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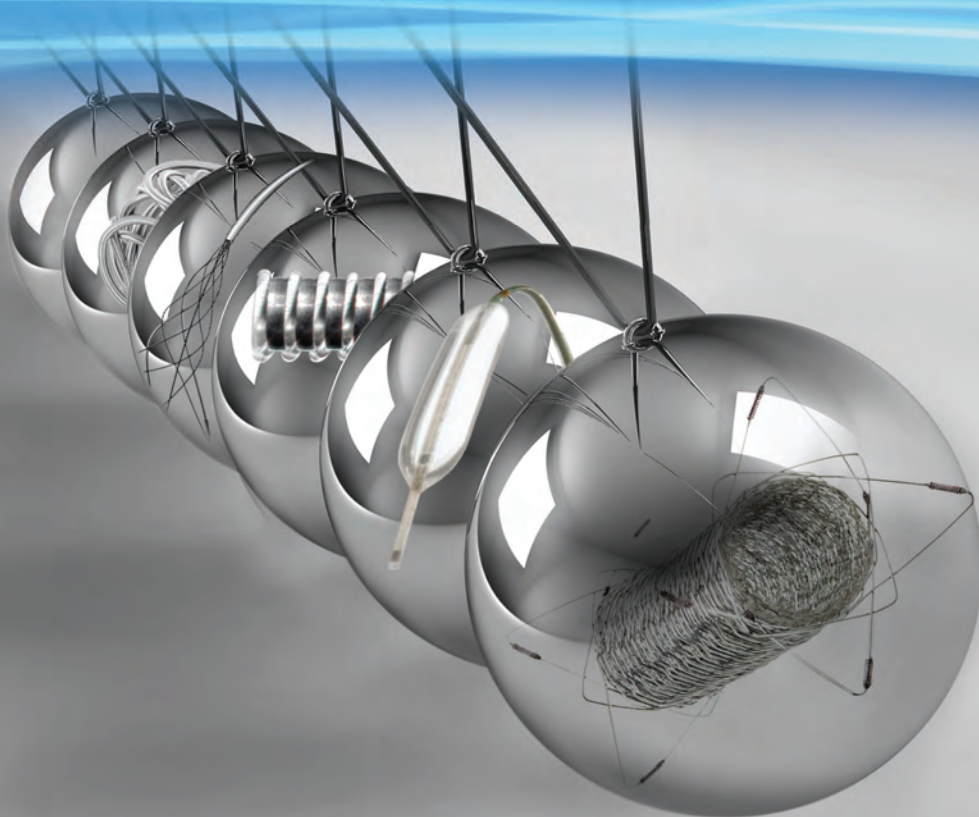
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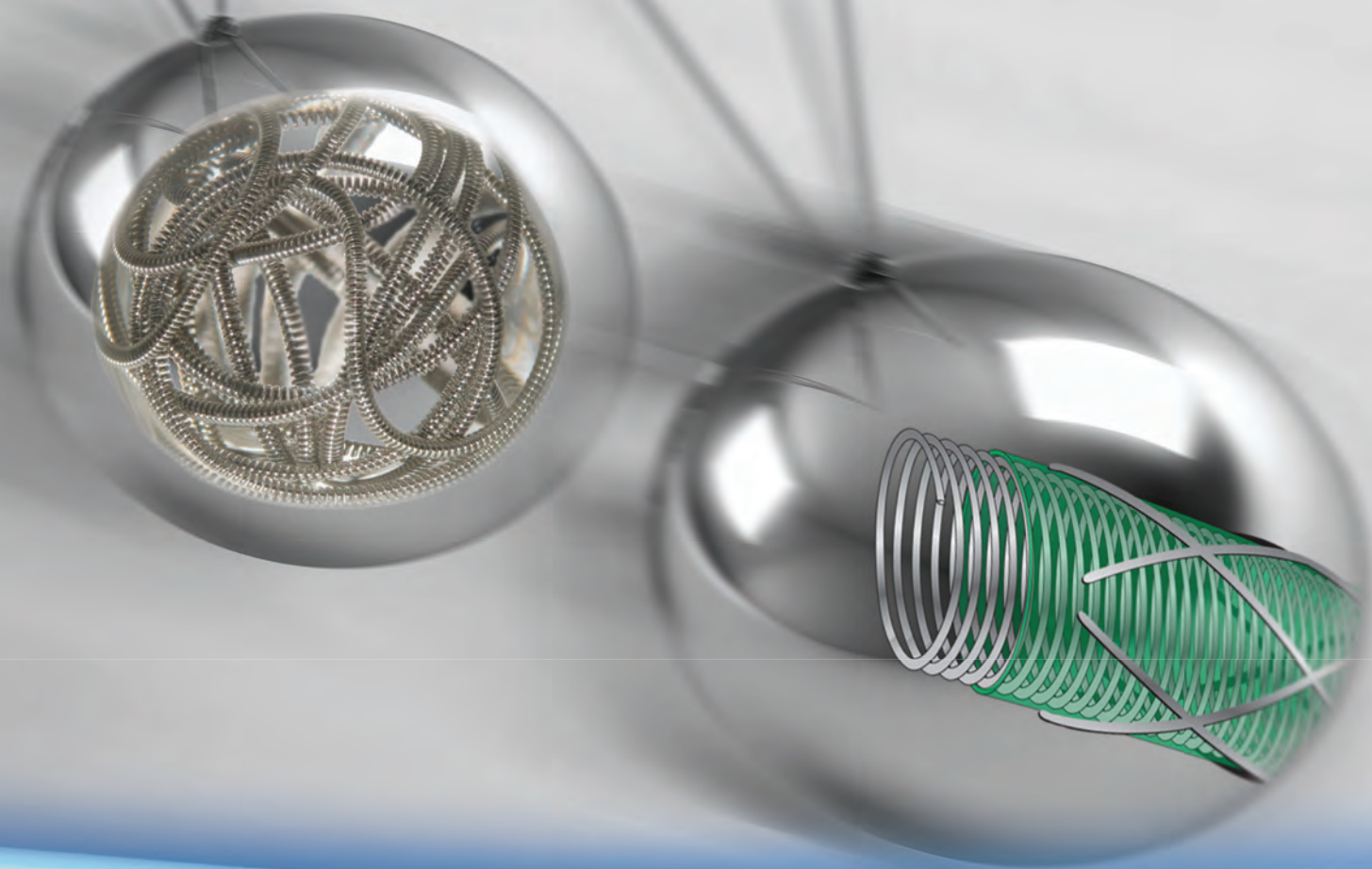
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The Scientific Method: A Need for Something Better?

M. Castillo, *Editor-in-Chief*

Here is the last part of the triptych that started with the “Perspectives” on brainstorming that was followed by the one on verbal overshadowing. I have decided to keep this for last because it deals with and in many ways attempts to debunk the use of the scientific method as the Holy Grail of research. Needless to say, the topic is controversial and will anger some.

In the “natural sciences,” advances occur through research that employs the scientific method. Just imagine trying to publish an original investigation or getting funds for a project without using it! Although research in the pure (fundamental) sciences (eg, biology, physics, and chemistry) must adhere to it, investigations pertaining to soft (a pejorative term) sciences (eg, sociology, economics, and anthropology) do not use it and yet produce valid ideas important enough to be published in peer-reviewed journals and even win Nobel Prizes.

The scientific method is better thought of as a set of “methods” or different techniques used to prove or disprove 1 or more hypotheses. A hypothesis is a proposed explanation for observed phenomena. These phenomena are, in general, empirical—that is, they are gathered by observation and/or experimentation. “Hypothesis” is a term often confused with “theory.” A theory is the end result of a previously tested hypothesis, meaning a proved set of principles that explain observed phenomena. Thus, a hypothesis is sometimes called a “working hypothesis,” to avoid this confusion. A working hypothesis needs to be proved or disproved by investigation. The entire approach employed to validate a hypothesis is more broadly called the “hypothetico-deductivism” method. Not all hypotheses are proved by empirical testing, and most of what we know and accept as truth about the economy and ancient civilizations is solely based on . . . just observation and thoughts. Conversely, the deep thinkers in the non-natural disciplines see many things wrong with the scientific method because it does not entirely reflect the chaotic environment that we live in—that is, the scientific method is rigid and constrained in its design and produces results that are isolated from real environments and that only address specific issues.

One of the most important features of the scientific method is its repeatability. The experiments performed to prove a working hypothesis must clearly record all details so that others may replicate them and eventually allow the hypothesis to become widely accepted. Objectivity must be used in experiments to reduce bias. “Bias” refers to the inclination to favor one perspective over others. The opposite of bias is “neutrality,” and all experiments (and their peer review) need to be devoid of bias and be neutral. In medicine, bias is also a part of conflict of interest and produces corrupt results. In medicine, conflict of interest is often due to relationships with the pharmaceutical/device industries. The

American Journal of Neuroradiology (AJNR), as do most other serious journals, requires that contributors fill out the standard disclosure form regarding conflict of interest proposed by the International Committee of Medical Journal Editors, and it publishes these at the end of articles.¹

Like many other scientific advances, the scientific method originated in the Muslim world. About 1000 years ago, the Iraqi mathematician Ibn al-Haytham was already using it. In the Western world, the scientific method was first welcomed by astronomers such as Galileo and Kepler, and after the 17th century, its use became widespread. As we now know it, the scientific method dates only from the 1930s. The first step in the scientific method is observation from which one formulates a question. From that question, the hypothesis is generated. A hypothesis must be phrased in a way that it can be proved or disproved (“falsifiable”). The so-called “null hypothesis” represents the default position. For example, if you are trying to prove the relationship between 2 phenomena, the null hypothesis may be a statement that there is no relationship between the observed phenomena. The next step is to test the hypothesis via 1 or more experiments. The best experiments, at least in medicine, are those that are blinded and accompanied by control groups (not submitted to the same experiments). Third is the analysis of the data obtained. The results may support the working hypothesis or “falsify” (disprove) it, leading to the creation of a new hypothesis again to be tested scientifically. Not surprising, the structure of abstracts and articles published in *AJNR* and other scientific journals reflects the 4 steps in the scientific method (Background and Purpose, Materials and Methods, Results, and Conclusions). Another way in which our journals adhere to the scientific method is peer review—that is, every part of the article must be open to review by others who look for possible mistakes and biases. The last part of the modern scientific method is publication.

Despite its rigid structure, the scientific method still depends on the most human capabilities: creativity, imagination, and intelligence; and without these, it cannot exist. Documentation of experiments is always flawed because everything cannot be recorded. One of the most significant problems with the scientific method is the lack of importance placed on observations that lie outside of the main hypothesis (related to lateral thinking). No matter how carefully you record what you observe, if these observations are not also submitted to the method, they cannot be accepted. This is a common problem found by paleontologists who really have no way of testing their observations; yet many of their observations (primary and secondary) are accepted as valid. Also, think about the works of Sigmund Freud that led to improved understanding of psychological development and related disorders; most were based just on observations. Many argue that because the scientific method discards observations extemporaneous to it, this actually limits the growth of scientific knowledge. Because a hypothesis only reflects current knowledge, data that contradict it may be discarded only to later become important.

Because the scientific method is basically a “trial-and-error” scheme, progress is slow. In older disciplines, there may not have been enough knowledge to develop good theories, which led to

the creation of bad theories that have resulted in significant delay of progress. It can also be said that progress is many times fortuitous; while one is trying to test a hypothesis, completely unexpected and often accidental results lead to new discoveries. Just imagine how many important data have been discarded because the results did not fit the initial hypothesis.

A lot of time goes into the trial-and-error phase of an experiment, so why do it when we already know perfectly well what to expect from the results? Just peruse *AJNR*, and most proposed hypotheses are proved true! Hypotheses proved false are never sexy, and journals are generally not interested in publishing such studies. In the scientific method, unexpected results are not trusted, while expected and understood ones are immediately trusted. The fact that we do “this” to observe “that” may be very misleading in the long run.² However, in reality, many controversies could have been avoided if instead of calling it “The Scientific Method,” we simply would have called it “A Scientific Method,” leaving space for development of other methods and acceptance of those used by other disciplines. Some argue that it was called “scientific” because the ones who invented it were arrogant and pretentious.

The term “science” comes from the Latin “scientia,” meaning knowledge. Aristotle equated science with reliability because it could be rationally and logically explained. Curiously, science was, for many centuries, a part of the greater discipline of philosophy. In the 14th and 15th centuries, “natural philosophy” was born; by the start of the 17th century, it had become “natural sciences.” It was during the 16th century that Francis Bacon popularized the inductive reasoning methods that would thereafter become known as the scientific method. Western reasoning is based on our faith in truth, many times absolute truth. Beginning assumptions that then become hypotheses are subjectively accepted as being true; thus, the scientific method took longer to be accepted by Eastern civilizations whose concept of truth differs from ours. It is possible that the scientific method is the greatest unifying activity of the human race. Although medicine and philosophy have been separated from each other by centuries, there is a current trend to unite both again.

The specialty of psychiatry did not become “scientific” until the widespread use of medications and therapeutic procedures offered the possibility of being examined by the scientific method. In the United States and Europe, the number of psychoanalysts has progressively declined; and most surprising, philosophers are taking their place.³ The benefits philosophy offers are that it puts patients first, supports new models of service delivery, and reconnects researchers in different disciplines (it is the advances in neurosciences that demand answers to the more abstract questions that define a human “being”). Philosophy provides psychiatrists with much-needed generic thinking skills; and because philosophy is more widespread than psychiatry and recognizes its importance, it provides a more universal and open environment.⁴ This is an example of a soft discipline merging with a hard one (medicine) for the improvement of us all. However, this is not the case in other areas.

For about 10 years, the National Science Foundation has sponsored the “Empirical Implications of Theoretical Models” initiative in political science.⁵ A major complaint is that most political

science literature consists of noncumulative empirical studies and very few have a “formal” component. The formal part refers to accumulation of data and use of statistics to prove or disprove an observation (thus, the use of the scientific method). For academics in political science, the problem is that some journals no longer accept publications that are based on unproven theoretic models, and this poses a significant problem to the “non-natural” sciences.⁶ In this case, the social sciences try to emulate the “hard” sciences, and this may not be the best approach. These academics and others think that using the scientific method in such instances emphasizes predictions rather than ideas, focuses learning on material activities rather than on a deep understanding of a subject, and lacks epistemic framing relevant to a discipline.⁷ So, is there a better approach than the scientific method?

A provocative method called “model-based inquiry” respects the precepts of the scientific method (that knowledge is testable, revisable, explanatory, conjectural, and generative).⁷ While the scientific method attempts to find patterns in natural phenomena, the model-based inquiry method attempts to develop defensible explanations. This new system sees models as tools for explanations and not explanations proper and allows going beyond data; thus, new hypotheses, new concepts, and new predictions can be generated at any point along the inquiry, something not allowed within the rigidity of the traditional scientific method.

In a different approach, the National Science Foundation charged scientists, philosophers, and educators from the University of California at Berkeley to come up with a “dynamic” alternative to the scientific method.⁸ The proposed method accepts input from serendipitous occurrences and emphasizes that science is a dynamic process engaging many individuals and activities. Unlike the traditional scientific method, this new one accepts data that do not fit into organized and neat conclusions. Science is about discovery, not the justifications it seems to emphasize.⁹

Obviously, I am not proposing that we immediately get rid of the traditional scientific method. Until another one is proved better, it should continue to be the cornerstone of our endeavors. However, in a world where information will grow more in the next 50 years than in the past 400 years, where the Internet has 1 trillion links, where 300 billion e-mail messages are generated every day, and 200 million Tweets occur daily, ask yourself whether it is still valid to use the same scientific method that was invented nearly 400 years ago?

REFERENCES

1. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research—Conflicts of Interest. International Committee of Medical Journal Editors, http://www.icmje.org/ethical_4conflicts.html. Accessed October 2, 2012
2. Halwes T. The Myth of the Magical Scientific Method. <http://dharma-haven.org/science/myth-of-scientific-method.htm>. Accessed October 2, 2012
3. Conn JH. **The decline of psychoanalysis: the end of an era, or here we go again.** *JAMA* 1974;228:711–12
4. Fulford KW, Stanghellini G, Broome M. **What can philosophy do for psychiatry?** *World Psychiatry* 2004;3:130–35

5. EITM. Empirical implications of theoretical models. <http://www.nsf.gov/sbe/ses/polisci/reports/pdf/eitmreport.pdf>. Accessed October 2, 2012
6. Clarke KA, Primo DM. Overcoming the 'physics envy.' <http://www.nytimes.com/2012/04/01/opinion/sunday/the-social-sciences-physics-envy.html>. Accessed October 2, 2012
7. Windschitl M, Thompson J, Braaten M. **Beyond the scientific method: model-based inquiry as a new paradigm of preference for school science investigations.** *Science Education* 2008;92:941–67
8. Musante S. A dynamic alternative to the scientific method: AIBS eye on education. http://www.aibs.org/eye-on-education/eye_on_education_2009_01.html. Accessed October 2, 2012
9. Understanding science. How science really works. <http://undsci.berkeley.edu>. Accessed October 2, 2012

EDITORIAL

Acute Stroke Imaging Research Roadmap II and International Survey of Acute Stroke Imaging Capabilities: We Need Your Help!

M. Wintermark and S.J. Warach,
on behalf of the STIR and Virtual International Stroke Trials
Archive (VISTA)-Imaging Investigators

Performing neuroimaging in the setting of a clinical trial, across multiple sites, is challenging because it involves standardizing acquisition and processing imaging protocols on multiple types of scanners by using multiple different platforms. The challenge is even more pronounced for cutting-edge imaging techniques such as arterial spin-labeling or diffusion tensor imaging. Mechanisms are therefore needed to translate and test advanced imaging methods across centers, to encourage the use of advanced imaging in acute settings, to stimulate closer academic-industry collaborations, and to promote the retrospective and prospective collection and pooling of imaging data while keeping in mind practical considerations such as clinical feasibility.

This daunting task has been tackled by the Stroke Imaging Research (STIR) group, a consortium of neuroradiologists, neurologists, imaging scientists, and emergency physicians with an interest in stroke imaging. STIR had a series of meetings in 2012 and 2013, where heated debates led to consensus recommendations as part of a stroke imaging research roadmap. This roadmap was published in *Stroke*¹ and should be read by all radiologists interested in stroke research because it contains some very important recommendations in terms of standardization of image acquisition and processing for stroke and how imaging should be incorporated in stroke clinical trials. To view the paper use the link in this issue's table of contents, or go directly to: <http://stroke.ahajournals.org/lookup/doi/10.1161/STROKEAHA.113.002015>.

STIR proposes a specific, standardized terminology for acute stroke imaging, aligned with the National Institute of Neurological Disorders and Stroke Common Data Elements,² including a modified TICI scale to assess reperfusion on cerebral conven-

tional angiography. STIR also introduces the concept of "Treatment-Relevant Acute Imaging Targets" (TRAIT), which is meant to capture imaging elements needed for inclusion (or exclusion) into specific treatment protocols. TRAIT acts as a shorthand term to describe the collection of specific imaging metrics used in protocols and simultaneously reminds trial designers to ensure that imaging is directed to the key anatomic or physiologic targets of their specific intervention.

STIR proposes the establishment of a calibration process for measuring ischemic core and penumbral software, as well as the population of the STIR clinical and imaging data repository to facilitate this calibration process. STIR recognizes that imaging techniques continuously evolve and that there will always be a newer, better ischemic core or penumbral imaging technique or processing software. Therefore, it is desirable to find a balance between continued attempts to improve on existing methods versus determining whether existing methods are good enough to be used in current clinical trials. At this time, STIR does not assess or recommend how to use ischemic core and penumbral information for prognosis, prediction of response to treatment, and/or selection of patients for reperfusion therapy. These are better answered in well-designed clinical trials or prospective validation studies.

Finally, STIR recommends the creation of a stroke neuroimaging network involving a collaboration between sites to promote scientific collaboration and education in a distributed fashion and further advance imaging protocols and software reuse, and data and model sharing. As a first step towards the creation of this network, STIR is conducting an international survey for which we need your help. Please take 15 minutes to fill out the survey, which can be found at <https://www.surveymonkey.com/s/DQRDYB2>. Thank you in advance for your collaboration!

REFERENCES

1. Wintermark M, Albers GW, Broderick JP, et al. **Acute Stroke Imaging Research Roadmap II.** *Stroke* 2013 Jul 16 [Epub ahead of print]
2. http://www.ninds.nih.gov/research/clinical_research/toolkit/common_data_elements.htm Accessed July 1 2013

EDITORIAL

Mechanical Thrombectomy after IMS III, Synthesis, and MR-RESCUE

L. Pierot, J. Gralla, C. Cognard, and P. White

Three recent publications report the neutral results of 3 randomized studies (Synthesis Expansion, Interventional Management of Stroke [IMS] III, and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR-RESCUE]) comparing IV thrombolysis therapy with the endovascular treatment (EVT) of acute ischemic stroke (AIS).^{1–3} The simultaneous publication of these 3 reports might lead to the erroneous conclusion that endovascular treatment has no place in the management of AIS. However, the role of endovascular therapy for the treatment must be more carefully considered, given the tremendous

evolution that imaging and endovascular treatment modalities have undergone over the past several years. Careful analysis of the IMS III, Synthesis, and MR-RESCUE studies shows that these reports have shortcomings as the result of changes in imaging and device technology and study designs.

Over the years, treatment of AIS has evolved to include IV thrombolysis and endovascular treatment. Several randomized studies of IV thrombolysis indicated little to no protection of ischemic brain before it was first reported that IV tPA administered within the first 3 hours after stroke onset had protective effects.⁴

The endovascular treatment of AIS has evolved, moving from intra-arterial (IA) chemical thrombolysis to mechanical thrombectomy. IA chemical thrombolysis was evaluated in several randomized trials that demonstrated its efficacy and safety.⁵ The next advancement in endovascular treatment of AIS was mechanical thrombectomy. Originally, this was performed with no specific tools by the injection of saline within the clot, disruption of the clot with a microguidewire, and “angioplasty” of the clot with remodeling balloons. Subsequently, dedicated, first-generation devices, such as the Merci and Penumbra devices, were developed to catch or aspirate the clot by different means. These first-generation devices were followed by second-generation devices (eg, “stentrievors” such as Solitaire), which were developed to promptly restore blood flow through retrieval of the clot.⁶

Until now, there have been no randomized, controlled trials (RCTs) that compared endovascular treatment with IV tPA for the management of AIS. IMS III, Synthesis, and MR-RESCUE are the first RCTs comparing EVT with IV tPA for the management of AIS and therefore merit attention.

IMS III is an international, phase 3, randomized, open-label clinical trial with a blinded outcome, comparing a combined approach of IV tPA followed by endovascular treatment with standard IV tPA treatment. From August 2006 to April 2012, 656 participants in 58 centers underwent random assignment (approximately 2 patients per center per year). The trial was stopped early because of futility, as defined by the prespecified aim (10% difference in Rankin scale score of ≤ 2 at 90 days). The proportion of patients with good outcome was slightly but not significantly higher in the EVT group (40.8% in the EVT arm and 38.7% in the IV tPA arm). There was also no significant difference between the 2 groups in mortality rate at 90 days as well as in the rate of symptomatic intracerebral hemorrhage within 30 hours after initiation of tPA. During the long inclusion period (close to 6 years), imaging and endovascular treatment modalities underwent a tremendous evolution, and utilization of this new technology was only partially implemented in the IMS III protocol, leading to major weaknesses in assessing the data. Only 306 of 656 participants (46.6%) had preoperative CTA, and it was not used for inclusion. Clearly, the inclusion of patients without a major arterial occlusion in a randomized trial dealing with endovascular recanalization illustrates an important weakness of the IMS III trial. Moreover, in patients for whom CTA was obtained, the rate of partial or complete recanalization was different in the EVT and IV tPA groups (81% and 35%, respectively, for an occlusion in the internal carotid artery; 86% and 68% for an M1 occlusion; and 88% and 77% for an M2 occlusion). Therefore, in terms of recanalization, mechanical thrombectomy performed better than IV

tPA alone for all locations, and, as demonstrated in IMS III, the proportion of patients with good clinical outcome increased with greater reperfusion, indicating that when analyzed this way, mechanical thrombectomy is associated with good clinical outcome. Another important limitation of the IMS III study is that the modalities of endovascular treatment were heterogeneous: IA tPA administration (37.8% of patients), mechanical thrombectomy with first-generation devices (34.3%), and only 1.2% with second-generation devices. As the SWIFT trial has clearly demonstrated, the second-generation devices are more efficacious than first-generation devices in terms of both recanalization and clinical outcome.⁶ Thus, the results of IMS III were outdated before they were published.

Synthesis is an Italian randomized, multicenter clinical trial with a blinded end point, comparing standard IV tPA treatment (initiated within 4.5 hours after symptom onset) to endovascular treatment (within 6 hours after symptom onset). Patients who were assigned to the EVT group did not receive IV tPA. All EVT modalities were authorized. The demonstration of vessel occlusion was not a precondition for inclusion in this trial. From February 2008 to April 2012, 362 patients underwent random assignment (3.5 patients per center per year). The primary end point (disability-free survival at 90 days, mRS 0 or 1) was similar in both groups (30.4% in the endovascular group and 34.8% in the IV tPA group). Symptomatic intracranial hemorrhage within 7 days occurred in 6% of patients in both groups. Additionally, death at 90 days was not significantly different between the 2 groups.

Although the inclusion period was shorter in Synthesis than in IMS III (4 versus 6 years), the same important limitations were encountered in Synthesis. Modern CT or MR modalities were not used to visualize vessel occlusion or evaluate penumbra. Additionally, EVT was mostly IA tPA, and second-generation devices were not commonly used (13.9%). Two other important limitations were encountered in Synthesis. Patients with NIHSS score as low as 2 were included, and they have a very high probability of having a good recovery at 3 months regardless of treatment given. Also, IV tPA was not given in the endovascular group. Synthesis compared IV tPA treatment with isolated endovascular treatment and not with combined IV tPA treatment and mechanical thrombectomy. As a consequence, the endovascular group received treatment 1 hour later than the IV tPA group, which, in part, explains the relative equivalence of endovascular treatment and IV tPA treatment. Given this, it is not surprising that the Synthesis study reconfirms the IMS III finding regarding the limited efficacy of endovascular treatment performed with obsolete tools.

The MR-RESCUE trial was a small, phase 2b, randomized, controlled, open-label, multicenter trial conducted at 22 sites in North America (0.7 patient per center per year). Patients between the ages of 18–85 years with NIHSS scores of 6–29 who had a large-vessel, anterior circulation ischemic stroke were randomly assigned within 8 hours after the onset of symptoms to undergo either mechanical embolectomy (with first-generation devices) or to undergo standard medical care. All patients underwent pretreatment multimodal CT or MR imaging of the brain, which permitted stratification according to the presence of a favorable penumbral pattern versus a nonpenumbral pattern. Among 118 eligible patients (recruited over 7 years), 64 were assigned to the

embolectomy group and 54 were assigned to the standard care group. In total, 68 of 118 patients (57.6%) had a favorable penumbra pattern after pretreatment imaging. The 118 patients were classified into 4 groups: embolectomy/penumbra (34 patients); standard care/penumbra (34 patients); embolectomy/nonpenumbra (30 patients); and standard care/nonpenumbra (20 patients). Statistical analysis testing to determine whether there was an interaction between treatment assignment and penumbra pattern determined no significance. Mean 90-day mRS scores were not significantly different between the groups. The number of patients with good outcome at 90 days (mRS 0–2) was also not significantly different between the groups. Death rates also did not significantly differ.

Unlike the IMS III or Synthesis trials, pretreatment evaluation was more precise, with CTA or MRA used to depict large-vessel proximal anterior circulation occlusion, and multi-modal CT or MR imaging of the brain was used to evaluate penumbra status. However, the MR-RESCUE trial still had several drawbacks. The number of patients in each group was small (≤ 30 patients), leading a low statistical power for their analysis. As in Synthesis and IMS III, first-generation thrombectomy devices were used, and it is now clear that efficacy is limited with these devices relative to second-generation thrombectomy devices. Additionally, the management of penumbra patterns is not easy to use in real time. Despite the development of specific models, the study software processed only 58% of cases successfully in real time. Additionally, the final pattern assignment changed after core laboratory postprocessing in an alarmingly high percentage of cases (8%). Also, the use of 2 different imaging modalities (CT and MR) to evaluate penumbra further complicates the findings in this study. It should also be noted that the time to enrollment for all patients in this study, regardless of assigned group, was relatively long (from 5.2–5.8 hours), and this must have played a large role in the overall disappointing clinical outcomes in the trial.

In summary, IMS III, Synthesis, and MR-RESCUE are 3 important trials that perfectly illustrate the difficulty of randomization for techniques that are in rapid evolution.

The main weaknesses of these trials are:

- Long period of inclusion (all studies): Difficulty in the recruitment of patients was encountered in most RCTs dealing with endovascular treatment. Mechanical thrombectomy is not yet a validated treatment, and, by not including all their relevant patients in RCTs, physicians take the risk of having this technique not validated.
- Small number of patients per center per year (all studies).
- Inappropriate preoperative imaging including absence of CTA or MRA to detect an occlusion of a major arterial trunk (IMS III and Synthesis).
- No evaluation of the salvageable brain with perfusion CT or MR (IMS III and Synthesis).
- Comparison of IV tPA to EVT alone (Synthesis and MR-

RESCUE): It does not appear to be the best course of action because the combined approach (endovascular treatment plus IV tPA) allows the physician to start treatment early and to synergize the efficacy of chemical and mechanical thrombolysis.

- Heterogeneity of the endovascular techniques used, with most of them no longer used. IA administration of fibrinolytics, as well as treatment with first-generation thrombectomy devices, has become outdated with the development of second-generation, stent-based thrombectomy devices. The clinical impact of the use of these novel devices has been impressively illustrated by the recent SWIFT trial.⁶

Analysis of the IMS III, Synthesis, and MR-RESCUE studies reveals what steps must be taken next in evaluating the role of endovascular therapy for the treatment of AIS. Analyzing these studies clearly shows that the selection of patients (clinical status, initial extension of ischemic lesion, depiction of arterial occlusion depicted, evaluation of salvageable brain) and the therapeutic methods evaluated are key elements that must be addressed in the design of future studies.

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REFERENCES

1. Ciccone A, Valvassori L, Nichelatti M, et al. **Endovascular treatment for acute ischemic stroke.** *N Engl J Med* 2013;368:904–13
2. Broderick JP, Palesch YY, Demchuk AM, et al. **Endovascular treatment after intravenous t-PA versus t-PA alone for stroke.** *N Engl J Med* 2013;368:893–903
3. Kidwell CS, Jahan R, Gornbein J, et al. **A trial of imaging selection and endovascular treatment for ischemic stroke.** *N Engl J Med* 2013;368:914–23
4. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. **Tissue plasminogen activator for acute ischemic stroke.** *N Engl J Med* 1995;333:1581–87
5. Furlan A, Higashida R, Wechsler L, et al. **Intraarterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial.** *JAMA* 1999;282:2003–11
6. Saver JL, Jahan R, Levy EI, et al. **Solitaire flow restoration device versus Merci retriever in patients with acute ischaemic stroke (SWIFT): a randomized, parallel-group, non-inferiority trial.** *Lancet* 2012;380:1241–49

Imaging of Cosmetic Facial Implants and Grafts

C.J. Schatz and D.T. Ginat



ABSTRACT

SUMMARY: A wide variety of implants and grafts have been used for cosmetic facial surgery, including forehead, nose, cheek, lip, and chin augmentation. Some of the implant materials include silicone, expanded polytetrafluoroethylene (Gore-Tex), hydroxylapatite, and porous polyethylene (Medpor). Grafts include bone and cartilage, which can be prepared as “Turkish Delight” for rhinoplasty. Imaged facial implants and grafts can be encountered incidentally or purposely to evaluate complications. Many of these materials have distinct radiologic imaging features and should not be misinterpreted as pathology. Conversely, implant complications should be appropriately recognized by using a focused imaging approach. The purpose of this article was to review the different types of cosmetic facial implants and grafts with an emphasis on their expected and complicated radiologic imaging appearances.

According to the American Society of Plastic Surgeons, a total of 243,777 rhinoplasty surgeries, 46,931 forehead lift surgeries, 20,680 chin augmentation surgeries, and 11,996 cheek implant surgeries were performed in the United States in 2011.¹ On occasion, patients who have undergone facial augmentation procedures present for radiologic imaging. Therefore, it is important to be familiar with the common types of cosmetic facial implants and their complications. The imaging features of these implants differ on the basis of location and composition. Often, implants are used at the same time in different locations to achieve balanced proportions of facial tissues. The imaging features of commonly used material for cosmetic facial implants are reviewed in the following sections and in the Table.²⁻⁵ It is important to recognize the expected imaging appearances of implants and their complications to avoid misdiagnosing these as neoplastic processes, for instance.^{6,7}

AUGMENTATION TECHNIQUES

Forehead

Cosmetic forehead augmentation (browplasty) can be performed for the treatment of frown lines and to mitigate bony deficiencies.^{8,9} Popular materials used in the midforehead include soft expanded

polytetrafluoroethylene strips and silicone implants.⁷ The expanded polytetrafluoroethylene strips (Gore-Tex; W.L. Gore & Associates, Newark, Delaware) are usually 1- to 2-mm thick and positioned in a vertical orientation (Fig 1). On the other hand, shield-shaped silicone implants can cover a relatively larger area, and irregular edges and perforations limit implant motion and capsular contraction.⁸

Cheek

Cheek augmentation (malarplasty) consists of adding volume to either the malar or submalar space or a combination of these to compensate for osseous and soft-tissue deficiencies and to elevate the cheek subcutaneous tissues.¹⁰⁻¹² Specifically, submalar implants are positioned over the anterior walls of the maxilla (Fig 2). On the other hand, malar implants are positioned over the malar eminences and zygomatic bones in a more superior and lateral position (Fig 3). Combined malar-submalar implants span both the malar eminence and the submalar triangle.

The implants are typically inserted into the subperiosteal pocket via a transoral approach through the canine fossa.¹⁰ In the past, ovoid “button” implants were used for cheek augmentation. Currently, Silastic (Dow Corning, Auburn, Michigan) shell implants are especially popular and have characteristic crescent shapes to match the contours of the underlying anatomy. The implants are available in a variety of sizes and can be further customized intraoperatively. Small holes are sometimes incorporated into the implant to promote tissue ingrowth. In addition, the implants can be secured with sutures or screws. Other materials that have been used for midface augmentation include porous polytetrafluoroethylene (Medpor; Stryker, Allendale, New Jersey) and expanded polytetrafluoroethylene (Gore-Tex).^{10,12}

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Facial implant materials

Material	Properties and Uses	Imaging Appearance
Silicone rubber (Silastic)	Rubber elastomer, well-tolerated and easily customizable, soft pliable consistency; indications: chin, lateral jaw, cheek, and nose augmentation	CT: variable attenuation, usually denser than soft tissue, but less dense than bone and best discerned using bone windows; MRI: very low signal intensity on T1- and T2-weighted sequences
Expanded polytetrafluoroethylene (Gore-Tex)	Biocompatible, long-lasting but can be removed surgically; indications: lower face lift, nasal and forehead augmentation	CT: higher attenuation relative to soft tissues, but less dense than bone; MRI: hypointense to fat on T1- and T2-weighted sequences
Polytetrafluoroethylene (Teflon) Porous polyethylene (Medpor)	Obsolete Inert and biocompatible, low complication rate, permanent; indications: lower face and nasal augmentation; also used for orbital and auricular reconstruction; fibrovascular ingrowth can render removal difficult	Imaging features similar to those of Gore-Tex CT: attenuation between fat and water; MRI: hypointense to fat on T1- and T2-weighted sequences; enhancement may occur due to fibrovascular ingrowth
Hydroxylapatite	Inert and biocompatible; blocks of hydroxylapatite can allow fibrovascular ingrowth and bony incorporation	CT: hyperdense, hyperattenuation similar to that of bone; the implant can become incorporated into and inseparable from the adjacent bone; MRI: low signal on T1 and T2; enhancement may occur due to fibrovascular ingrowth
Bone	Occasionally used for rhinoplasty, cheek, and chin augmentation; harvest sites include iliac crest, cranium, turbinates, rib	CT: same as normal bone elsewhere; cortex and trabecular can be identified unless resorption has occurred MRI: high T1 and T2 marrow signal and low-signal cortex are often discernible; in the early postoperative period, marrow edema within the graft may appear as low T1 and high T2 signal
Cartilage	Often used in rhinoplasty and sometimes chin augmentation; harvest sites include nasal septum, conchal cartilage, and costal cartilage; can be part of osteochondral grafts; can be diced and wrapped in Surgicel (Turkish Delight)	CT: soft-tissue density; may form a rim of calcification or ossification; MRI: usually low T2 and high T2 signal

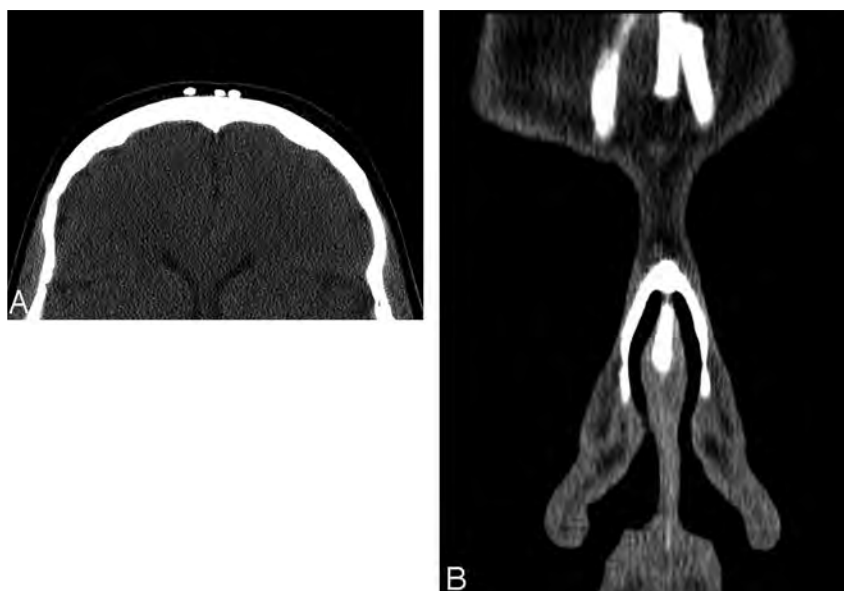


FIG 1. Forehead implants. Axial (A) and coronal (B) CT images show thin strips of expanded polytetrafluoroethylene in the midline of the forehead in the region of the glabella.

Nasal

Cosmetic rhinoplasty consists of altering the shape of the nose to achieve a more attractive form and relationship with the sur-

rounding facial structures, while attempting to preserve the normal functions of the nose. Augmentation rhinoplasty consists of

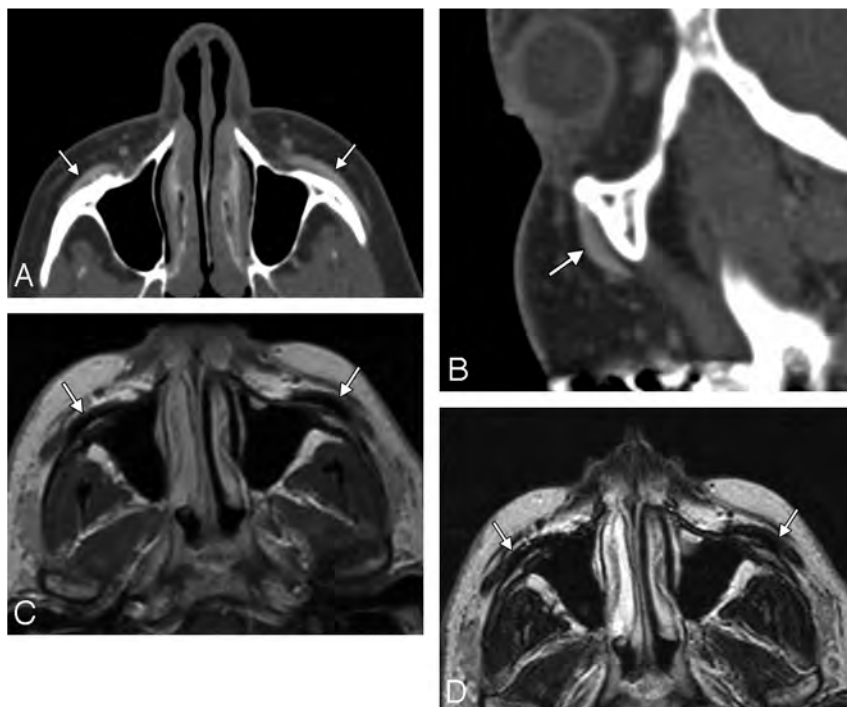


FIG 2. Malar implants. Axial (A) and sagittal (B) CT images show bilateral hyperattenuated silicone implants (*arrows*) overlying the malar eminences. The silicone implants (*arrows*) are hypointense on T1 (C) and T2 (D) MR images.

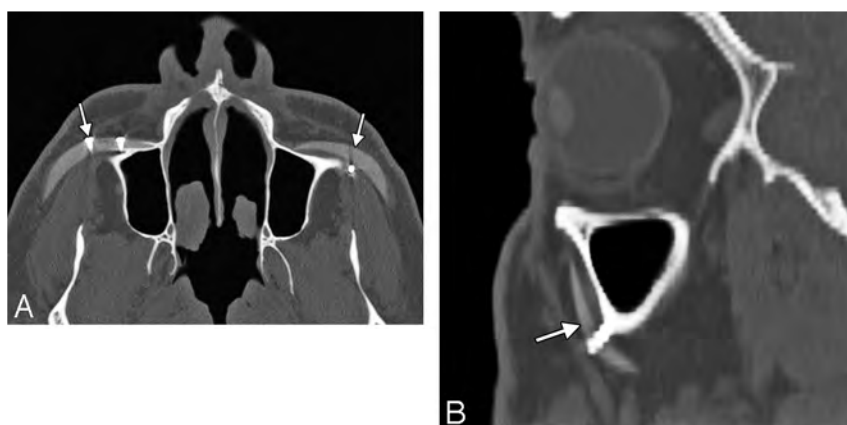


FIG 3. Submalar implants. Axial (A) and sagittal (B) CT images show bilateral silicone implants (*arrows*) secured to the underlying maxillary bone via screws.

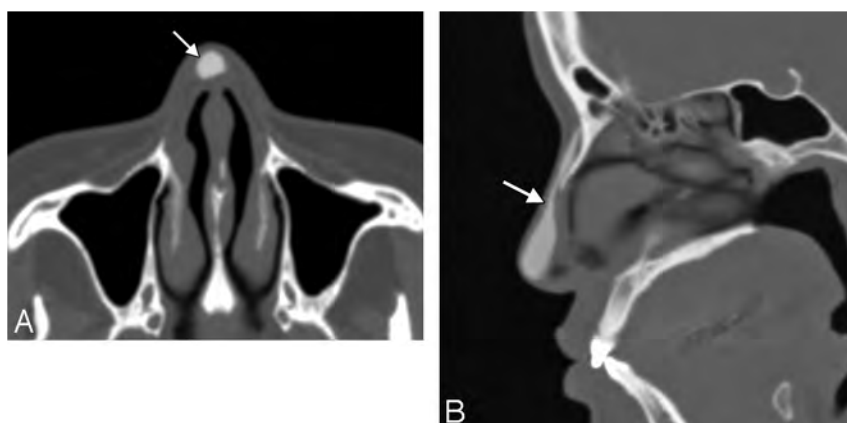


FIG 4. Rhinoplasty with a dorsal Silastic implant. Axial (A) and sagittal (B) CT images show the hyperattenuated implant (*arrows*) in the midline of the nasal dorsum. Note that the implant is thicker toward the tip than over the nasal bones.

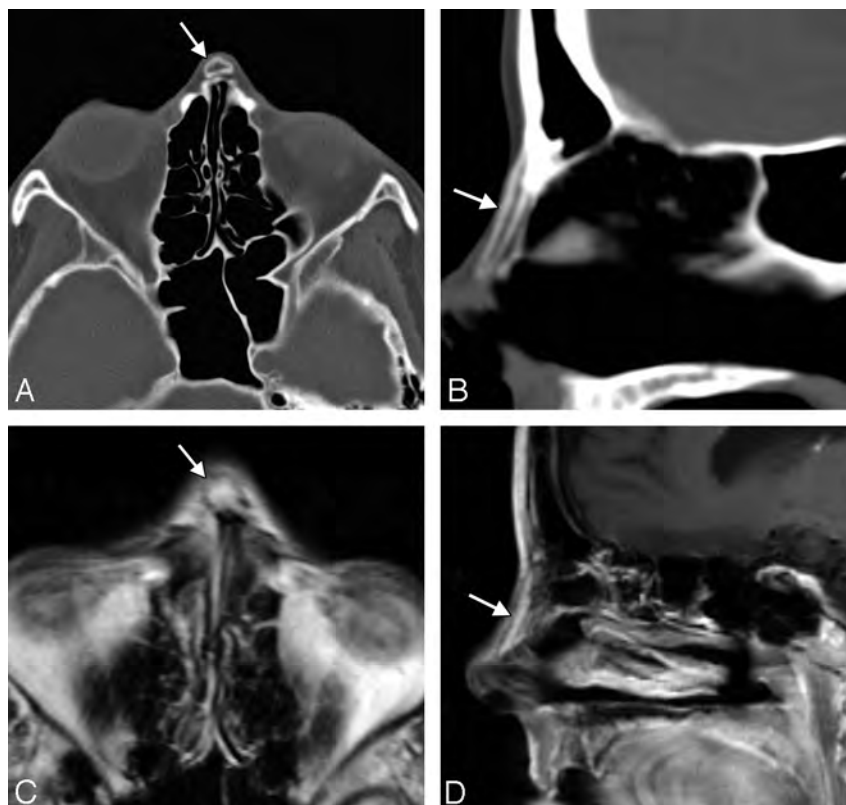


FIG 5. Rhinoplasty with a dorsal bone graft. Axial (A) and sagittal (B) CT images show a linear bone graft positioned along the dorsum of the nose (arrows). Axial T2 (C) and sagittal postcontrast T1 (D) MR images show hyperintense fatty marrow within the bone graft (arrows).



FIG 6. Premaxillary implant. Axial CT image shows a hyperattenuated silicone implant positioned anterior to the midline of the maxilla (arrow).

adding material to the nose and can be performed by using autograft, such as bone (Fig 4), or alloplastic implants, such as silicone rubber (Fig 5).^{13,14} Satisfactory results have also been obtained with cartilage grafts, Medpor, Gore-Tex, and Mersilene (Ethicon, Cincinnati, Ohio) mesh.¹⁻¹⁸ “Turkish Delight” is a unique augmentation preparation used for rhinoplasty composed of diced cartilage mixed with a small amount of the patient’s blood and wrapped in Surgicel (Ethicon).¹⁹ Variations of Turkish Delight, consisting of diced polyethylene, have also been used.¹⁷ Different portions of the nose can undergo augmentation, including the nasal dorsum, tip, columella, and combinations of these.

Premaxillary augmentation can be performed as an adjunct to

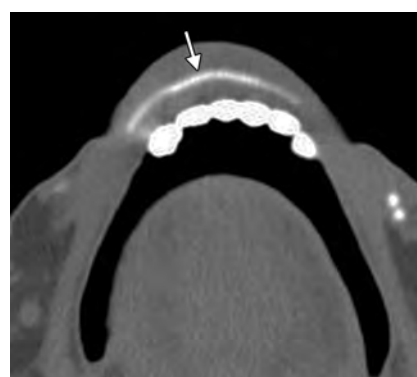


FIG 7. Lip implant. Axial CT image shows a hyperattenuated, thin, curved expanded polytetrafluoroethylene lower lip implant (arrow). Also note the presence of hyperattenuated fillers in the region of the oral commissures.

rhinoplasty to treat an excessively deep infranasal sulcus (premaxillary underprojection) and an acute nasolabial angle.^{20,21} This can be accomplished by using osteochondral grafts or a strip of alloplastic material, such as silicone, positioned in the midline just inferior to the anterior nasal spine of the maxilla (Fig 6). Some silicone implants have a bat-wing configuration.²⁰

Lip

Surgical augmentation of the lips (cheiloplasty) can be performed to mitigate the changes that occur with aging, such as the development of perioral rhytides and diminished fullness and ante-



FIG 8. Chin augmentation with cartilage graft. Axial CT image shows a chunk of soft tissue with a peripheral rim of hyperattenuation (calcification or ossification) anterior to the mentum (arrow).



FIG 9. Chin augmentation with silicone implant. Frontal 3D CT surface rendering shows a midline crescent-shaped implant positioned inferior to the mental foramina.

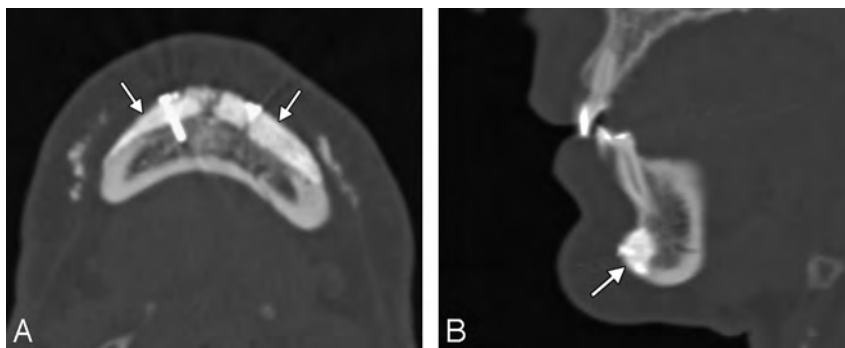


FIG 10. Chin augmentation with hydroxylapatite. Axial (A) and sagittal (B) CT images show the bilateral hyperattenuated implants (arrows) secured to the mandible with screws. The implant appears to have become incorporated into the underlying bone.



FIG 11. Chin augmentation with Medpor. Axial (A) and sagittal (B) CT images show a low-attenuation implant (arrows) anterior to the body of the mandible.

rior projection.²² Lip augmentation can also be performed in response to fashion trends, in which full lips are deemed a desirable trait.²² A variety of implants are available for lip augmentation, including fat grafts, musculoaponeurotic system grafts, acellular human dermis, and expanded polytetrafluoroethylene.²²⁻²⁵ These can be inserted via incisions made medial to the oral commissures and by threading the implant deep to the submucosal plane.²² The implants are often given a trapezoidal shape, so that these are thinner laterally to conform to the natural tapering of the

lips toward the oral commissures. Gore-Tex lip implants typically measure <3 mm in thickness so that these are not excessively stiff.²⁴

Chin

Cosmetic chin augmentation (mentoplasty) can be performed to treat a deficient chin projection, which results from soft-tissue atrophy and retrusion of the mandible.^{26,27} Ideally the chin should extend to the level of the vermilion border of the lower lip



FIG 12. Submental implant. Sagittal CT image shows the hyperattenuated silicone implant (arrow) positioned inferior to the mentum.

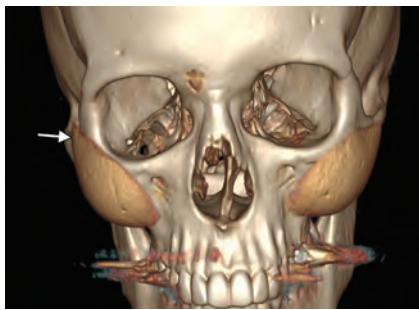


FIG 13. Implant migration. 3D CT image shows superior displacement of the right cheek implant (arrow), which occurred as a result of trauma. Compare it with the normal position of the contralateral implant.

in the sagittal plane.²⁶ Autogenous materials, such as cartilage grafts, have been used in chin augmentation for more than a century (Fig 7). Such grafts can be readily procured during concomitant reduction rhinoplasty, for instance. However, autografts have a tendency to resorb, resulting in loss of cosmetic effect. Consequently, alloplastic chin implants, including Gore-Tex (Fig 8), Medpor (Fig 9), Silastic (Fig 10), and hydroxylapatite (Fig 11), have been introduced.^{28,29} Most chin implants are crescent-shaped and wider centrally than laterally and are positioned approximately in the midline. Alternate designs such as cleft chin implants that are focally narrow in the midline are also available and should not be thought abnormal. Chin implants are usually



FIG 15. Implant infection. Axial fat-suppressed T1-weighted MR image shows abnormal enhancement surrounding a fluid-filled right cheek implant pocket (arrow), which extends through the right lateral cheek subcutaneous tissues to an overlying skin defect, representing a draining sinus (arrowhead). An external marker is positioned over the draining sinus.

inserted in a subperiosteal pocket anterior to the pogonion and inferior to the mental foramen.

Relatively stiff submental chin implants (Fig 12) can be inserted in conjunction with liposuction to tighten the skin and optimize the neck-chin angle.³⁰ A variant of the chin implant is the prejowl implant, which serves to fill in a prominent prejowl sulcus and is often used in conjunction with a midface lift.^{26,27} The prejowl implants extend farther posteriorly and are thicker laterally compared with chin implants.

COMPLICATIONS

Essentially all cosmetic facial implants and grafts can incur complications, which include infection, migration or displacement, extrusion, foreign body reaction, heterotopic bone formation, and bone erosion. These complications often warrant imaging evaluation and subsequent surgical removal of the implants. The rate of alloplastic implant removal due to complications has been reported to be 1.9%–4.9%.^{16,31} Imaging for early postoperative hematomas and seromas is not routinely performed unless these are larger than expected, there is an increase in size, or there are other associated complications.

Implant-related infections usually occur within the first 2 weeks of surgery and have been reported to occur in 3.2% of nasal dorsum implants, 3.8% of malar implants, and 5.3% of chin implants.^{31,32} Proplast (Vitek, Valencia, California) Teflon (DuPont, Wilmington, Delaware), which is an ultraporous composite material, has fallen out of use due to the relatively high incidence

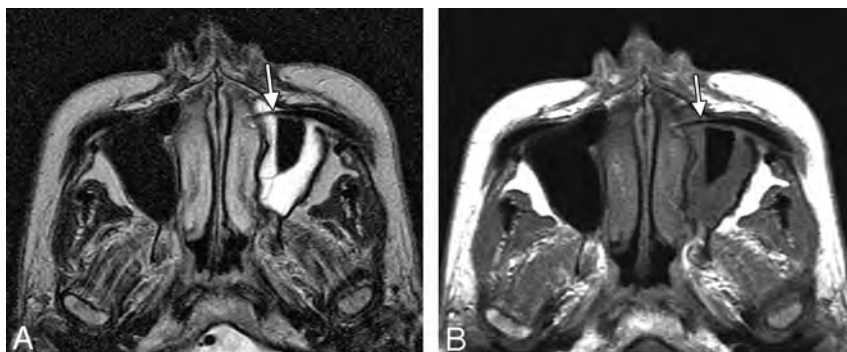


FIG 14. Implant extrusion. Axial T2 (A) and T1 (B) MR images show that the right cheek silicone implant has eroded through the anterior maxillary wall and has partially extruded into the maxillary sinus (arrow). There is associated left maxillary sinusitis.

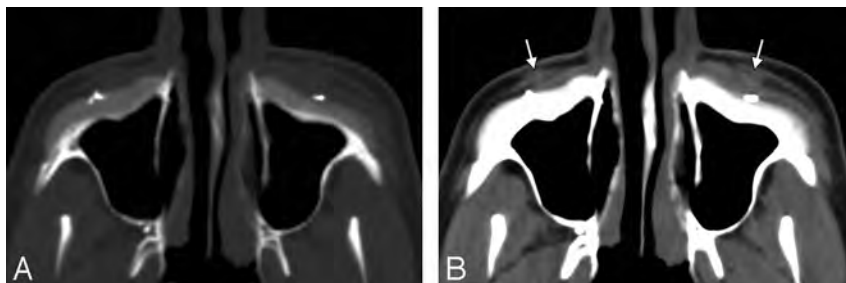


FIG 16. Cheek implant inflammation with foreign body giant cell reaction. The patient presented with bilateral cheek swelling many years after receiving the implants. Axial CT images in bone (A) and soft-tissue (B) windows show bilateral Proplast Teflon implants with inflammatory changes in the overlying soft tissues (arrows). Note the crude morphology of the implants, which date to the early 1990s. The implants were subsequently removed, and pathology demonstrated a combination of attenuated fibrous tissue with focal foreign body giant cell reaction and acute chronic inflammation.

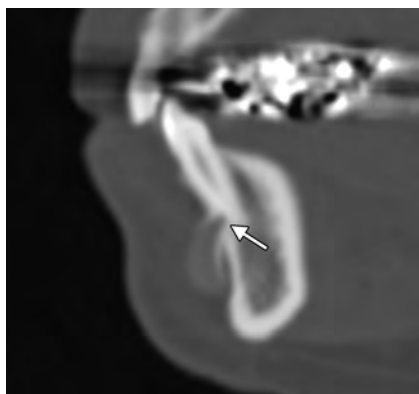


FIG 17. Chin implant bone erosion. Sagittal CT image shows that the Silastic implant has eroded through the underlying cortex, abutting the tooth apices (arrow).

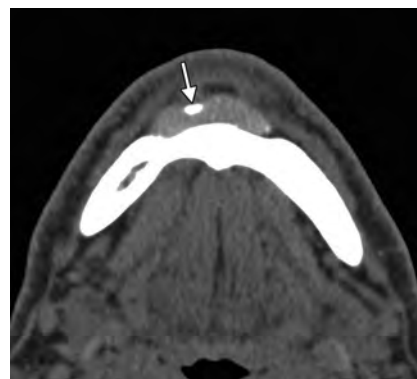


FIG 18. Chin implant heterotopic bone formation. Axial CT image shows a hyperattenuated focus along the margin of the silicone chin implant (arrow) at the expected location of the periosteal covering.

of complications, such as infection, which are reported to occur in 16% of cases.³³ Implant infections can manifest as cellulitis, abscess, draining sinuses, and/or osteomyelitis. MR imaging is particularly sensitive for delineating the extent of the infections, especially early in the course of disease. Fat-suppressed postcontrast T1-weighted sequences are particularly useful and often show enhancement within and surrounding the implant pocket (Fig 13). If there is incomplete fat suppression due to technical problems, short tau inversion recovery sequences can be helpful. Placement of external markers over palpable lesions and draining sinuses can facilitate determination of the necessary FOV and subsequent interpretation because the disease involvement can sometimes extend far away from the implant itself. Late infections can mimic malignancy, such as squamous cell carcinoma.⁷ Infections can also be associated with implant displacement and extrusion.

Chronic inflammation and foreign body giant cell reaction tend to be most exuberant with Proplast Teflon but can also be encountered with newer alloplastic implants, such as Medpor.^{33,34} On histology, intracytoplasmic phagocytosis of disintegrated implant material is characteristic. Cross-sectional imaging can reveal ill-defined soft tissue surrounding the implants (Fig 14). The abnormal soft tissues can enhance and form more focal masslike areas as well.

Implant migration or displacement is an uncommon complication that can certainly result in undesirable changes in cosmesis as well as serious complications, such as scleral erosion.³⁵ 3D CT surface renderings are particularly useful for delineating the po-

sitioning of the implants (Fig 15). Although sutures, screws, fibrous capsule formation, fibrovascular in-growth, and osseous incorporation can secure implants in position, the implants can become displaced by trauma, fluid collections, and bone erosion.

Bone erosion is a relatively frequent finding, occurring with most Silastic chin implants.^{36,37} The degree of erosion is usually mild and benign in nature; however, the implants can expose dental roots, resulting in pain (Fig 16). Chin implants can also erode into the mental foramen and compress the nerve. CT with dental scanning parameters is the technique of choice for evaluating symptomatic bone erosion caused by chin implants.³⁶

Implant extrusion is a rare event that is predisposed by an underlying infection, which can make the overlying tissues relatively friable.³⁸ Implants can extrude through the overlying skin or incision site, such as the intraoral approach for cheek implants, and even into the maxillary sinuses by eroding of the cheek implant through the anterior maxillary sinus wall (Fig 17).³⁹

Heterotopic new bone formation is not infrequently noted adjacent to implants, particularly those in a subperiosteal location. It is usually thin and linear in a distribution corresponding to the periosteum and is of little clinical significance.³⁶ However, heterotopic ossification is occasionally nodular (Fig 18) and can cause cosmetic deformity.² CT is the technique of choice for evaluating heterotopic ossification because some implants can display signal characteristics that are nearly identical to heterotopic bone on MR imaging.

CONCLUSIONS

Many types of implants and grafts are now available for facial augmentation. Radiologic imaging plays an important role in the assessment of cosmetic facial implants. MR imaging and CT with multiplanar reformats and, in some cases, 3D surface renderings are useful modalities for characterizing facial implants and their complications.

REFERENCES

1. 2011 Cosmetic plastic surgery statistics. Cosmetic Procedure Trends. <http://www.plasticsurgery.org/Documents/news-resources/statistics/2011-statistics/2011-cosmetic-procedures-trends-statistics.pdf>. Accessed April 20, 2012
2. Schatz CJ, Ginat DT. **Imaging of facial cosmesis**. In: Ginat DT, Westesson PL, eds. *Atlas of Post-Surgical Neuroradiology*. Berlin, Germany: Springer-Verlag; 2012. In press
3. Ginat DT, Schatz CJ. **Imaging features of midface injectable fillers and associated complications**. *AJNR Am J Neuroradiol*. 2012 Jul 26 [Epub ahead of print]
4. Coskun U, Ozturk S, Zor F, et al. **Imaging of porous polyethylene implant by using multidetector spiral computed tomography**. *J Craniofac Surg* 2008;19:156–58
5. Galluzzi P, De Francesco S, Giacalone G, et al. **Contrast-enhanced magnetic resonance imaging of fibrovascular tissue ingrowth within synthetic hydroxyapatite orbital implants in children**. *Eur J Ophthalmol* 2011;21:521–28
6. Gonçalves ES, Almeida AS, Soares S, et al. **Silicone implant for chin augmentation mimicking a low-grade liposarcoma**. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:e21–23
7. Bain CJ, Odili J. **Late infection of an alloplastic chin implant masquerading as squamous cell carcinoma**. *J Plast Reconstr Aesthet Surg* 2012; 65:e151–52
8. Wong JK. **Forehead augmentation with alloplastic implants**. *Facial Plast Surg Clin North Am* 2010;18:71–77
9. Mandel MA. **Treatment of glabellar frown lines using silicone implants**. *Ann Plast Surg* 1991;27:110–04
10. Binder WJ, Azizzadeh B. **Malar and submalar augmentation**. *Facial Plast Surg Clin North Am* 2008;16:11–32, v
11. Binder WJ. **Facial rejuvenation and volumization using implants**. *Facial Plast Surg* 2011;27:86–97
12. Matros E, Momoh A, Yaremchuk MJ. **The aging midfacial skeleton: implications for rejuvenation and reconstruction using implants**. *Facial Plast Surg* 2009;25:252–59
13. Ward JL, Garri JJ, Wolfe SA. **The osseous genioplasty**. *Clin Plast Surg* 2007;34:485–500
14. Erlich MA, Parhiscar A. **Nasal dorsal augmentation with silicone implants**. *Facial Plast Surg* 2003;19:325–30
15. Gentile P, Cervelli V. **Nasal dorsum reconstruction with 11th rib cartilage and auricular cartilage grafts**. *Ann Plast Surg* 2009;62: 63–66
16. Conrad K, Torgerson CS, Gillman GS. **Applications of Gore-Tex implants in rhinoplasty reexamined after 17 years**. *Arch Facial Plast Surg* 2008;10:224–31
17. Richardson S, Agni NA, Pasha Z. **Modified Turkish delight: morcellized polyethylene dorsal graft for rhinoplasty**. *Int J Oral Maxillofac Surg* 2011;40:979–82
18. Berghaus A, Stelter K. **Alloplastic materials in rhinoplasty**. *Curr Opin Otolaryngol Head Neck Surg* 2006;14:270–77
19. Erol OO. **The Turkish delight: a pliable graft for rhinoplasty**. *Plast Reconstr Surg* 2000;105:2229–41, discussion 2242–43
20. Fanous N, Yoskovitch A. **Premaxillary augmentation: adjunct to rhinoplasty**. *Plast Reconstr Surg* 2000;106:707–12
21. Kim WS, Kim CH, Yoon JH. **Premaxillary augmentation using autologous costal cartilage as an adjunct to rhinoplasty**. *J Plast Reconstr Aesthet Surg* 2010;63:e686–90
22. Byrne PJ, Hilger PA. **Lip augmentation**. *Facial Plast Surg* 2004;20:31–38
23. Hanke CW. **A new ePTFE soft tissue implant for natural-looking augmentation of lips and wrinkles**. *Dermatol Surg* 2002;28:901–08
24. Linder RM. **Permanent lip augmentation employing polytetrafluoroethylene grafts**. *Plast Reconstr Surg* 1992;90:1083–90, discussion 1091–92
25. Clymer MA. **Evolution in techniques: lip augmentation**. *Facial Plast Surg* 2007;23:21–26
26. Shire JR. **The importance of the prejowl notch in face lifting: the prejowl implant**. *Facial Plast Surg Clin North Am* 2008;16:87–97, vi
27. Romo T, Yalamanchili H, Sclafani AP. **Chin and prejowl augmentation in the management of the aging jawline**. *Facial Plast Surg* 2005;21:38–46
28. Choe KS, Stucki-McCormick SU. **Chin augmentation**. *Facial Plast Surg* 2000;16:45–54
29. Cottrell DA, Wolford LM. **Long-term evaluation of the use of coral-line hydroxyapatite in orthognathic surgery**. *J Oral Maxillofac Surg* 1998;56:935–41, discussion 941–42
30. Newman J, Dolsky RL, Mai ST. **Submental liposuction extraction with hard chin augmentation**. *Arch Otolaryngol* 1984;110:454–57
31. Wang TD. **Multicenter evaluation of subcutaneous augmentation material implants**. *Arch Facial Plast Surg* 2003;5:153–54
32. Niamtu J 3rd. **Essentials of cheek and midface implants**. *J Oral Maxillofac Surg* 2010;68:1420–29
33. Whear NM, Cousley RR, Liew C, et al. **Post-operative infection of Proplast facial implants**. *Br J Oral Maxillofac Surg* 1993;31:292–95
34. Gosau M, Draenert FG, Ihrler S. **Facial augmentation with porous polyethylene (Medpor): histological evidence of intense foreign body reaction**. *J Biomed Mater Res B Appl Biomater* 2008;87:83–87
35. Menon V, Gupta H. **An unusual complication of malar augmentation: transconjunctival exposure and scleral erosion**. *Ophthal Plast Reconstr Surg* 2012;28:e7–9
36. Abrahams JJ, Caceres C. **Mandibular erosion from Silastic implants: evaluation with a dental CT software program**. *AJNR Am J Neuroradiol* 1998;19:519–22
37. Matarasso A, Elias AC, Elias RL. **Labial incompetence: a marker for progressive bone resorption in Silastic chin augmentation**. *Plast Reconstr Surg* 1996;98:1007–14, discussion 1015
38. Graham BS, Thiringer JK, Barrett TL. **Nasal tip ulceration from infection and extrusion of a nasal alloplastic implant**. *J Am Acad Dermatol* 2001;44:362–64
39. Adams JR, Kawamoto HK. **Late infection following aesthetic malar augmentation with Proplast implants**. *Plast Reconstr Surg* 1995;95:382–84

^1H -MR Spectroscopy in the Human Spinal Cord

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ABSTRACT

SUMMARY: MR spectroscopy allows insight into the chemical composition of human tissue noninvasively. Thereby it can help to better characterize pathologic processes affecting the spinal cord and may provide important clinical markers for differential diagnosis. However, due to technical challenges, it has been rarely applied to the spinal cord. The aim of this review was to summarize the technical development and clinical studies using MR spectroscopy in the spinal cord. Main challenges of applying MR spectroscopy in the spinal cord are discussed, and a description of a state-of-the-art scan protocol is given. In conclusion, MR spectroscopy is a promising tool for research and diagnosis of the spinal cord because it can provide additional information complementary to other noninvasive imaging methods. However, the application of MR spectroscopy in the spinal cord is not straightforward, and great care is required to attain optimal spectral quality.

ABBREVIATIONS: CRLB = Cramér-Rao lower bounds; ECG = electrocardiogram; FWHM = full width at half maximum; IVS = inner-volume suppression; OVS = outer-volume suppression

MR spectroscopy enables the determination of metabolite concentrations in a predefined region of interest in the human body, both noninvasively and in vivo. In contrast to other MR imaging techniques, such as diffusion-weighted imaging, blood oxygen level-dependent contrast imaging, or structural MR imaging methods, MR spectroscopy provides information about the chemical microenvironment from atomic nuclei in a variety of functional groups. This allows detection of changes in the concentration of various metabolites for investigating healthy tissue and pathologic processes and exercise- or drug-induced changes. In vivo, MR spectroscopy is mainly based on proton (^1H), carbon (^{13}C), or phosphorous (^{31}P) nuclei. Due to the 100% natural abundance and the highest gyromagnetic ratio of protons¹ among the above-mentioned nuclei, ^1H -MR is the most sensitive in vivo spectroscopy method. In addition,

^1H -MR spectroscopy requires the same hardware as clinical MR imaging and can thus be integrated into clinical scan protocols in an efficient way. Hence ^1H -MR spectroscopy became a promising tool for basic physiologic studies and clinical diagnosis.

CLINICAL RELEVANCE OF MR SPECTROSCOPY IN THE SPINAL CORD

Traumatic injuries, neoplastic disorders, infections, inflammations, and degenerative changes cause microstructural and/or metabolic changes in neural tissue and may have an immediate and strong impact on quality of life, especially when occurring in the spinal cord. Symptoms can range from chronic pain or focal alterations in sensations or motor functions to severe states such as complete paralysis or organ failure. Appropriate patient treatment requires a diagnostic approach that enables reliable differential diagnosis; therapy planning and monitoring, including planning of biopsies, surgeries, and radiation therapy; and monitoring treatment response to specific cancer, neuroprotective, anti-inflammatory, or rehabilitative treatments. MR spectroscopy has been applied for several years in the investigation of pathologic processes involving the brain and has gained an increased acceptance among the clinicians by its potential in differentiating high- versus low-grade tumors,² distinguishing tumor from nontumoral tissue,² differentiating solid lesions from cysts or abscesses,³ monitoring the results of treatment, and occasionally predicting outcome.⁴

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The information obtained by MR spectroscopy may often prevent unnecessary invasive interventions, thus avoiding further negative impact on patient outcome. These applications have just begun to be implemented in the evaluation of patients with spinal cord disease. Other potential applications specific to the spinal cord include investigation of neuroregeneration and reorganization following spinal cord injury and monitoring during rehabilitation or pharmacologic therapies. The response to therapy may be predicted on the basis of specific biomarkers (eg, *N*-acetylaspartate, choline, creatine) to enable personalized treatment. MR spectroscopy quantifies multiple metabolite concentrations that reflect the state of energy metabolism, myelination, neuronal attenuation and function, glial impairments, or altered membrane turnover and, therefore, can be a valuable tool for the investigation of spinal cord pathologies.

TECHNICAL PROBLEMS OF MR SPECTROSCOPY APPLIED TO THE SPINAL CORD

The application of this promising technique to the spinal cord requires comprehensive expertise. The following methodologic challenges, related specifically to the application of MR spectroscopy in the human spinal cord, have hindered its application in the clinical settings for many years:

- 1) Strong susceptibility changes, related to the anatomic tissue heterogeneity (vertebral bodies, CSF, muscle tissue, and so forth) around the spinal cord, lead to spatially periodic distortions of the static magnetic (B_0) field along the spinal cord.⁵ This distorts the line shape of the spectra and reduces the SNR.

- 2) The small diameter of the spinal cord (approximately 1 cm in the cervical cord and even lower in the thoracic and lumbar cord⁶) limits the possible voxel size, resulting in a low SNR and potentially imprecise quantification of metabolite concentrations.

- 3) The attainable SNR is also limited by the relatively great distance from the region of interest to the receive coils; for example, in the cervical spinal cord, the distance is approximately 5 cm in all directions and can reach >15 cm in the lower cord regions.

- 4) The pulsatile flow of the CSF, caused by waves of arterial pressure transmitted via brain contractions due to the fixed total volume inside the skull to the CSF,⁶ can reduce the spectral quality (eg, impaired water suppression, distorted line shape and phase). The induced spinal cord motion does not seem to be critical because the maximum transversal displacement in the cervical region is approximately 0.6 mm in the anteroposterior direction.⁷

- 5) Subject motion is another severe problem because voxel dimensions are in the range of millimeters and are maximized to include as much spinal cord tissue as possible for increasing the SNR. Hence, patient motion in the range of millimeters (which is not unlikely considering the relatively long scanning times needed for spectroscopy) would already move the position of the voxels considerably out of the spinal cord. The result might be the contamination of the spectra with resonances of non-neural tissues, such as lipids, from nearby bone marrow or muscles and a further reduction of the SNR for the metabolites of interest.

- 6) Dynamic changes of the static magnetic field induced by cardiac, respiratory, and subject motion or hardware instabilities lead to inconsistent spectral averaging and hence to line broaden-

ing and thus to further SNR reduction and increased spectral overlap. Related frequency and phase shifts can also alter quantification results and impair water suppression.⁸

- 7) Anatomic variability, subject motion, or pathophysiologic changes of the electromagnetic tissue properties may affect the transmit (B_1) field and hence alter desired flip angles, localization profiles, and SNR.

- 8) With conventional MR spectroscopy localization techniques such as the point-resolved spectroscopic sequence, the signal of different metabolites stems from slightly different regions (chemical shift displacement artifact¹). If one considers the small size of the spinal cord, the excitation volumes for some metabolites might be shifted partially out of the cord region. This has to be considered to minimize measurement errors with regard to relative metabolite concentrations (see "Inner- and Outer-Volume Suppression").

All of the above-mentioned technical problems lead to a reduction of the spectral quality and thus to a reduction in the amount of reliably detectable metabolites (eg, Cramér-Rao lower bounds ≤ 20), which diminish the clinically usable information content. Therefore, optimizing and improving spectral quality is necessary to obtain meaningful data.

CONSIDERATIONS FOR SPINAL CORD MR SPECTROSCOPY PROTOCOLS

The following issues should be addressed in the scan protocol to optimize the spectral quality and to enable reliable metabolite quantification in the human spinal cord *in vivo*.

Optimizing SNR

To optimize SNR, moving to higher field strength (currently from 1.5T,^{3,9-15} >2T,^{5,16} and 3T^{14,15,17-30} to 7T³¹) is an obvious solution. However, spinal cord MR spectroscopy at a very high field strength (≥ 3 T) may provide increased SNR but is not readily available and requires further hardware and sequence development to address increased B_0 and B_1 inhomogeneity problems. Clinically relevant 3T protocols use point-resolved spectroscopic sequence³² volume localization,^{5,9-28,31,33} which, in contrast to a stimulated echo-acquisition mode³⁴ as used by Kim et al,³ provides more SNR. Usually the body coil is used for excitation, while a possibly close-fitting multichannel surface-coil array used for reception is an efficient way to maximize the obtainable SNR.²⁹⁻³¹

Voxel Placement

To measure exclusively cord tissue, to gain optimal SNR and B_0 shim quality, one must apply effort to ensure accurate voxel placement. Cooke et al⁵ recommended a voxel size of $9 \times 7 \times 35$ mm³ and appropriate placement so that the lower limit of the voxel level is aligned with the inferior border of the C2 vertebral body. In some investigations, the voxel dimensions are kept constant but smaller than the previously recommended size, to ensure that the voxel size fits even in subjects with a small spinal cord diameter,^{9,14,19,22,29,30,33,36,37} whereas others adapt the voxel size to each individual subject.^{17,18,20,21} Edden et al²⁶ introduced 1D proton MR spectroscopy imaging in the spinal cord at 3T. However, the huge excitation volume of $90 \times 10 \times 12$ mm³ might be difficult to apply in a curved spinal cord.

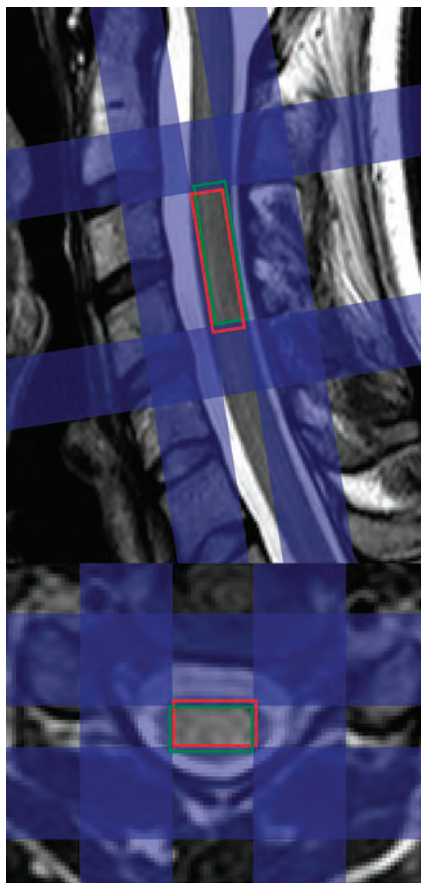


FIG 1. Exemplary planning based on sagittal and axial T2-weighted turbo spin-echo images of the cervical spinal cord. Due to the chemical shift displacement artifact, the signal of different metabolites stems from different regions. For example, spectral voxels from NAA (red voxel) and myo-inositol (green voxel) are shifted against each other. Applying narrow (approximately 10 mm) sharp-edged inner-volume saturation bands (blue) with high bandwidths (>10 kHz) reduces this artifact. The saturation pulses above and below the spectroscopy voxel also facilitate flow compensation.

For correct voxel placement, high-resolution images (eg, high-resolution T2-weighted turbo spin-echo¹⁷) of the spinal cord must be acquired (Fig 1). The voxel position should also be checked frequently to avoid misplacement due to subject motion (Fig 2). Therefore, some groups divide the spectroscopic acquisition into blocks interleaved with images to check for the correct voxel placement.^{5,16,19,30}

Inner- and Outer-Volume Suppression

Localized saturation bands are frequently used to reduce CSF flow artifacts, to suppress signals from outside the voxel, and to overcome the chemical shift displacement artifacts (see “Technical Problem” 8).¹ To that broadband, radio-frequency pulses with a small transition bandwidth should be used.

OVS. Saturation bands outside the spectroscopy voxel can help to enhance localization efficiency by suppressing signals from outside the voxel (ie, lipids) and acting as flow compensation.^{9,10,15,20,21,24-26}

IVS. Because saturation pulses can be designed to have a much higher bandwidth (>10 kHz) than the localization pulses, the chemical shift displacement artifacts can be substantially reduced by saturating the nonoverlapping areas of the metabolite-specific excitation volumes. Henning et al¹⁷ demonstrated how IVS can be applied in the spinal cord (Fig 1). This technique was also used in Hock et al^{18,19,29,30} in combination with a reduced thickness of the saturation band (10 mm), which further reduced the chemical shift displacement artifact and sharpened the saturation section profile.

ECG/Respiratory Triggering/Gating

Cooke et al⁵ suggested pulse triggering to reduce the influence of CSF flow and spinal cord motion. However, in some studies, pulse triggering/gating was not used, mainly to reduce acquisition time.²¹ For pulse triggering, either the ECG^{14,17,19,25} or infrared finger pulse oximeters can be used. Cooke et al⁵ used a pulse oximeter, and they stated that a gating delay of 400 ms after cardiac electrical systole provides the most stable spectra, whereas Henning et al¹⁷ used an ECG device with a delay of 300 ms. In contrast, Hock et al^{18,19,29,30} used a trigger delay of about 700 ms because the flow curve reaches a minimum at about 650 ms after the R peak of the ECG.⁶ They could show that ECG triggering also applied during the preparation phases improves the spectral quality and the robustness of the acquisition.²⁹

Respiratory triggering and gating were not used for MR spectroscopy in the human spinal cord until now. However, distinct dynamic B0 field fluctuations occur due to breathing at high B0 fields and/or during acquisitions in lower regions of the spinal cord. A recent technique to reduce the influence of dynamic B0 changes is the phase and frequency alignment of each free induction decay by using non-water-suppressed ¹H-MR spectroscopy before spectral averaging (compare with the section “Water and Fat Suppression”).^{19,30} Nevertheless, whether the use of respiratory triggering/gating is feasible is yet to be investigated because it might lead to severe scanning-time prolongation. More advanced solutions such as real-time B0 shim updating, as recently demonstrated for breast MR spectroscopy,³⁸ are also promising for spinal cord MR spectroscopy.

B0 Shimming

Static B0 inhomogeneity is one of the major problems in MR spectroscopy of the spinal cord because it leads to broadening of the resonance lines and hence to a further reduction of the achievable SNR and spectral resolution. Unfortunately, many authors are not specific in describing their B0 shimming routine. Different B0 shimming techniques like manual B0 shimming,^{11,13,15} B0 shimming based on static B0 maps,^{17,18,23} and iterative B0 shimming or a projection-based B0 shimming³⁹⁻⁴² approach^{18,19,26,29,30} have been used to reduce B0 field distortions. Hock et al^{18,29} compared different B0 shimming techniques and demonstrated that ECG-triggered, second order, projection-based B0 shimming resulted in the best spectral quality (full width at half maximum of the water peak around 9 Hz at 3T) and reproducibility. The use of a third³¹ or even higher order or dedicated local B0 shim coils might further improve these results in the future.

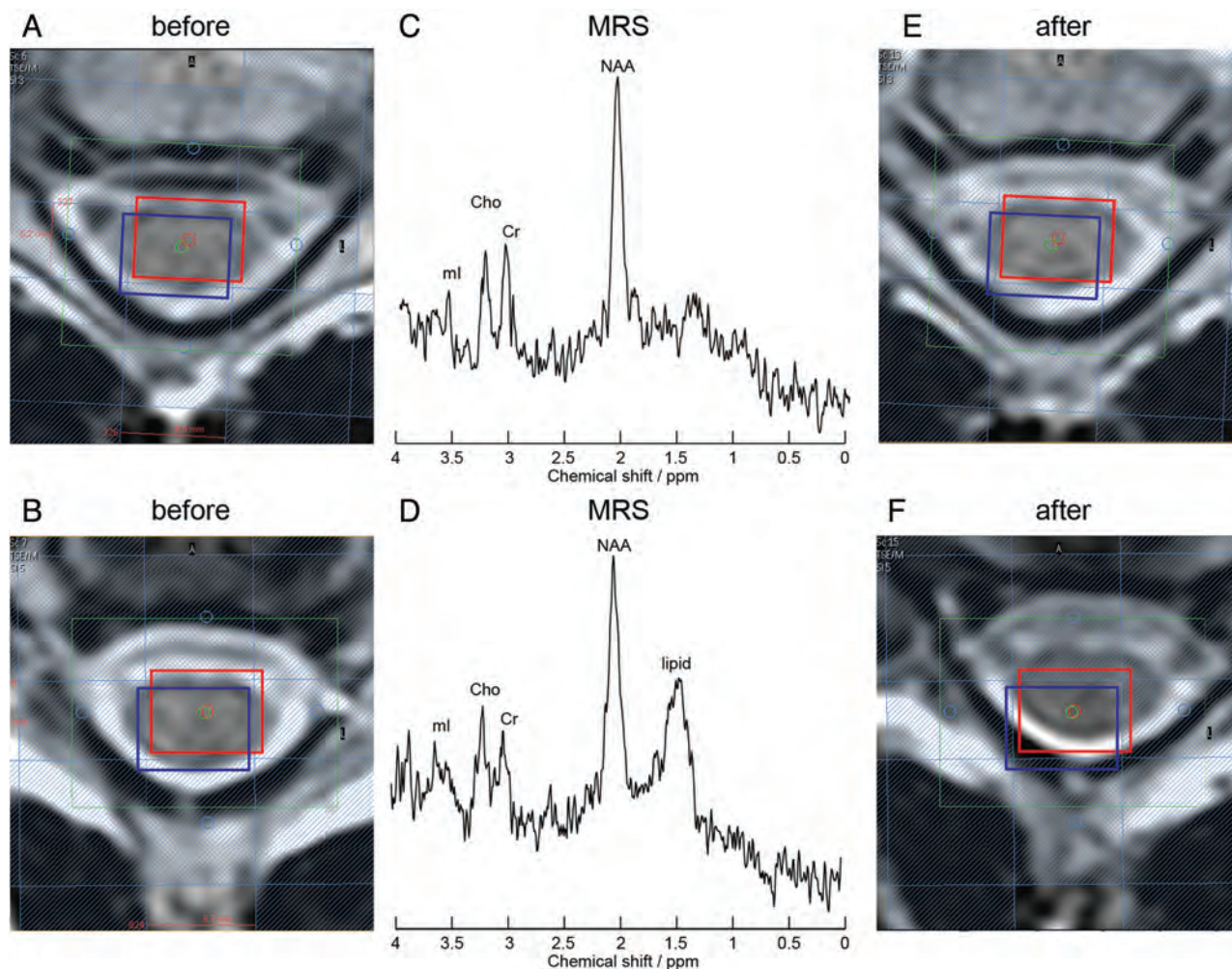


FIG 2. Effect of patient motion. Axial T2-weighted images with planning of the measurement voxel (red box, NAA; blue box, myo-inositol; green, B0 shim volume; blue transparent, IVS) before (A and B) and after (E and F) MR spectroscopy acquisition (C and D). Increased line width, lower SNR, and additional lipid peaks may occur in motion-affected measurements (D) compared with non-motion-affected acquisitions (C).

Water and Fat Suppression

The concentration of water in nervous system tissue is much higher than the concentration of metabolites¹; thus, the water peak around 4.7 ppm dominates the spectrum and can lead to baseline distortions and gradient vibration-induced signal modulations.¹ Therefore, the water peak is usually suppressed (or reduced), for example, with chemical shift selective⁴³ water suppression,^{3,5,9,16,20-23,27,28} or with asymmetric variable power RF pulses with optimized relaxation delays (VAPOR).^{29,30,44} In addition, Hock et al^{19,30} showed that MR spectroscopy in the spinal cord is possible without water suppression by using the metabolite-cycling technique.⁴⁵ The advantage of this technique for spinal cord MR spectroscopy is that the high water peak can be used for frequency and phase alignment of single acquisitions before spectral averaging, which reduces the resulting line width of the spectrum and thus increases the obtainable SNR. Some groups^{12,24,26} used a combined water and fat suppression, for example, by application of dual-band hyperbolic secant pulses.⁴⁶ However, lipid concentration is very low in the healthy spinal cord; thus, it will not disturb the spectrum as severely as the water peak. Thus, the lipid peak does not need to be suppressed. In

addition, an elevated lipid signal can be used as an indicator of subject motion (voxel position displaced to an area with high lipid concentration [Fig 2]) or inefficient spectral localization. Another argument for not using fat suppression is the potential suppression of metabolites lying in the frequency range of the fat-suppression pulse, such as lactate or macromolecules, which may provide important information on the nature of pathologic tissues.

Cervical Spinal Cord and Beyond

Most publications show spinal cord MR spectroscopy results of the upper part of the cervical region.^{3,5,9-28} Additional problems in lower regions are the following: 1) a reduced diameter of the spinal cord,⁶ which further reduces the possible voxel size and thus the SNR; 2) a larger distance between coils and the region of interest (in the thoracic part around 5–15 cm); and 3) increased spatial and temporal B0 and B1 inhomogeneity caused by the higher impact of cardiac and respiratory motion due to the closer proximity of the heart and lungs. However, 3 publications^{3,17,25} have shown decent results in lower cord regions in cases of large

tumors obliterating the subarachnoid spaces and thus reducing the CSF flow and allowing an increased voxel size.

Acquisition Settings

Settings for TE range from TE = 30⁵ to 43²⁵ ms over 144²⁴ to 288²⁵ ms. Short TEs enable higher SNR and detection of metabolites with short T2 times. On the other hand, a long TE can be used additionally to differentiate, for example, the lactate peak around 1.3 ppm from lipid resonances.²⁵ The settings for the TR range from TR = 590¹⁵ to 3000⁵ ms (mostly 2000 ms as in Henning et al¹⁷), and the excitation flip angles are usually set to 90° as in Henning et al.¹⁷ Adaptations of these values considering the Ernst angle (see de Graaf¹) might be useful.

In addition, a trade-off has to be made by setting the number of repetitions. A high number of repetitions can improve the SNR (with the square root of repetitions) but is also associated with long scanning time and increased sensitivity to subject motion. In the literature, repetition values from 160²³ to 512¹⁷ can be found. Furthermore, 512 ms acquisition time is commonly used as in Henning et al¹⁷ and Hock et al.³⁰

Postprocessing: Quantification and Display of the Results

Postprocessing includes averaging of the free induction decays, Fourier transformation, phase and eddy current correction, and time-domain filtering. Therefore, additional acquisitions of unsuppressed water spectra are frequently added^{12,17,20,21,23,24,29,30} for phase and eddy current correction with the technique described by Klose.⁴⁷ However, if the metabolite-cycling technique demonstrated in Hock et al^{19,30} is used, these corrections can be performed without additional acquisition of non-water-suppressed spectra, and additional phase and frequency alignment can be applied before spectral averaging.

Quantification of metabolite concentrations is the main goal of spinal cord MR spectroscopy. Some groups show absolute quantification results,^{5,9,10,16,21,26} while others show concentration ratios.^{11,13,15,17,19,20,22,23,27-30} However, metabolite quantification may be complicated by several technical pitfalls. An overview of the quantification challenge can be found in Heinzer-Schweizer⁴⁸ and de Graaf.¹ While some authors used quantification software provided by the scanner manufacturer or their own fitting tools,^{5,11-15,24,26} most authors used the LCModel⁴⁹ (Stephen Provencher, Oakville, Ontario, Canada)^{9,10,17,19-23,27,28} or jMRUI (http://www.mrui.uab.es/mrui/mrui_Overview.shtml)^{16,35,50} for fitting the spectra, which improves the comparability of the results. However, the wide range of quantification results in healthy volunteers (On-line Table 1) highlights the difficulty of this procedure and its reliance on different acquisition and quantification methods. Primary requirements for a dependable quantification are high spectral quality (high SNR and small line width) and an artifact-free signal. Cramér-Rao lower bounds of each metabolite fit, mean and SD of the line width and SNR (eg, of the highest metabolite peak), coefficient of variation of the measurements, plots of single subjects, and group average spectra are necessary to give the reader a chance to evaluate the reliability of the results. Unfortunately, few publications provide sufficient quality indicators as can be seen in On-line Tables 1 and 2.

Currently, spinal cord MR spectroscopy allows the investigation of 4 major metabolites in healthy volunteers: NAA, Cho, Cr, and myo-inositol. Moreover, additional metabolites like lactate or glutamate/glutamine may become visible in patients. In addition, information about macromolecules and lipid can be retrieved from spectra but may show a dramatic intersubject variability. A further increase of the SNR may be the key to uncovering additional metabolites: Hock et al^{19,30,36} also could detect scyllo-inositol with CRLB below 25% by using non-water-suppressed proton MR spectroscopy.

STATE-OF-THE-ART PROTOCOL

In conclusion, a state-of-the-art protocol includes the following: high-resolution localization images to verify the voxel position frequently; point-resolved spectroscopic sequence localization with short TEs (≤ 30 ms); an acquisition time of 512 ms; an SNR efficiency-optimized excitation flip angle and TR pair (for an excitation flip angle of 90°, a TR ≥ 2000 ms should be used); IVS; optimized water-suppression or non-water-suppressed ¹H-MR spectroscopy with frequency alignment of single free induction decays; ECG triggering; ECG-triggered, projection-based, higher order shimming to ensure a narrow line width (< 0.1 ppm); a high number of averages (eg, 512 resulting in a total scanning time of approximately 17 minutes); and sophisticated hardware (eg, high field strength [≥ 3 T] and dedicated spine coil arrays) enabling a high SNR (≥ 4).

MR SPECTROSCOPY OF THE HUMAN SPINAL CORD: CLINICAL STUDIES

Molar metabolite concentrations and concentration ratios measured with MR spectroscopy in the spinal cord in healthy volunteers are summarized in On-line Table 1. Unfortunately, there is a lack of quality indicators in many publications. In addition, in some studies, sample spectra indicate high artifact content (lipid peaks, phase shifts, ghostings, water-peak-affected baseline). However, data published by Marliani et al²¹ and Hock et al^{19,29,30} (Fig 3) feature acceptable SNR, low line width, low CRLB, and sample spectra free of major artifacts, making the results reliable. The differences among these studies are most likely attributed to the different water-suppression techniques used, which influence the spectra baseline. Because of the absence of a criterion standard for measuring metabolite concentrations in vivo, additional measurements and cross-validation against invasive methods (ie, in biopsies of patients or postmortem examinations) are needed to verify the results.

A review of the literature revealed several publications using ¹H-MR spectroscopy in clinical studies in which different pathologies were investigated.

Five investigations focused on multiple sclerosis and reported a general reduction in the NAA/Cr ratio in the spinal cord of patients with MS (On-line Table 2).^{9,12,16,20,33} One of these studies published by Marliani et al²⁰ exhibited a proper spectral quality documented by relatively high SNR, low line width, and sample spectra. They studied 15 patients with relapsing-remitting MS with at least 1 lesion in the measurement voxel (On-line Table 2), and they compared the results with those in healthy subjects.²¹ Besides the decrease of NAA/Cr, they found an additional significant decrease of NAA/Cho and an increase in Cho/Cr and myo-inositol/Cr in patients with MS.

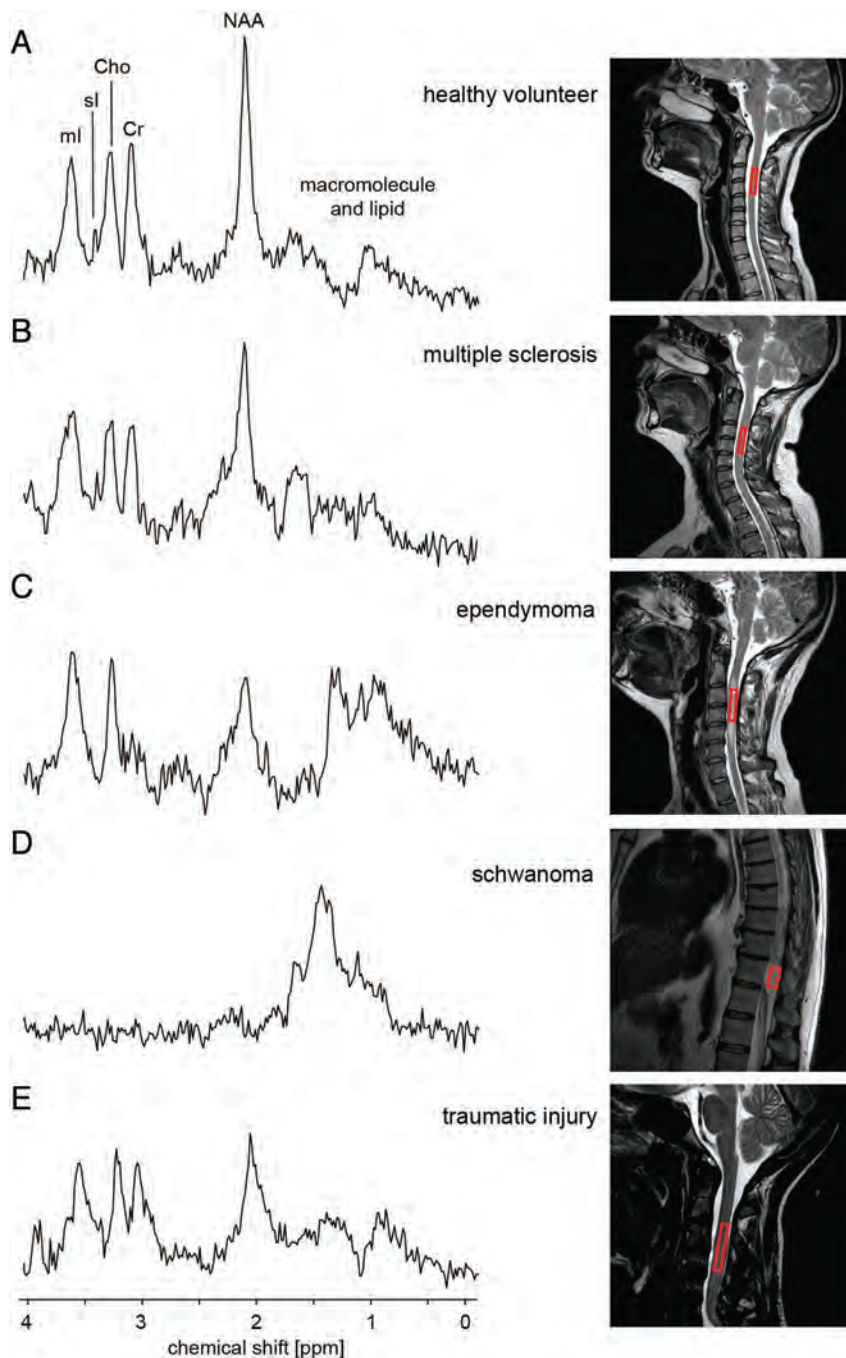


FIG 3. In contrast to controls,³⁰ spectra (A) measured in different pathologies (B–E)^{33,37} in the spinal cord show a distinct change in the metabolite fingerprint, with high correlation to con-natural MR spectroscopy acquisitions in the brain. Spectra measured in the normal-appearing spinal cord of patients with MS³³ show an increase of myo-inositol/Cr and Cho/Cr and a decrease in NAA/Cr. The extradural tumor (schwannoma) shown in D does not contain any metabolite observable in healthy neural tissue.³³ In contrast, the biopsy-confirmed ependymoma exhibited strongly reduced NAA/Cr, increased Cho/Cr, and strongly increased myo-inositol/Cr, in addition to increased lipid and lactate, compared to controls.³³ The spectra measured in a patient after a traumatic injury³⁷ also show a reduction in the NAA/Cr.

Four publications investigated tumors in the human spinal cord. Kim et al³ investigated 14 mass lesions. They reported specific MR spectroscopy changes, similar to changes seen in MR spectroscopy of central nervous system tumors. They provided

exemplary spectra measured in vivo and ex vivo. However, they did not show any quantification or metabolite ratios and quality evaluation of their results. Dydak et al²⁵ investigated 1 patient with a tumor in the cervical spinal cord. They showed that lactate and myo-inositol are increased compared with healthy spinal cord tissue by visual inspection of the spectrum, but they also did not provide metabolite concentrations and quality indicators. Henning et al¹⁷ reported 2 patients with spinal cord tumor (1 located at C4–5 and 1 at T9) with sufficient shim of 12 Hz (FWHM of the water peak) at 3T. Besides a decrease of NAA and Cr, an increase of Cho and myo-inositol was observed. In addition, they reported an increased lactate and glutamine/glutamate peak in the tumor tissue (On-line Table 2). However, the spectra had a low SNR. Finally, Hock et al³³ presented 3 patients with neoplastic spinal cord lesions and compared the spectra with those from 13 healthy volunteers and 13 patients with MS (On-line Table 2 and Fig 3). Spectra were of good quality, and low CRLB were provided. However just acquisitions with short TEs were acquired. The measured ependymoma showed strongly reduced NAA/Cr, increased Cho/Cr, and strongly increased myo-inositol/Cr in addition to lipids and lactate compared to metabolite over Cr ratios measured in healthy controls.

Holly et al¹¹ investigated 21 patients with cervical spondylotic myelopathy and compared the results (On-line Table 2) with those in 13 healthy volunteers (On-line Table 1). Voxels with the unusually large size of $10 \times 10 \times 15$ – 20 mm were placed at the C2 level (because the spinal cord has a diameter of approximately 10 mm, a significant amount of surrounding tissue or CSF must have been included in the voxel). They reported insufficient B0 shim values between 18 and 25 Hz at 1.5T; no CRLB and no SNR values were given. The displayed exemplary spectra seem to have low spectral quality (low SNR, probably phase-shifted). Furthermore, an additional acquisition with longer TEs to differentiate lactate and lipid

would be beneficial to verify the presence of lactate in this patient group.

Rapalino et al¹³ investigated cervical spondylosis in 8 patients (On-line Table 2) and compared the results with those in 6

healthy volunteers. They noticed a decrease of the NAA/Cr ratio and an increase of Cho/NAA in patients, without presenting quality indicators apart from 2 exemplary spectra with relatively low SNR.

Carew et al²² and Pineda-Alonso et al²⁸ used their previously published methods²⁷ to investigate amyotrophic lateral sclerosis in 14 patients (On-line Table 2) and 16 controls (On-line Table 1). They could show that NAA/Cr and NAA/myo-inositol were reduced in patients with amyotrophic lateral sclerosis, and the reduction correlated significantly with clinical parameters. However, in the presented sample spectrum, a baseline distortion most likely due to a widespread water peak indicating insufficient water suppression could be observed, which might have negatively impacted spectral quantification.

De Vita et al²³ presented data from 14 healthy volunteers (On-line Table 1) and 8 patients (On-line Table 2) after brachial plexus root re-implantation. They found a significant increase of the myo-inositol/Cr ratios in the patient data sets. The data quality was documented with exemplary spectra, line-width information, and CRLB, but no SNRs. However it seems that the SNRs of their data are quite low and a difference in data quality between patients and volunteers was seen, which should be discussed.

Hock et al³⁷ also presented data of patients with traumatic injuries (On-line Table 2). A decrease in NAA/Cr and an increase of myo-inositol/Cr were observed. However, the spectral quality was reduced in these patients in comparison with healthy volunteers and patients with MS, most likely due to implants and the presence of hemorrhage (Fig 3).

All published studies report specific changes when comparing patients with healthy volunteers, indicating the feasibility and the potential of applying MR spectroscopy to the spinal cord. Especially, NAA and myo-inositol seem to be meaningful markers for the investigation of various diseases. However, more studies with high spectral quality in larger patient cohorts are needed to increase diagnostic confidence with respect to the degree that MR spectroscopy can enhance specific differential diagnoses or to provide a tool for monitoring the course of a disease.

THE FUTURE OF MR SPECTROSCOPY IN THE SPINAL CORD

MR spectroscopy has the potential to evolve into a powerful tool for the investigation of biochemical changes in the spinal cord. The significant MR spectroscopy changes present in patients with different disorders, compared with healthy subjects, corroborate the clinical diagnostic potential of this method. However, to yield reliable results, certain quality criteria, related to both data acquisition and quantification, of the various metabolites need to be presented. Therefore, SNR, CRLB, coefficient of variation, SD, and exemplary and average spectra are necessary to give an impression of the data quality. Furthermore, the significance and sensitivity have to be investigated in large subject cohorts and in the context of multimodal imaging protocols.

To accelerate the transfer of spinal cord ¹H-MR spectroscopy from research and development to clinical practice, further technical progress improving spectral quality and robustness is helpful. Furthermore, the applicability has to be enhanced (eg, automation of postprocessing and quantification steps), the total

scanning time should be minimized, and standardized acquisition and quantification protocols are necessary for comparison of the data.

Another unsolved problem is the spectral quality of the measurements in more caudal regions of the spinal cord (ie, the thoracic and lumbar regions). The additional challenges discussed above have prevented the acquisition of satisfactory MR spectroscopy results to date. Increasing SNR due to progress in technology may enable reliable measurements in these regions in the future.

CONCLUSIONS

MR spectroscopy of the spinal cord is a promising tool for research and diagnosis because it can provide additional information complementary to other noninvasive imaging methods. However, the application of MR spectroscopy in the spinal cord is not straightforward, and great care is required to attain optimal spectral quality.

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REFERENCES

- de Graaf RA. *In Vivo NMR Spectroscopy: Principles and Techniques*. 2nd ed. Chichester, West Sussex, UK: Wiley-Interscience; 2008:592
- Preul MC, Caramanos Z, Collins DL, et al. **Accurate, noninvasive diagnosis of human brain tumors by using proton magnetic resonance spectroscopy.** *Nat Med* 1996;2:323–25
- Kim YG, Choi GH, Kim DH, et al. **In vivo proton magnetic resonance spectroscopy of human spinal mass lesions.** *J Spinal Disord Tech* 2004;17:405–11
- Kollias S, Goldstein R, Cogen P, et al. **Prenatally detected myelomeningoceles: sonographic accuracy in estimation of the spinal level.** *Radiology* 1992;185:109–12
- Cooke FJ, Blamire AM, Manners DN, et al. **Quantitative proton magnetic resonance spectroscopy of the cervical spinal cord.** *Magn Reson Med* 2004;51:1122–28
- Loth F, Yardimci MA, Alperin N. **Hydrodynamic modeling of cerebrospinal fluid motion within the spinal cavity.** *J Biomech Eng* 2001;123:71–79
- Figley CR, Stroman PW. **Investigation of human cervical and upper thoracic spinal cord motion: implications for imaging spinal cord structure and function.** *Magn Reson Med* 2007;58:185–89
- Kreis R. **Issues of spectral quality in clinical 1H-magnetic resonance spectroscopy and a gallery of artifacts.** *NMR Biomed* 2004;17:361–81
- Ciccarelli O, Wheeler-Kingshott CA, McLean MA, et al. **Spinal cord spectroscopy and diffusion-based tractography to assess acute disability in multiple sclerosis.** *Brain* 2007;130:2220–31
- Gómez-Ansón B, MacManus DG, Parker GJ, et al. **In vivo 1H-magnetic resonance spectroscopy of the spinal cord in humans.** *Neuroradiology* 2000;42:515–17

11. Holly LT, Freitas B, McArthur DL, et al. **Proton magnetic resonance spectroscopy to evaluate spinal cord axonal injury in cervical spondylotic myelopathy.** *J Neurosurg Spine* 2009;10:194–200
12. Kendi AT, Tan FU, Kendi M, et al. **MR spectroscopy of cervical spinal cord in patients with multiple sclerosis.** *Neuroradiol* 2004;46:764–69
13. Rapalino O, Law M, Salibi N, et al. **Metabolite changes from MR spectroscopy in the cervical spinal cord in patients with cervical spondylosis.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Seattle, Washington. May 6–12, 2006:3139
14. Callot V, Le Fur Y, Ranjeva JP, et al. **Spinal cord diffusion tensor imaging (DTI) and 1H-MR spectroscopy (MRS) at 1.5T and 3T.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Stockholm, Sweden. May 1–7, 2010:2453
15. Rapalino O, Law M, Salibi N, et al. **In vivo MR spectroscopy in the human cervical spinal cord at 1.5 and 3 Tesla.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Seattle, Washington. May 6–12, 2006:3138
16. Blamire AM, Cader S, Lee M, et al. **Axonal damage in the spinal cord of multiple sclerosis patients detected by magnetic resonance spectroscopy.** *Magn Reson Med* 2007;58:880–85
17. Henning A, Schar M, Kollias SS, et al. **Quantitative magnetic resonance spectroscopy in the entire human cervical spinal cord and beyond at 3T.** *Magn Reson Med* 2008;59:1250–58
18. Hock A, Henning A, Schär M, et al. **ECG-triggered FASTERMAP shimming allows for reproducible shim convergence in spinal cord spectroscopy.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Stockholm, Sweden. May 1–7, 2010:5042
19. Hock A, MacMillan EL, Fuchs A, et al. **Non-water suppressed proton MR spectroscopy allows spectral quality improvement in the human cervical spinal cord.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Québec, Canada. May 7–13, 2011:406
20. Marliani AF, Clementi V, Albini-Riccioli L, et al. **Quantitative cervical spinal cord 3T proton MR spectroscopy in multiple sclerosis.** *AJNR Am J Neuroradiol* 2010;31:180–84
21. Marliani AF, Clementi V, Albini-Riccioli L, et al. **Quantitative proton magnetic resonance spectroscopy of the human cervical spinal cord at 3 Tesla.** *Magn Reson Med* 2007;57:160–63
22. Carew JD, Nair G, Pineda-Alonso N, et al. **Magnetic resonance spectroscopy of the cervical cord in amyotrophic lateral sclerosis.** *Amyotroph Lateral Scler* 2011;12:185
23. de Vita E, Kachramanoglou C, Wheeler-Kingshott CA, et al. **Spinal cord 1H-MR spectroscopy in patients after brachial plexus root re-implantation.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Montreal, Québec, Canada. May 7–13, 2011:4290
24. Dubey P, Smith M, Bonekamp D, et al. **Proton MR spectroscopic imaging of the human cervical spine at 3 Tesla.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Miami Beach, Florida. May 7–13, 2005:812
25. Dydak U, Kollias S, Schär M, et al. **MR spectroscopy in different regions of the spinal cord and in spinal cord tumors.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Miami Beach, Florida. May 7–13, 2005:813
26. Edden RA, Bonekamp D, Smith MA, et al. **Proton MR spectroscopic imaging of the medulla and cervical spinal cord.** *J Magn Reson Imaging* 2007;26:1101–05
27. Pineda-Alonso N, Benatar M, Smith R, et al. **Reliability of 1H-MRS of the cervical spine at 3T.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Toronto, Ontario, Canada. May 3–9, 2008:02287
28. Pineda-Alonso N, Benatar M, Hu X, et al. **Proton magnetic resonance spectroscopy (1H-MRS) on the spinal cord in amyotrophic lateral sclerosis (ALS) at 3T.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Honolulu, Hawaii. April 18–24, 2009:3325
29. Hock A, Fuchs A, Boesiger P, et al. **Electrocardiogram-triggered higher order projection based B0-shimming allows for fast and reproducible shim convergence in spinal cord 1H magnetic resonance spectroscopy.** *NMR Biomed*. 2013;26:329–35
30. Hock A, MacMillan EL, Fuchs A, et al. **Non-water-suppressed proton MR spectroscopy improves spectral quality in the human spinal cord.** *Magn Reson Med* 2013;69:1253–60
31. Henning A, Koning W, Fuchs A, et al. **1H MRS in the human spinal cord at 7T using a combined RF shimming and travelling wave transmit approach.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Victoria, Australia. May 5–11, 2012:0711
32. Bottomley PA. **Spatial localization in NMR spectroscopy in vivo.** *Ann N Y Acad Sci* 1987;508:333–48
33. Hock A, Fuchs A, Boesiger P, et al. **Spinal cord MR spectroscopy in neoplastic lesions.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Victoria, Australia. May 5–11, 2012:0838
34. Frahm J, Merboldt KD, Hänicke W. **Localized proton spectroscopy using stimulated echoes.** *J Magn Reson* 1987;72:502–08
35. Pijnappert WW, van den Boogaart A, de Beer R, et al. **SVD-based quantification of magnetic resonance signals.** *J Magn Reson* 1992;97:122–34
36. Hock A, Fuchs A, MacMillan EL, et al. **Scyllo-inositol detection in the human spinal cord.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Victoria, Australia. May 5–11, 2012:1815
37. Hock A, Petrou N, Zweers P, et al. **MR spectroscopy in the spinal cord of patients with traumatic injuries.** In: *Proceedings of the Annual Meeting of the International Society of Magnetic Resonance in Medicine*, Victoria, Australia. May 5–11, 2012:1047
38. Boer VO, van de Bank BL, van Vliet G, et al. **Direct B0 field monitoring and real time B0 field updating in the human breast at 7 Tesla.** *Magn Reson Med* 2012;67:586–91
39. Gruetter R. **Automatic, localized in vivo adjustment of all first-and second-order shim coils.** *Magn Reson Med* 1993;29:804–11
40. Gruetter R, Boesch C. **Fast, noniterative shimming of spatially localized signals. In vivo analysis of the magnetic field along axes.** *J Magn Reson* 1992;96:323–34
41. Gruetter R, Tkáč I. **Field mapping without reference scan using asymmetric echo-planar techniques.** *Magn Reson Med* 2000;43:319–23
42. Shen J, Rycyna RE, Rothman DL. **Improvements on an in vivo automatic shimming method [FASTERMAP].** *Magn Reson Med* 1997;38:834–39
43. Haase A, Frahm J, Hanicke W, et al. **1H NMR chemical shift selective (CHESS) imaging.** *Phys Med Biol* 1985;30:341–44
44. Tkac I, Starcuk Z, Choi IY, et al. **In vivo 1H NMR spectroscopy of rat brain at 1 ms echo time.** *Magn Reson Med* 1999;41:649–56
45. Dreher W, Leibfritz D. **New method for the simultaneous detection of metabolites and water in localized in vivo 1H nuclear magnetic resonance spectroscopy.** *Magn Reson Med* 2005;54:190–95
46. Smith MA, Gillen J, McMahon MT, et al. **Simultaneous water and lipid suppression for in vivo brain spectroscopy in humans.** *Magn Reson Med* 2005;54:691–96
47. Klose U. **In vivo proton spectroscopy in presence of eddy currents.** *Magn Reson Med* 1990;14:26–30
48. Heinzer-Schweizer S, De Zanche N, Pavan M, et al. **In-vivo assessment of tissue metabolite levels using 1H MRS and the Electric Reference To access In vivo Concentrations (ERETIC) method.** *NMR in Biomedicine* 2010;23:406–13
49. Provencher SW. **Estimation of metabolite concentrations from localized in vivo proton NMR spectra.** *Magn Reson Med* 1993;30:672–79
50. Stefan D, Di Cesare F, Andrasescu A, et al. **Quantitation of magnetic resonance spectroscopy signals: the jMRUI software package.** *Measurement Science and Technology* 2009;20:104035

Inherited Forms of Creutzfeldt-Jakob Disease

A.J. Degnan and L.M. Levy

ABBREVIATIONS: CJD = Creutzfeldt-Jakob Disease; *PRNP* = prion protein gene

INTRODUCTION

Protein infectious agent or “prion” is a concept developed by Stanley Prusiner in the 1980s of a form of infectious disease involving proteins rather than traditional pathogens.¹ More accurately, prion disease is a heterogeneous collection of neurodegenerative diseases characterized by alteration of a naturally occurring prion protein to a malformed protein with varying forms of presentation and transmission other than infection. Within the largest group of prion diseases—Creutzfeldt-Jakob disease—there are sporadic, familial, iatrogenic, and variant forms. CJD is an endemic disease with worldwide distribution; estimates of the incidence of sporadic or idiopathic CJD vary from 1 to 2 cases per million population annually.

WHAT IS THE NORMAL FUNCTION OF THE PRION PROTEIN?

The etiology of CJD entails a misfolding of the prion protein, but there is presently no consensus on a specific function for this protein. In light of its central role in a neurodegenerative disease, it is expected that the prion protein performs important functions in the brain, which, when disrupted, may lead to impairment of neurologic function. Prions are thought to serve in neuronal signaling as a membrane protein with cell signal-transduction properties.² Many authors argue that the prion protein plays a role in some cognitive tasks as supported by the association of conditions with cognitive impairment and prion protein gene mutations, but there is some contention in the literature on this topic.^{3–5}

HOW DOES ABNORMAL PRION PROTEIN CAUSE DISEASE?

The misfolded prion protein is marked by a shift from α -helices present in normal proteins to β -pleated sheets due to changes in the amino acid sequence. This abnormal protein accumulates within the brain, possibly further propagated by a direct change in the conformation of neighboring normal protein by contact with the abnormal prion protein. Subsequently, neuronal death leads to spongiosis within affected regions throughout the brain; there is also accumulation of τ protein concomitant with neuron loss. These changes occur while there is a wide variety of neurologic deficits ranging from rapid dementia, ataxia, and extra-pyramidal symptoms to psychiatric manifestations.

WHAT ARE THE GENETICS OF FAMILIAL CJD?

Familial CJD (and related inherited prion diseases: fatal familial insomnia and Gerstmann-Straussler-Scheinker disease) manifests in a variety of different forms caused by changes to *PRNP* on chromosome 20 that may occur with deletion, insertion, or point mutations—all in autosomal dominant patterns of inheritance. *PRNP* mutations are highly penetrant, meaning that the presence of a *PRNP* mutation all but guarantees the eventual progression of CJD in an individual. However, beyond pathognomonic *PRNP* mutations (for which particular types of familial CJD are named), there are also polymorphic codons elsewhere within the gene. One location in particular is the codon 129, which codes for either methionine or valine and is the target of molecular diagnostic tests of CJD.⁶ This codon is frequently involved in all forms of CJD, and methionine homozygosity appears to constitute the most common polymorphism associated with an increased risk for CJD.⁷ More recent work argues for a protective effect of heterozygosity at codon 129 as protection against kuru (an unusual form of prion disease associated with cannibalism in a specific population of Papua New Guinea).⁸ Thus, variance in CJD presentations pivots primarily on the nature of the *PRNP* mutation and then is further modified by polymorphisms within codon 129 on both the mutated and wild alleles.

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WHAT ARE SOME FORMS OF FAMILIAL CJD?

The most common form of inherited CJD involves the E200K (lysine [K] in lieu of the glutamate [E]) mutation, which has been noted in an assortment familial clusters including Libyan Jews (most prominently) and families in Slovakia and South America—this manifestation shares great similarity to sporadic CJD both clinically and on diagnostic imaging.^{9,10} The next most common mutation is V210I (isoleucine [I] in lieu of valine [V]), but this condition does not have a clear pattern.^{10,11} To date, approximately 30 mutations associated with inherited prion disease have been identified in a diverse group of populations, and it is likely that, with increased awareness and improved molecular tools, more mutations will be observed.^{6,10}

REFERENCES

1. Prusiner SB. **Biology and genetics of prion diseases.** *Annu Rev Microbiol* 1994;48:655–86
2. Mouillet-Richard S, Ermonval M, Chebassier C, et al. **Signal transduction through prion protein.** *Science* 2000;289:1925–28
3. Combarros O, Sanchez-Guerra M, Llorca J, et al. **Polymorphism at codon 129 of the prion protein gene is not associated with sporadic AD.** *Neurology* 2000;55:593–95
4. Croes EA, Dermaut B, Houwing-Duistermaat JJ, et al. **Early cognitive decline is associated with prion protein codon 129 polymorphism.** *Ann Neurol* 2003;54:275–76
5. Riemenschneider M, Klopp N, Xiang W, et al. **Prion protein codon 129 polymorphism and risk of Alzheimer disease.** *Neurology* 2004;63:364–66
6. Puoti G, Bizzi A, Forloni G, et al. **Sporadic human prion diseases: molecular insights and diagnosis.** *Lancet Neurol* 2012;11:618–28
7. Head MW, Ironside JW. **Review: Creutzfeldt-Jakob disease: prion protein type, disease phenotype and agent strain.** *Neuropathol Appl Neurobiol* 2012;38:296–310
8. Mead S, Whitfield J, Poulter M, et al. **A novel protective prion protein variant that colocalizes with kuru exposure.** *N Engl J Med* 2009;361:2056–65
9. Colombo R. **Age and origin of the PRNP E200K mutation causing familial Creutzfeldt-Jacob disease in Libyan Jews.** *Am J Hum Genet* 2000;67:528–31
10. Schelzke G, Kretzschmar HA, Zerr I. **Clinical aspects of common genetic Creutzfeldt-Jakob disease.** *Eur J Epidemiol* 2012;27:147–49
11. Kovács GG, Puopolo M, Ladogana A, et al. **Genetic prion disease: the EURO-CJD experience.** *Hum Genet* 2005;118:166–74

Metabolite Differences in the Lenticular Nucleus in Type 2 Diabetes Mellitus Shown by Proton MR Spectroscopy

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ABSTRACT

BACKGROUND AND PURPOSE: Previous studies by using proton MR spectroscopy found metabolite abnormalities in the cerebral cortex and white matter of patients with type 2 diabetes mellitus. The present study was undertaken to detect metabolite differences in the lenticular nuclei and thalamus in patients with T2DM.

MATERIALS AND METHODS: Twenty subjects with T2DM and 22 age-matched control subjects underwent single-voxel MR spectroscopy in the left and right lenticular nuclei and left and right thalami. NAA/Cr and Cho/Cr ratios were calculated. Brain lactic acid, fasting blood glucose, and glycosylated hemoglobin levels were also monitored.

RESULTS: The NAA/Cr ratio was lower in the left lenticular nuclei of subjects with T2DM ($P = .007$), whereas the Cho/Cr ratio was increased in both the and right lenticular nuclei ($P = .001$). The NAA/Cr ratio was negatively correlated with FBG in the left ($r = -0.573$, $P = .008$) and right nuclei ($r = -0.564$, $P = .010$). It was also negatively correlated to HbA1c in the left ($r = -0.560$, $P = .010$) and right ($r = -0.453$, $P = .045$) nuclei. The Cho/Cr ratio was positively correlated with these variables ($P < .05$). No significant differences in NAA/Cr or Cho/Cr ratios were observed in the thalamus of patients with T2DM. Lactic acid was not detected in any of the patients in the study.

CONCLUSIONS: The different metabolic statuses of the lenticular nuclei and thalamus suggest different effects of T2DM in each of these brain nuclei, with the lenticular nuclei being more vulnerable than the thalamus. The abnormal metabolic status was observed before lesions had appeared in these brain areas.

ABBREVIATIONS: T2DM = type 2 diabetes mellitus; DM = diabetes mellitus; FBG = fasting blood glucose; HbA1c = glycosylated hemoglobin

Proton MR spectroscopy can be used to determine the resonance peaks of many kinds of brain metabolites and neurotransmitters but is most often used to monitor NAA, Cho, Cr, and lactic acid.¹ NAA is a marker for neurons and axons, reflecting the

number and functional status of neurons.² Cho, mainly distributed in the glial cells, is involved in cell membrane composition and myelin formation. Cr is associated with energy metabolism.²

Type 2 diabetes mellitus is an extremely prevalent metabolic disease, which is associated with a variety of acute and chronic complications. Previous works have shown that DM causes metabolic changes in the brain, especially in the cerebral cortex and white matter.³⁻⁵

Most studies suggest that diabetes affects either the number or the function of central neurons, which is mirrored by a reduction in NAA levels and a lower NAA/Cr ratio.⁴⁻⁶ Studies investigating the effects of diabetes on Cho metabolism have produced inconsistent results. Studies by Kreis and Ross⁵ and Biessels et al⁶ reported no difference in Cho/Cr ratios in diabetic rats or in brain tissue from patients with diabetes. However, Sahin et al⁷ found evidence of a lower Cho/Cr ratio in the parietal and frontal lobe white matter in patients with T2DM, which was inversely related to HbA1c levels. Other works demonstrated an increase in the Cho/Cr ratio in the left occipital lobe gray matter of patients with T2DM but found no significant difference in the Cho/Cr ratio between patients and controls in the bilateral frontal and left parietal lobe white matter.⁸

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While many studies have investigated the effects of diabetes in the brain cortex, few have investigated its effect in specific brain nuclei such as the lenticular nuclei and thalamus. Previous studies report that motor defects such as hemichorea may occur in patients with diabetes with lesions in the striatum. MR imaging indicated that this may be caused by lesions in the lenticular nuclei and was evidenced by lower NAA/Cr ratios and increased Cho/Cr in these patients.^{9,10} On the basis of these findings, it may be speculated that T2DM might result in metabolic abnormalities in the basal ganglia, even in the absence of visible lesions in those areas.

In the present study, we used ¹H-MR spectroscopy to observe whether the metabolism within the lenticular nuclei and thalamus was altered in patients with T2DM and to explore the impact of T2DM on brain nuclei.

MATERIALS AND METHODS

Study Design

Subjects were selected for the study from the Department of Neurology, Second Affiliated Hospital of Dalian Medical University, between March 2011 and December 2011. The subjects included 20 patients (7 men and 13 women) with T2DM (age range, 51–85 years) and 22 control subjects (9 men and 13 women) between 52 and 80 years of age.

Patients with T2DM met the 1999 World Health Organization diagnostic criteria for diabetes¹¹ and were using oral medication or insulin to control blood glucose. The duration of T2DM ranged from 1 month to 30 years. Those who came to the hospital during the same time but without DM were selected as control subjects. All of the subjects enrolled in the study were right-handed. None of the subjects had coexisting systemic diseases, head trauma, cognitive dysfunction, thyroid dysfunction, alcohol dependence, hemichorea, infectious diseases of the central nervous system, or epilepsy. Those with impaired glucose tolerance or impaired fasting glucose regulation were excluded from the study. None of the subjects had a history of hypoglycemia.

Institutional ethics approval was obtained from the Second Affiliated Hospital of Dalian Medical University. All study subjects provided informed consent before entering the study.

Measurement of Brain Metabolites

Studies were performed on a 1.5T Signa MR imaging system (GE Healthcare, Milwaukee, Wisconsin). Conventional axial, sagittal, and coronal spin-echo scans and axial fast spin-echo scans, including T1- and T2-weighted images, were obtained before spectroscopy to rule out any lesions or structural abnormalities. T2-weighted imaging was performed by using the following parameters: TR/TE, 4300/105.3 ms; *k*-space matrix, 320 × 256; FOV, 24 × 24 cm; section thickness, 6 mm; space, 1 mm. The axial section showing the most anterior extent of the anterior margin of the genu of the corpus callosum was chosen as the reference image on which to center the voxels for both locations.¹²

Single-voxel spectroscopy was performed on all subjects with a circularly polarized head coil by using a point-resolved spectroscopy sequence (TR/TE, 1000/144 ms) with 128 averages. Due to the less complex spectra and increased reproducibility of the measurements, the long-TE point-resolved spectroscopy sequence

was chosen as the primary pulse sequence. Voxels were placed in the bilateral lenticular nuclei (10 × 10 × 10 mm) and thalamus (10 × 10 × 10 mm), respectively, avoiding the CSF of the lateral ventricles, sulci, and cistern. Voxel-based shimming was performed to optimize field homogeneity before acquiring the spectra. Water suppression was performed by applying a chemical shift selective saturation-pulse technique provided by the vendor. Postprocessing of the spectral data was performed by using vendor-provided software (FuncTool 2, GE Healthcare).

The integral values of the metabolite peaks of NAA, Cho, and Cr were observed at 2.12, 3.29 and 3.11 ppm, respectively. Metabolite ratios were obtained for NAA/Cr and Cho/Cr.

Fasting blood glucose and glycosylated hemoglobin levels were monitored in all subjects.

Statistical Analysis

Statistical analyses were performed by using the Statistical Package for the Social Sciences, Version 16.0 for Windows (SPSS, Chicago, Illinois). Data were presented as means and SDs. The Shapiro-Wilk test was used for the normality of all continuous variables. An independent *t* test was used for comparison of the metabolite ratios between the T2DM group and the controls, and the Mann-Whitney *U* test was used to assess the differences of FBG and HbA1c between the 2 groups. Categorical data were compared by using analysis of variance. Correlations were estimated by using Spearman rank correlation coefficients. *P* < .05 was considered statistically significant.

RESULTS

Figures 1 and 2 show the regions of interest in the right lenticular nucleus and thalamus together with corresponding MR spectra for Cho, Cr, and NAA.

FBG in patients with T2DM was in the range of 5.85–15.96 mmol/L, and in the control group, it ranged from 5.05 to 5.90 mmol/L (*P* = .000). The HbA1c was also statistically significantly higher in the T2DM group (5.8%–14.3%) than in the control group (4.4%–5.6%, *P* = .000). There was no significant difference in the occurrence of high blood pressure between the 2 groups (85% versus 77.3%).

Metabolite ratios for the right and left lenticular nuclei and thalamus are shown in Table 1. The NAA/Cr ratio in the left lenticular nuclei was significantly lower in the patients with T2DM than in healthy control subjects (*P* = .007), but no significant difference in this ratio was found between patients and controls in the right lenticular nuclei (*P* = .071).

The Cho/Cr ratios in the left and right lenticular nuclei were both significantly higher in patients with T2DM than in controls (*P* = .001 for both sides). No statistically significant difference in NAA/Cr or Cho/Cr ratios between patients with T2DM and controls was found in the bilateral thalami.

In both patients and controls, metabolite ratios in the left brain nuclei and thalamus were not statistically significantly different from those on the right side of the brain. Lactic acid was not observed in the nuclei of any of the patients.

HbA1c and FBG were negatively correlated with NAA/Cr ra-

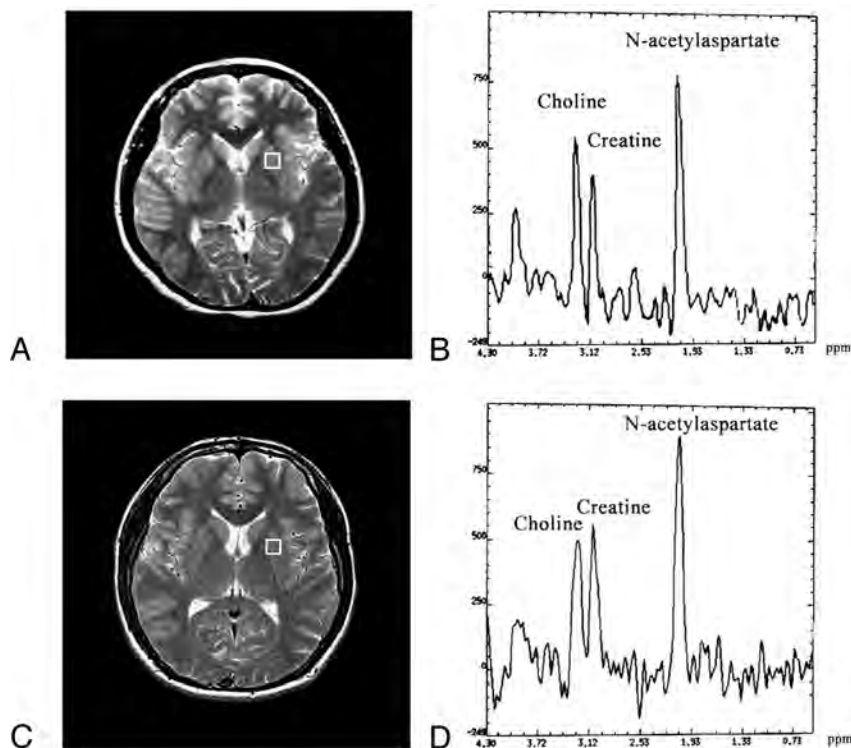


FIG 1. A and C, Regions of interest used for ^1H -MR spectroscopy in a patient with T2DM (female, 57 years of age) and a control subject (female, 58 years of age). B, Spectrum of the patient with T2DM obtained from the left lenticular nucleus. D, Spectrum of the control subject obtained from the left lenticular nucleus.

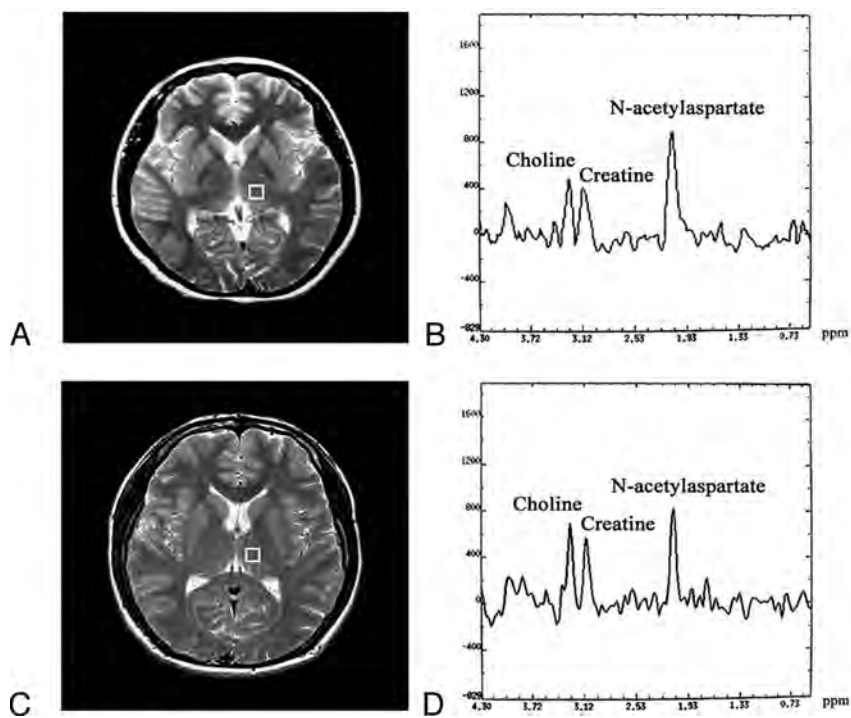


FIG 2. A and C, Region of interest in the left thalamus used for ^1H -MR spectroscopy in the same patients in Fig 1 with T2DM and control subject. B and D, Spectra of the patient with T2DM is above and the control subject is below.

tios in the left and right lenticular nuclei of patients in the T2DM group (Table 2). There was also a positive correlation between the Cho/Cr ratio and HbA1c and FBG in the T2DM group. Figure 3

shows the significant correlations between the metabolite ratios in the left lenticular nucleus and FBG as well as HbA1c.

DISCUSSION

Diabetes mellitus is a metabolic disorder with alterations of carbohydrate metabolism and biochemical metabolism of the brain.³ Our findings show lower levels of NAA/Cr in the left lenticular nucleus and increased Cho/Cr levels in both the left and right lenticula of subjects with T2DM. Both FBG and HbA1c were negatively correlated with the NAA/Cr ratio in the left nuclei as well as the right, while the Cho/Cr ratio was positively correlated. No significant differences in NAA/Cr or Cho/Cr ratios were observed in the thalamus of patients with T2DM.

Lower NAA/Cr levels observed in the left lenticular nucleus of patients with T2DM suggest that the number or the functional state of the neuron in the lenticular nucleus was affected by diabetes. This was consistent with previous studies reporting that diabetes could affect the neuronal function, resulting lower NAA or NAA/Cr ratios in some regions of the brain.^{4,5}

The increased Cho/Cr ratios in the lenticular nuclei may have been related to ≥ 1 of the following reasons: First, long-term high blood glucose levels could cause blood viscosity to increase and then disturb the macro- and micro-vascular function and structure, which might result in vessel dysfunction and cerebral arteriosclerosis.^{13,14} The abnormal vascular function might further contribute to hypoperfusion, ischemia, and hypoxia. Energy depletion caused by ischemia would increase the Cho concentration by reducing the synthesis and enhancing the hydrolysis of acetylcholine.^{15,16}

Second, choline is a mixture of molecular sources predominantly found in cell membranes.¹⁷ Therefore, a second explanation for the increased Cho levels is that hypoxia resulting from local hypoperfusion may cause a breakdown of myelin and decomposition or hydrolysis of cell membranes.⁹

Finally, increased Cho in T2DM may be a result of reactive glial proliferation, which may occur as a secondary response to neuronal dysfunction in the presence of relative tissue hypoxia.¹⁸

Table 1: NAA/Cr and Cho/Cr ratios (mean $\pm$ SD) in the lenticular nuclei and thalamus of control subjects and patients with T2DM

	Left			Right		
	Controls (n = 22)	T2DM (n = 20)	P ^a	Controls (n = 22)	T2DM (n = 20)	P ^b
Lenticular nuclei						
NAA/Cr	1.61 $\pm$ 0.19	1.41 $\pm$ 0.26	.007	1.57 $\pm$ 0.20	1.45 $\pm$ 0.24	.071
Cho/Cr	0.99 $\pm$ 0.19	1.23 $\pm$ 0.24	.001	0.98 $\pm$ 0.16	1.18 $\pm$ 0.20	.001
Thalamus						
NAA/Cr	1.70 $\pm$ 0.16	1.64 $\pm$ 0.16	.222	1.72 $\pm$ 0.15	1.65 $\pm$ 0.18	.221
Cho/Cr	1.13 $\pm$ 0.15	1.17 $\pm$ 0.16	.479	1.15 $\pm$ 0.15	1.21 $\pm$ 0.16	.236

^a Comparison of metabolite ratios in the left nuclei between patients and controls.

^b Comparison of metabolite ratios in the right nuclei between patients and controls.

Table 2: Spearman rank correlations between lenticular nuclei metabolite ratios and FBG and HbA1c in patients with T2DM

	Left				Right			
	NAA/Cr		Cho/Cr		NAA/Cr		Cho/Cr	
	r	P Value	r	P Value	r	P Value	r	P Value
FBG (mmol/L)	−0.573	.008	0.735	.000	−0.564	.010	0.608	.004
HbA1c (%)	−0.560	.010	0.838	.000	−0.453	.045	0.619	.004

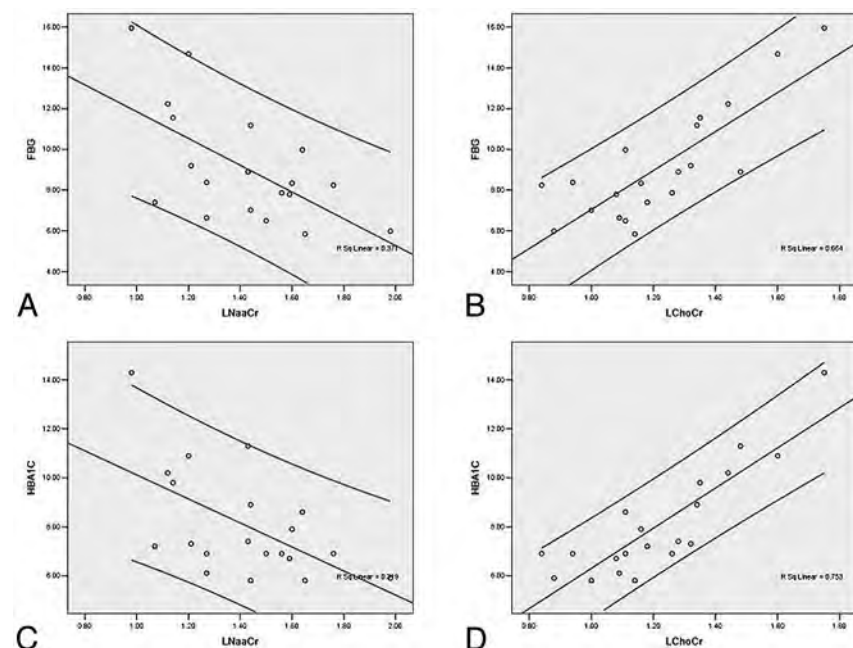


FIG 3. Significant correlations for the lenticular nucleus (left side) between metabolite ratios and FBG as well as HbA1c. A and B, Correlations between FBG and NAA/Cr and Cho/Cr. C and D, Correlations between HbA1c and NAA/Cr and Cho/Cr.

Despite the metabolic changes observed in the lenticular nuclei, we were unable to demonstrate any significant differences in Cho/Cr ratios in the thalamus, suggesting that dysfunction of cellular membrane metabolites or abnormalities of neuronal energy metabolites do not occur in this part of the brain.

In the study of Tiehuis et al,¹⁹ HbA1c was found to have no significant effect on the metabolite ratios in the corona radiata. We did, however, find that the NAA/Cr ratio in the lenticular nuclei of patients with T2DM was negatively related to FBG and HbA1c, while Cho/Cr was positively related to these 2 variables. These findings are partly supported by previously published results that suggested that neuronal damage was more serious in

patients with diabetes with poor glycemic control than in well-controlled patients.⁷ It is thought that chronic high blood glucose levels alter neuron metabolism, protein synthesis, and expression, as well as the apoptosis of a gene that may accelerate neuronal degeneration.²⁰ The positive association between Cho/Cr and FBG and HbA1c also suggests that the Cho levels may be increased under conditions of high blood glucose and hypoxia, resulting from the sequence of events described above.

Our finding that differences of metabolites were observed only in the lenticular nucleus but not in the thalamus suggests that the lenticular nucleus might be more vulnerable than the thalamus because of differences in vascular anatomy. The lenticular nuclei are supplied by the penetrating arteries called lenticulostriate arteries, which originate from the middle cerebral arteries. These are penetrating end arteries that lack collaterals. This pattern of vascular anatomy may make the lenticular nuclei particularly sensitive to the changes of blood flow and more susceptible to metabolic change. The thalamus is supplied by a more robust arterial network that includes the posterior perforating arteries (the tuberthalamic artery, thalamogeniculate artery, and anterior choroidal artery) as well as the medial and lateral posterior choroidal arteries. The collateral circulation of the thalamus is also abundant. Blood supply to the thalamus is mainly from the posterior cerebral cycle. The thalamus is also partly supplied by the anterior cerebral cycle, because the anterior choroidal artery, which is involved in the blood supply of subthalamus, also arises from the middle cerebral artery. The specialized

blood supply to the thalamus might make it less sensitive to changes in blood flow, and consequently, its tolerance to ischemia is better than that of the lenticular nucleus.

Lactate resulting from the mismatch between glycolysis and oxygen supply is a product of anaerobic metabolism, and it is a hallmark for the detection of cerebral ischemia.²¹ However, none of the patients with T2DM in our study had lactic acid detected. We speculated that this was because ischemia resulting from T2DM was not enough to cause anaerobic metabolism. However, this speculation needs to be proved by further study.

Our finding that significant differences in NAA/Cr ratios between patients and controls were only present in the left lenticular

nucleus suggests that the metabolic changes of the left lenticular nucleus play a more important role in T2DM. It is probable that the left hemisphere is more vulnerable than the right because of a “dominant hemisphere” effect. All subjects in the study were right-handed, which might explain why metabolite changes were more obvious in the left hemisphere. We speculated that the dominant hemisphere is more likely to be in the state of energy shortage because its energy requirements might be higher. Under hypoxic conditions, this would make this hemisphere more susceptible to nerve tissue damage, metabolic abnormalities, and dysfunction.

CONCLUSIONS

¹H-MR spectroscopy contributed to the early detection of brain damage. The abnormal metabolic status was observed in the brain areas that appeared with normal structure in MR imaging. Different metabolic statuses of the lenticular nuclei and thalamus were observed, suggesting different effects of T2DM in each of these brain nuclei, with the lenticula being more vulnerable than the thalamus. However, we could not show now whether the perfusion of these 2 areas was different. Further study is needed to verify the perfusion state of both areas.

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REFERENCES

- Ross B, Bluml S. Magnetic resonance spectroscopy of the human brain. *Anat Rec* 2001;265:54–84
- Miller BL. A review of chemical issues in ¹H NMR spectroscopy: N-acetyl-L-aspartate, creatine and choline. *NMR Biomed* 1991;4:47–52
- Geissler A, Frund R, Scholmerich J, et al. Alterations of cerebral metabolism in patients with diabetes mellitus studied by proton magnetic resonance spectroscopy. *Exp Clin Endocrinol Diabetes* 2003;111:421–27
- Kario K, Ishikawa J, Hoshida S, et al. Diabetic brain damage in hypertension: role of renin-angiotensin system. *Hypertension* 2005;45:887–93
- Kreis R, Ross BD. Cerebral metabolic disturbances in patients with subacute and chronic diabetes mellitus: detection with proton MR spectroscopy. *Radiology* 1992;184:123–30
- Biessels GJ, Braun KP, de Graaf RA, et al. Cerebral metabolism in streptozotocin-diabetic rats: an in vivo magnetic resonance spectroscopy study. *Diabetologia* 2001;44:346–53
- Sahin I, Alkan A, Keskin L, et al. Evaluation of in vivo cerebral metabolism on proton magnetic resonance spectroscopy in patients with impaired glucose tolerance and type 2 diabetes mellitus. *J Diabetes Complications* 2008;22:254–60
- Modi S, Bhattacharya M, Sekhri T, et al. Assessment of the metabolic profile in type 2 diabetes mellitus and hypothyroidism through proton MR spectroscopy. *Magn Reson Imaging* 2008;26:420–25
- Higa M, Kaneko Y, Inokuchi T. Two cases of hyperglycemic chorea in diabetic patients. *Diabet Med* 2004;21:196–98
- Lai PH, Chen PC, Chang MH, et al. In vivo proton MR spectroscopy of chorea-ballismus in diabetes mellitus. *Neuroradiology* 2001;43:525–31
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2000;23(suppl 1):S4–19
- Ajilore O, Haroon E, Kumaran S, et al. Measurement of brain metabolites in patients with type 2 diabetes and major depression using proton magnetic resonance spectroscopy. *Neuropsychopharmacology* 2007;32:1224–31
- Keymel S, Heinen Y, Balzer J, et al. Characterization of macro- and microvascular function and structure in patients with type 2 diabetes mellitus. *Am J Cardiovasc Dis* 2011;1: 68–75
- Jones RL, Peterson CM. Hematologic alterations in diabetes mellitus. *Am J Med* 1981;70:339–52
- Djuricic B, Olson SR, Assaf HM, et al. Formation of free choline in brain tissue during in vitro energy deprivation. *J Cereb Blood Flow Metab* 1991;11:308–13
- Scremin OU, Jenden DJ. Focal ischemia enhances choline output and decreases acetylcholine output from rat cerebral cortex. *Stroke* 1989;20:92–95
- Blüml S, Seymour KJ, Ross BD. Developmental changes in choline- and ethanolamine-containing compounds measured with proton-decoupled (31)P MRS in in vivo human brain. *Magn Reson Med* 1999;42:643–54
- Mäkimattila S, Malmberg-Ceder K, Hakkinen AM, et al. Brain metabolic alterations in patients with type 1 diabetes-hyperglycemia-induced injury. *J Cereb Blood Flow Metab* 2004;24:1393–99
- Tiehuis A, van der Meer F, Mali W, et al. MR spectroscopy of cerebral white matter in type 2 diabetes; no association with clinical variables and cognitive performance. *Neuroradiology* 2010;52:155–61
- Li L, Holscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. *Brain Res Rev* 2007;56:384–402
- Saunders DE. MR spectroscopy in stroke. *Br Med Bull* 2000;56: 334–45

Comparison of 10 TTP and Tmax Estimation Techniques for MR Perfusion-Diffusion Mismatch Quantification in Acute Stroke

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ABSTRACT

BACKGROUND AND PURPOSE: The mismatch between lesions identified in perfusion- and diffusion-weighted MR imaging is typically used to identify tissue at risk of infarction in acute stroke. The purpose of this study was to analyze the variability of mismatch volumes resulting from different time-to-peak or time-to-maximum estimation techniques used for hypoperfused tissue definition.

MATERIALS AND METHODS: Data of 50 patients with middle cerebral artery stroke and intracranial vessel occlusion imaged within 6 hours of symptom onset were analyzed. Therefore, 10 different TTP/Tmax techniques and delay thresholds between +2 and +12 seconds were used for calculation of perfusion lesions. Diffusion lesions were semiautomatically segmented and used for mismatch quantification after registration.

RESULTS: Mean volumetric differences up to 40 and 100 mL in individual patients were found between the mismatch volumes calculated by the 10 TTP/Tmax estimation techniques for typically used delay thresholds. The application of typical criteria for the identification of patients with a clinically relevant mismatch volume resulted in different mismatch classifications in $\leq 24\%$ of all cases, depending on the TTP/Tmax estimation method used.

CONCLUSIONS: High variations of tissue-at-risk volumes have to be expected when using different TTP/Tmax estimation techniques. An adaption of different techniques by using correction formulas may enable more comparable study results until a standard has been established by agreement.

ABBREVIATIONS: GVM = γ -variate model; LDRWM = local density random walk model; LNM = log-normal model; RLCFM = reference-based linear curve fit model; Tmax = time-to-maximum

Multiparametric MR imaging is currently widely established for diagnosis of patients with acute stroke,¹ whereas diffusion-weighted and time-resolved perfusion-weighted MR imaging datasets are especially relevant for today's clinical routine. DWI can display ischemic brain tissue with decreased diffusion within minutes from onset. A lesion that is visible in the DWI image sequence is typically assumed to represent the core of an

ischemic lesion that is unlikely to recover from therapy. PWI allows identifying hypoperfused tissue resulting from a present vascular occlusion. It has been hypothesized that the volumetric difference between these 2 lesions, the so-called PWI-DWI mismatch, allows a quantitative definition of potentially salvageable brain tissue at risk, which reflects the ischemic penumbra.²⁻⁴ It is further assumed that a quantification of this mismatch volume allows identifying patients who are likely to benefit from thrombolysis, even in an extended time window after symptom onset.^{5,6} The definition and quantification of the ischemic penumbra is, therefore, increasingly performed for patient selection in randomized controlled trials with treatment beyond the time window that is approved for thrombolytic therapy.⁷⁻⁹

Although a Tmax (see below) bolus delay of >6 seconds has become an accepted threshold for the definition of a relevant hypoperfusion in recent stroke thrombolysis trials, no official guidelines have been established on how the PWI-DWI mismatch should be calculated. While the identification of acute ischemic lesions on DWI is quite straightforward, the interpretation of PWI is rather challenging. One reason is that several parameters

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can be used for perfusion map calculation. Examples of these parameters comprise the cerebral blood volume, cerebral blood flow, mean transit time, time-to-peak, and time-to-maximum. Several studies have been performed in the past to evaluate the performance of these parameters regarding the ability to predict the final infarct volume, with contradictory outcomes.^{10,11} However, recent trials mainly focus on the time-to-peak and time-to-maximum parameter for PWI-DWI mismatch quantification. For quantitative analyses, the perfusion lesion is typically defined by $TTP > TTP + \tau$ or $Tmax > \tau$, where TTP describes a mean value within healthy tissue in the contralateral hemisphere and τ , a given temporal delay threshold.

Several studies have been conducted to identify the optimal delay threshold τ for tissue outcome prediction. However, the findings of these studies are ambiguous, with identified optimal delay thresholds ranging from 4 to 6 seconds, depending on the applied methods and validations.^{4,12,13} Secondary analyses of data from the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) have resulted in a similar refinement of the relevant mismatch criterion by a $Tmax$ delay of >6 seconds, which was used in the EXtending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial.⁹

Several factors may influence the PWI analysis, such as the use and localization of the arterial input function.^{14,15} Apart from this, there is another important aspect of PWI analysis that has not attracted much attention; that is the method for computation of TTP or $Tmax$ parameter maps. Consequently, the method selection may influence the quantitative perfusion lesion definition and subsequent treatment decisions.

The aim of this work was to analyze the impact of different $TTP/Tmax$ estimation techniques on tissue-at-risk quantification at different delay thresholds. It was hypothesized that different hemodynamic models result in relevant differences of tissue-at-risk volumes, with a noticeable effect on the number of patients labeled as exhibiting a relevant PWI-DWI mismatch according to currently used definitions.

METHODS AND MATERIALS

Patients and Imaging Protocol

Fifty nonconsecutive datasets of patients with an acute ischemic stroke in the MCA territory admitted to our hospital since 2004 were analyzed in this study. The selection criterion was a sufficient image quality without movement artifacts so that biased results due to suboptimal image quality could be neglected. Moreover, only patients with an intracranial vessel occlusion identified on time-of-flight MRA were included in this study. The site of vessel occlusion predicts the extent of acute ischemia.¹⁶ Thus, to include perfusion lesions over the entire distribution range, we selected patients with 4 different occlusion types: carotid-T occlusion; “tandem-occlusion” combining extra- or intracranial ICA with MCA mainstem occlusion (MCA + ICA); MCA mainstem occlusion; and MCA branch occlusion.

All MR imaging measurements were performed on a 1.5T Sonata scanner (Siemens, Erlangen, Germany). The PWI datasets were acquired after application of contrast agent (approximately 15 mL of gadopentetate dimeglumine [Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, New Jersey]) by using a TR = 1500

ms, TE = 37 ms, and flip angle = 90°; image in-plane image resolution = 0.94 mm²; and 24 sections with 5-mm section thickness. Each acquired PWI dataset contained forty 3D datasets. The DWI sequences were acquired by applying diffusion gradients in 3 directions with strong diffusion-weighting ($b=1000$ s/mm², TR = 3500 ms, TE = 89 ms, flip angle = 90°; image in-plane image resolution = 0.94 mm²; and 24 sections with 5-mm section thickness).

Informed consent was obtained from all patients. The study was approved by the local ethics committee.

TTP and Tmax Estimation Techniques

The TTP of a given tissue concentration curve, which can be extracted from each voxel of the PWI dataset, is defined as the time point at which the curve achieves its signal peak. One possibility to calculate this parameter is to determine it directly from the tissue-concentration curves by using the discrete sample points. However, there are 2 main drawbacks when extracting the TTP parameter model independently by using the raw PWI concentration curves: noise artifacts and limited temporal resolution due to the discrete representation.

Thus, hemodynamic model curves are typically used to overcome these limitations. These model curves are fitted to the tissue-concentration curves before TTP estimation. After they are fitted, the adapted model functions can be used for TTP estimation with supposed higher precision.

The following 4 hemodynamic models (Fig 1) have been implemented and used for this study: the simplified γ -variate model,¹⁷ the local density random walk model,¹⁸ the modified log-normal model,¹⁹ and the reference-based linear curve fit model.²⁰

The TTP estimation does not account for the shape of the arterial-indicator dilution curves.²¹ Therefore, deconvolution-based $Tmax$ estimation, which is based on the indicator-dilution theory,²² has been proposed as a more precise alternative to direct TTP estimation. The $Tmax$ parameter is defined as the time point at which the residue function $R(t)$ reaches its maximum. Practically, the residue function can be calculated by using the following relation:

$$1) \quad C_T(t) = CBF \times R(t) \otimes C_a(t),$$

where $C_T(t)$ denotes the tissue concentration curve; $C_a(t)$, the arterial input function; $R(t)$, the residue function; CBF, the cerebral blood flow; and $\otimes$, the convolution parameter. Several approaches have been presented in the past that can be used to solve this equation, whereas the singular-value decomposition approach²³ has been found to achieve good results.

Contrast agent delays among arterial, brain tissue, and venous structures lead to nonidentical recirculation portions in the measured indicator dilution curves because indicator dilution curves are finite. As a result of this, the estimated residue functions may exhibit shape and amplitude errors.²⁴ Theoretically, this problem can be solved by fitting of the aforementioned hemodynamic models to the arterial input function and tissue curves before $Tmax$ estimation.

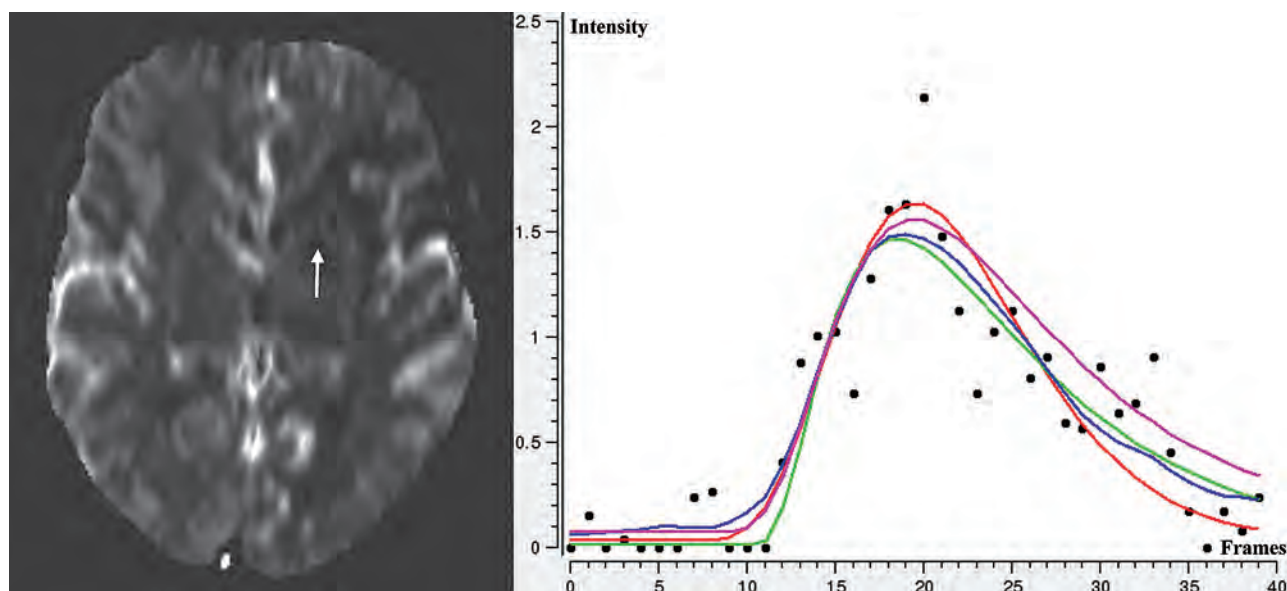


FIG 1. Selected section from a PWI dataset (left) and concentration time curve (black dotted) for a location within the perfusion lesion (arrow) with fitted hemodynamic model curves: γ -variate model (red), local density random walk model (green), log-normal model (magenta), and reference-based linear curve fit model (blue).

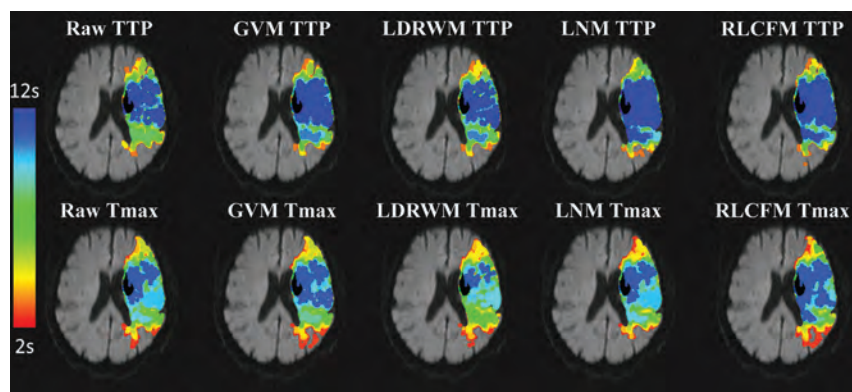


FIG 2. Selected section from a DWI dataset with a corresponding DWI lesion (black) and overlaid tissue-at-risk volumes for delay thresholds between 2 and 12 seconds calculated by using the 10 different TTP/Tmax estimation methods.

Image Processing

4D PWI datasets display the passage of the paramagnetic contrast agent, which results in a shortening of the T2 and T2* relaxation times and therefore in a reduction of signal intensities. For this reason, the signal functions $S(t)$ need to be converted to concentration curves $C(t)$ to enable an application of the aforementioned TTP/Tmax estimation techniques by using the following formula:

$$2) \quad C(t) = -\frac{k}{TE} \ln\left(\frac{S(t)}{S_0}\right),$$

where S_0 denotes the baseline MR signal intensity; TE, the echo time; and k , a proportionality constant.

After conversion, TTP/Tmax perfusion maps were calculated in a voxel wise manner for each PWI dataset by using the mentioned 10 different TTP/Tmax estimation methods (model-independent TTP estimation by using the raw curves, GVM, LDRWM, LNM, and RLCFM as well as model-independent Tmax estimation by using the raw curves, GVM, LDRWM, LNM, and RLCFM).

The arterial input function, required for Tmax estimation, was selected in all datasets from the contralateral middle cerebral artery. The deconvolution, required for Tmax estimation, was performed by using the standard singular value decomposition and a truncation threshold of 0.2.

For quantification of the PWI-DWI mismatch volume, we manually encircled the visible lesions, including a safety margin at each affected section in the DWI dataset. A second healthy volume of interest was then placed in the contralateral unaffected hemisphere in the corresponding brain tissue, so that the resulting defined volume represented an

approximation of the mirrored lesion volume. This healthy volume of interest was then used for calculation of the mean μ and SD σ of the DWI signal intensities, which were then applied for a refinement of the defined coarse DWI lesion volume of interest. Here, all voxels with a signal intensity $I(x) > \mu + 2\sigma$ are retained, while all other voxels are rejected from the final lesion definition.

After this process, the first PWI dataset was registered to the DWI dataset for each patient by using rigid-transformation, linear interpolation, and maximization of the mutual information. The resulting transformation was then used to align the corresponding calculated 10 TTP/Tmax maps of a patient to the DWI dataset by using a linear interpolation.

After registration, the healthy volume of interest as used for the DWI lesion was also used for determination of the mean TTP or Tmax values for each calculated parameter map, which were used for bolus-delay correction of the TTP and Tmax values. The

normalization of the Tmax maps was required because the standard singular value decomposition used in this work is sensitive to arterial bolus delay.²¹

These mean values were then applied for automatic PWI lesion definition by using an automatic segmentation method. Here, all voxels within the DWI lesion were used as seeds for a volume-growing by using lower delay thresholds of $\tau = 2, 3, \dots, 12$ seconds. For each volume-growing segmentation result, morphologic opening (erosion followed by a dilation) followed by a largest connected component analysis was performed for leakage correction.

Finally, the mismatch volumes were calculated for each TTP/Tmax estimation technique and delay threshold by voxelwise subtraction of the DWI lesion from the PWI lesion (Fig 2).

All image-processing steps were performed in this study by using the in-house-developed software tool AnToNIa,²⁵ which was especially extended to enable all described image-based analyses. Apart from the DWI lesion definition, all mentioned TTP and Tmax estimation methods are implemented in this tool. Furthermore, the registration of the TTP/Tmax maps to the DWI dataset and the subsequent method for PWI-DWI mismatch definition are integrated in the software tool.

Statistics

Statistical analysis was performed by using the Pearson correlation coefficient to examine the strength of the association between all TTP/Tmax estimation methods for all delay thresholds applied by using the Statistical Package for the Social Sciences (Version 18.0; SPSS, Chicago, Illinois).

For assessment of intermodel TTP/Tmax correction formulas, the analysis distribution of the data was checked and subsequently log-transformed. Random intercept regression analyses (with patient as a random effect) were performed to model one TTP/Tmax parameter on the basis of another. Model-based estimates with 95% confidence intervals are reported. Nominal *P* values < .05, two-sided, were considered significant. No multiplicity correction was performed. The regression analyses were performed by using SAS 9.2 (SAS Institute, Cary, North Carolina).

As a result of this analysis, a mismatch volume V_T calculated by 1 TTP/Tmax estimation technique for a given delay threshold T_T can be artificially corrected to the corresponding mismatch volume V_R as calculated by another TTP/Tmax estimation method at the same delay threshold by using the following formula:

$$3) \quad V_R = \exp(A + \log(V_T) \times B + T_T \times C),$$

where *A*, *B*, and *C* are correction-specific parameters obtained by the random intercept regression analyses.

RESULTS

Patient Characteristics

The mean patient age was 66 years (median: 66 years; range: 37–88 years), and the mean time from symptom onset to MR imaging was 154 minutes (median: 127 minutes; range: 60–310 minutes). The infarct was located on the right hemisphere in 22 cases. The median NIHSS score on admission was 15 (range, 3–23).

Ten patients presented a carotid-T occlusion; 10 patients, an ICA+MCA occlusion; 20 patients, an MCA mainstem occlusion; and 10 patients, an MCA branch occlusion.

PWI-DWI Mismatch Volumes

The mean DWI lesion volume was 26.4 ± 29.39 mL. The median DWI lesion volume was 19.6 mL (interquartile range, 8–63 mL) for carotid-T occlusions, 13.7 mL (interquartile range, 10–16 mL) for MCA+ICA occlusions, 16.1 mL (interquartile range, 9–22 mL) for MCA mainstem occlusions, and 14.1 mL (interquartile range, 8–19 mL) for MCA branch occlusions.

The results of the PWI-DWI mismatch volumes for the 10 different TTP/Tmax estimation techniques and 11 delay thresholds are illustrated in On-line Fig 2, stratified for the different occlusion types. Overall, the results suggest that the mismatch volumes of all TTP/Tmax estimation techniques are highly correlated because the curve shapes are very similar. Although the general shapes of the resulting curves are very similar, differences regarding the magnitude can be observed. More precisely, the mean volumetric PWI-DWI mismatch differences ranged from only 1.7 to 40.7 mL (corresponding to percentage differences up to 70%) among the results of the 10 TTP/Tmax estimation methods for the most widely used delay range between >4 and >8 seconds. In general, Tmax-based mismatch quantification usually led to smaller mismatch volumes compared with the corresponding TTP-based quantification by using the same model (Fig 2).

Stratification of the results for occlusion type revealed the largest mean mismatch volumes for carotid-T occlusions, comparably smaller mismatch volumes for MCA+ICA, isolated MCA mainstem occlusions, and the smallest mismatch volumes for MCA branch occlusions. Within the first 3 mentioned occlusion type groups, differences in mean PWI-DWI mismatch volume ranged between 0.47 mL and 53.3 mL for the different estimation methods for delay thresholds between >4 and >8 seconds. In contrast, MCA branch occlusions presented considerably smaller marked differences, ranging from 0.54 to 25.2 mL between the average mismatch volumes calculated by the different TTP/Tmax estimation methods.

Patient-specific comparison of individual mismatch volumes determined by the 10 TTP/Tmax estimation techniques revealed volumetric differences up to 100 mL for delay thresholds between >4 and >8 seconds in single patients. Even the most widely used model-independent and GVM TTP/Tmax estimation techniques led to volumetric differences up to 75 mL within this delay threshold range in individual patients.

Number of Patients with “Relevant” Mismatch

In decision-making or image-based inclusion criteria of clinical trials, a mismatch considered “relevant” for identifying patients to be treated or not treated is usually defined by the mismatch ratio rather than the plain mismatch volume. Thus, the mismatch volumes were converted to mismatch ratios in a next step. Overall, the graphs for the mismatch ratios stratified for the different occlusion types show the same tendencies as the raw mismatch volumes (On-line Fig 1).

To further relate these findings to clinical decision-making, we calculated the number of patients complying with the penumbral

inclusion criteria used in the EXTEND trial for each TTP/Tmax estimation method. More precisely, patients exhibiting a PWI-DWI mismatch ratio of $>20\%$ and a PWI-DWI mismatch volume of >10 mL at a temporal delay of >6 seconds⁹ were considered as presenting a relevant mismatch volume. The results of this evaluation are shown in On-line Fig 3 (top), which displays the number of patients included by each TTP/Tmax estimation technique stratified for each occlusion type. Noticeable discrepancies regarding the number of patients fulfilling these mismatch criteria can be seen. Over the entire sample, the number of patients classified as presenting “no mismatch” ranged from only 3 (RLCFM TTP) to 15 patients (LDRWM TTP and Tmax), depending on the TTP/Tmax estimation method used.

Correlation Analysis and Correction Formulas

Crosswise correlation analysis of the tissue-at-risk volumes at the different delay thresholds determined by the different TTP/Tmax estimation techniques revealed highly significant strong correlation coefficients, ranging from 0.896 to 0.998.

These findings support the assumption that the tissue-at-risk volumes derived from the different TTP/Tmax estimation techniques are comparable to some extent and a correction between the models is feasible. Quantitatively, the correction formulas allowed an adaptation with a nonlogarithmized mean standard error of 3.64 mL (minimum, 0.84 mL; maximum, 7.46 mL) over all TTP/Tmax estimation techniques and delay thresholds (On-line Table). In general, a conversion from TTP to Tmax or vice versa led to higher standard errors (mean standard error, 4.28 mL) than the conversion between 2 TTP and 2 Tmax estimation methods (mean standard error, 2.96 mL). The correction parameters derived from the random intercept regression analyses can be found in the On-line Table.

To investigate a possible clinical benefit associated with these correction formulas, we exemplarily analyzed whether this adaptation is beneficial in terms of reduced differences regarding the definition of patients with a relevant mismatch volume. Therefore, all tissue-at-risk volumes determined by the different TTP/Tmax estimation methods were corrected to the corresponding mismatch quantification resulting from the model-independent TTP estimation. The results of this evaluation are illustrated in On-line Fig 3 (bottom). Compared with the identification of patients with a relevant PWI-DWI mismatch by using the model-independent TTP estimation method, differences of up to 7 patients were found for the other TTP/Tmax estimation methods before correction. After correction, maximum differences in patient numbers fulfilling the mismatch criterion decreased to only 2 patients.

DISCUSSION

The main finding of this study is the observation that different TTP and Tmax estimation methods lead to considerable differences of perfusion lesion volumes and calculated perfusion-diffusion mismatch volumes. In this sample of 50 patients with acute ischemic stroke with different occlusion types, the mean mismatch volumes differed up to 40 mL among different TTP/Tmax estimation methods. Moreover, for individual patients, the differences in lesion volumes increased up to 100 mL. These findings

are novel because there is no previous systematic comparison of different TTP/Tmax estimation methods in patients with acute ischemic stroke.

The PWI-DWI mismatch definition may be influenced by several parameters to different extents, which is beyond the focus of this study. Among others, these parameters comprise the injection protocol (injection volume and injection rate), MR imaging parameters, usage and techniques for preprocessing including deconvolution, perfusion parameter selection, arterial input function localization, image registration accuracy, and finally the definition of thresholds to define critical hypoperfusion.^{11,14,15,21} Although several studies have evaluated the impact of 1 or more of these different parameters directly or indirectly, the influence of the TTP/Tmax estimation technique has not gained much attention. So far, only 1 study has been conducted comparing direct TTP and deconvolution-based Tmax estimation.¹³ With PET as a criterion standard, it was concluded that deconvoluted Tmax does not perform significantly better than the direct TTP estimation. Moreover, the optimal TTP delay threshold was estimated at 4.2 seconds, while the optimal Tmax threshold was determined at 5.5 seconds in this study. This finding also substantiates the conclusions of this work that different TTP and Tmax methods lead to volumetric differences of perfusion lesions when applying inappropriate delay thresholds. However, only model-independent direct TTP and Tmax estimation was evaluated in this PET study,¹³ while the use of hemodynamic model curves was not investigated.

The numerous possible influence factors and the heterogeneity of techniques and parameters pose a vital challenge to acute stroke perfusion image analysis, making direct comparisons between studies that employed different methods complex, if not impossible.²⁶ Stroke researchers have addressed this problem by a consensus statement of an Acute Stroke Research Imaging Roadmap.²⁷ Nevertheless, a recent systematic review still identified substantial heterogeneity of perfusion image acquisition and postprocessing as well as considerable under-reporting of methodology in scientific publications.²⁶ The present study sheds light on an essential part of the postprocessing pipeline that has not been the focus of most stroke imaging researchers until now.

Besides this rather scientific problem, the results of this study also have an immediate clinical implication. The identification of tissue at risk by estimation of perfusion and diffusion lesions is increasingly used to guide treatment decisions in acute stroke.^{1,5,6} While differences in perfusion lesion extent as observed in this study may not make a difference in the case of a large perfusion lesion with a clear mismatch, they may be decisive in borderline cases in which the decision, whether a relevant mismatch is present, is not eye-catching. This possibility applies especially to clinical trials that use a penumbral MR imaging pattern to identify a target population of patients with acute stroke.⁷⁻⁹ In these trials, a clear definition of mismatch has to be used, and differences in perfusion lesion quantification, as reported in this study, may determine whether the patients have a mismatch. If one applies the relevant mismatch definition that is currently used in the EXTEND trial,⁹ the TTP/Tmax estimation methods tested in this study resulted in a different mismatch classification in $\leq 24\%$ of all cases (12/50).

Especially in the setting of multicenter trials, this difference carries the risk of significant inclusion heterogeneity, which, in the end, may even influence the results of the trial. A number of re-analyses of data from the EPITHET have demonstrated that only slight modifications of the definition of mismatch, such as the use of coregistered images to calculate mismatch volume instead of simple volume subtraction, may change the trial from a negative to a positive one with respect to the primary end point.²⁸ Thus, especially in a clinical trial or any study involving multiple sites, standardization of image acquisition and processing represents a key factor to assure homogeneous results.

It was not an aim of this study to identify the optimal TTP/Tmax estimation technique or the best delay threshold. However, the results of this study revealed that the definition of an optimal delay threshold may only be valid for a certain TTP/Tmax estimation technique.

This study indicates a way to overcome the problem of heterogeneous TTP/Tmax estimation algorithms used in stroke research by calculating correction formulas to convert results from one estimation model into another. Although the results of different studies will still not be directly comparable, a rough adjustment appears possible by using the described correction formulas. However, the correction formulas have only been evaluated exemplarily in this work so that no conclusions can be drawn from this regarding a possible general application. It may be possible that the calculated parameters of the correction formulas depend on the contrast agent injection protocol, PWI acquisition parameters, or localization of the arterial input function. Therefore, further evaluations of the presented correction formulas are required.

A suboptimal fitting of a hemodynamic model curve to the arterial input function may lead to a systematic error for the whole Tmax map calculation. Thus, special care needs to be taken to ensure optimal fitting to the arterial input function in this case.

Apart from this problem, an occluded vessel may lead to considerable perfusion changes so that the concentration curves do not exhibit a typical shape in the worst case. Thus, an optimal model curve fitting may not be possible in certain stroke areas because the underlying assumptions are not valid. The reference-based linear curve fitting approach²⁰ recently has been suggested, which differs from the other hemodynamic models in that no explicit assumption about typical concentration curve shape is made, to overcome this problem. The results of this study suggest that this approach leads to bigger mismatch volumes compared with the other TTP/Tmax estimation methods. This finding may be ascribed to better curve fitting in areas that are affected by a severe perfusion disturbance.

Finally, the arterial input function was selected in all datasets from the contralateral middle cerebral artery and was used in a standard singular value decomposition approach for Tmax estimation. Therefore, it may be interesting for further studies to evaluate more sophisticated deconvolution techniques²¹ in combination with varying global or even local arterial input functions.

CONCLUSIONS

High variations of tissue-at-risk volumes, which may also be clinically relevant, have to be expected when using different

TTP/Tmax estimation techniques. An adaption of different techniques using correction formulas may enable more comparable study results until a standard has been established by agreement.

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REFERENCES

- Muir KW, Buchan A, von Kummer R, et al. **Imaging of acute stroke.** *Lancet Neurol* 2006;5:755–68
- Butcher KS, Parsons M, MacGregor L, et al. **Refining the perfusion-diffusion mismatch hypothesis.** *Stroke* 2005;36:1153–59
- Neumann-Haefelin T, Wittsack HJ, Wenserski F, et al. **Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke.** *Stroke* 1999;30:1591–97
- Sobesky J, Zaro Weber O, Lehnhardt FG, et al. **Which time-to-peak threshold best identifies penumbral flow? A comparison of perfusion-weighted magnetic resonance imaging and positron emission tomography in acute ischemic stroke.** *Stroke* 2004;35:2843–47
- Thomalla G, Schwark C, Sobesky J, et al. **Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients: comparison of a German multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials.** *Stroke* 2006;37:852–58
- Schellinger PD, Thomalla G, Fiehler J, et al. **MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients.** *Stroke* 2007;38:2640–45
- Hacke W, Furlan AJ, Al-Rawi Y, et al. **Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study.** *Lancet Neurol* 2009;8:141–50
- Davis SM, Donnan GA, Parsons MW, et al. **Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial.** *Lancet Neurol* 2008;7:299–309
- Ma H, Parsons MW, Christensen S, et al. **A multicentre, randomized, double-blinded, placebo-controlled phase III study to investigate EXTending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND).** *Int J Stroke* 2012;7:74–80
- Schaefer PW, Hunter GJ, He J, et al. **Predicting cerebral ischemic infarct volume with diffusion and perfusion MR imaging.** *AJNR Am J Neuroradiol* 2002;23:1785–94
- Kane I, Carpenter T, Chappell F, et al. **Comparison of 10 different magnetic resonance perfusion imaging processing methods in acute ischemic stroke: effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores, and radiologic outcomes.** *Stroke* 2007;38:3158–64
- Olivot JM, Mlynash M, Thijs VN, et al. **Optimal Tmax threshold for predicting penumbral tissue in acute stroke.** *Stroke* 2009;40:469–75
- Zaro-Weber O, Moeller-Hartmann W, Heiss WD, et al. **Maps of time to maximum and time to peak for mismatch definition in clinical stroke studies validated with positron emission tomography.** *Stroke* 2010;41:2817–21
- Ebinger M, Brunecker P, Jungehulsing GJ, et al. **Reliable perfusion maps in stroke MRI using arterial input functions derived from distal middle cerebral artery branches.** *Stroke* 2010;41:95–101
- Christensen S, Mouridsen K, Wu O, et al. **Comparison of 10 perfusion MRI parameters in 97 sub-6-hour stroke patients using voxel-based receiver operating characteristics analysis.** *Stroke* 2009;40:2055–61
- Fiehler J, Knudsen K, Thomalla G, et al. **Vascular occlusion sites determine differences in lesion growth from early apparent diffu-**

- sion coefficient lesion to final infarct. *AJNR Am J Neuroradiol* 2005;26:1056–61
17. Madsen MT. **A simplified formulation of the gamma variate function.** *Phys Med Biol* 1992;37:1597–600
 18. Bogaard JM, Smith SJ, Versprille A, et al. **Physiological interpretation of the skewness of indicator-dilution curves; theoretical considerations and a practical application.** *Basic Res Cardiol* 1984;79:479–93
 19. Linton RA, Linton NW, Band DM. **A new method of analysing indicator dilution curves.** *Cardiovasc Res* 1995;30:930–38
 20. Forkert ND, Fiehler J, Ries T, et al. **Reference-based linear curve fitting for bolus arrival time estimation in 4D MRA and MR perfusion-weighted image sequences.** *Magn Reson Med* 2011;65:289–94
 21. Kudo K, Sasaki M, Ostergaard L, et al. **Susceptibility of Tmax to tracer delay on perfusion analysis: quantitative evaluation of various deconvolution algorithms using digital phantoms.** *J Cereb Blood Flow Metab* 2011;31:908–12
 22. Meier P, Zierler KL. **On the theory of the indicator-dilution method for measurement of blood flow and volume.** *J Appl Physiol* 1954;6:731–44
 23. Ostergaard L, Weisskoff RM, Chesler DA, et al. **High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I. Mathematical approach and statistical analysis.** *Magn Reson Med* 1996;36:715–25
 24. Straka M, Albers GW, Bammer R. **Real-time diffusion-perfusion mismatch analysis in acute stroke.** *J Magn Reson Imaging* 2010;32:1024–37
 25. Thomalla G, Cheng B, Ebinger M, et al. **DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study.** *Lancet Neurol* 2011;10:978–86
 26. Dani KA, Thomas RG, Chappell FM, et al. **Systematic review of perfusion imaging with computed tomography and magnetic resonance in acute ischemic stroke: heterogeneity of acquisition and postprocessing parameters: a translational medicine research collaboration multicentre acute stroke imaging study.** *Stroke* 2012;43:563–66
 27. Wintermark M, Albers GW, Alexandrov AV, et al. **Acute stroke imaging research roadmap.** *Stroke* 2008;39:1621–28
 28. Nagakane Y, Christensen S, Brekenfeld C, et al. **EPITHET: positive result after reanalysis using baseline diffusion-weighted imaging/perfusion-weighted imaging co-registration.** *Stroke* 2011;42:59–64

Chronic Hemodynamic Compromise and Cerebral Ischemic Events in Asymptomatic or Remote Symptomatic Large-Artery Intracranial Occlusive Disease

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ABSTRACT

BACKGROUND AND PURPOSE: In asymptomatic or remote symptomatic LAICOD, the risk of ischemic events is low in general, but there may be a subgroup of higher risk patients who require aggressive medical management. The purpose of this study was to determine whether chronic hemodynamic compromise is a predictor of ischemic events in asymptomatic or remote symptomatic LAICOD.

MATERIALS AND METHODS: We prospectively studied 51 asymptomatic, 19 coexistent asymptomatic, and 19 remote (>6 months) symptomatic patients with atherosclerotic intracranial internal carotid artery or middle cerebral artery disease by using ^{15}O -PET. MP was defined as decreased CBF, increased OEF, and a decreased CBF/CBV ratio. All patients were followed up for 2 years or until occurrence of stroke or TIA or death.

RESULTS: Bypass surgery was performed in 4 patients (2 with MP). Three cerebral ischemic events (1 TIA in an asymptomatic patient, 1 stroke, and 1 TIA in a remote symptomatic patient) occurred in the vascular territory ipsilateral to LAICOD. Kaplan-Meier analysis with censoring at the time of bypass surgery revealed that the incidence of ipsilateral ischemic events in patients with MP (2/5) was significantly higher than that in patients without MP (1/84) (log-rank test; $P < .0001$). The relative risk conferred by MP was 83.1 (95% confidence interval, 6.8–1017.4; $P < .001$). The incidence of ipsilateral ischemic events in patients with decreased CBF/CBV (2/9) was also significantly higher than that of patients without it (1/80) ($P = .0001$).

CONCLUSIONS: Chronic hemodynamic compromise may be a predictor of ischemic events in both asymptomatic and remote symptomatic LAICOD.

ABBREVIATIONS: CI = confidence interval; CMRO_2 = cerebral metabolic rate of oxygen; LAICOD = large-artery intracranial occlusive disease; MP = misery perfusion; OEF = oxygen extraction fraction

LAICOD has emerged as the most common stroke subtype worldwide, and recent symptomatic LAICOD (within 3 months) is associated with a high risk of recurrent stroke.^{1,2} Aggressive medical management is recommended to prevent recurrent stroke for this subset of high-risk patients.³ On the other hand, in asymptomatic or remote symptomatic LAICOD, the risk of ischemic events is relatively low.^{4,5} If a patient has asymptomatic LAICOD or presents for evaluation after the initial symptoms and does not experience subsequent events, a

more conservative approach is recommended. However, there may be a subgroup of higher risk patients who require aggressive medical management.

Hemodynamic factors may be important in LAICOD prognosis.^{6–9} Patients with LAICOD with hemodynamic symptoms were reported to be at high risk for subsequent ischemic events.¹⁰ Previous studies of mixed patient populations with symptomatic large-artery extracranial and intracranial occlusive disease suggest that chronic hemodynamic compromise, as indicated by increased OEF (also known as MP)¹¹ on ^{15}O -PET¹² or severely decreased vasodilatory capacity, is a risk factor for subsequent ischemic stroke.^{13–17} However, the relationship between hemodynamic compromise and asymptomatic or remote symptomatic LAICOD prognosis is unknown. The purpose of this observational study was to determine whether chronic hemodynamic compromise on ^{15}O -PET is a predictor of subsequent ischemic events in asymptomatic or remote (>6 months) symptomatic atherosclerotic intracranial disease of the ICA or MCA.

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Table 1: Baseline patient characteristics

Characteristic	Category			
	Asymptomatic	Coexistent	Remote	Controls
No. of patients	51	19	19	7
MP (No.)	1	1	3	—
Increased OEF	7	4	6	—
Decreased CBF/CBV	1	3	5	—
Age (mean) (yr)	63 ± 9	63 ± 9	65 ± 8	47 ± 7
Men/women (No.)	31:20	13:6	13:6	4:3
Cerebral infarction (No.)	20	7	17	—
Asymptomatic bilateral lacunar infarcts (No.)	8	3	3	—
Qualifying artery (No. of occlusions/stenoses)	9/42	5/14	7/12	—
Intracranial ICA (occlusions/stenoses)	26 (3/23)	9 (1/8)	4 (1/3)	—
MCA (occlusion/stenosis)	25 (6/19)	10 (4/6)	15 (6/9)	—
Other asymptomatic stenoses >50% (No.)	18	—	2	—
Other medical illness (No.)				
Hypertension	27	11	15	0
Diabetes mellitus	14	10	5	0
Ischemic heart disease	9	7	4	0
Hypercholesterolemia	10	5	8	0
Smoking habit (current and former) (No.)	11	4	5	0
Antiplatelet agents	33	18	17	0
Bypass surgery (MP) (No.)	2 (1)	0	2 (1)	—

Note:—Asymptomatic indicates asymptomatic artery disease; Coexistent, coexistent asymptomatic artery disease; Remote, remote symptomatic artery disease.

MATERIALS AND METHODS

Patients

We studied 51 consecutive patients with asymptomatic atherosclerotic LAICOD (asymptomatic group). We included 31 men and 20 women (age range, 44–90 years; mean, 63 ± 9 years; Table 1). Patients were first referred to the PET unit at Shiga Medical Center from the outpatient clinic or other hospitals in the Shiga Prefecture between 1999 and 2008 to undergo hemodynamic parameter evaluation as part of clinical assessment to determine the need for extracranial–intracranial bypass. Although the benefit from bypass surgery in patients with MP remains to be proved, the operation is nevertheless performed in some patients in Japan and elsewhere. The inclusion criteria were the following: 1) occlusion or stenosis (>50% diameter reduction) of the intracranial ICA or MCA as documented by conventional or MR angiography,¹⁸ and 2) absence of previous symptoms or signs of ischemia in the diseased intracranial ICA or MCA territory. The exclusion criteria were the following: 1) history of vascular reconstruction surgery, or 2) potential sources of cardiogenic embolism, including recent myocardial infarction (within 3 weeks), known atrial fibrillation, mitral stenosis, mitral valve prosthesis, dilated cardiomyopathy, sick sinus syndrome, or subacute bacterial endocarditis.

During the same study period, we also studied 19 consecutive patients with asymptomatic LAICOD coexistent with symptomatic large-artery disease who met the inclusion criteria above (coexistent group) and 19 consecutive patients with remote (>6 months; median, 45 months; range, 6.4–142 months) symptomatic LAICOD without subsequent events (remote group) (Table 1). These patients were selected from candidates for the observational study of symptomatic large-artery disease reported elsewhere.¹⁷ Patients were first referred to the PET unit at Shiga Medical Center from the outpatient clinic or other hospitals in the Shiga Prefecture to undergo hemodynamic parameter evaluation as part of clinical assessment to determine the need for bypass surgery. The inclusion

criteria for symptomatic large-artery disease were the following: 1) occlusion of the extracranial ICA or occlusion or stenosis (>50% diameter reduction) of the intracranial ICA or MCA as documented by conventional or MR angiography,¹⁸ 2) history of TIA or stroke involving the relevant ICA or MCA territory, and 3) ability to independently carry out daily activities (<3 on the modified Rankin Scale). The exclusion criteria were the same as described above.

In asymptomatic (never symptomatic) patients, arterial disease was suspected on the basis of the findings of MR angiography or echo angiography performed during screening for cerebral arterial disease in patients with coronary artery disease or those presenting with dizziness, vertigo, or headache. In 20 of the 51 patients, MR imaging revealed minor abnormalities in the MCA territory of the hemisphere with arterial disease. Eight patient MRIs showed asymptomatic lacunar infarcts in the bilateral basal ganglia (putamen, globus pallidus, and caudate nucleus) that were identified as hyperintense regions on fluid-attenuated inversion recovery images and hypointense areas on T1-weighted images. Diseased arteries included intracranial ICA occlusion in 3 cases, intracranial ICA stenosis in 23 cases, MCA occlusion in 6 cases, and MCA stenosis in 19 cases. Other asymptomatic arterial stenoses (>50% diameter reduction)^{18,19} were found in 16 cases (18 arteries), including contralateral ICA disease in 8 cases, contralateral MCA disease in 4 cases, and vertebral artery disease in 6 cases. The findings on MR imaging or angiography in coexistent asymptomatic or remote symptomatic patients are listed in Table 1. Vascular risk factors, including hypertension, diabetes mellitus, ischemic heart disease, hypercholesterolemia, and smoking status were determined from patient history recorded at the time of PET examination. Hypertension, diabetes mellitus, ischemic heart disease, and hypercholesterolemia were judged as present on the basis of treatment history. The ethics committee of our center approved the study protocol, and each patient provided written informed consent.

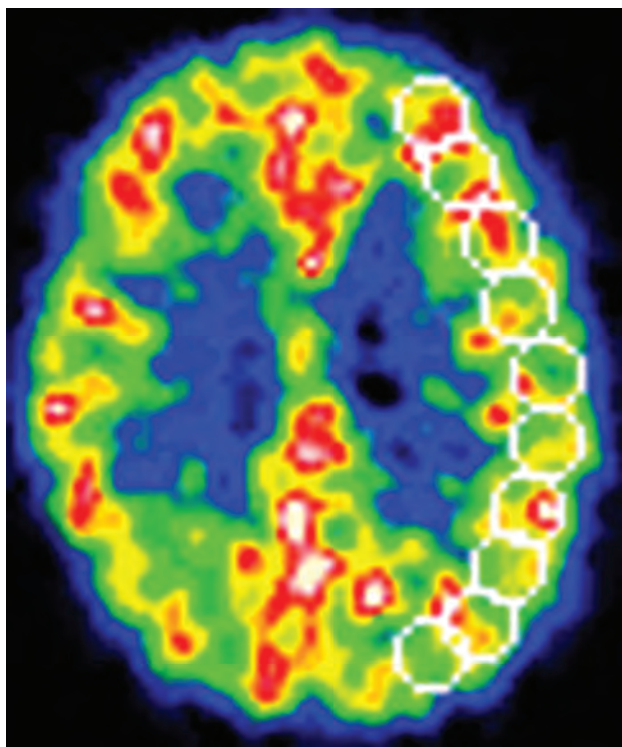


FIG 1. An example of the ROIs on the CBF image.

PET Measurements

All patients underwent ^{15}O -PET scans with a whole-body Advance PET scanner (GE Healthcare, Milwaukee, Wisconsin), which permits simultaneous acquisition of 35 sections with intersection spacing of 4.25 mm.²⁰ Intrinsic scanner resolution was 4.6–5.7 mm in the transaxial direction and 4.0–5.3 mm in the axial direction. As part of the scanning procedure but before tracer administration, germanium 68/gallium 68 transmission scanning was performed for 10 minutes for attenuation correction. To reconstruct the PET data, we blurred images to 6.0-mm full width at half maximum in the transaxial direction with a Hanning filter. Functional images were reconstructed as 128×128 pixels, with each pixel representing an area of 2.0×2.0 mm.

A series of oxygen 15 (^{15}O) gas studies was performed. The patients continuously inhaled C^{15}O_2 , and $^{15}\text{O}_2$ through a face mask.²⁰ The scanning time was 5 minutes, and arterial blood was manually sampled from the brachial artery 3 times during each scan. Radiotracer radioactivity in whole blood and plasma was measured by using a well counter. Bolus inhalation of C^{15}O and 3-minute scanning was used to measure CBV. Arterial samples were manually obtained twice during scanning, and radiotracer radioactivity was measured in whole-blood samples. CBF, CMRO_2 , and OEF were calculated by using the steady-state method.²¹ CMRO_2 and OEF were corrected by CBV.²² The CBF/CBV ratio was calculated pixel-by-pixel as an indicator of cerebral perfusion pressure.²³

Data Analysis

We analyzed 10 tomographic planes from 46.25 to 84.5 mm above and parallel to the orbitomeatal line, which corresponded to the levels of the basal ganglia and thalamus to the centrum semiovale.

The ROIs were placed on the CBF images. Each image was examined by placing 10–12 circular ROIs (diameter, 16 mm) over the outer cortical gray matter in each hemisphere (Fig 1). According to the atlas, the ROIs in all 10 images covered the distribution of the MCA and the watershed areas between the MCA and other cerebral arteries.²⁴ The same ROIs were transferred to the other images. The mean value for the hemisphere affected by ICA or MCA disease was calculated as the average of the values for all circular ROIs. In asymptomatic (never symptomatic) patients with bilateral disease, the hemisphere supplied by the more severely diseased ICA or MCA is referred to here as the “affected hemisphere.” In patients with cerebral cortex infarction, the circular ROIs that included hypointense areas on T1-weighted MR images were excluded from analysis by using a method that correlated PET images with MR images.¹⁶ We did not use coregistered MR imaging to define the ROIs.

Normal control values of the ^{15}O -PET variables were obtained from 7 healthy volunteers (4 men and 3 women; mean age, 47 ± 7 years) who underwent routine neurologic examinations and MR imaging scans. The OEF value obtained from these 14 control hemispheres was $44.5\% \pm 3.8\%$. Hemispheric OEF values beyond the upper 95% limit defined in healthy subjects (above 52.9%) represented increased OEF. Comparative values for CBF and CBF/CBV in healthy controls were 44.6 ± 4.5 and 11.4 ± 1.8 , respectively. Hemispheric CBF and CBF/CBV values below 35.0 mL/100 g/min and 7.6/min, respectively, were considered abnormal.

Patients with increased OEF, decreased CBF, and decreased CBF/CBV in hemispheres with arterial disease were categorized as having MP. This definition differed from that in our previous study, which only considered increased OEF.^{15,16} It was adopted because increased OEF without decreased perfusion pressure may not indicate MP.^{17,23} Patients with increased OEF in our previous study also had decreased CBF and CBF/CBV,¹⁵ which is consistent with MP in the present study. Patients were categorized as having or not having MP by an investigator who was unaware of their clinical status.

Follow-Up and Outcome

Attending physicians were informed of ^{15}O -PET findings, but risk factor treatment and pharmacologic or surgical interventions were left to individual clinical judgment. Asymptomatic patients who received medical treatment and all symptomatic patients were examined at 1- or 2-month intervals after ^{15}O -PET in the outpatient clinic of our center or at other hospitals in the Shiga Prefecture. An interim history was obtained, and a neurologic examination was performed at each visit. We contacted 2 asymptomatic patients without medical treatment or their next of kin by telephone every 6 months. In patients who experienced subsequent ischemic events (stroke or TIA), MR images or CT images were obtained and compared with the initial images to confirm stroke, and MR angiography was performed to study changes in arterial disease. The end point was an ipsilateral ischemic event (stroke or TIA). “Stroke” was defined as the acute onset of a new focal neurologic deficit of cerebral origin persisting for more than 24 hours without primary intracranial hemorrhage on CT or MR imaging. “TIA” was defined as the development of focal symptoms of presumed cerebrovascular ischemic origin lasting <24 hours.

Table 2: Baseline values of PET variables in the hemispheres ipsilateral to intracranial artery disease and in healthy controls^a

Variable	Category			
	Asymptomatic	Coexistent	Remote	Controls
CBF (mL/100 g/min)	39.5 ± 7.3	36.3 ± 7.8	34.0 ± 6.6 ^b	44.6 ± 4.5
CMRO ₂ (mL/100 g/min)	3.29 ± 0.50	2.96 ± 0.44	2.89 ± 0.42	3.43 ± 0.33
OEF (%)	48.0 ± 5.9	50.7 ± 6.8	50.3 ± 5.8	44.5 ± 3.8
CBV (mL/100 g)	3.53 ± 0.54	3.85 ± 0.83	3.84 ± 0.75	3.98 ± 0.48
CBF/CBV (per min)	11.3 ± 2.1	9.8 ± 2.7	9.2 ± 2.6	11.4 ± 1.8

Note:—Asymptomatic indicates asymptomatic artery disease; Coexistent, coexistent asymptomatic artery disease; Remote, remote symptomatic artery disease.

^a Values are means.

^b $P < .001$ vs corresponding value in healthy controls (1-way ANOVA and post hoc Scheffe analysis).

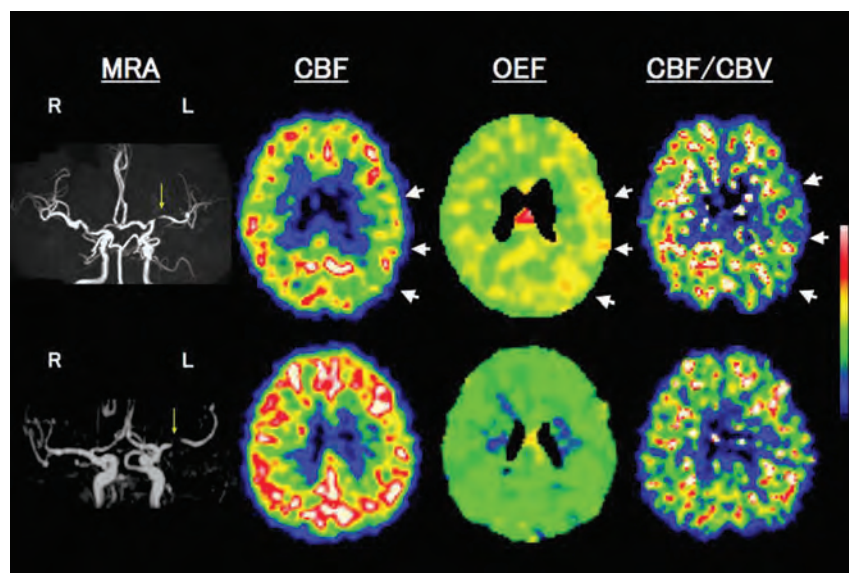


FIG 2. Upper row shows examples of PET images for a patient with left (L) remote (41 months) symptomatic MCA stenosis with MP. MRA shows severe stenosis of the L MCA. PET study shows reduced CBF, increased OEF, and decreased CBF/CBV in the L hemisphere with MCA stenosis (arrows). A subsequent transient ischemic attack (a transient episode of sensory aphasia) occurred 14 days after the PET study. Lower row shows a patient with L asymptomatic MCA stenosis with normal cerebral hemodynamics.

Statistical Analysis

Baseline values of 5 PET variables were compared among 3 LAICOD types and healthy controls by using 1-way analysis of variance and post hoc Scheffe analysis; significance was established at $P < .01$ (.05/5) by performing a Bonferroni correction. The incidence of subsequent cerebral ischemic events was compared between groups by using the Fisher exact test or Mantel-Cox log-rank statistics and Kaplan-Meier survival curves. Survival analysis began on the day of the ¹⁵O-PET examination, which was considered the date of entry into the study. Analysis was performed with censoring at the time of bypass surgery. Multivariate analysis by using the Cox proportional hazards model was used to test the effect of multiple variables on the occurrence of ischemic events. Age, sex, subgroup (asymptomatic, coexistent asymptomatic, or remote symptomatic LAICOD), antiplatelet agent, arterial occlusion, MCA disease, other asymptomatic major cerebral arterial stenoses, cerebral infarction, bilateral asymptomatic lacunar infarcts, complications (hypertension, diabetes mellitus, prior ischemic heart disease, or hypercholesterolemia), smoking habits, and MP were considered covariates. Forward stepwise selection was performed, and variables demonstrating a significant rela-

tionship ($P < .05$) with an outcome event were included in the final model.

RESULTS

On the basis of OEF, CBF, and CBF/CBV values in the hemisphere supplied by the asymptomatic or remote symptomatic artery, 5 patients (5.6%) had MP and 84 did not (Table 1). Seventeen patients had increased OEF, while 9 patients had decreased CBF/CBV. Baseline values of PET variables in the 3 groups are shown in Table 2. No significant difference was found for any variable among the 3 patient groups, while CBF in remote symptomatic patients was only significantly decreased compared with healthy controls.

All patients were followed up for 2 years or until a cerebral ischemic event or death. Four patients (4.5%), including 2 with MP (1 intracranial ICA stenosis and 1 intracranial ICA occlusion) and 2 without (2 MCA occlusions), underwent bypass surgery an average of 2.4 months after PET examinations (range, 0.5–4.0 months). Three cerebral ischemic events occurred in the vascular territory ipsilateral to LAICOD. All 3 events occurred in medically treated patients. One stroke and 1 TIA occurred in remote symptomatic patients with remote artery disease and MP; 1 patient with left intracranial ICA stenosis developed infarction in the posterior limb of the left internal capsule, resulting in right hemiparesis; and 1 patient with left

MCA stenosis developed a transient episode of sensory aphasia (Fig 2). One TIA occurred in an asymptomatic patient without MP, and a patient with right MCA occlusion developed a transient weakness of the left upper limb. Four surgically treated patients had no ischemic events after surgery. All of the asymptomatic or remote symptomatic patients survived the 2-year follow-up period, and 1 patient with coexistent asymptomatic artery disease and MP died of myocardial infarction after 12 months.

In patients with and without MP, the 2-year incidences of ipsilateral stroke and TIA were 2/5 (40%) and 1/84 (1.2%), respectively (Fisher exact test; $P = .0075$). Kaplan-Meier analysis with censoring at the time of bypass surgery revealed that the incidence of ipsilateral ischemic events in patients with MP was significantly higher than that of patients without MP ($P < .0001$; Fig 3, left). Multivariate analysis with the Cox proportional hazards model demonstrated that only MP was a significant independent predictor for ipsilateral ischemic events. The relative risk conferred by MP was 83.1 (95% confidence interval, 6.8–1017.4; $P < .001$).

The ipsilateral ischemic event incidence in patients with decreased CBF/CBV (2/9) was significantly higher than that of pa-

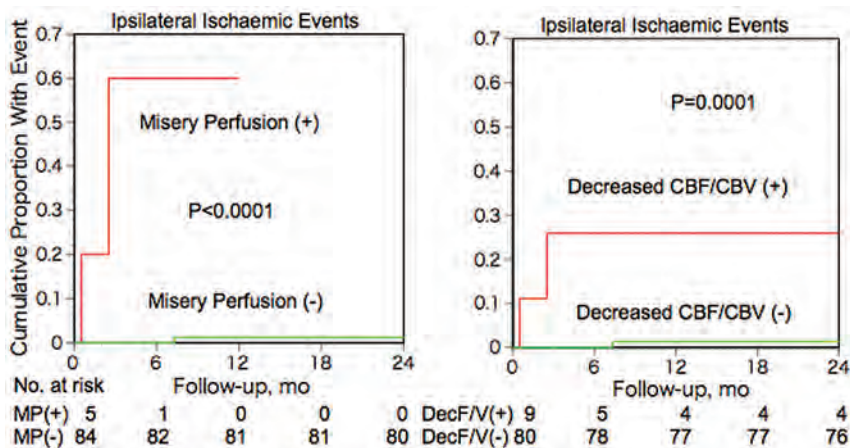


FIG 3. Kaplan-Meier cumulative failure curves for ipsilateral ischemic events in patients with and without misery perfusion (left) or decreased CBF/CBV (right). The number of patients who remained event-free and available for follow-up evaluation during each 6-month interval is shown at the bottom of the graph.

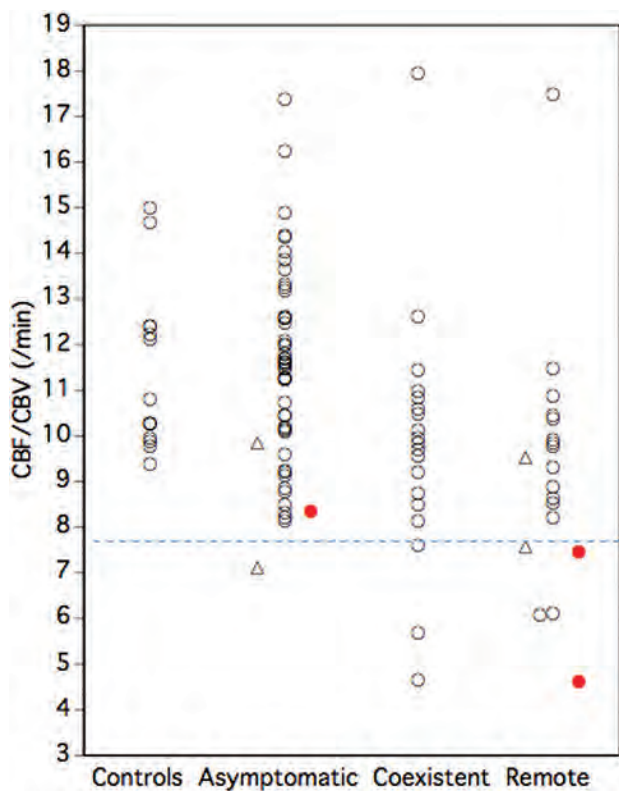


FIG 4. Relationship between decreased CBF/CBV and ischemic events. Closed circles (red) indicate patients with ischemic events. A dashed line (blue) denotes the lower 95% limit defined in healthy controls. Triangles indicate patients who underwent bypass surgery.

tients without decreased CBF/CBV (1/80) (Fisher exact test; $P = .026$) (Fig 4), while no significant difference was found between that of patients with increased OEF (2/17) and patients without increased OEF (1/72) (Fisher exact test; $P = .092$). Kaplan-Meier analysis with censoring at the time of bypass surgery revealed that the incidence of ipsilateral ischemic events in patients with increased OEF or decreased CBF/CBV was significantly higher than that of patients without it (log-rank test; $P < .05$ and $P = .0001$, respectively) (Fig 3, right). When increased OEF or decreased

CBF/CBV was used as a covariate instead of MP, multivariate analysis with the Cox proportional hazards model demonstrated that only decreased CBF/CBV was a significant independent predictor for ipsilateral ischemic events; increased OEF was not. The relative risk values conferred by decreased CBF/CBV and increased OEF were 24.8 (95% CI, 2.2–277.3; $P < .01$) and 9.8 (95% CI, 0.8–108.4; $P = .063$), respectively.

DISCUSSION

This study demonstrated that chronic hemodynamic compromise on ^{15}O -PET is a predictor of subsequent ischemic events in the hemispheres with asymptomatic or remote (>6 months) symptomatic atherosclerotic intracranial disease of the ICA or MCA.

The 2-year incidence of ipsilateral ischemic events in patients with MP (2/5) or decreased CBF/CBV (2/9) was significantly higher than that of patients without MP (1/84) or decreased CBF/CBV (1/80), respectively. Evaluation of chronic hemodynamic compromise may identify a subgroup of higher risk patients in asymptomatic or remote (>6 months) symptomatic LAICOD that has a low risk of ischemic events in general.⁴

No studies have investigated the relationship between chronic hemodynamic compromise on ^{15}O -PET and asymptomatic or remote symptomatic LAICOD prognosis. Previous studies of symptomatic atherosclerotic large-artery disease, including LAICOD, suggested that patients with chronic hemodynamic compromise are at high risk for subsequent stroke.^{13–17} Thus, chronic hemodynamic compromise may also confer a higher risk of ischemic events in patients with asymptomatic or remote symptomatic LAICOD. The results of this study support this hypothesis, though only a few patients in this small sample experienced subsequent ischemic events. However, our findings are consistent with the benign prognosis of asymptomatic LAICOD reported by several studies.^{4,25–28} Correct evaluations of hemodynamic status by using ^{15}O -PET could identify a small subgroup of higher risk patients among low-risk patients with LAICOD. MP was the best predictor of ischemic events, and decreased CBF/CBV also predicted ischemic events, though the predictive value of decreased CBF/CBV was lower than that of MP. The CBF/CBV is the reciprocal of the expression for vascular MTT, which can be evaluated by perfusion imaging with MR imaging or CT in routine clinical practice.^{29,30} The ability of perfusion MR imaging or CT methods to predict the risk of future ischemic events should be studied in a larger patient sample.⁶ In the future, the combination of perfusion imaging with oxygen imaging by using MR imaging, which may detect MP, would allow greater accuracy in identifying higher risk patients.^{31,32}

In asymptomatic or remote symptomatic LAICOD, cerebral hemodynamics and metabolism have not been studied specifically. In this study, the degree of hemodynamic compromise at baseline was mild. However, cerebral atherosclerosis is a dynamic

disease that can progress or regress.³³ Thus, to improve long-term prognosis in patients with asymptomatic or remote (>6 months) symptomatic atherosclerotic LAICOD, preventing hemodynamic deterioration due to the progression of artery disease may be important. This could be achieved by appropriately managing atherogenic risk factors. In patients with carotid occlusion, asymptomatic hemodynamic deterioration has been demonstrated to cause subsequent hemodynamic stroke during long-term (>2 years) follow-up.³⁴ Hemodynamic assessment at baseline may be useful to identify patients who require aggressive medical management. Furthermore, follow-up evaluation of hemodynamic status and cerebral atherosclerosis might identify patients whose stroke risk is increased in asymptomatic or remote symptomatic atherosclerotic LAICOD.

The major limitation of this study was that only a few ischemic events occurred in the small patient sample. Because our cohort comprised patients who were examined on a PET unit, our results are subject to referral or selection bias. Patients perceived to be at high risk for ischemic events might have been more readily referred for ¹⁵O-PET investigation. Despite the possibility of overestimation of ischemic-event risk, asymptomatic or remote symptomatic LAICOD had a low risk of ischemic events and a low incidence of MP, suggesting that benign prognosis may be associated with less hemodynamic impairment in these patients. Because only a few patients experienced subsequent ischemic events, we were unable to establish a conclusive relationship between hemodynamic compromise and ischemic event risk. Future MR imaging or CT studies by using MTT measurements should be performed in a large number of patients.

This study has other limitations. It is debatable whether TIAs without infarction are clinically important. However, the 90-day risk of ischemic stroke was reported to be 6.9% after TIA in patients with intracranial artery stenosis.³⁵ Thus, detection of patients at high risk for TIA is meaningful for preventing subsequent stroke. Thirty-six percent of patients were diagnosed by MR angiography, which could have overestimated stenosis. The selection of bypass surgery was left to the individual clinical judgment of attending physicians, which may have caused selection bias. The lack of coregistered MR imaging to define the ROIs might have limited correct stratification of the patient groups. However, calculation of the mean hemispheric value by using ROIs placed compactly on multiple image sections could help to diminish this error. In some patients, hemodynamic compromise severity might not have been reflected by the ¹⁵O-PET variables in the whole hemisphere; they may have been more regional. The healthy control subjects were younger than the patients. With ¹⁵O-PET, in the cerebral cortical ROIs of the MCA distribution, CBF, CMRO₂, and CBV were reported to decrease with age, while OEF and CBF/CBV did not change with age.³⁶ Thus, the degree of hemodynamic compromise evaluated with OEF and CBF/CBV may not be affected by the inadequate matching for age.

CONCLUSIONS

In the hemispheres with asymptomatic or remote (>6 months) symptomatic atherosclerotic LAICOD, those with chronic hemodynamic compromise, specifically MP or decreased CBF/CBV, appear to be at high risk for cerebral ischemic events under stan-

dard medical therapy. This small subgroup of patients with higher risk LAICOD may need aggressive medical management and can be identified by detecting increased MTT by using perfusion MR imaging or CT imaging in routine clinical practice.

REFERENCES

1. Gorelick PB, Wong KS, Bae HJ, et al. **Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier.** *Stroke* 2008;39:2396–99
2. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. **Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis.** *N Engl J Med* 2005;352:1305–16
3. Chimowitz M, Lynn M, Derdeyn C, et al. **Stenting versus aggressive medical therapy for intracranial arterial stenosis.** *N Engl J Med* 2011;365:993–1003
4. Taylor RA, Kasner SE. **Natural history of asymptomatic intracranial arterial stenosis.** *J Neuroimaging* 2009;19(suppl 1):17S–19S
5. Kasner SE, Chimowitz MI, Lynn MJ, et al. **Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis.** *Circulation* 2006;113:555–63
6. Fargen KM, Velat GJ, Lawson MF, et al. **Flow failure from intracranial atherosclerotic disease: a rationale for endovascular intervention in a population with recurrent symptoms despite maximal medical therapy.** *J Neurointerv Surg* 2013;5:e17
7. Liebeskind DS, Cotsonis GA, Saver JL, et al. **Collaterals dramatically alter stroke risk in intracranial atherosclerosis.** *Ann Neurol* 2011;69:63–74
8. Powers WJ. **Cerebral hemodynamics in ischemic cerebrovascular disease.** *Ann Neurol* 1991;29:231–40
9. Yamauchi H, Fukuyama H, Fujimoto N, et al. **Significance of low perfusion with increased oxygen extraction fraction in a case of internal carotid artery stenosis.** *Stroke* 1992;23:431–32
10. Mazighi M, Tanasescu R, Ducrocq X, et al. **Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study.** *Neurology* 2006;66:1187–91
11. Baron JC, Bousser MG, Rey A, et al. **Reversal of focal “misery-perfusion syndrome” by extra-intracranial arterial bypass in hemodynamic cerebral ischemia: a case study with ¹⁵O positron emission tomography.** *Stroke* 1981;12:454–59
12. Baron JC, Jones T. **Oxygen metabolism, oxygen extraction and positron emission tomography: historical perspective and impact on basic and clinical neuroscience.** *Neuroimage* 2012;61:492–504
13. Kuroda S, Houkin K, Kamiyama H, et al. **Long-term prognosis of medically treated patients with internal carotid or middle cerebral artery occlusion: can acetazolamide test predict it?** *Stroke* 2001;32:2110–16
14. Ogasawara K, Ogawa A, Yoshimoto T. **Cerebrovascular reactivity to acetazolamide and outcome in patients with symptomatic internal carotid or middle cerebral artery occlusion: a xenon-133 single-photon emission computed tomography study.** *Stroke* 2002;33:1857–62
15. Yamauchi H, Fukuyama H, Nagahama Y, et al. **Evidence of misery perfusion and risk for recurrent stroke in major cerebral arterial occlusive diseases from PET.** *J Neurol Neurosurg Psychiatry* 1996;61:18–25
16. Yamauchi H, Fukuyama H, Nagahama Y, et al. **Significance of increased oxygen extraction fraction in 5-year prognosis of major cerebral arterial occlusive diseases.** *J Nucl Med* 1999;40:1992–98
17. Yamauchi H, Higashi T, Kagawa S, et al. **Is misery perfusion still a predictor of stroke in symptomatic major cerebral artery disease?** *Brain* 2012;135:2515–26
18. Samuels OB, Joseph GJ, Lynn MJ, et al. **A standardized method for measuring intracranial arterial stenosis.** *AJNR Am J Neuroradiol* 2000;21:643–46
19. **Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis: North American Symptom-**

- atic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1991;325:445–53
20. Okazawa H, Yamauchi H, Sugimoto K, et al. **Quantitative comparison of the bolus and steady-state methods for measurement of cerebral perfusion and oxygen metabolism: positron emission tomography study using ^{15}O gas and water.** *J Cereb Blood Flow Metab* 2001;21:793–803
21. Frackowiak RS, Lenzi GL, Jones T, et al. **Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure, and normal values.** *J Comput Assist Tomogr* 1980;4:727–36
22. Lammertsma AA, Jones T. **Correction for the presence of intravascular oxygen-15 in the steady-state technique for measuring regional oxygen extraction ratio in the brain. 1. Description of the method.** *J Cereb Blood Flow Metab* 1983;3:416–24
23. Schumann P, Touzani O, Young AR, et al. **Evaluation of the ratio of cerebral blood flow to cerebral blood volume as an index of local cerebral perfusion pressure.** *Brain* 1998;121(pt 7):1369–79
24. Yamauchi H, Fukuyama H, Kimura J, et al. **Hemodynamics in internal carotid artery occlusion examined by positron emission tomography.** *Stroke* 1990;21:1400–06
25. Kern R, Steinke W, Daffertshofer M, et al. **Stroke recurrences in patients with symptomatic vs asymptomatic middle cerebral artery disease.** *Neurology* 2005;65:859–64
26. Kremer C, Schaettin T, Georgiadis D, et al. **Prognosis of asymptomatic stenosis of the middle cerebral artery.** *J Neurol Neurosurg Psychiatry* 2004;75:1300–03
27. Nahab F, Cotsonis G, Lynn M, et al. **Prevalence and prognosis of coexistent asymptomatic intracranial stenosis.** *Stroke* 2008;39:1039–41
28. Ni J, Yao M, Gao S, et al. **Stroke risk and prognostic factors of asymptomatic middle cerebral artery atherosclerotic stenosis.** *J Neurol Sci* 2011;301:63–65
29. Kajimoto K, Moriwaki H, Yamada N, et al. **Cerebral hemodynamic evaluation using perfusion-weighted magnetic resonance imaging: comparison with positron emission tomography values in chronic occlusive carotid disease.** *Stroke* 2003;34:1662–66
30. Dani KA, Thomas RG, Chappell FM, et al. **Computed tomography and magnetic resonance perfusion imaging in ischemic stroke: definitions and thresholds.** *Ann Neurol* 2011;70:384–401
31. Seiler A, Jurcoane A, Magerkurth J, et al. **T2' imaging within perfusion-restricted tissue in high-grade occlusive carotid disease.** *Stroke* 2012;43:1831–36
32. Jensen-Kondering U, Baron JC. **Oxygen imaging by MRI: can blood oxygen level-dependent imaging depict the ischemic penumbra?** *Stroke* 2012;43:2264–69
33. Mok VC, Lam WW, Chen XY, et al. **Statins for asymptomatic middle cerebral artery stenosis: the regression of cerebral artery stenosis study.** *Cerebrovasc Dis* 2009;28:18–25
34. Yamauchi H, Fukuyama H, Nagahama Y, et al. **Long-term changes of hemodynamics and metabolism after carotid artery occlusion.** *Neurology* 2000;54:2095–102
35. Ovbiagele B, Cruz-Flores S, Lynn MJ, et al. **Early stroke risk after transient ischemic attack among individuals with symptomatic intracranial artery stenosis.** *Arch Neurol* 2008;65:733–37
36. Leenders KL, Perani D, Lammertsma AA, et al. **Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age.** *Brain* 1990;113:27–47

Perivascular Spaces Are Associated with Atherosclerosis: An Insight from the Northern Manhattan Study

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ABSTRACT

BACKGROUND AND PURPOSE: Perivascular spaces are potential spaces found between brain blood vessels and surrounding leptomeninges that have been associated with cardiovascular risk factors and dementia, but less is known about their relationship to atherosclerosis. We tested the hypothesis that perivascular spaces are associated with atherosclerosis.

MATERIALS AND METHODS: Participants from the Northern Manhattan Study who remained stroke-free were invited to participate in an MR imaging substudy. Parenchymal hypointensities of <3 mm identified on brain axial T1-weighted MR imaging were scored as perivascular spaces. A semiquantitative score was created to express the degree of brain involvement. Generalized linear models were used to assess statistical associations with carotid plaque as a surrogate marker of atherosclerosis.

RESULTS: The studied sample included 706 participants (mean age, 72.6 ± 8.0 years; 60% women, 61% Hispanic, 68% with hypertension, 19% with diabetes, and 57% with high cholesterol). The perivascular spaces score ranged from 0 to 19 with 52% of the sample having a perivascular spaces score of ≤ 4 . In unadjusted analysis, perivascular spaces were associated with age ($\beta = 0.01$ per year, $P < .001$), non-Hispanic black race-ethnicity ($\beta = 0.16$, $P = .02$), hypertension ($\beta = 0.24$, $P < .001$), and carotid plaque ($\beta = 0.22$, $P < .001$). In multivariable analysis, only age ($\beta = 0.01$, $P = .02$), hypertension ($\beta = 0.17$, $P = .01$), and carotid plaque ($\beta = 0.22$, $P < .001$) remained independently associated with perivascular spaces.

CONCLUSIONS: Perivascular spaces were more frequently found in older participants, in those with hypertension, and in the presence of carotid plaque. These results suggest that mechanisms leading to atherosclerosis might also lead to an increased number of perivascular spaces. These results need confirmation in prospective studies.

ABBREVIATIONS: PVS = perivascular spaces; HTN = hypertension

Perivascular spaces in the brain have been described for more than a century, but their pathologic significance has not been settled.^{1,2} A definition of PVS can be summarized as a potential space between blood vessels created by surrounding leptomeninges as they travel through the CSF space and penetrate the brain parenchyma, acting as an isolating sheath from the CSF compartment.³ Among some physiologic functions attributed to PVS are the trafficking of inflammatory cells to and from the brain and drainage of interneural fluid to the systemic circulation through the lymphatic system.^{4,5}

When these spaces dilate, they can be observed directly in postmortem brain sections or on brain MR imaging or CT.⁶ Pathologic and radiologic studies that have evaluated the significance of PVS have yielded conflicting results. In some cases, PVS have been described as an age-related phenomenon without pathologic associations, while in others, they are more frequently found in individuals with disease.⁷⁻⁹ The reasons underlying these discrepancies are various, including the heterogeneous populations studied and differing study methods. The importance of correctly identifying PVS and understanding their pathophysiology is highlighted by their association with a worse cardiovascular profile, cerebral small-vessel disease (leukoaraiosis), and worse cognition.^{10,11} Whether PVS are biomarkers of cardiovascular risk-factor severity and indicators of a pathophysiologic process or simply innocent bystanders remains to be clarified.

If PVS are more frequent in individuals with cardiovascular risk factors, then atherosclerosis should be more prevalent in those with PVS. However, this hypothesis has not been tested. In addition, few

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community-based studies have examined the prevalence of PVS in the general population or their association with vascular risk factors and atherosclerosis.^{6,11} We examined the prevalence and correlates of PVS in the urban Northern Manhattan population that includes Hispanic white and non-Hispanic black individuals known to be at greater risk of stroke than non-Hispanic whites.¹²

MATERIALS AND METHODS

The Northern Manhattan Study includes a prospective population-based cohort of participants enrolled from the Northern Manhattan neighborhood between 1993 and 2001 by using random digit dialing. An overall response rate was 68% as previously described.¹³ Eligible participants were stroke-free at baseline, aged 40 years or older, and had resided in Northern Manhattan for at least 3 months in a household with a telephone. Between 2003 and 2008, all surviving participants remaining stroke-free were invited to participate in an MR imaging substudy. Participants were eligible if they were older than 55 years of age and had no contraindication to MR imaging. For this analysis, only subjects with MR images in DICOM format were included because the software used did not support other formats. All participants signed written informed consent, and the study was approved by the local institutional review board.

Data were obtained from participants (99%) or proxies by using standardized data-collection instruments. Participants self-identified their ethnicity as Hispanic or non-Hispanic and race as white, black, or other. Standard techniques were used to measure blood pressure, height, weight, and fasting glucose levels. "Hypertension" was defined as a systolic blood pressure of 140 mm Hg or a diastolic blood pressure of ≥ 90 mm Hg, physician diagnosis, or self-report of a history of hypertension or antihypertensive use. "Diabetes mellitus" was defined as fasting blood glucose of ≥ 126 mg/dL or self-report of such a history or insulin or hypoglycemic use. "Dyslipidemia" was defined as total cholesterol of >200 mg/dL or use of cholesterol-lowering medications. Smoking was categorized as never, former, and current smoker (within 1 year). "History of cardiac disease" was defined as self-report of atrial fibrillation, myocardial infarction, angina, or coronary artery bypass grafting. Carotid plaque in any of the carotid artery segments (the common carotid artery, bifurcation, and internal carotid artery) was assessed by high-resolution B-mode carotid sonography (LOGIQ 700; GE Healthcare, Milwaukee, Wisconsin) using a standardized sonography imaging protocol with excellent inter- and intrareader reliability, as previously described.¹⁴ It was defined as an area of focal wall thickening $>50\%$ greater than the surrounding wall thickness and coded as "present" or "not."

Imaging was performed on a dedicated 1.5T research MR imaging system (Philips Healthcare, Best, the Netherlands) by using a standardized protocol. The MR imaging sequences used in the current study were axial FLAIR and axial T1. The 3D T1 image had a section thickness of 1.5 mm with no gap, a TE of 2.1 ms, a TR of 20 ms, and a flip angle of 20° . The FLAIR images were acquired in the multi-section turbo spin-echo mode with an FOV of 250 mm, a rectangular FOV of 80%, an acquisition matrix of 192×133 scaled to 256×256 in reconstruction, a 3-mm section thickness with no gap, a TE of 144 ms, a TR of 5500 ms, an inversion recovery delay of 1900 ms, and a flip angle of 90° .

Parenchymal hypointensities observed in 3D axial T1 with an effective diameter of <3 mm and an absent FLAIR hyperintensity were considered to represent perivascular spaces (Fig 1). Due to the large number of small hypointensities observed in some cases, we used a semiquantitative score to express the degree of brain involvement per section: 0 = no voids observed in the region, 1 = 1–3 voids, and 2 = ≥ 4 voids. The supratentorial brain was divided into 12 sections: 1 section for the white matter of each lobe (ie, frontal, temporal, parietal, and occipital) and 4 sections in the basal ganglia. The brain stem and the cerebellum were considered as 1 separate region (14 sections, with a possible score ranging from 0 to 28; Fig 2). Intrareader reliability was assessed in a 10% random sample and was found to be excellent for the PVS score (rating by J.G., first author; intraclass correlation coefficient = 0.90).

Statistical Analysis

Differences among participants studied in this analysis versus those excluded were evaluated with Student *t* tests for continuous variables and χ^2 tests for categorical variables. The main outcome variable was the PVS score, but we also used the median of the PVS distribution to categorize the presence of PVS for secondary analysis. We built separate generalized linear models with the continuous PVS score as the outcome and sample demographic, clinical, and ancillary characteristics as the predictor variables. In a secondary analysis, we evaluated the continuous PVS score by anatomic region to see whether the association differed by location and the dichotomized PVS score to evaluate the effect size of predictors on the prevalence of PVS by using odds ratios. We used Poisson distributions to fit the continuous PVS score (count) distribution and binomial distributions for the dichotomized PVS score to obtain the odds ratios and their 95% confidence intervals. A *P* value $\leq .05$ was considered statistically significant by using type III effects in the generalized linear models. A random sample of 10% was used to assess intrareader reliability by using an intraclass correlation coefficient or κ value, depending on the type of variable measured. The analysis was performed with SAS software, Version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Population Characteristics

Of 1290 participants who underwent brain MR imaging, we rated PVS in 706 participants (limited to data available in the DICOM format). The sample mean age was 71.6 ± 8.0 years, 60% were women, 61% were Hispanic, 20% were non-Hispanic black, and 19% were non-Hispanic white. Hypertension was present in 68%; diabetes, in 19%; hypercholesterolemia, in 57%; smoking, in 52% (36% were former smokers and 16% current smokers); and a history of cardiac disease, in 16%. There were no advanced plaques (those producing hemodynamic stenosis of $>40\%$) among subjects included in this study. Small, nonstenotic carotid plaque was found in 55% of the participants. Those individuals included in this analysis were slightly older and more likely to be non-Hispanic black and less likely to have dyslipidemia (Table 1).

Perivascular Spaces Score

The PVS score ranged from 0 to 19, with 52% of the sample having a PVS score of ≤ 4 (median = 4; Fig 3, Table 1). The percentage of

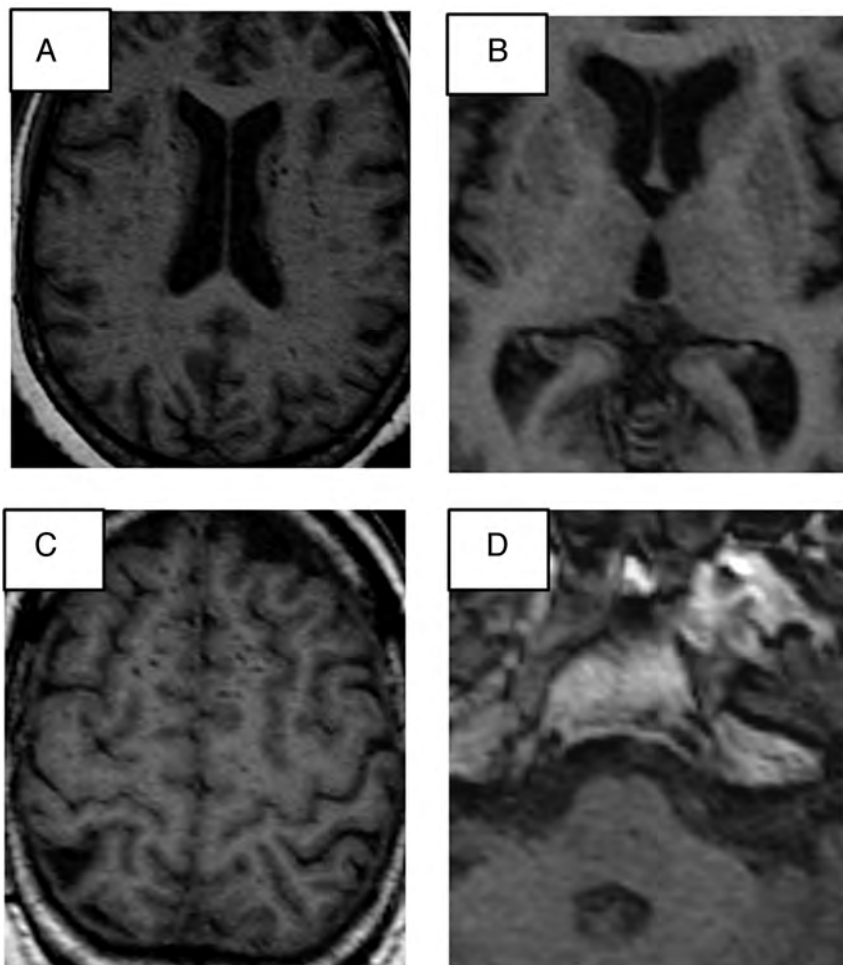


FIG 1. A, Multiple hyperintensities appear in both caudate heads and the corona radiata white matter tracts, suggestive of perivascular spaces. B, Small voids (hypointensities) can be observed in the lateral margins of both putamina. C, Example of multiple perivascular spaces high in the medial frontal convexity. D, A small perivascular space is observed in the pons.

participants with PVS scores of >4 increased with age. It was 39% in those between 55 and 64.9 years, 48% in those 65–74.9 years, 55% in those 75–84.9 years, and 57% in those 85 years or older. The proportion of participants who had nonstenotic carotid plaque and a PVS score of >4 was 55% compared with 40% in those without carotid plaque. In unadjusted analysis, the PVS score was higher with older age ($\beta = 0.01$, $P < .001$), black race ($\beta = 0.16$, $P = .02$), HTN ($\beta = 0.24$, $P < .001$), and the presence of carotid plaque ($\beta = 0.22$, $P < .001$). It was lower in participants who reported taking antihypertensive medications ($\beta = -0.19$, $P = .04$), antihyperglycemics ($\beta = -0.23$, $P = .008$), and cholesterol-lowering drugs ($\beta = -0.26$, $P = .003$). Being male was marginally associated with a lower PVS score ($\beta = -0.11$, $P = .06$).

No associations were noted between the PVS score and systolic blood pressure, diastolic blood pressure, pulse pressure, dyslipidemia, low-attenuation lipoprotein cholesterol levels, diabetes, current or former smoking, body mass index, or history of cardiac disease. In multivariable analysis, age ($\beta = 0.01$, $P = .02$), HTN ($\beta = 0.17$, $P = .01$), and the presence of carotid plaque ($\beta = 0.22$, $P < .001$) were significant predictors of a higher PVS score (Table 2), while taking cholesterol-lowering medications was a predictor of lower PVS scores ($\beta = -0.23$, $P = .01$). Using the

same variables in a multivariate model with binomial distribution to predict the prevalence of PVS (ie, PVS score ≥ 5) reproduced the same independent association of PVS with age (OR, 1.03; 95% CI, 1.06–1.05), HTN (OR, 1.58; 95% CI, 1.05–2.38), the presence of carotid plaque (OR, 1.71; 95% CI, 1.18–2.47), and taking cholesterol-lowering medications (OR, 0.65; 95% CI, 0.44–0.94).

Perivascular Spaces by Anatomic Region

Analysis of the PVS scores demonstrated variation in the degree of involvement by anatomic region. While $>73\%$ of participants had PVS in either the subcortical white matter or basal ganglia, only 18% of the sample had infratentorial lesions. Using the same multivariable model used for the global PVS scores, we found important differences in the PVS score by anatomic locations (Table 2). Perivascular scores in the subcortical white matter were more frequent in women than in men. They were not associated with HTN or hypercholesterolemia but were associated with the presence of carotid plaque. The basal ganglia PVS were more frequent in those with a history of cardiac disease and less frequent in the context of dyslipidemia. The infratentorial PVS score was greater among current smokers and hypertensive participants. The effect estimates for the association of carotid plaque with

the infratentorial PVS score had the same magnitude as in other anatomic regions but did not reach statistical significance.

DISCUSSION

Our study demonstrates that PVS were more frequent in older participants, in the presence of HTN, and in those with carotid atherosclerotic plaques. Carotid plaque was found to be among the strongest and most consistent predictors of PVS, suggesting a biologic link between PVS and atherosclerosis, though we cannot evaluate causality in this observational study. It seems unlikely that the development of PVS causes atherosclerosis, but the biophysics are poorly understood. For example, it is not known whether a tendency to form PVS might influence the response of an arterial tree to variations in blood flow or wall shear stress that might encourage local atherosclerotic plaque formation. It also seems unlikely that small, nonstenotic carotid plaques observed in our study had an impact on cerebral hemodynamics that might have affected PVS formation because flow is not thought to be altered until the degree of stenosis reaches $>80\%$.¹⁵ Even in the case of carotid stenosis of $>80\%$, it is unlikely that dampening of cerebral blood flow underlies the association between PVS

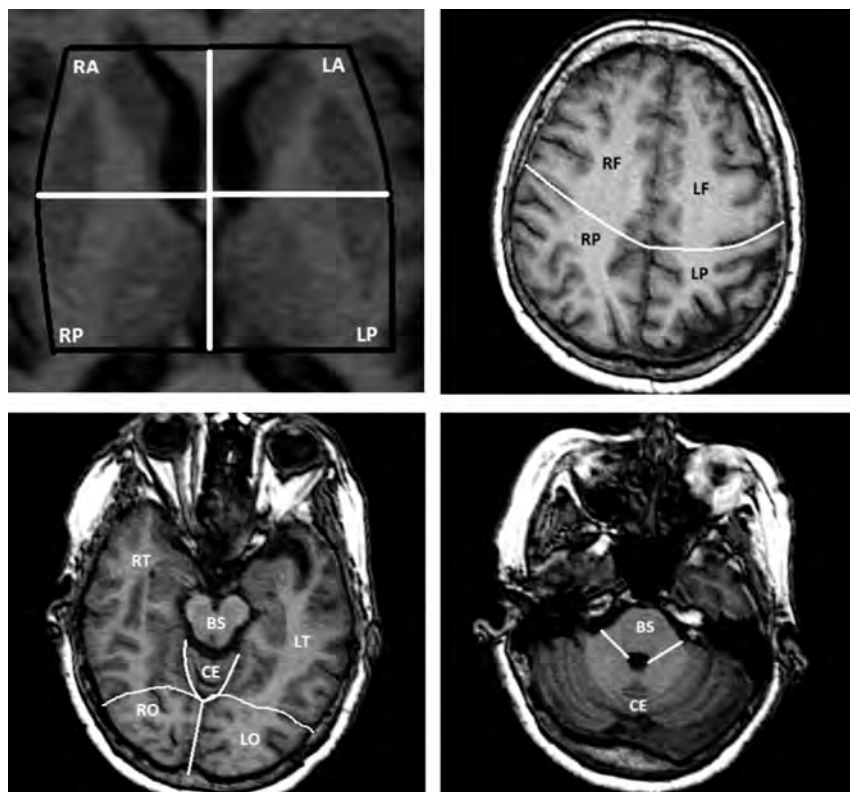


FIG 2. Division used to score perivascular spaces by anatomic regions. R indicates right; L, left; A, anterior; P, posterior; F, frontal; T, temporal; P, parietal; O, occipital; CE, cerebellum; BS, brain stem.

Table 1: Characteristics of the studied sample compared with the NOMAS MRI subsample

	NOMAS MRI Study Included Sample (n = 706)	NOMAS MRI Study Excluded Sample (n = 585)	P Value ^a
Age (yr)	71.6 ± 8.0	69.4 ± 9.9	<.01
Female sex (%)	60.4	60.5	.95
Ethnicity (%)			
Non-Hispanic white	15.9	13.5	<.01
Non-Hispanic black	20.3	13.7	
Hispanic	61.1	71.1	
Hypertension (%)	68.5	64.6	.15
Diabetes (%)	18.9	20.0	.61
Hypercholesterolemia (%)	56.6	63.2	.02
Current smoking (%)	15.9	16.2	.86
Previous cardiac disease (%)	16.3	16.9	.77
Carotid plaque (%)	55.0	55.5	.85
Perivascular spaces score			
Mean	5.0	Not applicable	Not applicable
Median	4.0		
25th percentile	2.0		
50th percentile	4.0		
75th percentile	7.0		

Note:—NOMAS indicates the Northern Manhattan Study.

^aTwo-tailed *t* test was used to obtain *P* values for age differences, while the χ^2 test was used for all other comparisons.

and HTN.^{16,17} The association of PVS with carotid plaque may represent a shared association with atherosclerotic risk factors. Another explanation may be that PVS are an epiphenomenon of the presence of atherosclerosis in other vessels. Other possible mediators in the development of PVS may be arterial stiffness and pulse-wave reflection, because both increase with age and atherosclerosis. Increased arterial stiffness in large ar-

teries can be associated with increased pulsatility to richly vascularized organs, such as the brain.^{18,19} In turn, greater pulsatility in brain penetrator arteries could lead to PVS as a consequence of atherosclerosis and aging.¹⁶ This hypothesis requires further investigation.

Hypertension seems to be one of the most consistent cardiovascular risk factors associated with the presence and number of PVS.^{10,20,21} In a similar population-based MR imaging study of dementia and stroke-free participants, the presence and severity of PVS were associated with HTN.¹⁰ Additionally, the severity of their PVS score was associated with other markers of small-vessel disease such as white matter hyperintensities and male sex. Other studies, though from more selected populations, have also reproduced the association of PVS and HTN.^{20,21} The reasons underlying this association are difficult to explain with cross-sectional data, but it is plausible that an increase in intraluminal pressure might lead to greater extravasation of fluid through the small arteries into these spaces. This hypothesis is supported by rat experiments in which sustained HTN led to increased permeability of endothelial cells and fluid-induced damage to surrounding brain parenchyma.²² Due to the close proximity of PVS to brain parenchyma, elevated pulsatility in these areas could lead to enlargement of perivascular spaces.¹⁶ Also, small penetrating arteries receive their flow from large arteries, with a large drop in caliber that might expose the smaller vessels to greater pulsatility and mechanical forces. For example, from an average MCA diameter of 3.0 mm, the diameter of lenticulostriate arteries drops to 0.5–0.9 mm.^{23,24} Furthermore, a bifurcation angle between 70 and 110° is associated with increased wall shear stress in the branching vessel (the lenticulostriate arteries leave the MCA at an angle of approximately 90°).²⁵ This

greater angle could partially explain why one of the most common anatomic locations of PVS is the basal ganglia, at the origin of the lenticulostriates.^{10,26–28}

However, other factors might be involved. The association of HTN with PVS has not always been reproduced, and the brain stem is the least affected region, even though a similar drop in diameter occurs from the basilar artery to small penetrators.^{6,27,28}

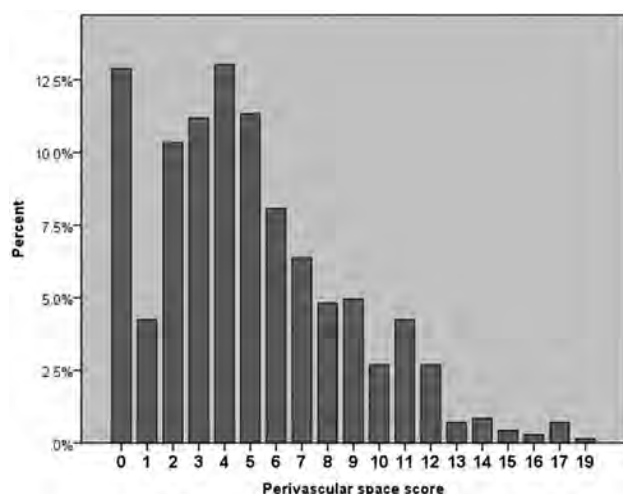


FIG 3. Distribution of PVS scores in the studied sample.

An alternate explanation for the predisposition of the basal ganglia to develop PVS might be the existence of the more complex, doubled-layered microstructure of the PVS compartments in this region compared with the cortex.²⁹ More studies are needed to assess this hypothesis.

The prevalence of PVS in our sample increased with age after adjusting for other covariates; this finding suggests that PVS might be a manifestation of aging. The high prevalence of PVS in older individuals compared with the lower prevalence in younger groups supports this finding.^{10,30} However, PVS are also found in children, in whom their presence has been associated with behavioral and neurologic symptoms.^{9,31} Perivascular spaces associated with neuropsychiatric abnormalities in children are most likely of a different etiology than those of middle-aged and older individuals with cardiovascular risk factors. While serotonin has been

invoked to explain the relationship between PVS and migraine in children, inflammation has been cited as the leading process in the presence of PVS in patients with multiple sclerosis and other brain inflammatory processes.^{7,31-33} Although low-attenuation lipoprotein cholesterol levels were not associated with PVS, taking cholesterol-lowering medications was a strong negative predictor of PVS in this study. We found that taking antihypertensive or hypoglycemic medications was also associated with a lower PVS score. These findings taken together might suggest that controlling vascular risk factors leads to a reduction in PVS prevalence. A role of inflammation in the development of PVS is also possible in adults with cardiovascular risk factors. The link between PVS and inflammation will be pursued in our cohort in the future.

The analysis of PVS by brain anatomic areas revealed consistent findings across all locations for most of the included variables except smoking. Current smoking was associated with greater infratentorial PVS scores. Rather than suggesting a biologic relationship of smoking with PVS in the posterior circulation, this association might represent misclassification of small infarcts as PVS in the brain stem and cerebellum. Although PVS are present in the brain stem, the occurrence of infarcts is considered more likely.^{23,28,34} The lack of a significant association between carotid plaque and infratentorial PVS might be related to the lower prevalence of PVS in this region.

This study has noteworthy limitations. Our study included a stroke-free, unselected population with a high prevalence of cardiovascular risk factors, but it may not be generalizable to other nonurban US populations and further studies are needed in other groups. Using axial images as the only plane for measuring PVS diameters could underestimate the volumes of thin, vertically oriented voids of >3 mm, but the use of FLAIR to look for evidence of gliotic changes suggestive of infarction minimizes misclassification. The lack of prospective data hampers inferences about the

Table 2: Adjusted β coefficients^a of predictors of the overall perivascular space scores and by anatomic regions

	Perivascular Space Score by Anatomic Region							
	Overall Score		Subcortical White Matter		Basal Ganglia		Infratentorial	
	β Coefficient	P Value	β Coefficient	P Value	β Coefficient	P Value	β Coefficient	P Value
Age	0.01	.02	0.008	.15	0.01	.02	0.02	.19
Male sex	-0.11	.12	-0.21	.01	0.05	.52	-0.35	.08
Race								
White	Ref		Ref		Ref		Ref	
Black	0.004	.96	0.11	.37	-0.07	.51	-0.47	.12
Hispanic	-0.11	.17	-0.06	.57	-0.15	.10	-0.20	.40
Body mass index	-0.004	.53	-0.004	.61	-0.003	.64	-0.008	.63
Smoking								
Never	Ref		Ref		Ref		Ref	
Former	0.02	.35	0.05	.55	-0.05	.52	0.35	.07
Current	0.08	.78	0.14	.20	-0.04	.61	0.76	.001
Hypertension	0.17	.01	0.11	.20	0.20	.02	0.59	.008
Antihypertensive medications	-0.11	.09	-0.13	.13	-0.09	.24	-0.28	.24
Diabetes	0.03	.71	0.06	.51	-0.003	.96	-0.04	.88
Hypoglycemic medications	-0.18	.19	-0.19	.10	-0.03	.79	-0.31	.40
Hypercholesterolemia	-0.12	.21	0.01	.93	-0.14	.02	-0.16	.38
Cholesterol-lowering medications	-0.24	.02	-0.22	.08	-0.22	.08	-0.76	.04
History of cardiac disease	0.07	.32	-0.02	.81	0.15	.05	0.26	.23
Carotid plaque	0.22	<.001	0.29	<.001	0.16	0.02	0.22	.21

Note:—Ref indicates reference group.

^a Coefficients were adjusted for all other demographic variables plus medications to treat hypertension, diabetes, and hypercholesterolemia.

cause of PVS. More important, it remains unknown whether PVS have a role as a biomarker for identifying individuals at high risk of developing cerebrovascular disease that would require a different diagnostic and treatment approach. Additional limitations to this study include the survivor bias of the MR imaging cohort and a lack of data on the inter-rater reliability of our PVS scoring system, though the intrarater reliability was high.

CONCLUSIONS

In this population-based race/ethnically diverse sample, we found that PVS were associated with age and several vascular risk factors and were strongly related to carotid plaque. Prospective data are needed to confirm the importance of these subclinical MR imaging findings in relation to cardiovascular risk, dementia, and other clinical outcomes.

Disclosures: Jose Gutierrez—UNRELATED: Grants/Grants Pending: American Heart Association. Tatjana Rundek—UNRELATED: Grant: National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS). * Comments: R01 and K24. Mitchell S.V. Elkind—RELATED: Grant: Bristol-Myers Squibb (BMS)-Sanofi Partnership, * diaDexus Inc. * Comments: research on stroke biomarkers, Consulting Fee or Honorarium: BMS-Pfizer Partnership. Comments: use of anticoagulants for stroke prevention, Fees for Participation in Review Activities such as Data Monitoring Boards, Statistical Analysis, Endpoint Committees, and the Like: Jarvik Heart, Comments: Clinical Event Committee for an artificial heart trial, Other: Organon, Boehringer-Ingelheim, Comments: NuvaRing and stroke; Pradaxa and hemorrhage, UNRELATED: Board Membership: American Heart Association, American Stroke Association, Comments: board membership, New York City and Founders Affiliate, Expert Testimony: Organon, Boehringer-Ingelheim, Comments: Nuvaring and stroke, PRADAXA and hemorrhage, Payment for Development of Education Presentations: QuantiaMD, Comments: cholesterol and stroke prevention, Other: American Academy of Neurology, Comments: Associate Editor of society journal, Neurology. Ralph L. Sacco—RELATED: Grant: NIH. * Comments: Northern Manhattan Study NINDS grants (NINDS R37 NS029993). Clinton B. Wright—RELATED: NIH. * Comments: grants (K02 NS 059729; R01 HL08623), UNRELATED: Consultancy: Merck, Comments: stroke adjudication for clinical trial, Grants/Grants Pending: NIH, American Heart Association, Royalties: UpToDate, Comments: author of 2 chapters on vascular dementia. *Money paid to the institution.

REFERENCES

- Durand-Fardel M. *Traite Clinique et Pratique des Maladies des Vieillards*. Paris, France: Germer Bailliere; 1854
- Poirier J, Derouesne C. **The concept of cerebral lacunae from 1838 to the present** [in French]. *Rev Neurol (Paris)* 1985;141:3–17
- Greenfield JG, Blackwood W, Corsellis JA. *Greenfield's Neuropathology*. 3rd ed. London: E. Arnold; 1976:239
- Bradbury MW, Cserr HF, Westrop RJ. **Drainage of cerebral interstitial fluid into deep cervical lymph of the rabbit**. *Am J Physiol* 1981;240:F329–36
- Millen JW, Woollam DH. **The reticular perivascular tissue of the central nervous system**. *J Neurol Neurosurg Psychiatry* 1954;17:286–94
- Pulicino PM, Miller LL, Alexandrov AV, et al. **Infraputaminall 'lacunes': clinical and pathological correlations**. *Stroke* 1995;26:1598–602
- Wuerfel J, Haertle M, Waiczies H, et al. **Perivascular spaces—MRI marker of inflammatory activity in the brain?** *Brain* 2008;131:2332–40
- Cumurciuc R, Guichard JP, Reizine D, et al. **Dilation of Virchow-Robin spaces in CADASIL**. *Eur J Neurol* 2006;13:187–90
- Rollins NK, Deline C, Morriss MC. **Prevalence and clinical significance of dilated Virchow-Robin spaces in childhood**. *Radiology* 1993;189:53–57
- Zhu YC, Tzourio C, Soumare A, et al. **Severity of dilated Virchow-Robin spaces is associated with age, blood pressure, and MRI markers of small vessel disease: a population-based study**. *Stroke* 2010;41:2483–90
- MacLulich AM, Wardlaw JM, Ferguson KJ, et al. **Enlarged perivascular spaces are associated with cognitive function in healthy elderly men**. *J Neurol Neurosurg Psychiatry* 2004;75:1519–23
- Sacco RL, Boden-Albala B, Gan R, et al. **Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study**. *Am J Epidemiol* 1998;147:259–68
- Boden-Albala B, Cammack S, Chong J, et al. **Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS)**. *Diabetes Care* 2008;31:1132–37
- Rundek T, Arif H, Boden-Albala B, et al. **Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study**. *Neurology* 2008;70:1200–07
- Hartmann A, Mast H, Thompson JL, et al. **Transcranial Doppler waveform blunting in severe extracranial carotid artery stenosis**. *Cerebrovasc Dis* 2000;10:33–38
- Hughes W. **Hypothesis**. *Lancet* 1965;286:19–21
- Hughes W, Dodgson MC, MacLennan DC. **Chronic cerebral hypertensive disease**. *Lancet* 1954;267:770–74
- Mitchell GF, Parise H, Benjamin EJ, et al. **Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study**. *Hypertension* 2004;43:1239–45
- Mitchell GF. **Arterial stiffness and wave reflection: biomarkers of cardiovascular risk**. *Artery Res* 2009;3:56–64
- Awad IA, Johnson PC, Spetzler RF, et al. **Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations**. *Stroke* 1986;17:1090–97
- Cole FM, Yates PO. **Comparative incidence of cerebrovascular lesions in normotensive and hypertensive patients**. *Neurology* 1968;18:255–59
- Suzuki K, Masawa N, Takatama M. **Pathogenesis of état criblé in experimental hypertensive rats**. *J Stroke Cerebrovasc Dis* 2001;10:106–12
- Fisher CM. **Lacunes: small, deep cerebral infarcts**. *Neurology* 1965;15:774–84
- El-Barhoun EN, Gledhill SR, Pitman AG. **Circle of Willis artery diameters on MR angiography: an Australian reference database**. *J Med Imaging Radiat Oncol* 2009;53:248–60
- Noren D, Palmer HJ, Frame MD. **Predicted wall shear rate gradients in T-type arteriolar bifurcations**. *Biorheology* 2000;37:325–40
- Patankar TF, Mitra D, Varma A, et al. **Dilatation of the Virchow-Robin space is a sensitive indicator of cerebral microvascular disease: study in elderly patients with dementia**. *AJNR Am J Neuroradiol* 2005;26:1512–20
- Groeschel S, Chong WK, Surtees R, et al. **Virchow-Robin spaces on magnetic resonance images: normative data, their dilatation, and a review of the literature**. *Neuroradiology* 2006;48:745–54
- Bokura H, Kobayashi S, Yamaguchi S. **Distinguishing silent lacunar infarction from enlarged Virchow-Robin spaces: a magnetic resonance imaging and pathological study**. *J Neurol* 1998;245:116–22
- Pollock H, Hutchings M, Weller RO, et al. **Perivascular spaces in the basal ganglia of the human brain: their relationship to lacunes**. *J Anat* 1997;191(pt 3):337–46
- Jungreis CA, Kanal E, Hirsch WL, et al. **Normal perivascular spaces mimicking lacunar infarction: MR imaging**. *Radiology* 1988;169:101–04
- Schick S, Gahleitner A, Wober-Bingol C, et al. **Virchow-Robin spaces in childhood migraine**. *Neuroradiology* 1999;41:283–87
- Kwee RM, Kwee TC. **Virchow-Robin spaces at MR imaging**. *Radiographics* 2007;27:1071–86
- Achiron A, Faibel M. **Sandlike appearance of Virchow-Robin spaces in early multiple sclerosis: a novel neuroradiologic marker**. *AJNR Am J Neuroradiol* 2002;23:376–80
- Elster AD, Richardson DN. **Focal high signal on MR scans of the midbrain caused by enlarged perivascular spaces: MR-pathologic correlation**. *AJR Am J Roentgenol* 1991;156:157–60

Morphologic Characteristics of Atherosclerotic Middle Cerebral Arteries on 3T High-Resolution MRI

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ABSTRACT

BACKGROUND AND PURPOSE: There are limited studies on the morphologic characteristics of MCA atherosclerotic stenosis. Our aim was to quantitatively assess the remodeling pattern and plaque distribution of atherosclerotic MCAs with 3T high-resolution MR imaging.

MATERIALS AND METHODS: Eighty-seven consecutive patients with symptomatic atherosclerotic stenoses at the M1 segment of the MCA on DSA (50%–99%) were enrolled. The remodeling index was calculated as the Vessel Area at Maximal Lumen Narrowing/Reference Vessel Area. A remodeling index ≥ 1.0 was defined as positive remodeling, and a remodeling index < 1.0 , as negative remodeling. Plaque distribution at the maximal lumen narrowing site was classified on the basis of the involvement of the superior, inferior, dorsal, or ventral MCA wall.

RESULTS: Forty-three of 87 patients were excluded due to poor imaging quality ($n = 8$) or scan plane obliquity secondary to a tortuous M1 segment of the MCA or an MCA ostium lesion or angled lesion ($n = 35$). Of 44 patients in the final analysis, negative remodeling was found in 19 (43.2%) lesions, and positive remodeling, in 25 (56.8%) lesions. At maximal lumen narrowing sites, lesions with negative remodeling had less vessel area, wall area, and percentage of plaque burden ($P < .0001$) and a lower eccentricity index ($P = .023$), compared with lesions with positive remodeling. The plaque involved the superior and dorsal walls in 15 (34.1%) of 44 patients.

CONCLUSIONS: 2D high-resolution MR imaging can help assess the remodeling pattern and plaque distribution of MCA stenosis, but the imaging and postprocessing protocol for remodeling assessment needs to be improved in the tortuous course of the MCA and in MCA ostium or angled lesions.

ABBREVIATIONS: MLN = maximal lumen narrowing; NR = negative remodeling; PR = positive remodeling; PTAS = percutaneous transluminal angioplasty and stenting; SAMMPRIS = Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis

Previous studies of coronary arteries confirmed that vessels may respond to plaque growth by either outward enlargement of the vessel wall (positive remodeling) or vessel shrinkage (negative re-

modeling).¹ Pre-existing remodeling was important in the immediate success and clinical outcome following coronary interventions.^{2,3} In addition, the existence of plaque close to a branch vessel ostium has been shown to increase the risk of branch occlusion after coronary stent placement.⁴ In light of the disappointing results⁵ of the Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Arterial Stenosis (SAMMPRIS) trial, we are reminded that lesion morphology of the intracranial artery may also be a prominent factor that influences the rate of periprocedural complications.^{6,7} Knowledge of the wall characteristics of the MCA may be useful in interpreting the data of the SAMMPRIS trial, selecting patients for percutaneous transluminal angioplasty and stenting (PTAS), and designing individualized operating plans.

High-resolution MR imaging has been increasingly used in recent years to identify the wall features of the intracranial artery.^{8–12} However, the remodeling pattern and the plaque distribution of MCA atherosclerotic stenosis remains poorly understood. The aim of this prospective study was to quantitatively investigate remodeling patterns and plaque distribution in patients with symptomatic MCA stenosis with 3T high-resolution MR imaging.

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All the images were assessed and measured by X.Z. (reader 1) and B.Z. (reader 2).

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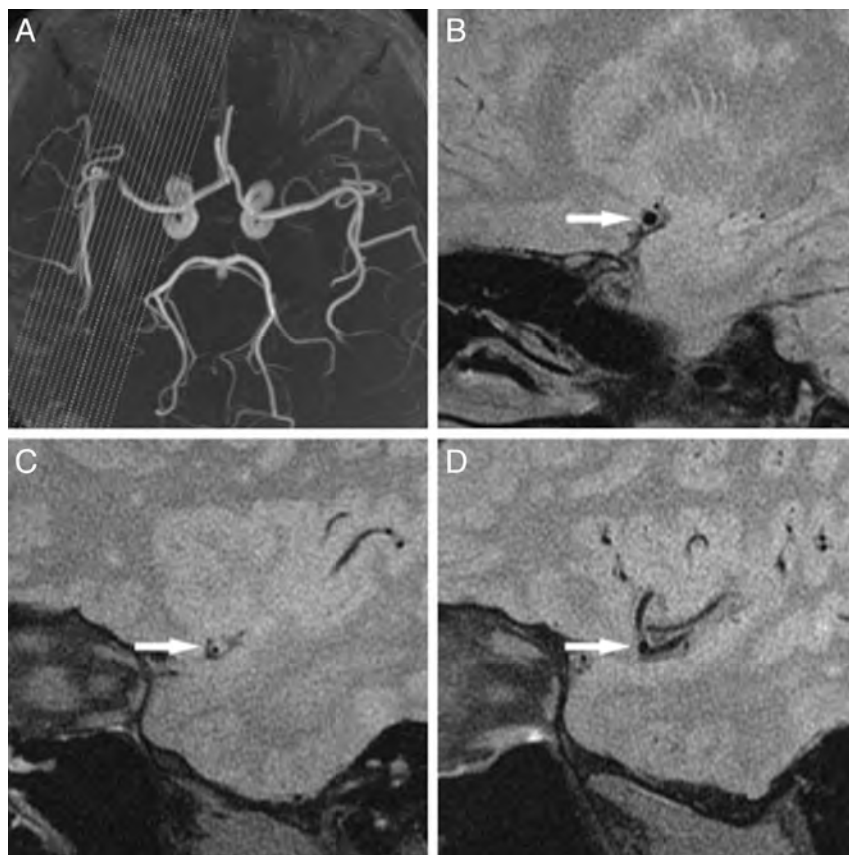


FIG 1. An example of an excluded case. MRA (A) shows the obvious angled stenosis located at the distal M1 segment near M2 of the MCA. Suitable cross-sectional images can be obtained at the proximal (B, arrow) and MLN (C, arrow) but not the distal (D, arrow) site.

MATERIALS AND METHODS

Patients

This observational cross-sectional study was approved by our institutional ethics committees. Before each high-resolution MR imaging examination, written informed consent was obtained. Patients were enrolled in this study according to the following criteria: 1) ischemic stroke or TIA in the target MCA territory within 90 days; 2) 50%–99% stenosis at the M1 segment of the MCA on DSA; and 3) ≥ 2 atherosclerotic risk factors, including hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, and obesity as described previously.¹⁰ According to the traditional clinical definition, we defined ischemic stroke as a new focal neurologic deficit of sudden onset lasting >24 hours and not caused by hemorrhage, and TIA is the acute onset of a focal neurologic deficit lasting <24 hours. We excluded patients with the following conditions: 1) contraindications to MR imaging; 2) nonatherosclerotic vasculopathy, such as dissection, arteritis, or Moyamoya disease; 3) fewer than 2 atherosclerotic risk factors; 4) coexistent $>50\%$ supra-aortic cerebrovasculature stenosis on DSA; and 5) evidence of cardioembolism.

Between December 2009 and May 2011, eighty-seven consecutive patients with symptomatic atherosclerotic stenosis at the M1 segment of the MCA on DSA (50%–99%) were enrolled in this study.

Imaging Protocol

Cross-sectional imaging was performed by using a 3T MR imaging scanner (Signa, TwinSpeed 3T; GE Healthcare, Milwaukee,

Wisconsin) and an 8-channel phased array head coil. 3D time-of-flight MRA was performed purely for image positioning with the following parameters: TR/TE = 21/3.2 ms, FOV = 16×16 cm, thickness = 1 mm, matrix = 256×256 , and NEX = 1. On the basis of the MRA, the scan plane was angled to ensure that the cross-sectional images were perpendicular to the M1 segment of the MCA (Figs 1A, 2A, and 3A). Then, proton attenuation-weighted images of 12–17 sections were acquired with an FSE sequence. The parameters for proton attenuation-weighted images were as follows: TR/TE = 4000/12.9 ms, FOV = 16×16 cm, thickness = 2 mm, matrix = 384×256 , NEX = 2, and echo-train length = 10. The cross-sectional voxel size was 0.6×0.6 mm on time-of-flight images and 0.4×0.6 mm on proton attenuation-weighted images. Fat suppression was applied to reduce fat signal from the surrounding scalp. A zero-fill interpolation 512-matrix technique was used to enhance spatial resolution. The total imaging time was 7–10 minutes.

Morphologic Measurement and Calculation of the MCA Wall

Two trained readers with >1 year of experience in reading intracranial MR images,

blinded to the clinical information of the patients, assessed image quality by consensus by using a previously developed 4-point scale (1 = poor quality, 4 = excellent).¹³ Images of poor image quality were excluded from the final analysis. Quantitative measurement was performed on the proton attenuation-weighted images with a score of ≥ 2 by using FuncTool II software (GE Healthcare) from a Sun ADW4.3 workstation (GE Healthcare). The images were zoomed to 400%. The window width and level were adjusted to optimize the conspicuity of the vessel contour. In the MCA cross-sectional images, the contour of the outer wall and lumen at the maximal lumen narrowing site and reference site was traced manually to measure the vessel area and luminal area by reader 1, blinded to the clinical information of the patients. The reference sites used were the nearest plaque-free or minimally diseased segments proximal and distal to the maximal lumen narrowing (MLN) sites.

Due to the vessel tapering, the reference vessel area was calculated as the average of the distal and proximal vessel area, and luminal area, was calculated as the average of the distal and proximal luminal area. Wall area was calculated by Vessel Area – Luminal Area. Plaque size was estimated by Wall Area at the MLN site – Reference Wall Area. Because plaque size varies with vessel size and larger vessels usually have larger plaques, we used the percentage of plaque burden to correct for vessel sizes. The percentage of plaque burden was calculated by using the following formula: (Plaque Size/Vessel Area at MLN site) $\times 100\%$. The degree of stenosis on high-resolution MR imaging

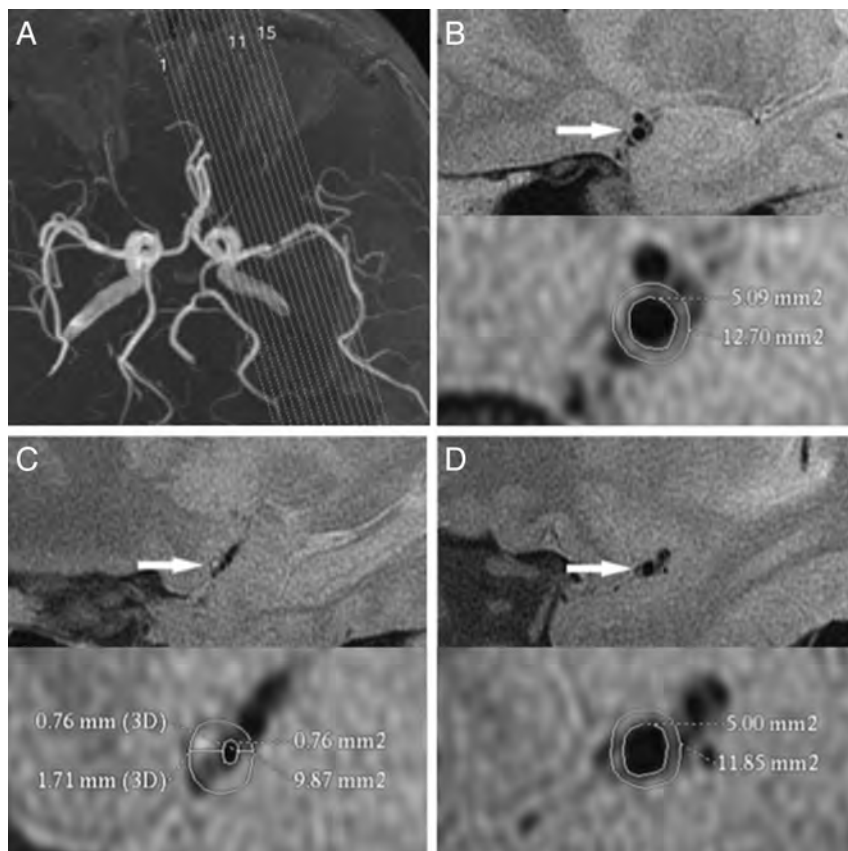


FIG 2. A 37-year-old man with hypertension, hypercholesterolemia, and cigarette smoking history who presented with aphasia, a cognitive disorder, and right-side numbness for 60 days. MRA (A) shows stenosis located at the straight M1 segment of the MCA. The proximal (B, arrow), MLN (C, arrow), and distal (D, arrow) site of the left MCA are shown. The vessel area or luminal area is measured (demonstrated by the magnified view in the inset). The reference vessel area is 12.3 mm², and the remodeling index at the MLN site is 0.8 < 1.00 (NR). The eccentricity index is 0.6. B. The plaque location is mainly on the ventral wall (arrow). The wall area is 7.6 mm² at the proximal, 9.1 mm² at the MLN, and 6.9 mm² at the distal site. The reference wall area is 7.2 mm². Plaque size is 1.9 mm², and percentage of plaque burden is 19.1%.

was calculated as follows: $(1 - \text{Luminal Area at the MLN Site/Reference Luminal Area}) \times 100\%$.¹ The remodeling index was calculated as follows: $\text{Vessel Area at MLN Site/Reference Vessel Area}$. Positive remodeling (PR) was defined as a remodeling index ≥ 1.0 ; negative remodeling (NR), as a remodeling < 1.0 .¹ Patterns of the remodeling were classified into 2 subgroups (PR and NR).

The thickest and thinnest wall segments on the cross-sectional image at the MLN site were identified by visual inspection, and maximal and minimal wall thicknesses were measured manually by the same reader (reader 1). The eccentricity index of the MLN site was calculated as follows: $(\text{Maximal Wall Thickness} - \text{Minimal Wall Thickness})/\text{Maximal Wall Thickness}$.¹⁴ The maximal wall thickness at the reference site was the average of maximal wall thickness distal and proximal to the MLN site. All cross-sectional images at MLN sites were classified on the basis of their plaque orientation being centered on the superior, inferior, dorsal, or ventral side of the vessel.¹⁵ Each cross-sectional image at the MLN site was grouped into 1 of the 4 quadrants. In cases in which the plaque was distributed on >1 quadrant, the quadrant with the maximal wall thickness was chosen.

To assess interobserver variability and intraobserver variability, the 2 readers independently remeasured the vessel area, lumi-

nal area, maximal wall thickness, and minimal wall thickness at MLN sites of the initial 10 consecutive patients 2 months later. Subjects, included 2 patients (score 2), 6 patients (score 3), and 2 patients (score 4).

Statistical Analysis

The intraclass correlation coefficient was used to find the intraobserver or interobserver reproducibility for the measurements of vessel area, luminal area, maximal wall thickness, and minimal wall thickness. Continuous variables were described as means $\pm$ SD or as an interquartile range (if not normally distributed). The continuous variable between the 2 groups was compared by using the Student *t* test or Mann-Whitney *U* test (when the continuous variable was not normally distributed). Categorical variables were compared by using the χ^2 test or Fisher exact test. The Statistical Package for the Social Sciences, Version 11.5 (SPSS, Chicago, Illinois) was used as the statistical analysis software. All reported *P* values were 2-sided, and a *P* value $< .05$ was considered statistically significant.

RESULTS

Patients

From the 87 patients enrolled in this study, 8 (9.2%) were excluded due to poor image quality and 79 (90.8%) had images suitable for analysis (image quality, ≥ 2) to depict the MCA wall. In the final anal-

ysis, 35 patients were also excluded because cross-sectional images perpendicular to the MCA at reference sites ($n = 34$) or at the MLN site ($n = 1$) could not be acquired due to a tortuous course of the MCA or a lesion at the MCA ostia or an angled lesion (Fig 1). Therefore, 44 patients (39 men and 5 women) were included in the final analysis. There were no significant differences in the clinical characteristics between the included patients and excluded patients (Table 1). The mean age of included patients was 47.8 ± 9.9 years. The image quality was 2 in 8 patients, 3 in 26 patients, and 4 in 10 patients. The mean time from qualifying events to high-resolution MR imaging was 33.8 ± 19.0 days.

Morphologic Measurement and Calculation of the MCA Wall

The intraobserver and interobserver reproducibility was high for measurements of the vessel area, luminal area, maximal wall thickness, and minimal wall thickness (Table 2).

At the reference site, the vessel area was 14.8 ± 3.3 mm², the luminal area was 5.3 ± 1.8 mm², the wall area was 9.5 ± 1.7 mm², and the maximal wall thickness was 0.9 ± 0.1 mm. At the MLN site, the vessel area was 15.4 ± 4.8 mm², the luminal area was 0.8 ± 0.6 mm², and the wall area was 14.6 ± 4.7 mm². Thus,

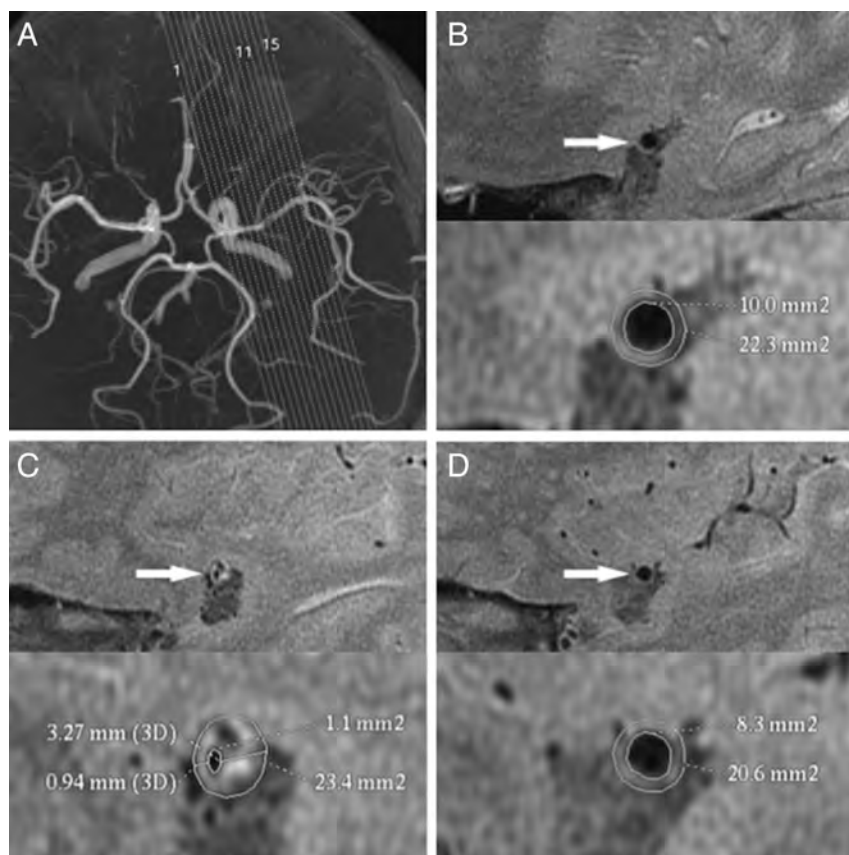


FIG 3. A 74-year-old man with hypertension and hypercholesterolemia who presented with aphasia for 27 days. MRA (A) shows stenosis located at the nearly straight M1 segment of the MCA. The proximal (B, arrow), MLN (C, arrow), and distal (D, arrow) site of left MCA are surrounded by more CSF due to age-related brain involution compared with the case in Fig 2. The vessel area or lumen area is measured (demonstrated by the magnified view in the inset). The reference vessel area is 21.5 mm², and the remodeling index at the MLN is 1.1 > 1.00 (PR). The eccentricity index is 0.7. B, The plaque location is mainly on the ventral and superior walls (arrow). The wall area is 12.3 mm² at the proximal, 22.3 mm² at the MLN, and 12.3 mm² at the distal site. The reference wall area is 12.3 mm². Plaque size is 10.0 mm², and the percentage of plaque burden is 42.7%. Compared with the case in Fig 2, this case has a larger vessel area, wall area, plaque size, percentage of plaque burden, and eccentricity index.

Table 1: Clinical characteristics between included patients and excluded patients

Characteristics	Included Patients (n = 44)	Excluded Patients (n = 43)	P Value
Age (yr) (mean) (SD)	47.8 (9.9)	47.7 (11.4)	.966
Men (No.) (%)	39 (88.6)	37 (86.1)	.716
Hypertension (No.) (%)	29 (65.9)	26 (60.5)	.599
Hypercholesterolemia (No.) (%)	42 (95.5)	42 (97.7)	1.000
Diabetes mellitus (No.) (%)	8 (18.2)	10 (23.3)	.559
Smoking (No.) (%)	30 (68.2)	31 (72.1)	.690
Obesity (No.) (%)	7 (15.9)	3 (7.0)	.332
Three or more risk factors (No.) (%)	23 (52.3)	22 (51.2)	.918
Stroke as qualifying event (No.) (%)	27 (61.4)	26 (60.5)	.932
NIHSS scores at admission (median) (interquartile range)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	.916
Time from qualifying event to high-resolution MRI, days (mean) (SD)	33.8 (19.0)	33.3 (21.2)	.905

plaque size was 5.1 ± 4.5 mm², percentage of plaque burden was $28.1 \pm 21.1\%$, degree of stenosis was $82.8 \pm 14.2\%$, and remodeling index was 1.1 ± 0.3 . At the MLN sites, the maximal wall

thickness was 2.5 ± 0.6 mm, the minimal wall thickness was 1.0 ± 0.3 mm, and the eccentricity index was 0.6 ± 0.2 .

NR was found in 19 (43.2%) lesions (Fig 2), and PR, in 25 (56.8%) lesions (Fig 3). There was no significant difference in the clinical characteristics between the lesions with NR and PR (Table 3). The wall morphologic characteristics are outlined in Table 4. At MLN sites, lesions with NR, compared with lesions with PR, had less vessel area, wall area, plaque size, and percentage of plaque burden ($P < .0001$). At the same time, lesions with NR had a significantly lower maximal wall thickness ($P < .0001$) and eccentricity index than did lesions with PR (0.5 versus 0.6, $P = .023$). However, there was no difference in the luminal area, minimal wall thickness, and degree of stenosis between the lesions with NR and PR. At reference sites, NR lesions had greater maximal wall thickness than PR lesions, with a trend toward significance; however, there was no significant difference in vessel area, luminal area, and wall area between the 2 groups.

Plaques were located at the superior wall in 10 (22.7%) patients, the dorsal wall in 5 (11.4%) patients, the inferior wall in 13 (29.6%) patients, and the ventral wall in 16 (36.4%) patients (Fig 2). In total, the plaque involved the superior and dorsal walls in 34.1% of patients (Fig 3).

DISCUSSION

The use of high-resolution MR imaging could permit evaluation of the remodeling

of intracranial arteries.^{8–12} A previous study showed that the remodeling index could be assessed quantitatively with 1.5T high-resolution MR imaging.⁸ Compared with 1.5T, a 3T MR imaging system has higher SNR and has recently been used to identify the remodeling pattern of intracranial arteries.^{10,11} The results showed that NR and PR also occur in the MCA and basilar arteries.^{10,11} However, the remodeling index depends on the reference vessel area. Using only proximal or distal segments as a reference site in previous studies may have resulted in underestimation or overestimation of the remodeling index due to the natural tapering of the MCA.¹¹ In contrast, we used the average of reference site areas distal and proximal to the stenosis for remodeling calculation to help overcome the obstacle of natural tapering of the MCA. In addition, the positioning of 2D sections in 1 scan for the tortuous MCA makes 2D images more prone to obliquity artifacts, especially for the reference sites, leading to the overestimation of the true vessel area and wall thickness. To minimize errors, we excluded 35 patients because cross-sectional images perpendicular to the long axis of the MCA were unavailable.

Table 2: Intraobserver and interobserver variability

	Intraclass Correlation Coefficient (95% CI)	
	Intraobserver	Interobserver
Vessel area	0.917 (0.666–0.979)	0.906 (0.620–0.977)
Luminal area	0.833 (0.329–0.959)	0.898 (0.589–0.975)
Maximal wall thickness	0.962 (0.847–0.991)	0.916 (0.663–0.979)
Minimal wall thickness	0.876 (0.501–0.969)	0.851 (0.399–0.963)

Table 3: Clinical characteristics between the NR and PR groups

Characteristics	NR Group (n = 19)	PR Group (n = 25)	P Value
Age (yr) (mean) (SD)	48.0 (8.4)	47.8 (11.0)	.951
Men (No.) (%)	15 (79.0)	24 (96.0)	.198
Hypertension (No.) (%)	13 (68.4)	16 (64.0)	.759
Hypercholesterolemia (No.) (%)	19 (100)	23 (92.0)	.498
Diabetes mellitus (No.) (%)	5 (26.3)	3 (12.0)	.409
Smoking (No.) (%)	11 (57.9)	19 (76.0)	.202
Obesity (No.) (%)	5 (26.3)	2 (8.0)	.219
Three or more risk factors (No.) (%)	12 (63.2)	11 (44.0)	.208
Stroke as qualifying event (No.) (%)	13 (68.4)	14 (56.0)	.402
NIHSS scores at admission, median (interquartile range)	0.0 (0.0–2.0)	0.0 (0.0–0.5)	.419
Time from qualifying event to high-resolution MRI (days) (mean) (SD)	33.8 (17.4)	33.8 (20.5)	1.000

Table 4: Wall characteristics of symptomatic atherosclerotic MCA stenosis

Variables ^a	NR Group (n = 19)	PR Group (n = 25)	P Value
At reference site			
Vessel area (mm ²)	15.5 (3.3)	14.3 (3.2)	.228
Luminal area (mm ²)	5.5 (1.6)	5.2 (1.9)	.516
Wall area (mm ²)	10.0 (1.8)	9.1 (1.6)	.103
Maximal wall thickness (mm)	1.0 (0.1)	0.9 (0.1)	.058
At MLN site			
Vessel area (mm ²)	12.4 (3.3)	17.8 (4.5)	<.0001
Luminal area (mm ²)	0.8 (0.6)	0.8 (0.5)	0.804
Wall area (mm ²)	11.6 (3.3)	16.9 (4.3)	<.0001
Plaque size (mm ²)	1.6 (2.3)	7.8 (3.8)	<.0001
Percentage of plaque burden (%)	9.9 (16.8)	42.0 (11.1)	<.0001
Degree of stenosis (%)	84.5 (13.8)	81.5 (14.6)	.497
Maximal wall thickness (mm)	2.1 (0.5)	2.8 (0.5)	<.0001
Minimal wall thickness, (mm)	0.9 (0.3)	1.0 (0.2)	.381
Eccentricity index	0.5 (0.2)	0.6 (0.1)	.023
Remodeling index	0.8 (0.1)	1.3 (0.3)	<.0001

^a Variables are expressed as mean and SD.

Our findings emphasized that NR was almost as frequent as PR in symptomatic atherosclerotic MCA stenosis and NR lesions had less wall area and percentage of plaque burden. At reference sites, NR lesions had greater maximal wall thickness than PR lesions, with a trend toward significance; however, the difference may have no meaning, given the in-plane resolution. In addition, the remodeling pattern was associated with the eccentricity index, and PR lesions had a larger eccentricity index (0.6 versus 0.5, $P = .023$). These findings have potential implications for the mechanisms of arterial PR because it has been thought that in coronary atherosclerosis, PR mainly occurs as a consequence of the outward stretch of the vessel wall behind the plaque, as a direct response to the plaque release of metalloproteinases.¹

Intracranial atherosclerotic stenosis is associated with a high risk of recurrent stroke, despite treatment with aspirin and standard management of vascular risk factors. Intracranial PTAS emerged as a valuable tool for patients refractory to medical therapy.^{16,17} In the PTAS procedure, the operators select the size of the balloon or stent on the basis of the reference vessel diameter during luminal imaging. However, for the patients with NR, sizing of the balloon may not take into account the diminished outer wall diameter and may increase the risk of vessel injury or even rupture when the balloon is inflated. Previous studies with coronary intervention have shown that patients with PR had the highest rate of major adverse cardiac events; in contrast, patients with NR may face high rates of in-hospital complications, including postinterventional dissection.^{2,3} The consequences of SAMMPRIS suggest that the remodeling pattern may also be a prominent factor that influences the rate of periprocedural complications. In future studies, we will use a wall imaging technique to study the remodeling pattern of other intracranial arteries (such as the ICA) and will assess the influence of local remodeling patterns on periprocedural complications in patients with intracranial PTAS.

Intracranial PTAS also showed that patients presenting with perforator ischemia may have an increased risk of perioperative stroke.⁶ PTAS restores the luminal diameter by pushing the plaque outward against the wall of the artery, which can cause plaque shifting, occluding the penetrating arteries. An eccentric plaque location on the superior and dorsal walls of the MCA, where most of perforators arise, may increase the risk of perforator occlusion. In this study, 34.1% of the lesions mainly involved the superior and dorsal MCA walls. These findings are meaningful. Patients with perforator syndromes were also included in SAMMPRIS. This feature may help explain the high risk of perioperative stroke. Patients with plaques near penetrating artery orifices may face a higher risk of perforator stroke. For those patients, a subsized balloon with low balloon inflation pressure may help reduce the risk of perforator stroke.¹⁸

We found that measurement reproducibility for vessel and luminal areas in the MCA was lower than the results of a previous study of the basilar artery.¹⁰ This finding seemed due to the confluence of the MCA with adjacent brain parenchyma, with little surrounding CSF reducing the conspicuity of its outer wall. By contrast, abundant CSF around the basilar artery may improve wall conspicuity. We obtained good measurement reproducibility with more CSF surrounding the MCA due to age-related brain involution, especially compared with the relatively young volunteers in a previous study.¹⁹

We excluded nearly half of the patients from final analysis in this study, with most cases related to obliquity of the scan plane and tortuous vessels. This choice caused a high exclusion rate and makes the current protocol inefficient for assessment of remodeling in clinical practice. Approaches to arterial wall imaging involving 3D acquisitions with short time durations are promising.¹⁹ These techniques, with the aid of multiple planar reconstruction, may help reduce the number of excluded cases and may be ideal for assessment of arterial remodeling in tortuous intracranial vessels.

Other limitations are as follows: First, values of vessel area and wall thickness may be overestimated. The overestimation may

arise from lower in-plane and through-plane spatial resolution. This would lead to partial volume effects, resulting in an overestimation of the true vessel area and wall thickness, especially for reference sites. Another significant issue was that no effective technique for inflow and CSF suppression was applied in this study. Incomplete inflow or surrounding CSF suppression might mimic the vessel wall, causing an additional overestimation of the true vessel wall thickness. Second, although the proximal and distal minimally diseased vessels were also selected as reference sites in some cases, the number of lesions with negative remodeling may have been overestimated or underestimated due to remodeling of the reference sites in response to early-stage atherosclerosis.

CONCLUSIONS

2D high-resolution MR imaging can help assess the remodeling pattern and plaque distribution of MCA stenosis, but the imaging and postprocessing protocol for remodeling assessment needs to be improved in the tortuous course of the MCA or MCA ostium lesions or angled lesions due to artifacts and technical challenges related to obliquity.

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REFERENCES

1. Varnava AM. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation* 2002;105:939–43
2. Wexberg P, Gyöngyösi M, Sperker W, et al. Pre-existing arterial remodeling is associated with in-hospital and late adverse cardiac events after coronary interventions in patients with stable angina pectoris. *J Am Coll Cardiol* 2000;36:1860–69
3. Yamagishi M, Terashima M, Awano K, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol* 2000;35:106–11
4. Aliabadi D, Tilli FV, Bowers TR, et al. Incidence and angiographic predictors of side branch occlusion following high-pressure intracoronary stenting. *Am J Cardiol* 1997;80:994–97
5. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365:993–1003
6. Abou-Chebl A, Steinmetz H. Critique of “Stenting versus aggressive medical therapy for intracranial arterial stenosis” by Chimowitz et al in the New England Journal of Medicine. *Stroke* 2012;43:616–20
7. Marks MP. Is there a future for endovascular treatment of intracranial atherosclerotic disease after Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis (SAMMPRIS)? *Stroke* 2012;43:580–84
8. Lam WW, Wong KS, So NM, et al. Plaque volume measurement by magnetic resonance imaging as an index of remodeling of middle cerebral artery: correlation with transcranial color Doppler and magnetic resonance angiography. *Cerebrovasc Dis* 2004;17:166–69
9. Ryu CW, Jahng GH, Kim EJ, et al. High resolution wall and lumen MRI of the middle cerebral arteries at 3 Tesla. *Cerebrovasc Dis* 2009;27:433–42
10. Ma N, Jiang WJ, Lou X, et al. Arterial remodeling of advanced basilar atherosclerosis: a 3-Tesla MRI study. *Neurology* 2010;75:253–58
11. Xu WH, Li ML, Gao S, et al. In vivo high-resolution MR imaging of symptomatic and asymptomatic middle cerebral artery atherosclerotic stenosis. *Atherosclerosis* 2010;212:507–11
12. Klein IF, Lavalley PC, Touboul PJ, et al. In vivo middle cerebral artery plaque imaging by high-resolution MRI. *Neurology* 2006;67:327–29
13. Underhill HR, Yarnykh VL, Hatsukami TS, et al. Carotid plaque morphology and composition: initial comparison between 1.5- and 3.0-T magnetic field strengths. *Radiology* 2008;248:550–60
14. Li F, McDermott M, Li D, et al. The association of lesion eccentricity with plaque morphology and components in the superficial femoral artery: a high-spatial-resolution, multi-contrast weighted CMR study. *J Cardiovasc Magn Reson* 2010;12:37
15. Xu WH, Li ML, Gao S, et al. Plaque distribution of stenotic middle cerebral artery and its clinical relevance. *Stroke* 2011;42:2957–59
16. Jiang WJ, Cheng-Ching E, Abou-Chebl A, et al. Multicenter analysis of stenting in symptomatic intracranial atherosclerosis. *Neurosurgery* 2012;70:25–30, discussion 31
17. Jiang WJ, Yu W, Du B, et al. Outcome of patients with $\geq 70\%$ symptomatic intracranial stenosis after Wingspan stenting. *Stroke* 2011;42:1971–75
18. Jiang WJ, Yu W, Ma N, et al. High resolution MRI guided endovascular intervention of basilar artery disease. *J NeuroInterv Surg* 2011;3:375–78
19. Qiao Y, Steinman DA, Qin Q, et al. Intracranial arterial wall imaging using three-dimensional high isotropic resolution black blood MRI at 3.0 Tesla. *J Magn Reson Imaging* 2011;34:22–30

Multiparameter MR Imaging in the 6-OPRI Variant of Inherited Prion Disease

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ABSTRACT

BACKGROUND AND PURPOSE: Inherited prion diseases represent over 15% of human prion cases and are a frequent cause of early onset dementia. The purpose of this study was to define the distribution of changes in cerebral volumetric and microstructural parenchymal tissues in a specific inherited human prion disease mutation combining VBM with VBA of cerebral MTR and MD.

MATERIALS AND METHODS: VBM and VBA of cerebral MTR and MD were performed in 16 healthy control participants and 9 patients with the 6-OPRI mutation. An analysis of covariance consisting of diagnostic grouping with age and total intracranial volume as covariates was performed.

RESULTS: On VBM, there was a significant reduction in gray matter volume in patients compared with control participants in the basal ganglia, perisylvian cortex, lingual gyrus, and precuneus. Significant MTR reduction and MD increases were more anatomically extensive than volume differences on VBM in the same cortical areas, but MTR and MD changes were not seen in the basal ganglia.

CONCLUSIONS: Gray matter and WM changes were seen in brain areas associated with motor and cognitive functions known to be impaired in patients with the 6-OPRI mutation. There were some differences in the anatomic distribution of MTR-VBA and MD-VBA changes compared with VBM, likely to reflect regional variations in the type and degree of the respective pathophysiologic substrates. Combined analysis of complementary multiparameter MR imaging data furthers our understanding of prion disease pathophysiology.

ABBREVIATIONS: IPD = inherited prion disease; MD = mean diffusivity; MTR = magnetization transfer ratio; VBA = voxel-based analysis; VBM = voxel-based morphometry

Human prion diseases are rapidly progressive, uniformly fatal neurodegenerative disorders¹ that can be inherited (IPD), occur sporadically, or be caused by iatrogenic or dietary infection. The discovery of variant Creutzfeldt-Jakob disease² has not been followed by a major epidemic; however, the exis-

tence of subclinical infections³ and the evidence for secondary transmission by blood transfusion^{4,5} reinforce the public health relevance of these conditions.

Most of the literature on prion disease imaging has focused on the acquired and sporadic forms rather than IPD. In prevalence studies, 15% of prion disease cases are IPD, a cause of early-onset dementia, with more than 30 different prion protein gene (*PRNP*) mutations identified.⁶ The clinical phenotypes vary widely, with some mutations having a phenotype similar to sporadic Creutzfeldt-Jakob disease (eg, *E200K*), whereas others can mimic hereditary ataxias (eg, *P102L*) or Alzheimer disease (eg, some cases of 4-OPRI).⁷ The findings on conventional MR imaging are similarly variable.

In the United Kingdom, large kindreds presenting with 6 additional repeats in the octapeptide region (6-OPRI mutation), have been followed up for more than 2 decades with detailed reports of clinical symptoms⁸ and neuropsychological features⁹ but without systematic analysis of imaging findings. These pa-

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tients characteristically present with frontoparietal dysfunction progressing for 7–15 years (mean, 11 years) that culminates in an akinetic mute state. Visuospatial, frontal executive, and nominal skills are significantly impaired in this patient group, and apraxia is an important early feature.

Brain atrophy has rarely been quantified in IPD, apart from a case report of a presymptomatic *P102L* gene carrier demonstrating early parietal atrophy¹⁰ and a recent demonstration of parietal and occipital cortical thinning in patients with the 6-*OPRI* mutation.⁹ Quantitative MR imaging techniques such as MTR and MD mapping have revealed significant regional and whole-brain differences between patients with symptomatic prion disease and control participants.^{11–14} However, these studies used region-of-interest or histogram analyses, possibly missing or diluting regionally specific changes.

VBA of structural images (VBM)¹⁵ or MR imaging measures such as MD or MTR overcome these limitations because they do not require a priori anatomic hypotheses. These tools have not been applied in IPD, except for patients with the *E200K* mutation.^{16–18}

We performed VBM, MTR-VBA, and MD-VBA in a cohort of patients with IPD who have the 6-*OPRI* mutation, some of whom were previously studied with alternative methods.^{12,13} We hypothesized that this multiparametric approach would localize brain abnormalities corresponding to known clinical symptoms and neuropsychological deficits and, further, that MTR and MD would quantify microstructural changes even in areas without significant volume loss on VBM.

MATERIALS AND METHODS

Patients

Patients attended the National Prion Clinic at the National Hospital for Neurology and Neurosurgery, London, United Kingdom, and were recruited into the UK MRC PRION-1 trial.¹⁹ Ethical approval was granted by the Eastern Multicentre Research Ethics Committee, Cambridge, United Kingdom.

Full neurologic, Mini-Mental State Examination,²⁰ and Clinical Dementia Rating Scale sum of boxes=^{8,21} were recorded. Where several individual patient MR imaging datasets were available, the dataset acquired when the patient's Clinical Dementia Rating Scale was closest to the group median (Clinical Dementia Rating Scale=8) was selected. This approach allowed us to have a more homogeneous cohort and minimize the Clinical Dementia Rating Scale SD across the patient group.

Nine individuals with the 6-*OPRI* mutation were studied (6-*OPRI* group: mean age, 38.1 ± 3.6 years; median Mini-Mental State Examination, 19 [range 11–27]; all codon 129MM). Sixteen healthy volunteers with no history of neurologic disorder were included (Controls group: mean age, 37.1 ± 10.7 years; all Mini-Mental State Examination, 30); Table 1.

MR Imaging Acquisition

MR imaging was performed at 1.5T (GE Healthcare, Milwaukee, Wisconsin) by using the standard transmit/receive head coil. Sequences included the following:

Table 1: Patient demographics and clinical data

	Control Group	6- <i>OPRI</i> Group	P Value
N	16 (8 M)	9 (4 M)	—
Age (y)	37.1 ± 10.7	38.1 ± 3.6	ns
MMSE	30 (30–30)	19 (11–27)	<.001
CDR	—	8 (2–14)	.002 ^a

Note:—CDR indicates Clinical Dementia Rating Scale; M, male; N, number; MMSE, Mini-Mental State Examination; ns, not significant ($P \geq 0.1$); 6-*OPRI*, 6-octapeptide repeat insertion. Age values are mean ± SD. MMSE and CDR values are median (range).

^a All comparisons were performed with the Mann-Whitney *U* test, except for CDR, for which the Wilcoxon test vs CDR = 0 was performed.

- 1) Structural T1-weighted imaging (3D inversion recovery-spoiled gradient recalled-echo sequence [TR, 6.4 ms; TE, 14.5 ms; TI, 650 ms; flip angle, 15°; number of 1.5-mm partitions, 124; FOV, 24 × 18 cm²; matrix, 256 × 192; total acquisition time, 9 minutes, 48 seconds]).
- 2) DWI with diffusion-weighting (“*b*”) (single-shot echo-planar imaging [TR, 10 s; number of 5-mm sections, 30; FOV, 26 × 26 cm²; matrix, 96 × 128]) with diffusion-weighting factors (“*b*-values”) of 0 (B0) and 1000 s/mm² (*b* = 1000: TE, 101 ms; 1 average; acquisition time 1 minute, 20 seconds) and of 0 and 3000 s/mm² (*b* = 3000: TE, 136 ms; 3 averages; acquisition time 4 minutes) applied sequentially along 3 orthogonal axes. MD was calculated as:

$$MD_{1k,3k} = \ln(S_0/S_{1k,3k})/b_{1k,3k}^{22}$$

where S_0 and $S_{1k,3k}$ are respectively the local signal intensities of the B0 and mean of DWI (*b* = 1000 or *b* = 3000) acquired in 3 orthogonal directions (as only 3 gradient sensitization directions were used, this variable is actually an approximation of the mean diffusivity that could be measured with 6 or more directions).

- 3) MTR imaging (interleaved 2D, gradient-echo sequence, similar to the EuroMT sequence²³ [TR, 1500 ms; TE, 15.4 ms; flip angle, 70°; number of 5-mm sections, 30; FOV, 24 × 18 cm²; matrix, 256 × 192; acquisition time 12 minutes]). Magnetization transfer presaturation was achieved with a Gaussian pulse of duration 12.8 ms and peak amplitude 23.2 μT giving a nominal bandwidth of 125 Hz, applied 2 kHz off water resonance. Scans with and without presaturation were interleaved for each TR period, ensuring exact coregistration of the pixels on saturated (Msat) and unsaturated (M0) images.²⁴ MTR was calculated from M0 and Msat images as $MTR = (1 - Msat/M0) \times 100$ in percentage units.
- 4) Fast spin-echo T2-weighted (TR, 6000 ms; TE, 106 ms; number of 5-mm sections, 22; FOV, 24 × 18 cm²; matrix, 256 × 224; 2 averages) and FLAIR imaging (TR, 9897 ms; TE, 161 ms; TI, 2473 ms; number of 5-mm sections, 22; FOV, 24 × 24 cm²; matrix, 256 × 224).

Imaging Analysis: Qualitative Analysis by Visual Inspection

The T2-weighted, FLAIR, and DWI images were reviewed independently (in an unblinded fashion) by 2 consultant neuroradiologists with experience in prion disease. Pathologic signal changes were assessed in the caudate, putamen, and thalamus and in the cortex of the frontal, parietal, temporal, and occipital lobes. When a discrepancy was identified, the images were re-reviewed

in a consensus reading and a κ statistic calculated to assess the level of agreement.

Imaging Analysis: Quantitative MR Imaging

VBM Spatial Preprocessing. Spatial processing for VBM was performed for structural data by using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) as follows:

- 1) SPM8's "unified segmentation," combining segmentation, bias correction, and normalization to the Montreal Neurological Institute space into a single generative model (SPM "Segment").²⁵ The rigid normalization transformation component was used to produce approximately aligned images for the following step.
- 2) Generation of a cohort specific template for gray matter and WM segments by using the DARTEL toolbox in SPM8²⁶ using all participants.
- 3) Warping and resampling of individual gray matter and WM segments, normalizing them to the cohort-specific template. Local intensities for each voxel were modulated (ie, multiplied by the ratio of voxel volume before and after normalization) to account for normalization-associated volume changes.²⁷

MTR-VBA Preprocessing. Rigid transformations between individual Msat images and corresponding T1 datasets were estimated and then combined with the warps computed for the T1 data to normalize individual MTR maps to the cohort VBM T1-template. As voxel MTR values are not directly related to voxel volume, data were not modulated.

MD-VBA Preprocessing. The MD ($b = 3000 \text{ s/mm}^2$) dataset was rigidly aligned with the MD ($b = 1000 \text{ s/mm}^2$) dataset (based on the corresponding B0 acquisitions). Affine transformations between MD and corresponding T1 images were estimated with the tool in NiftyReg (<http://sourceforge.net/projects/niftyreg/>)^{28,29} to partially correct echo-planar imaging-associated geometric distortion (based on the MD ($b = 1000 \text{ s/mm}^2$) B0 acquisitions). These transforms were then combined with the warps computed for the T1 data to normalize (with no modulation) individual MD ($b = 1000 \text{ s/mm}^2$) and MD ($b = 3000 \text{ s/mm}^2$) maps to the cohort VBM T1-template.

Statistical Analysis

An isotropic 6-mm full width at half maximum Gaussian kernel was applied to each of the 6 normalized datasets (gray matter, WM, MTR, MD ($b = 1000 \text{ s/mm}^2$), and MD ($b = 3000 \text{ s/mm}^2$)). An "objective" masking strategy³⁰ defined the voxels for subsequent statistical analysis on gray matter and WM segments separately; the resulting masks were combined for MTR and MD data analysis. For each dataset, the analysis involved an analysis of covariance consisting of diagnostic grouping (6-OPRI or controls) with individual age and total intracranial volume (estimated as the sum of gray matter, WM, and CSF segments) as covariates (using the same covariates for all analyses allowed for a more consistent model across modalities). Group differences between covariates were assessed with the 2-sample Mann-Whitney U test (PASW Statistics 18, SPSS, Chicago Illinois).

SPM-t maps ($P < .05$) after family-wise error multiple-comparison correction (with no cluster-extent threshold), and effect-

size maps showing group differences as percentages of the control group mean were produced. We also computed the affine transformation between the DARTEL space (in which the SPM results were computed) and Montreal Neurological Institute space. Using these parameters, we also transformed the SPM maps and effect-size maps onto Montreal Neurological Institute space for visualization. Results are thus displayed in the Montreal Neurological Institute space overlaid on the average of the warped and smoothed T1 volumes. All are presented by using the neurologic convention (right hemisphere displayed on the right).

ROIs

To quantify differences in MR imaging measures, 3 ROIs were defined on the right hemisphere of the average warped and smoothed T1-volume, in the thalamus, head of the caudate, and putamen (ROI volume range, 0.59–0.60 mL). The ROIs were then verified for individual datasets to ensure that the smoothing had not introduced CSF contamination. The ROI mean from the corresponding warped and smoothed datasets for each patient was computed and between-group differences assessed by the 2-sample Mann-Whitney U test. To account for multiple comparisons over the 3 regions (but not the 4 metrics, as these tests are being compared with each other, rather than simply being searched over), $P < .01$ was considered significant.

RESULTS

Between controls and patients with 6-OPRI, differences in age were not significant, in contrast to Mini-Mental State Examination and Clinical Dementia Rating Scale (Table 1). The total intracranial volumes were $1.42 \pm 0.14 \text{ L}$ (mean $\pm$ SD) in controls and $1.41 \pm 0.20 \text{ L}$ in patients with 6-OPRI and were not significantly different.

Qualitative Analysis

On initial assessment, both raters agreed that there was no pathologic signal change in 7 of the 9 patients. There were discrepancies in 2 patients where DWI signal hyperintensity in the frontal cortex was noted in 1 patient and FLAIR signal hyperintensity in the perihabenular region noted in another patient (κ score, 0.835). On consensus review of these cases, it was decided that the findings were artifactual and that there was no evidence of pathologic signal change.

Quantitative Analysis

VBM. Within the supratentorial cortex, extensive bilateral symmetric gray matter volume reduction was seen in the perisylvian cortex: central opercular, insular cortex, middle and superior temporal gyri; parietal cortex: angular, supramarginal, and post-central gyrus; and occipital cortex: lingual gyrus and cuneus. Less extensive gray matter reduction was also seen in the left superior frontal gyrus and cingulate gyrus. Within the deep gray nuclei, significant gray matter reduction was seen in the caudate and putamen bilaterally and within the posterior fossa; the cerebellar cortex bilaterally also showed significant gray matter reduction (Fig 1A).

The areas of significant WM reductions are more sparse and to a smaller extent. Significant areas of WM volume reduction in-

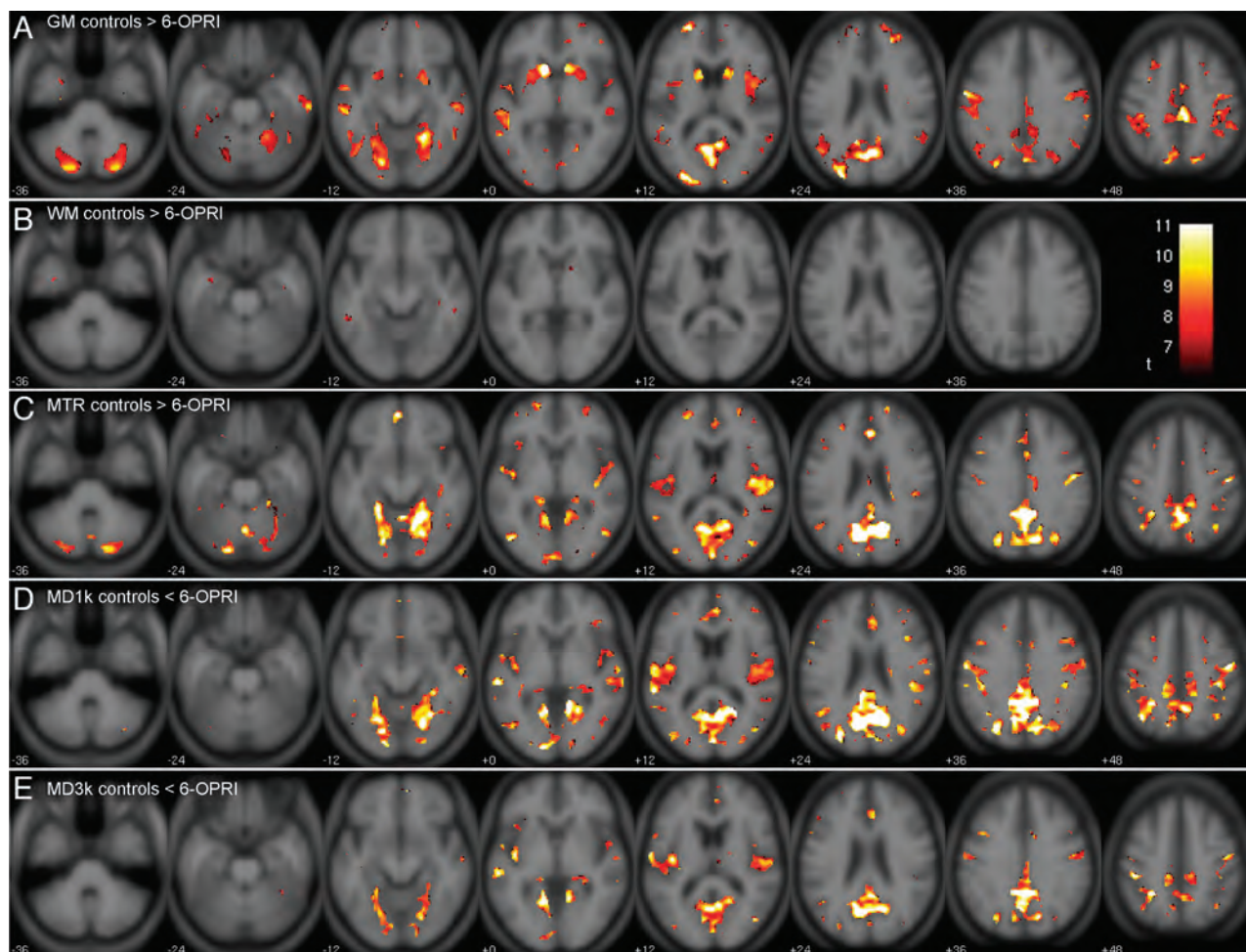


FIG 1. SPM-*t* maps for patients with the *6-OPRI* mutation compared with control participants. SPM-*t* maps showing significant differences between symptomatic patients with the *6-OPRI* mutation ($n = 9$) and healthy control participants ($n = 16$) for family-wise error $P < .05$. A, gray matter: controls $> 6-OPRI$, $t \geq 6.60$. B, WM: controls $> 6-OPRI$, $t \geq 6.07$. C, MTR: controls $> 6-OPRI$, $t \geq 6.86$. D, MD ($b = 1000 \text{ s/mm}^2$): controls $< 6-OPRI$, $t \geq 7.03$. E, MD ($b = 3000 \text{ s/mm}^2$): controls $< 6-OPRI$, $t \geq 6.96$. The color bar represents the t value range.

Table 2: Significant clusters for WM VBM (Controls $> 6-OPRI$)

k	Peak P Value (FWE corr)	Peak T	Peak Z	x	y	z	Description
175	$<.001$	10.59	6.16	-34	-4	-31	L temporal fusiform and parahippocampal gyri
176	.003	7.61	5.22	-52	-43	-3	L middle temporal gyrus
	.005	7.37	5.12	-56	-42	-12	L middle temporal gyrus
7	.017	6.66	4.83	-54	-29	-8	L middle temporal gyrus
6	.019	6.61	4.81	-39	-57	30	L angular gyrus
46	.006	7.25	5.08	-25	-31	-13	L hippocampus
45	.007	7.16	5.04	-26	-29	-8	L hippocampus and L parahippocampal gyrus
	.03	6.35	4.69	-20	-34	6	L thalamus
18	.035	6.27	4.66	-13	6	-3	L pallidum
97	.001	8.25	5.45	57	-35	-13	R middle temporal gyrus
	.017	6.67	4.83	49	-39	-9	R inferior temporal gyrus
	.018	6.66	4.83	47	-48	-11	R inferior temporal gyrus
148	.002	7.82	5.29	37	-12	-22	R temporal fusiform gyrus
	.003	7.72	5.26	37	-29	-13	R temporal fusiform gyrus
57	.009	7.01	4.98	26	-31	-6	R hippocampus
60	.012	6.86	4.92	13	8	-3	R pallidum
27	.004	7.58	5.21	2	-22	19	Midline-body of corpus callosum
3	.034	6.29	4.66	-5	-19	30	L body of corpus callosum
10	.022	6.54	4.78	5	-17	30	R body of corpus callosum

Note:—FWE corr indicates family-wise error corrected; L, left; MNI, Montreal Neurological Institute; R, right. k is the number of voxels within each cluster. All clusters of voxels above a voxel-level threshold FWE $P \leq .05$ of size $k > 2$ are shown. For the largest clusters, the table shows up to 3 local maxima more than 8 mm apart. The x, y, and z coordinates are in the MNI space. Peak-t and Peak-z values are within each cluster.

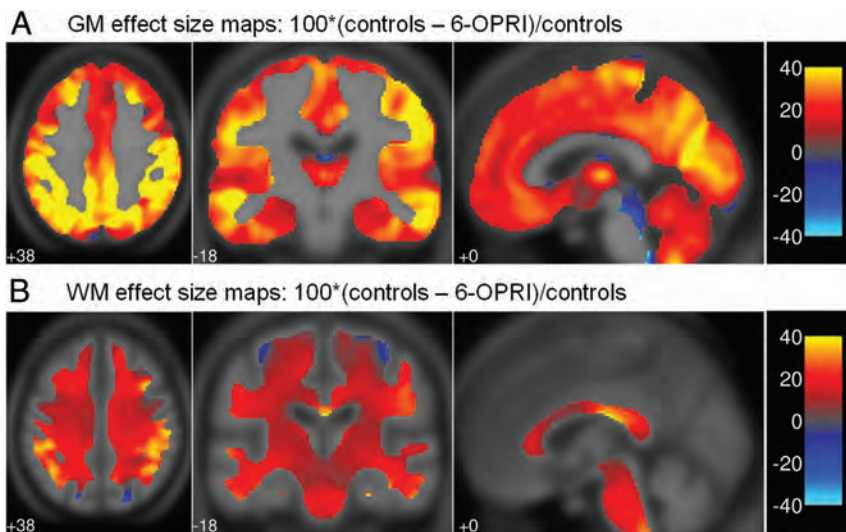


FIG 2. Effect size maps for all patients compared with control participants and patients with 6-OPRI compared with control participants. Effect size maps demonstrating the percentage difference between patients with 6-OPRI and controls in (A) gray matter volume and (B) WM volume calculated as $100 \times (\text{controls} - \text{all patients}) / \text{controls}$ displayed in the Montreal Neurological Institute space.

involved the anterior temporal lobes, the body of the corpus callosum, and hippocampus bilaterally (Fig 1B). A complete list of the coordinates and corresponding anatomic locations of the significant cluster peaks (for clusters with size $k > 2$) is presented in Table 2.

The effect maps (Fig 2A, 2B) demonstrated that the largest percentage differences were present in the insular cortex, middle and superior temporal gyri, angular and supramarginal gyri, lingual gyrus, and cuneus.

MTR. Significant MTR reductions in the 6-OPRI group were topographically similar in the supratentorial cortex to those seen on VBM, with extensive involvement of the perisylvian regions, and parietal and occipital cortices bilaterally, as described above (Fig 1C). Within the deep gray nuclei, significant MTR reductions were seen in the posteromedial thalamus bilaterally only. In the posterior fossa, extensive involvement of the cerebellar cortex was seen.

Regarding the number of suprathreshold voxels, changes were more anatomically extensive on MTR-VBA than on VBM in the perisylvian regions, cuneus, and precuneus, where there is the impression of involvement of the subcortical WM, with significant reductions in the posteromedial thalamus, not seen on VBM. However, MTR-VBA did not detect significant MTR reductions in the caudate nucleus, putamen, or middle temporal gyri where VBM showed differences (Fig 1C).

MD. MD ($b = 1000 \text{ s/mm}^2$). The largest clusters and most significant MD ($b = 1000 \text{ s/mm}^2$) increases were seen in the gray matter and subcortical WM of the perisylvian, parietal, and occipital lobes (Fig 1D) and in the posteromedial thalamus bilaterally. Regarding the number of suprathreshold voxels, changes were more anatomically extensive on MD-VBA than on VBM, similar to MTR-VBA. No significant differences were seen in the cerebellar hemispheres (as seen on MTR) or in the basal ganglia (as seen on VBM).

MD ($b = 3000 \text{ s/mm}^2$). Areas of significant MD ($b = 3000 \text{ s/mm}^2$) increase overlapped those seen with MD ($b = 1000$

s/mm^2), although the extent and significance were generally smaller (Fig 1D,E). Reduced significance could arise from either reduced effect size (group difference) or increased variability. We investigated these influences by evaluating the non-normalized group difference, and a form of coefficient of variation given by the square root of the mean squared residuals (SPM ResMS Image) divided by the average of the 2 group means from the analysis of covariance model. Both the group difference and the coefficient of variation were larger for MD ($b = 1000 \text{ s/mm}^2$) (data not shown), suggesting that the higher significance of MD ($b = 1000 \text{ s/mm}^2$) changes is the result of a greater effect size than for MD ($b = 3000 \text{ s/mm}^2$) and not simply a higher signal-to-noise ratio.

ROI Analysis

Mean values for patients with 6-OPRI differed significantly from controls in all 3 ROIs for tissue-segment volumes, MTR, and MD ($b = 1000 \text{ s/mm}^2$), and in the thalamic ROI only for MD ($b = 3000 \text{ s/mm}^2$) (Table 3).

DISCUSSION

This systematic study is the first to describe the distribution of gray matter and WM volume changes and voxelwise MTR and MD changes in patients with IPD who have the 6-OPRI mutation. We demonstrated anatomically specific mean tissue attenuation reduction in these patients that are consistent with previous qualitative reports. Using MTR and MD, we detected cortical and subcortical microstructural changes both coincident with and spatially independent of tissue volume changes. Some of these changes seem to be specific to the 6-OPRI IPD mutation.

Local Volume Reductions Assessed with VBM

Brain atrophy occurs in all forms of prion disease,^{8,31} but most reports are based on visual inspection rather than objective quantification. In an early case report, a presymptomatic *P102L* gene carrier demonstrated widespread supratentorial and cerebellar volume loss with relative sparing of the mesial temporal lobe structures.¹¹ In a recent study of patients with the 6-OPRI mutation, significant cortical thinning was seen in the precuneus, inferior parietal cortex, supramarginal gyrus, and lingula.⁹ Our study confirms these findings, with gray matter volume loss in such patients predominantly involving the perisylvian cortex, precuneus, and lingual gyrus and without significant involvement of the mesial temporal lobe structures.

These cortical changes relate well to clinical symptoms documented in patients with the 6-OPRI mutation. Apraxia is an important early feature and is generally associated with lesions to the dominant parietal lobe and, specifically, the supramarginal gyrus. Visuo-perceptual and visuo-spatial impairments known to be sensitive to right parietal damage are also common in this patient

Table 3: Mean values for tissue segment volumes, MTR, MD ($b = 1000 \text{ s/mm}^2$), and MD ($b = 3000 \text{ s/mm}^2$) in selected ROIs

Brain Region	Control Group	6-OPRI Group	P Value ^b
Right thalamus			
WM (tv) ^a	0.66 ± 0.07	0.57 ± 0.05	.002
MTR (%)	40.6 ± 1.2	38.9 ± 1.1	.002
MD1k ($\times 10^{-3} \text{ mm}^2/\text{s}$)	0.81 ± 0.03	0.88 ± 0.05	<.001
MD3k ($\times 10^{-3} \text{ mm}^2/\text{s}$)	0.63 ± 0.01	0.67 ± 0.03	<.001
Right caudate			
GM (tv)	0.74 ± 0.07	0.50 ± 0.08	<.001
MTR (%)	37.6 ± 1.1	33.8 ± 2.2	<.001
MD1k ($\times 10^{-3} \text{ mm}^2/\text{s}$)	0.79 ± 0.03	0.88 ± 0.10	.001
MD3k ($\times 10^{-3} \text{ mm}^2/\text{s}$)	0.63 ± 0.02	0.64 ± 0.03	NS
Right putamen			
GM (tv)	0.92 ± 0.12	0.60 ± 0.12	<.001
MTR (%)	38.6 ± 1.0	36.8 ± 1.1	.001
MD1k ($\times 10^{-3} \text{ mm}^2/\text{s}$)	0.78 ± 0.02	0.83 ± 0.07	.008
MD3k ($\times 10^{-3} \text{ mm}^2/\text{s}$)	0.65 ± 0.01	0.63 ± 0.03	.04

Note:—GM indicates gray matter; MD1k, mean diffusivity ($b=1000 \text{ s/mm}^2$); MD3k, mean diffusivity ($b=3000 \text{ s/mm}^2$); NS, not significant ($p \geq 0.1$); tv, modulated tissue segment fractional volume. Values are mean $\pm$ SD over subject group of the individual ROI means.

^aWM is reported here because the SPM8 segmentation routine classifies the thalamus as a predominantly WM structure.

^bP values are reported for the Mann-Whitney *U* test.

group.⁸ The explanation for the prominent cognitive features of memory loss and frontal executive dysfunction in this patient group³² is more complex.

Although the effect size maps (Fig 2) demonstrated some percentage difference in the mesial temporal lobes and prefrontal cortices, these volume losses were less marked compared with those in the cortical areas described above and did not prove to be statistically significant on VBM. Some of the memory and executive deficits seen in patients with 6-OPRI mutations could be explained by subcortical pathologic changes affecting the cortical circuits involved in these cognitive functions. This finding would be supported by the subcortical gray matter volume loss seen in the caudate nuclei and putamina, as well as the MD and MTR changes in the posteromedial thalami.

Thalamic and striatal involvement is well established in all forms of human prion disease.³³ The putamen and caudate nuclei receive input from diverse cortical areas, including the prefrontal and limbic structures with nonmotor output from the striatum projecting, via the mediodorsal and ventrolateral thalamic nuclei, to the dorsolateral prefrontal cortex, lateral orbitofrontal cortex, and the anterior cingulate.³⁴

Voxel-Based Analyses of MTR and MD

The MTR-VBA and MD-VBA did not show significant change in the basal ganglia; however, they demonstrated significant MTR reduction and significant MD increase in the posteromedial thalamus (not detected by VBM), cortical gray matter areas corresponding to those displaying VBM changes, and also in adjacent subcortical WM where no significant volume changes were detected. This finding suggests that MTR and MD data are a useful complement to T1-weighted structural data and are potentially more sensitive to subcortical WM and thalamic changes in prion diseases.

MTR-VBA

Our MTR findings are consistent with a previous study in which decreases in whole-brain and whole—gray matter segment MTR compared with controls were observed in patients with symptomatic prion disease, correlating with disease severity.¹³ An association between decreased postmortem gray matter MTR and increased spongiosis was also seen in that study. One possible explanation for the differences in regional distribution of changes shown by MTR-VBA and VBM here is the potential of MTR to reflect microstructural pathologic changes (such as spongiosis), occurring before or independent of macroscopic volume loss.

MD-VBA

Our findings of increased cerebral MD in patients with the 6-OPRI mutation have been reported in patients with IPD,^{11,35} specifically in the cerebellar cortex in patients with the *E200K* mutation¹⁸ and in the thalamus in variant Creutzfeldt-Jakob disease,^{36,37} thought to reflect increased gliosis.^{35,36} Opposite findings of decreased MD have been reported in sporadic Creutzfeldt-Jakob disease and in patients with the *E200K* mutation, specifically within the basal ganglia and thalamus,^{11,14} thought to reflect spongiform change. A relationship between macroscopic atrophy and microscopic changes reflected in increased MD may be expected; in other neurodegenerative disorders, whole-brain or regional MD values usually increase in association with brain atrophy.^{38,39} This increase in diffusivity has been associated with loss of neuronal cell bodies, synapses, and dendrites, causing an expansion of the extracellular space where water diffusivity is fastest.⁴⁰ Also, in prion diseases, this increase in diffusivity could reflect areas where neuronal loss and gliosis are becoming dominant over spongiform change but is too subtle to be detected by VBM.

High b-value DWI, relatively more sensitive to slowly diffusing tissue water components,⁴¹ provided greater pathologic sensitivity for spongiform change than conventional b-value DWI in a previous study of sporadic Creutzfeldt-Jakob disease¹¹ and in patients with IPD who have the *E200K* mutation frequently mimicking the sporadic Creutzfeldt-Jakob disease phenotype.¹⁴

However, in the former study¹¹, high b-value DWI was not more sensitive than conventional b-value DWI in the detection of increased ADC values in the pulvinar nucleus in patients with variant Creutzfeldt-Jakob disease, thought to have histopathologic features of gliosis. It is likely that in the context of gliosis and neuronal loss, fast diffusion components dominate the mean diffusivity so that high b-value DWI is less sensitive, as was observed in our study.

ROI Analysis

Although MD-VBA and MTR-VBA did not reveal significant changes in the basal ganglia, significant ROI MD increases and MTR decreases were seen in the thalamus, putamen, and caudate in the 6-OPRI subgroup relative to control participants. Voxel-based analyses may not provide a complete substitute but, rather, a complement to ROI analysis, the latter potentially avoiding smoothing across interregional or tissue boundaries. Cross-boundary smoothing in VBA complicates interpretation and can either reduce or increase statistical power, depending on whether the greatest underlying changes respect the observable tissue boundaries. Intergroup differences revealed on VBA and VBM may identify pathologically specific affected regions. These differences may then be more sensitively investigated on a subject-by-subject basis by ROI analysis, which may provide the most straightforward and interpretable way to monitor disease progression.

Study Limitations

Patients with the 6-OPRI mutation were the largest mutation subgroup to undergo MR imaging scanning in the PRION-1 trial, and our current study represents the largest group of such patients for which consistent multiparameter MR imaging measurements are available. Nevertheless, given the relatively small group size, our analysis should be considered preliminary.

Some types of IPD (*E200K*, *V201I*) have clinical and radiologic features similar to sporadic Creutzfeldt-Jakob disease,⁴² but apart from patients carrying the *P102L* mutation,⁹ the imaging features of other mutations are not well described in the literature. A comparison of 6-OPRI MR imaging findings with those from other IPD mutations would be particularly informative. Although we had access to another small set ($n = 8$) of patients with IPD who had other mutations, the subgroups were too small ($n = 4$, $n = 1$, $n = 1$, $n = 1$, $n = 1$) to achieve statistical power sufficient to provide robust conclusion on differences and similarities among mutations. Future trials enrolling larger patient numbers will be necessary for this type of analysis.

Our data suggest that in a number of brain regions, MTR and MD appear more sensitive to pathologic changes than the tissue-volume data inferred from the T1-weighted acquisition. A future study with a larger dataset may confirm this observation by seeking significant changes after adjusting for local atrophy by using voxelwise covariates (also known as biologic parametric mapping).^{43,44} Furthermore, for our current data we underline that the specific sensitivities (and statistical power) of the individual voxel-based analyses also depend on the acquisition signal-to-noise ratios in the respective protocols (eg, determined by specific sequence parameters, including nominal voxel sizes). We used the standard acquisition parameters optimized for each method at our institution; our current study was not designed to systematically compare protocols with matched signal-to-noise ratios.

Although the voxel-based analyses were performed on normalized images with a nominal isotropic resolution (1.5 mm),³ the DWI and MTR source data were acquired with a larger section thickness (5 mm) compared with the nominal 1.5-mm partition of the 3D structural images. Partial-volume averaging from CSF at the brain surface may thus be partly responsible for the larger

clusters detected proximal to the brain-CSF interfaces on MTR-VBA and MD-VBA. With this problem in mind, we took care to ensure that CSF contamination did not influence the manually drawn ROIs.

CONCLUSIONS

Our study is the first multiparameter voxel-based analysis of cerebral atrophy and microstructural changes in the 6-OPRI IPD mutation by using quantitative MR imaging. With VBM, we demonstrated regionally specific volume loss corresponding anatomically to clinical symptoms and providing an anatomic basis for the memory and executive function deficits seen clinically. We also showed that VBA of MTR and MD can detect microstructural changes in anatomic regions that do not demonstrate volume loss on VBM. This finding is likely to reflect a diverse anatomic distribution of histopathologic change driven by varying pathophysiologic processes. Combining regional measures from different but complementary MR imaging modalities can identify brain regions preferentially involved in the pathophysiology of prion disease and may provide markers of value in monitoring future therapies. Comparison of our data on patients with the 6-OPRI mutation with existing literature suggests that the distribution of structural and microstructural changes presented here is specific to this particular IPD mutation.

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REFERENCES

1. Collinge J. Prion diseases. In: Ledingham JGG, Warrell DA, eds. *Concise Oxford Textbook of Medicine*. New York: Oxford University Press, 2000;1307–11
2. Collinge J, Rossor M. A new variant of prion disease. *Lancet* 1996;347:916–17
3. Hill AF, Collinge J. Subclinical prion infection in humans and animals. *Br Med Bull* 2003;66:161–70
4. Llewellyn CA, Hewitt PE, Knight RS, et al. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004;363:417–21

5. Wroe SJ, Pal S, Siddique D, et al. **Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report.** *Lancet* 2006;368:2061–67
6. Mead S. **Prion disease genetics.** *Eur J Hum Genet* 2006;14:273–81
7. Kaski DN, Pennington C, Beck J, et al. **Inherited prion disease with 4-octapeptide repeat insertion: disease requires the interaction of multiple genetic risk factors.** *Brain* 2011;134:1829–38
8. Mead S, Poulter M, Beck J, et al. **Inherited prion disease with six octapeptide repeat insertional mutation—molecular analysis of phenotypic heterogeneity.** *Brain* 2006;129:2297–317
9. Alner K, Hyare H, Mead S, et al. **Distinct neuropsychological profiles correspond to distribution of cortical thinning in inherited prion disease caused by insertional mutation.** *J Neurol Neurosurg Psychiatry* 2012;83:109–14
10. Fox NC, Freeborough PA, Mekkaoui KF, et al. **Cerebral and cerebellar atrophy on serial magnetic resonance imaging in an initially symptom free subject at risk of familial prion disease.** *BMJ* 1997;315:856–57
11. Hyare H, Thornton J, Stevens J, et al. **High-b-value diffusion MR imaging and basal nuclei apparent diffusion coefficient measurements in variant and sporadic Creutzfeldt-Jakob disease.** *AJNR Am J Neuroradiol* 2010;31:521–26
12. Hyare H, Wroe S, Siddique D, et al. **Brain-water diffusion coefficients reflect the severity of inherited prion disease.** *Neurology* 2010;74:658–65
13. Siddique D, Hyare H, Wroe S, et al. **Magnetization transfer ratio may be a surrogate of spongiform change in human prion diseases.** *Brain* 2010;133:3058–68
14. Lee H, Hoffman C, Kingsley PB, et al. **Enhanced detection of diffusion reductions in Creutzfeldt-Jakob disease at a higher B factor.** *AJNR Am J Neuroradiol* 2010;31:49–54
15. Ashburner J, Friston KJ. **Voxel-based morphometry—the methods.** *Neuroimage* 2000;11:805–21
16. Lee H, Rosenmann H, Chapman J, et al. **Thalamo-striatal diffusion reductions precede disease onset in prion mutation carriers.** *Brain* 2009;132:2680–87
17. Lee H, Cohen OS, Rosenmann H, et al. **Cerebral white matter disruption in Creutzfeldt-Jakob disease.** *AJNR Am J Neuroradiol* 2012;33:1945–50
18. Cohen OS, Hoffmann C, Lee H, et al. **MRI detection of the cerebellar syndrome in Creutzfeldt-Jacob disease.** *Cerebellum* 2009;8:373–81
19. Collinge J, Gorham M, Hudson F, et al. **Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial.** *Lancet Neurol* 2009;8:334–44
20. Folstein MF, Folstein SE, McHugh PR. **“Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician.** *J Psychiatr Res* 1975;12:189–98
21. Hughes CP, Berg L, Danziger WL, et al. **A new clinical scale for the staging of dementia.** *Br J Psychiatry* 1982;140:566–72
22. Stejskal EO, Tanner JE. **Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient.** *J Chem Phys* 1965;42:288–92
23. Barker GJ, Schreiber WG, Gass A, et al. **A standardised method for measuring magnetisation transfer ratio on MR imagers from different manufacturers—the EuroMT sequence.** *MAGMA* 2005;18:76–80
24. Barker GJ, Tofts PS, Gass A. **An interleaved sequence for accurate and reproducible clinical measurement of magnetization transfer ratio.** *Magn Reson Imaging* 1996;14:403–11
25. Ashburner J, Friston KJ. **Unified segmentation.** *Neuroimage* 2005;26:839–51
26. Ashburner J. **A fast diffeomorphic image registration algorithm.** *Neuroimage* 2007;38:95–113
27. Mechelli A, Price CJ, Friston KJ, et al. **Voxel-based morphometry of the human brain: methods and applications.** *Curr Med Imag Rev* 2005;1:105–13
28. Ourselin S, Roche A, Subsol G, et al. **Reconstructing a 3D structure from serial histological sections.** *Image Vis Comput* 2001;19:25–31
29. Ourselin S, Stefanescu R, Pennec X. **Robust registration of multi-modal images: Towards real-time clinical applications.** In: *Proceedings of Medical Image Computing and Computer-Assisted Intervention (MICCAI)*, Tokyo, Japan, September 25–28, 2002:140–47
30. Ridgway GR, Omar R, Ourselin S, et al. **Issues with threshold masking in voxel-based morphometry of atrophied brains.** *Neuroimage* 2009;44:99–111
31. Arata H, Takashima H, Hirano R, et al. **Early clinical signs and imaging findings in Gerstmann-Sträussler-Scheinker syndrome (Pro102Leu).** *Neurology* 2006;66:1672–78
32. Cordery RJ, Alner K, Cipolotti L, et al. **The neuropsychology of variant CJD: a comparative study with inherited and sporadic forms of prion disease.** *J Neurol Neurosurg Psychiatry* 2005;76:330–36
33. Aguzzi A, Weissmann C. **Prion diseases.** *Haemophilia* 1998;4:619–27
34. Middleton FA, Strick PL. **Basal-ganglia ‘projections’ to the prefrontal cortex of the primate.** *Cereb Cortex* 2002;12:926–35
35. Haik S, Galanaud D, Linguraru MG, et al. **In vivo detection of thalamic gliosis: a pathoradiologic demonstration in familial fatal insomnia.** *Arch Neurol* 2008;65:545–49
36. Oppenheim C, Brandel JP, Hauw JJ, et al. **MRI and the second French case of vCJD.** *Lancet* 2000;356:253–54
37. Waldman AD, Jarman P, Merry RT. **Rapid echoplanar diffusion imaging in a case of variant Creutzfeldt-Jakob disease; where speed is of the essence.** *Neuroradiology* 2003;45:528–31
38. Kantarci K, Jack CR Jr, Xu YC, et al. **Mild cognitive impairment and Alzheimer disease: regional diffusivity of water.** *Radiology* 2001;219:101–07
39. Mascalchi M, Lolli F, Della Nave R, et al. **Huntington disease: volumetric, diffusion-weighted, and magnetization transfer MR imaging of brain.** *Radiology* 2004;232:867–73
40. Kantarci K, Petersen C, Boeve BF, et al. **DWI predicts future progression to Alzheimer disease in amnesic mild cognitive impairment.** *Neurology* 2006;64:902–04
41. Niendorf T, Dijkhuizen RM, Norris DG, et al. **Biexponential diffusion attenuation in various states of brain tissue: implications for diffusion-weighted imaging.** *Magn Reson Med* 1996;36:847–57
42. Breithaupt M, Romero C, Kallenberg K, et al. **Magnetic resonance imaging in E200K and V210I mutations of the prion protein gene.** *Alzheimer Dis Assoc Disord* 2013;27:87–90
43. Casanova R, Srikanth R, Baer A, et al. **Biological parametric mapping: A statistical toolbox for multimodality brain image analysis.** *Neuroimage* 2007;34:137–43
44. Oakes TR, Fox AS, Johnstone T, et al. **Integrating VBM into the general linear model with voxelwise anatomical covariates.** *Neuroimage* 2007;34:500–08

Imaging of the 6-*OPRI* Mutation Prion Disease: An Entity Distinct from Typical Creutzfeldt-Jakob Disease?

In the article “Multi-parameter MR Imaging in the 6-*OPRI* Variant of Inherited Prion Disease,” featured in this issue, De Vita et al¹ evaluate a particular mutation of human prion disease, thereby making an essential contribution to our understanding of the clinical and radiologic spectrum of this disorder. The surprising results suggest that the 6-octapeptide repeat insertion (6-*OPRI*) mutation does not demonstrate the typical imaging findings of some genetic variants of Creutzfeldt-Jakob disease (CJD), such as the *E200K* variant, which Prohovnik and colleagues established as clinically and radiographically equivalent to sporadic CJD in a study using high-b-value diffusion-weighted imaging and which other authors illustrated with the *V210I* mutation.^{2,3} Because it is not yet known whether this finding applies to other mutations, the study of De Vita et al may help in further understanding the diversity of familial CJD populations.

The group of individuals studied was found to have an inherited prion disease related to a 6-*OPRI* mutation in a cohort of families in the United Kingdom. Although the sample size was small, no other group has access to such a substantial number of cases with this particular mutation. The present study aimed to explore underinvestigated aspects of cerebral degeneration in this condition, namely systematic voxel-based morphometry, magnetization transfer, and more standard diffusivity methods.

When one reviews this article, it seems that more questions are raised surrounding the nature of this particular cohort of familial CJD. These findings and, more important, the lack of findings characteristic of sporadic CJD in other inherited prion diseases suggest that the 6-*OPRI* is distinctive, with divergent clinical and imaging findings. Could this constitute a great enough difference to be classified independent of other familial forms of CJD? Do these divergent imaging findings explain the prominent early cognitive and neurodevelopmental-pattern deficits in this specific mutation, which make it different from other familial prion diseases? CJD and other associated prion diseases related to the abnormal conformation of a normal protein found in the brain, though uncommon, feature prominently in the differential diagnosis in patients with presenile dementia. Sporadic, familial, iatrogenic, and variant (or new variant) forms of CJD exist. An extensive body of neuroimaging research during the past 2 decades

rapidly established the importance of MR imaging, particularly diffusion-weighted imaging, in solidifying the diagnosis of CJD.⁴ Multiple forms of familial CJD exist, with associated genetic mutations, and constitute a substantial minority of cases. The presence of autosomal dominant inherited mutations in cohorts of families with CJD offers the unique opportunity to model progression of imaging changes before symptoms.

Previous imaging evidence of this particular mutation demonstrated cortical thinning within predominantly the posterior frontal and parietal lobes.⁵ This present study extended the findings of this previous work in using voxel-based analysis of advanced MR imaging in several patients with 6-*OPRI* mutations. The authors discovered volume reductions, decreases in magnetization transfer ratio, and diffusivity increases within subcortical gray matter structures as well as some cortical structures including the perisylvian cortex and precuneus.

There are some clinical differences between patients with 6-*OPRI* and those with other prion-related mutations such as *P102-L* that may explain the divergent imaging profile. Patients with this particular mutation have lower premorbid cognitive functioning, which may predate the neurodegenerative changes. It is perhaps for this reason that cortical thinning and now the notable volume reduction and increased diffusivity in the cortical and subcortical gray matter structures feature prominently in this particular mutation, despite the absence of more typical morphologic imaging findings. This study notably differs from the imaging findings seen in other reported forms of familial CJD, including the *E200K* mutation and *V210I*, both of which are thought to resemble sporadic CJD with prototypical restricted diffusion in the basal ganglia and thalamus.³ Although there are substantial similarities among sporadic CJD, variant CJD, and several genetic variants on MR imaging,³ it is surprising that the 6-*OPRI* mutation appears to be very different from all other variants.

The authors of this work as well as others in the field of prion disease imaging benefitted greatly from the work of our late colleague, Isak Prohovnik, who, before his passing, assisted greatly in critiquing and amending the work of De Vita et al.¹ Dr Prohovnik's own research, particularly in establishing an extensive prospective imaging cohort of patients with the *E200K* mutation,

advanced the field of CJD imaging tremendously. In building on the pioneering work of our esteemed colleague, Isak Prohovnik, and applying his multidisciplinary approach combining clinical and imaging resources to the study of 6-OPRI, the authors of this study further advance our understanding of the diversity of prion diseases.

REFERENCES

1. De Vita E, Ridgway G, Scahill R, et al. **Multi-parameter MRI in the 6-OPRI variant of inherited prion disease.** *AJNR Am J Neuroradiol* 2013;34:1723–30
2. Lee H, Hoffman C, Kingsley PB, et al. **Enhanced detection of diffusion reductions in Creutzfeldt-Jakob disease at a higher B factor.** *AJNR Am J Neuroradiol* 2010;31:49–54
3. Breithaupt M, Romero C, Kallenberg K, et al. **Magnetic resonance imaging in E200K and V210I mutations of the prion protein gene.** *Alzheimer Dis Assoc Disord* 2013;27:87–90
4. Zerr I, Kallenberg K, Summers DM, et al. **Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease.** *Brain* 2009;132:2659–68
5. Alner K, Hyare H, Mead S, et al. **Distinct neuropsychological profiles correspond to distribution of cortical thinning in inherited prion disease caused by insertional mutation.** *J Neurol Neurosurg Psychiatry* 2012;83:109–14

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Sensorimotor Cortex Gamma-Aminobutyric Acid Concentration Correlates with Impaired Performance in Patients with MS

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ABSTRACT

BACKGROUND AND PURPOSE: Abnormalities in GABA concentration [GABA] have been associated with several neuropsychiatric disorders, and research has suggested that GABA may play a role in sensorimotor cortex function. We sought to determine whether identifying a change in [GABA] within the sensorimotor cortex of patients with MS has any effect on motor function and would provide information about the adaptive/compensatory mechanisms involved in the attempt to maintain motor function during disease progression.

MATERIALS AND METHODS: In 19 healthy controls and 30 patients with MS, we assessed task performance with the MS Functional Composite scale and its components (T25FW test, 9HPT, and PASAT). With in vivo MR spectroscopy, we measured [GABA] in the sensorimotor cortex and determined correlations between [GABA] and task performance. We also assessed the association between [GABA] and cortical activation volume after a bilateral finger-tapping task.

RESULTS: [GABA] was inversely correlated with 9HPT scores in patients with MS, indicating a worsening of performance with increased [GABA]. No significant correlation was observed between [GABA] and T25FW or PASAT scores. [GABA] was directly correlated with primary motor cortex activation volume after the finger-tapping task in patients with MS.

CONCLUSIONS: These results suggest that cortical [GABA] may be a marker of function and reorganization/adaptation of cortical gray matter in MS.

ABBREVIATIONS: 9HPT = Nine-Hole Peg Test; GABA = γ -aminobutyric acid; GM = gray matter; PASAT = Paced Auditory Serial Addition Test; PRESS = point-resolved spectroscopy sequence; T25FW = Timed 25-Foot Walk Test

Spectroscopic measurement of GABA has garnered attention in recent years because of the role of GABA as a major inhibitory transmitter in the human brain. Abnormalities in GABA concentration [GABA] have been associated with several neuropsychiatric disorders,¹ and recent reports have suggested that GABA may

play a role in sensorimotor cortex function in both healthy and disease states.²⁻⁹ In particular, GABA may be involved in brain plasticity, cortical adaptation, and reorganization in neurodegenerative disease processes. Reduction in GABA inhibition has been reported to facilitate long-term potentiation-like activity in the motor cortex.^{3,4} GABAergic inhibition has been identified as one of the mechanisms operating in use-dependent plasticity in the intact human motor cortex, which suggests similarities between the mechanisms underlying this form of plasticity and long-term potentiation.² The GABA agonist lorazepam is associated with suppression of profound reorganization in the somatosensory cortex, as demonstrated with motor-learning paradigms.⁸ [GABA] reduction in the sensorimotor cortex of healthy controls during motor learning has been reported⁵; and decreases in [GABA] in the sensorimotor cortex have been observed in patients with focal dystonia.⁶ Reduction of [GABA] in the sensorimotor cortex induced by acute deafferentation has also been reported.⁷ A recent study reported a positive correlation between the decrease in primary motor cortex (M1) [GABA] and the degree of motor learning as well as the motor learning-induced fMRI signal change within the M1.⁹

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MS frequently produces significant motor impairment in affected patients. Damage to both GM and WM components of the motor system has been reported in patients with MS.^{10,11} Functional imaging studies have suggested that adaptive and/or compensatory mechanisms are involved in the attempt to maintain motor function during disease progression.^{10,12–14} These studies generally have demonstrated an increase in the extent of functional cortical activation in patients with MS versus controls during performance of specific tasks; this increased brain activation has been interpreted as cortical reorganization and/or adaptation. Given the role of GABA in other disease processes, we hypothesized that identifying a change in [GABA] within the sensorimotor cortex of patients with MS would provide us with additional information about the ongoing disease process and these compensatory mechanisms.

In this study, we measured the sensorimotor cortex [GABA] in healthy controls and in patients with MS with MR spectroscopy. These [GABA] values were correlated with the MS Functional Composite¹⁵ scores and with scores of the individual components of the scale involving ambulatory, arm function, and cognitive tasks. Additionally, to investigate the potential role of GABA in cortical reorganization, we assessed the association between [GABA] and cortical activation volume following a bilateral finger-tapping task.

MATERIALS AND METHODS

Nineteen healthy controls and 30 patients with relapsing-remitting MS participated in this study. The patients had their last doses of steroids at least 8 weeks before the MR imaging and were clinically stable, with no changes in the Expanded Disability Status Scale for at least 8 weeks before imaging. From these participants, datasets for 8 controls and 13 patients were discarded because of unacceptable subject motion.^{16,17} GABA signal was either too low or inconclusive in the datasets for 1 control and 4 patients (the spectra were either too noisy to fit with the Advanced Method for Accurate, Robust, and Efficient Spectral fitting,¹⁸ or had other comparable peaks present in the edited spectra, possibly due to poor editing). Data from the remaining 10 healthy controls (8 women, 2 men; mean age = 38.4 ± 13.6 years; mean MS Functional Composite = 0.408 ± 0.445) and 13 patients with MS (10 women, 3 men; mean age = 47.2 ± 8.3 years; disease duration = 9.5 ± 7.0 years; mean Expanded Disability Status Scale score = 3.15 ± 2.30 ; mean MS Functional Composite = 0.212 ± 0.559) were included in this study. Sixteen of a total 96 time points were discarded in 1 acceptable dataset because of motion, while no other dataset had to be discarded among the acceptable studies. The local institutional review board approved the study procedures, and all patients and controls provided informed consent.

Behavioral Study

The behavioral study consisted of MS Functional Composite testing with 3 components: 1) the T25FW test, a measure of ambulation in which the time required for the subject to walk 25 feet back and forth is recorded; 2) the 9HPT, a measure of arm function and fine-motor coordination, in which the time taken by the subject to pick up and place 9 dowels in 9 holes is recorded¹⁹; and 3) the PASAT, a measure of cognition in which the subject is presented

with a series of 60 numbers spaced 2 seconds apart and asked to add the 2 most recent numbers and the number of correct responses is recorded.²⁰ The z score for each component and the total MS Functional Composite score for each subject were calculated with the methods outlined by the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force.^{15,21,22}

MR Imaging Study

MR images were obtained on a 3T Trio scanner (Siemens, Erlangen, Germany). A circularly polarized head coil was used. All patients and healthy volunteers were scanned with a sequence based on the MEGA-PRESS sequence that was designed by Mescher et al.²³

To identify motion-corrupted data for all controls and the first 25 patients with MS, we used water signal–based interleaved navigator pulses,¹⁷ a methodology that has been identified as an effective way to discard only the portion of data from a scan that is motion-corrupted and to therefore reduce possible misinterpretation of the edited spectra. For the last 5 patients with MS, we used an alternative method of motion detection. This method identified motion by collecting data in weak water-suppression mode to detect residual water-signal fluctuation.¹⁶ This change in the motion-identification method was implemented to improve the signal and ease of acquisition and has similar efficacy in detecting motion compared with the first method. Because the main MEGA-PRESS module used in the 2 methods is the same, a change in motion-detection method does not influence the measured GABA concentration. This was verified by scanning phantoms containing GABA of a known concentration. Three percent or more change in water signal is indicative of unacceptable motion in both methods.^{16,17}

The complete protocol consisted of the following scans, as discussed in our previous work²⁴:

- 1) A localizer scan.
- 2) Gradient-echo field mapping.
- 3) A whole-brain T1-weighted magnetization-prepared rapid acquisition of gradient echo scan with the following parameters: 144 axial sections; thickness = 1 mm; FOV = 25.6×25.6 cm; TR = 1900 ms; TE = 1.89 ms; flip angle = 8° ; 256×128 matrix; readout bandwidth = 125 kHz; and scan time = 8 minutes 5 seconds.
- 4) An fMRI scan: The gradient-echo echo-planar fMRI scan parameters were as follows: TR = 2000 ms; TE = 30 ms; flip angle = 90° ; number of transverse sections = 32; and section thickness = 4 mm without any intersection gap. Subjects performed self-paced bilateral finger tapping (index finger simultaneously in opposition to the thumb on each hand) in blocks of interleaved 32-second ON and 32-second OFF patterns. The voxel at the motor cortex was selected by using the real-time fMRI Student *t* statistic activation map-generation program Neuro 3D (Siemens). A single voxel ($2 \times 2 \times 2$ cm³) centered at the area of maximum activation in the precentral gyrus of the right hemisphere was selected for the spectroscopy scans from pixels with $t \geq 4.0$ ($P < .001$).

- 5) A MEGA-PRESS–based GABA editing scan with a water signal–based interleaved navigator scan¹⁷ by using the following parameters: voxel = $2 \times 2 \times 2$ cm³; TR = 2700 ms; TE = 68 ms;

number of excitations = 96; flip angle = 90°; unsuppressed water-excitation flip angle = 20°; edit pulse frequency = 1.90 ppm (the other 180° pulse was placed at 1.50 ppm to minimize macromolecule contamination²⁵); edit pulse width ~ 44 Hz (duration = 20 ms); and scanning time = 8 minutes 39 seconds. The navigator-based sequence was replaced with MEGA-PRESS in weak water-suppression mode for the last 5 patients.¹⁶

6) A metabolite nulling scan with an 180° inversion pulse added to the sequence used in scan 5 with a TI of 650 ms.²⁴ Even though pulsing at 1.90 and 1.50 ppm minimizes macromolecule contamination, this scan was added to ensure minimization of any residual macromolecule contamination resulting from shot-to-shot B0 variation.²⁶

7) A PRESS scan with TR = 2700 ms and number of excitations = 48.

8) A PRESS scan with TR = 2700 ms, number of excitations = 1, and no water suppression.

9) Repeat of the localizer scan.

A bite-bar was used during all scans to reduce head motion.

The MR spectroscopy data were analyzed with the jMRUI software package (<http://www.mrui.uab.es/mrui>)²⁷; we described the steps of this data analysis in detail in a previous study.²⁴ In brief, the data analysis consisted of the following: 1) discarding the first 4 measurements from each scan to ensure steady-state magnetization and identifying and discarding motion-corrupted data on the basis of fluctuation of the unsuppressed navigator water/residual water signal; 2) performing zero-order phase correction; 3) performing frequency-shift correction of the individual subspectra by using residual water as a reference; 4) summing the phase- and frequency-corrected subspectra; 5) performing residual water suppression with a Hankel-Lanczos singular-value decomposition filter²⁸; 6) performing apodization with a 5-Hz Gaussian filter; and 7) performing zero-filling. Finally, the OFF-resonance spectrum was subtracted from the ON-resonance spectrum to obtain the final edited spectrum.

Next, as we previously described,²⁴ the GM, WM, and CSF contributions to the voxel composition were determined with the fMRI of the Brain Automated Segmentation Tool (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FAST>) algorithm²⁹ of the fMRI of the Brain Software Library (<http://www.fmrib.ox.ac.uk/analysis/techrep/tr04ss2/tr04ss2/node19.html>)³⁰; the anatomic 3D magnetization-prepared rapid acquisition of gradient echo scan was used as the base image, and a mask was applied at the voxel location. The fraction volumes of gray matter, white matter, and CSF (f_{GM_vol} , f_{WM_vol} , and f_{vol_CSF}) were used to perform absolute quantification of the GABA level.

The absolute GABA level was obtained following a 2-step process as described in our previous study²⁴:

1) The [GABA]/[Cr] ratio was obtained in the first step from scans 5 and 6 by using the equation:

$$\frac{[GABA]}{[Cr]} = \frac{(G^* - M)}{I_{Cr} \times EE},$$

where G^* is the area under the 3.01-ppm peak in the edited spectrum, M is the area under the 2.99-ppm residual macromolecule peak in the metabolite-nulled spectrum after correcting for the relaxation effects, I_{Cr} is the area under the 3.93-ppm peak (meth-

ylene Cr) in the OFF-resonance spectrum, and EE is the editing factor. All areas were measured by using the Advanced Method for Accurate, Robust, and Efficient Spectral fitting algorithm.¹⁷ The editing factor EE was calculated following the method used by Terpstra et al²⁶ by comparing the unmodulated GABA relative to the glycine signal from a PRESS scan (TR = 2700 ms, TE = ms) with that from a MEGA-PRESS scan of the same voxel of a phantom containing GABA and glycine. Terpstra et al²⁶ had assumed an identical T2 of Cr methyl and C⁴H GABA resonances, and T2 of Cr methyl and methylene resonances were reported at the occipital lobe by Mlynárik et al³¹ at 3T. Assuming the T2 of Cr resonances in occipital and motor areas to be similar, we calculated the difference in T2 relaxation effect between Cr methyl and methylene at TE = 68 ms to be negligible, and the T2 of the Cr methylene and of the C⁴H GABA resonances was assumed to be identical in this study. In addition, the potential difference in the T1 relaxation effect at TR = 2700 ms was assumed to be negligible in this study, in line with the assumption of comparable T1 of all metabolites²³ and our observation of similar T1 of GABA and Cr from phantom scans. In this study, we used the methylene resonance of Cr instead of the methyl resonance because the latter can introduce a systematic error in [GABA]/[Cr] measurement.³²

2) Next, the creatine concentration, [Cr], was determined from scans 7 and 8 by using the following equation as in Gasparovic et al³³:

$$[Cr] = I_{Cr} \times \frac{(f_{GM} \times R_{H2O_GM} + f_{WM} \times R_{H2O_WM} + f_{CSF} \times R_{H2O_CSF})}{S_{H2O_obs} (1 - f_{CSF}) \times R_{Cr}} \times \frac{2}{\#H_{Cr}} \times H_2O,$$

where I_{Cr} is the area under the 3.93-ppm peak in scan 7, and f_{GM} , f_{WM} , and f_{CSF} are the fractions of GM, WM, and CSF water respectively. R_{H2O_GM} , R_{H2O_WM} , and R_{H2O_CSF} are the relaxation attenuation factors for water in GM, WM, and CSF respectively; S_{H2O_obs} is the area under the unsuppressed water peak in scan 8; R_{Cr} is the relaxation attenuation factor for Cr methylene resonance; $\#H_{Cr}$ ($n = 2$) is the number of protons in Cr methylene; and $[H_2O]$ (55 mol/L) is the concentration of pure water. f_{GM} , f_{WM} , and f_{CSF} were calculated by using f_{GM_vol} , f_{WM_vol} , and f_{vol_CSF} as in Bhattacharyya et al²⁴ and Gasparovic et al.³³

Finally, the GABA concentration was determined by taking the product of the [GABA]/[Cr] ratio and [Cr].

Because the water content in an MS lesion is $6.3 \pm 0.3\%$ higher than that in normal-appearing WM³⁴ and the water content in normal-appearing WM is approximately 2.2% higher than that in normal WM,³⁴ we made the necessary corrections for calculating [GABA] in patients with MS. It should be pointed out that the WM lesion content within spectroscopy voxels as determined from the T1-weighted image was only approximately 0.2%.

To account for the effect of voxel composition in patients with MS, we estimated [GABA] in GM and WM. It has recently been shown, with linear regression analysis, that [GABA] values within GM and WM in the sensorimotor region are 2.87 ± 0.61 and 0.33 ± 0.11 mmol/L, respectively, in healthy controls, which results in a GM/WM [GABA] ratio of 8.70 ± 3.44 .²⁴ Because

[GABA] in the cortical GM may vary among patients depending on the severity of disease, we determined that it was not feasible to perform linear regression analysis on patient data. To estimate the GM/WM [GABA] in patients, we therefore assumed that the ratio of GM and WM [GABA] was similar in patients with MS and controls. In the absence of any a priori knowledge, we performed the analysis several times by using different GM and WM [GABA] ratios, ranging from 5 to 11.

We analyzed the fMRI data to look for a correlation between activation volume and [GABA]. The first 4 volumes from the fMRI time-series were discarded. The remaining data were spatially filtered by using a 64-point radially symmetric 2D Hamming filter in the Fourier domain and were then retrospectively motion-corrected by using Analysis of Functional NeuroImages software (AFNI; <http://dbic.dartmouth.edu/wiki/index.php/AFNI>).³⁵ Data were analyzed for activation by least-squares fitting the time-series for each pixel to a boxcar reference function plus a slope.³⁶ Student *t* maps and a magnetization-prepared rapid acquisition of gradient echo scan for each subject were transformed into the standard stereotaxic space defined by Talairach and Tournoux³⁷ by using AFNI.³⁵ ROI analysis was performed by using the Human Motor Area Template (<http://lrlab.org/>), a set of ROI masks defining the M1, primary sensory cortex, dorsal premotor cortex, ventral premotor cortex, and supplemental motor area in Talairach space.³⁸ The number of activated voxels (Student *t* > 3.5, 1-sided, uncorrected $P < 3 \times 10^{-4}$) within the Human Motor Area Template ROI mask corresponding to M1 was determined. The right hemisphere of the brain was chosen for this analysis because the spectroscopy voxel was selected from within the right hemisphere for each subject.

RESULTS

Figure 1 shows spectra from 5 subjects (all patients) obtained by using a MEGA-PRESS sequence. Table 1 shows the [GABA]/[Cr] ratio, [Cr], and [GABA] in a $20 \times 20 \times 20$ mm³ voxel in the sensorimotor region of the healthy controls and patients with MS. [GABA]/[Cr] and [GABA] were not significantly different between controls and patients ($P = .10$ and 0.15 , respectively).

The calculated correlation coefficients between MS Functional Composite scores (and the components of the MS Functional Composite) and [GABA] are shown in Table 2. We observed a very strong inverse correlation between [GABA] and the 9HPT in patients with MS (Fig 2). Because the spectroscopy voxels were always selected from the right hemisphere, we repeated the same analysis by using 9HPT data for the contralateral (left) hand only. We also repeated the analysis by using only the cortical GM [GABA], for which we used the range of GM [GABA], as mentioned earlier. In all cases, significant inverse correlation between 9HPT scores and [GABA] was observed. Most interesting, the control subjects' data did not show any such correlation ($P = .78$). The [GABA]/[Cr] ratio did not significantly correlate with the MS Functional Composite or its components for either controls or patients. Combined plots of [GABA] versus 9HPT are shown in On-line Fig 1.

The total number of M1 voxels was 497 ± 50 and 498 ± 64 in controls and patients, respectively. The number of activated voxels in the controls (124 ± 92) was not significantly different from

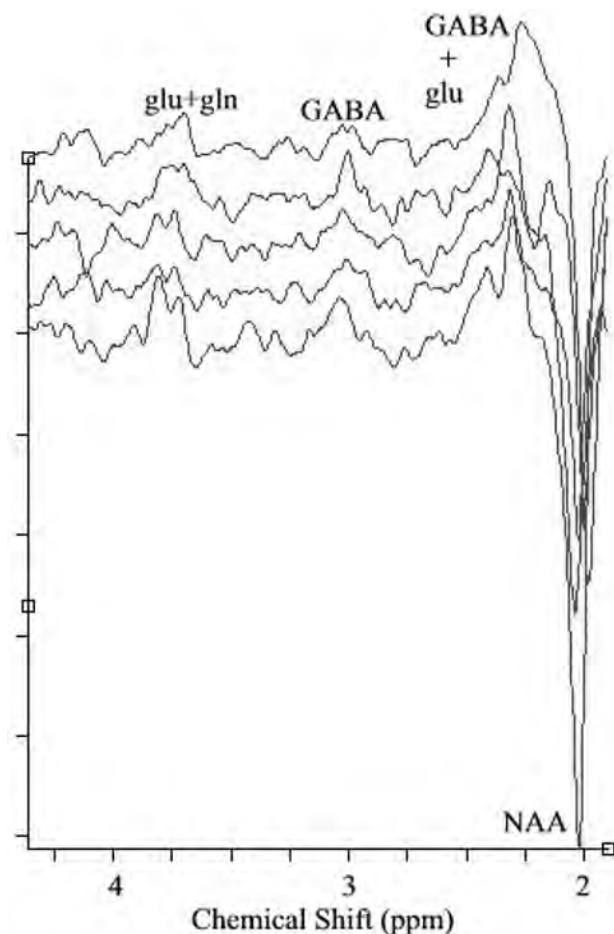


FIG 1. GABA-edited spectra from 5 subjects (all patients) obtained by using MEGA-PRESS sequence. NAA and coedited glutamate (glu) and glutamine (gln) can be seen in the spectra in addition to GABA.

Table 1: GABA and Cr concentrations in healthy controls and patients with MS^a

	Voxel Composition			[GABA]/[Cr]	[Cr] (mM)	[GABA] (mM)
	% GM	% WM	% CSF			
Controls (n = 10)	37 ± 7	52 ± 12	11 ± 8	0.15 ± 0.05	9.22 ± 0.85	1.43 ± 0.48
Patients (n = 13)	34 ± 7	49 ± 10	16 ± 5	0.19 ± 0.06	9.43 ± 1.43	1.71 ± 0.42

^a Values are means.

that in patients with MS (176 ± 63). The trend of our data suggests a significant correlation between the number of activated voxels (ie, activation volume) and [GABA] in the patients with MS ($P = .05$; Fig 3). No significant correlation was seen between activation volume and [GABA] in the healthy controls ($P = .81$). The [GABA]/[Cr] ratio did not have any significant correlation with primary cortex activation volume in either controls ($P = .90$) or patients ($P = .16$). Combined plots of [GABA] versus activation volume are shown in On-line Fig 2.

DISCUSSION

In this study, we found that [GABA] was inversely correlated with 9HPT scores in patients with MS, indicating a worsening of performance with increases in [GABA]. The [GABA] value was also directly correlated with primary motor cortex-activation volume after a bilateral finger-tapping task in patients with MS.

Table 2: Correlation coefficients of MSFC and components with GABA concentration and the ratio of GABA and Cr concentration

	GABA MSFC	GABA/Cr MSFC	GABA 9HPT	GABA/Cr 9HPT	GABA T25FW	GABA/Cr T25FW	GABA PASAT	GABA/Cr PASAT
Controls (n = 10)	-0.2233, <i>P</i> = .54	-0.1728, <i>P</i> = .63	0.1035, <i>P</i> = .78	0.1824, <i>P</i> = .61	-0.1680, <i>P</i> = .64	-0.0133, <i>P</i> = .97	-0.3341, <i>P</i> = .35	-0.3124, <i>P</i> = .38
Patients (n = 13)	-0.3324, <i>P</i> = .27	-0.2052, <i>P</i> = .50	-0.6750, ^a <i>P</i> = .01	-0.4807, <i>P</i> = .1	-0.3865, <i>P</i> = .19	-0.4155, <i>P</i> = .16	0.0504, <i>P</i> = .87	0.1161, <i>P</i> = .71

Note:—MSFC indicates Multiple Sclerosis Functional Composite.

^a Statistically significant.

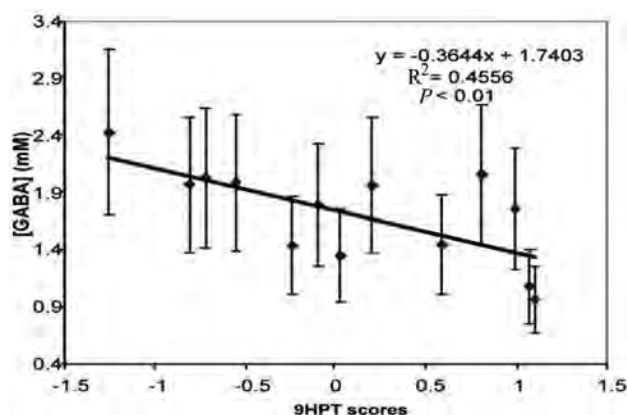


FIG 2. Inverse correlation of sensorimotor γ -aminobutyric acid concentration and Nine-Hole Peg Test scores in patients with multiple sclerosis. A fixed error bar of 30% is used for [GABA] in the plot.

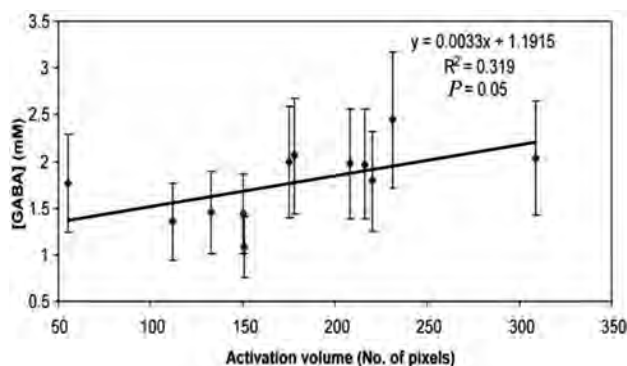


FIG 3. Correlation of sensorimotor γ -aminobutyric acid concentration and fMRI activation volume in patients with multiple sclerosis. A fixed error bar of 30% is used for [GABA] in the plot.

Recent histopathologic observations have suggested that GABA receptor levels may be reduced in the motor cortex of patients with MS,^{39,40} whereas our results suggest that [GABA] is increased within the motor cortex in patients who demonstrate poorer motor performance. The reasons for these different findings are unclear. It is possible that these varying results may reflect differences in the patient populations evaluated; the pathologic studies included predominantly patients with late end-stage chronic MS, whereas we included patients with relapsing-remitting MS.

The 9HPT is a clinical measure that probes dominant and nondominant hand and finger coordination and dexterity. Thus, this test more specifically addresses motor function in a manner similar to finger tapping, which was used for GABA spectroscopy voxel selection. In our study, no significant correlation was found between [GABA] and the T25FW or PASAT components of the MS Functional Composite in patients with MS. These results, in

conjunction with the inverse correlation between [GABA] and the 9HPT in study patients, suggest that [GABA] measurements within a given cortical region relate directly to the expected function of the underlying parenchyma rather than reflecting a generalized effect of global disease progression.

While several investigators have studied the relationship between GABA and motor plasticity in healthy controls,^{2,5,9,41} the work has focused on tasks involving motor learning. In this study, we adopted a task that does not involve motor learning. Our observation of lack of any correlation between sensorimotor [GABA] and M1 activation volume in healthy controls is in line with a previous observation of no sensorimotor [GABA] modulation during unlearnable nonrepetitive tasks.⁵ Cortical reorganization or adaptation has been found to take place in patients with MS as a compensatory mechanism for functioning.^{10,12-14} This reorganization/adaptation is manifested by increased activation, as measured by fMRI, involving a broader range of cortical regions in these patients versus controls. Reddy et al¹⁰ reported increased activation in the ipsilateral sensorimotor cortex with simple hand movements in patients with MS. In another study, a distinct pattern of cortical activation from disability and brain injury in MS was observed.¹³ The degree of adaptive cortical functional change has also been shown to be correlated with the extent of brain injury in patients with nondisabling MS.¹⁴ The underlying mechanism responsible for this cortical reorganization or adaptation is still unknown, and a cortical marker of adaptation has not previously been explored in great detail. Our observation of increased cortical [GABA] with increased motor activation suggests that GABA plays a role in this cortical adaptation process.

Although the inclusion criteria for datasets in our study reduced the final sample size, the increased reliability of GABA measurements was considerable; additionally, the inverse correlation between [GABA] and 9HPT scores and the correlation between [GABA] and the number of activated pixels were statistically significant.

Potential differences in self-paced finger tapping between individuals is a limitation of this study. Because motor learning has been reported to the sensorimotor cortex GABA levels,⁵ we chose self-paced finger tapping as the task for this study instead of having the subjects follow a specific pattern. Our experience with this in past studies^{42,43} is that similar paradigms have sufficiently light attention demands so that patients with MS can easily perform them with little training and the variability in performance is minimal.

Also some of the medications prescribed to the patients may have some effect on GABA levels. In addition, modulation of the occipital cortex GABA level during the menstrual period has been reported in literature⁴⁴ and may have some effect in our sensorimotor GABA measurement. However, function-specific correla-

tions suggest that the effect we are observing primarily arises from the MS disease process.

In addition, heterogeneity in subject population could potentially dilute some of the changes in the components in the MS Functional Composite. This is another potential limitation of the study. We have reported an interesting observation that suggests the role of the cortical GABA level in MS. At this stage, we are not in a position to comment on the mechanism of this observation at the cellular level or the implication of this in GABAergic drug medications. Another limitation of this study is the small subject population. The study was not powered to find changes in T25FW or PASAT. Further studies are needed to explore this, and we are pursuing that as well. However, our observation with the current sample size strongly suggests that sensorimotor [GABA] in MS is inversely related to the 9HPT and not correlated with the T25FW or PASAT.

A note on multiple comparisons is in order. Although multiple hypotheses were tested in the work reported here, we think that a Bonferroni correction is not warranted, due to the fact that we had a priori expectations for each of the tests. Our principal hypothesis was that a strong significant inverse correlation was observed between [GABA] and the 9HPT in patients. Because [GABA] was measured at the sensorimotor cortex and the 9HPT directly addresses a function that involves the sensorimotor cortex, we had a priori expectations that these would correlate. Similarly, because [GABA] was measured at the sensorimotor cortex and like the 9HPT, finger tapping directly addresses a function that involves the sensorimotor cortex, we had an a priori expectation that the volume of activation in the primary motor cortex would be correlated with [GABA]. On application of a strict multiple-comparison correction, the volume correlation loses significance. However, given the a priori nature of the comparison and the exploratory nature of the study, we think that such a correction is not warranted.

CONCLUSIONS

We found that [GABA] in the region of the sensorimotor cortex associated with hand activity in patients with MS was inversely correlated with performance on the 9HPT, a task that involves hand coordination. Additionally, [GABA] had no significant correlation with tasks not involving hand activity and the associated brain regions, suggesting that these results are functionally and anatomically specific. We also observed that [GABA] was directly correlated with activation volume in the primary motor cortex after self-paced bilateral finger tapping. No such correlations were observed between [GABA] and 9HPT performance or primary motor cortex activation in healthy controls. These results suggest that cortical [GABA] may play a role in and be a potential marker of function and reorganization/adaptation of cortical GM in patients with MS.

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REFERENCES

- Chang L, Cloak CC, Ernst T. **Magnetic resonance spectroscopy studies of GABA in neuropsychiatric disorders.** *J Clin Psychiatry* 2003; 64(suppl 3):7–14
- Bütefisch CM, Davis BC, Wise SP, et al. **Mechanisms of use-dependent plasticity in the human motor cortex.** *Proc Natl Acad Sci U S A* 2000;97:3661–65
- Castro-Alamancos MA, Connors BW. **Short-term synaptic enhancement and long-term potentiation in neocortex.** *Proc Natl Acad Sci U S A* 1996;93:1335–39
- Castro-Alamancos MA, Donoghue JP, Connors BW. **Different forms of synaptic plasticity in somatosensory and motor areas of the neocortex.** *J Neurosci* 1995;15:5324–33
- Floyer-Lea A, Wylezinska M, Kincses T, et al. **Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning.** *J Neurophysiol* 2006;95:1639–44
- Levy LM, Hallett M. **Impaired brain GABA in focal dystonia.** *Ann Neurol* 2002;51:93–101
- Levy LM, Ziemann U, Chen R, et al. **Rapid modulation of GABA in sensorimotor cortex induced by acute deafferentation.** *Ann Neurol* 2002;52:755–61
- Pleger B, Schwenkreis P, Dinse HR, et al. **Pharmacological suppression of plastic changes in human primary somatosensory cortex after motor learning.** *Exp Brain Res* 2003;148:525–32
- Stagg CJ, Bachtiar V, Johansen-Berg H. **The role of GABA in human motor learning.** *Curr Biol* 2011;21:480–84
- Reddy H, Narayanan S, Arnoutelis R, et al. **Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis.** *Brain* 2000;123(pt 11):2314–20
- Sailer M, Fischl B, Salat D, et al. **Focal thinning of the cerebral cortex in multiple sclerosis.** *Brain* 2003;126(pt 8):1734–44
- Rocca MA, Mezzapesa DM, Falini A, et al. **Evidence for axonal pathology and adaptive cortical reorganization in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis.** *Neuroimage* 2003;18:847–55
- Reddy H, Narayanan S, Woolrich M, et al. **Functional brain reorganization for hand movement in patients with multiple sclerosis: defining distinct effects of injury and disability.** *Brain* 2002;125(pt 12):2646–57
- Rocca MA, Falini A, Colombo B, et al. **Adaptive functional changes in the cerebral cortex of patients with nondisabling multiple sclerosis correlate with the extent of brain structural damage.** *Ann Neurol* 2002;51:330–39
- Cutter GR, Baier ML, Rudick RA, et al. **Development of a multiple sclerosis functional composite as a clinical trial outcome measure.** *Brain* 1999;122(pt 5):871–82
- Bhattacharyya PK, Beall EB, Lowe MJ. **Residual water for motion identification in J-difference editing.** In: *Proceedings of the International Society for Magnetic Resonance Workshop on Current Concepts of Motion Correction for MRI and MRS*, Kitzbühel, Tyrol, Austria. February 24–28, 2010
- Bhattacharyya PK, Lowe MJ, Phillips MD. **Spectral quality control in motion-corrupted single-voxel J-difference editing scans: an interleaved navigator approach.** *Magn Reson Med* 2007;58:808–12
- Vanhamme L, van den Boogaart A, Van Huffel S. **Improved method for accurate and efficient quantification of MRS data with use of prior knowledge.** *J Magn Reson* 1997;129:35–43
- Mathiowetz V, Volland G, Kashman N, et al. **Adult norms for the Box and Block Test of manual dexterity.** *Am J Occup Ther* 1985;39:386–91

20. Gronwall DM. **Paced Auditory Serial-Addition Task: a measure of recovery from concussion.** *Percept Mot Skills* 1977;44:367–73
21. Rudick R, Antel J, Confavreux C, et al. **Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force.** *Ann Neurol* 1997;42:379–82
22. Fischer JS, Rudick RA, Cutter GR, et al. **The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment—National MS Society Clinical Outcomes Assessment Task Force.** *Mult Scler* 1999;5:244–50
23. Mescher M, Merkle H, Kirsch J, et al. **Simultaneous in vivo spectral editing and water suppression.** *NMR Biomed* 1998;11:266–72
24. Bhattacharyya PK, Phillips MD, Stone LA, et al. **In vivo magnetic resonance spectroscopy measurement of gray-matter and white-matter gamma-aminobutyric acid concentration in sensorimotor cortex using a motion-controlled MEGA point-resolved spectroscopy sequence.** *Magn Reson Imaging* 2011;29:374–79
25. Henry PG, Dautry C, Hantraye P, et al. **Brain GABA editing without macromolecule contamination.** *Magn Reson Med* 2001;45:517–20
26. Terpstra M, Ugurbil K, Gruetter R. **Direct in vivo measurement of human cerebral GABA concentration using MEGA-editing at 7 Tesla.** *Magn Reson Med* 2002;47:1009–12
27. Naressi A, Couturier C, Devos JM, et al. **Java-based graphical user interface for the MRUI quantitation package.** *Magma* 2001;12:141–52
28. Pijnappel WW, van den Boogaart A, de Beer R, et al. **SVD-based quantification of magnetic resonance signals.** *J Magn Reson* 1992;97:122–34
29. Zhang Y, Brady M, Smith S. **Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm.** *IEEE Trans Med Imaging* 2001;20:45–57
30. Smith SM, Jenkinson M, Woolrich MW, et al. **Advances in functional and structural MR image analysis and implementation as FSL.** *Neuroimage* 2004;23(suppl 1):S208–19
31. Mlynárik V, Gruber S, Moser E. **Proton T (1) and T (2) relaxation times of human brain metabolites at 3 Tesla.** *NMR Biomed* 2001;14:325–31
32. Bhattacharyya PK. **Systematic error in the measurement of [GABA]/[Cr] ratio using methyl resonance of creatine.** In: *Proceedings of the International Society for Magnetic Resonance in Medicine Workshop on MR Spectroscopy and Neurotransmitter Function in Neuropsychiatric Disorders*, Quebec City, Quebec, Canada. November 7–10, 2008
33. Gasparovic C, Song T, Devier D, et al. **Use of tissue water as a concentration reference for proton spectroscopic imaging.** *Magn Reson Med* 2006;55:1219–26
34. Laule C, Vavasour IM, Moore GR, et al. **Water content and myelin water fraction in multiple sclerosis: a T2 relaxation study.** *J Neurol* 2004;251:284–93
35. Cox RW, Hyde JS. **Software tools for analysis and visualization of fMRI data.** *NMR Biomed* 1997;10:171–78
36. Lowe MJ, Russell DP. **Treatment of baseline drifts in fMRI time series analysis.** *J Comput Assist Tomogr* 1999;23:463–73
37. Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain.* New York: Thieme Medical; 1988
38. Mayka MA, Corcos DM, Leurgans SE, et al. **Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis.** *Neuroimage* 2006;31:1453–74
39. McDonough J, Dutta R, Gudiz T, et al. **Decreases in GABA and mitochondrial genes are implicated in MS cortical pathology through microarray analysis of postmortem MS cortex.** *Soc Neurosci Abstr* 2003;213:212
40. Dutta R, McDonough J, Yin X, et al. **Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients.** *Ann Neurol* 2006;59:478–89
41. Ziemann U, Muellbacher W, Hallett M, et al. **Modulation of practice-dependent plasticity in human motor cortex.** *Brain* 2001;124:1171–81
42. Horenstein C, Lowe MJ, Koenig KA, et al. **Comparison of unilateral and bilateral complex finger tapping-related activation in premotor and primary motor cortex.** *Hum Brain Mapp* 2009;30:1397–412
43. Lowe MJ, Beall EB, Sakaie KE, et al. **Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity.** *Hum Brain Mapp* 2008;29:818–27
44. Epperson CN, Haga K, Mason GF, et al. **Cortical gamma-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder: a proton magnetic resonance spectroscopy study.** *Arch Gen Psychiatry* 2002;59:851–58

Measuring Pulsatile Flow in Cerebral Arteries Using 4D Phase-Contrast MR Imaging

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ABSTRACT

BACKGROUND AND PURPOSE: 4D PCMRI can be used to quantify pulsatile hemodynamics in multiple cerebral arteries. The aim of this study was to compare 4D PCMRI and 2D PCMRI for assessments of pulsatile hemodynamics in major cerebral arteries.

MATERIALS AND METHODS: We scanned the internal carotid artery, the anterior cerebral artery, the basilar artery, and the middle cerebral artery in 10 subjects with a single 4D and multiple 2D PCMRI acquisitions by use of a 3T system and a 32-channel head coil. We assessed the agreement regarding net flow and the volume of arterial pulsatility (ΔV) for all vessels.

RESULTS: 2D and 4D PCMRI produced highly correlated results, with $r = 0.86$ and $r = 0.95$ for ΔV and net flow, respectively ($n = 69$ vessels). These values increased to $r = 0.93$ and $r = 0.97$, respectively, during investigation of a subset of measurements with $<5\%$ variation in heart rate between the 4D and 2D acquisition ($n = 31$ vessels). Significant differences were found for ICA and MCA net flow ($P = .004$ and $P < .001$, respectively) and MCA ΔV ($P = .006$). However, these differences were attenuated and no longer significant when the subset with stable heart rate ($n = 31$ vessels) was analyzed.

CONCLUSIONS: 4D PCMRI provides a powerful methodology to measure pulsatility of the larger cerebral arteries from a single acquisition. A large part of differences between measurements was attributed to physiologic variations. The results were consistent with 2D PCMRI.

ABBREVIATIONS: PCMRI = phase-contrast MR imaging; ACA = anterior cerebral artery; ΔV = volume of arterial pulsatility; PC-VIPR = phase contrast with vastly undersampled isotropic projection reconstruction; ΔHR = change in heart rate

Excessive arterial pulsatility has been linked to poorer cognitive performance and brain atrophy among the elderly.¹ Therefore, evaluation of this association is important for understanding pathophysiological processes related to cerebral aging and dementia. The pulsatility index, the resistive index, or a volume corresponding to vessel distention can be used to describe arterial pulsatility.

Whereas the indexes describe a mixture of vascular impedance, resistance, and compliance,^{2,3} the volume of arterial pulsatility represents the magnitude of accumulated downstream cyclic vessel distention, assuming a stationary downstream capillary flow,^{4,5} that is, the cyclic increase in arterial volume from the measurement level to the capillaries. Therefore, this measure is sensitive to the balance of factors such as downstream and upstream arterial compliance and cardiac stroke volume and thus provides a mechanically relevant alternative for analyzing vascular pulsatility.⁶

Traditionally, intracranial vascular pulsatility is estimated by use of Doppler sonography techniques¹ or 2D PCMRI scans.⁴ These methods are associated with laborious workflows and rely on a trained neurovascular imager to make skillful interpretations and vessel localizations during the acquisition. 4D PCMRI allows a desirable separation of image acquisition and image interpretation because flow is collected over a large volume and subsequently analyzed off-line.⁷

Heavily accelerated 4D PCMRI makes it possible to assess arterial flow in the entire intracranial space while maintaining an acceptable scan time.^{8,9} This approach significantly eases the

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workflow, possibly reduces total scan time, and ensures the proper capture of all vessels in the prescribed imaging volume. Such 4D PCMRI techniques for intracranial measurements have been validated in vivo,^{10,11} but evaluations regarding pulsatile hemodynamics are lacking.

In the present study, we apply a radially undersampled 4D approach, PC-VIPR,¹² to assess the volume of arterial pulsatility in major cerebral vessels. The main objective was to evaluate the agreement with conventional 2D PCMRI acquisitions.

MATERIALS AND METHODS

Subjects

Ten healthy volunteers (7 male) were recruited (age [mean $\pm$ SD], 37 ± 9 years; range, 29–53 years). The local ethical review board approved the study, and written informed consent was obtained from all participants.

MR Imaging

All scans were performed by use of a clinical 3T scanner (Discovery MR 750; GE Healthcare, Milwaukee, Wisconsin) with a 32-channel head coil. The imaging protocol started with a 3D time-of-flight acquisition, reconstructed in axial, sagittal, and coronal directions to provide vessel localization for the successive 2D PCMRI sequences. Second, 4D PCMRI data were acquired by use of a balanced 5-point¹³ PC-VIPR sequence, prescribed to cover the entire intracranial space. We used 16,000 radial projections; acquisition resolution, $300 \times 300 \times 300$; imaging volume, $22 \times 22 \times 22$ cm; reconstruction resolution, $320 \times 320 \times 320$ mm (zero padded interpolation); velocity encoding, 110 cm s^{-1} ; TR/TE, 6.5/2.7 ms; flip angle, 8° . Dynamic images were reconstructed by retrospective gating from the recorded peripheral pulse signal by use of temporal interpolation similar to view sharing in Cartesian acquisitions.¹⁴ Besides 3D velocity information for the 20 reconstructed time positions, a time-average complex difference image was reconstructed to provide anatomic detail of the vascular system. During the 9-minute 4D PCMRI acquisition, 5 2D PCMRI scans were planned by means of the time-of-flight images. The first measured left and right ICA and basilar artery at the level of the carotid C3–C4 segment¹⁵ (velocity encoding 80 cm s^{-1}). The second and third 2D PCMRI sequences measured the M1 segment of left and right MCA respectively (velocity encoding, 110 cm s^{-1}). The fourth and fifth 2D PCMRI sequences measured the A1 segment of left and right ACA, respectively (velocity encoding, 90 cm s^{-1}). Other 2D PCMRI parameters were TR/TE, 7.6–8.5/4.1–5.0 ms; 3-mm section thickness; 15° flip angle; in-plane resolution, 0.5×0.5 mm; 6 views per segment; and 2 averages. Thirty-two phases were reconstructed. Retrospective gating with peripheral sensor was used for all acquisitions.

Because the ICA has no branches close to the measurement location, this vessel segment provided the opportunity to investigate the internal consistency of the 4D PCMRI measurements. This consistency check was implemented by performing an additional segmentation, upstream and strictly separated (ie, no overlap) from the first segmentation, at carotid level C2–C3, in all ICAs. The separation distance between the 2 sections was approximately 1.5–2 cm, in the direction along the ICA.

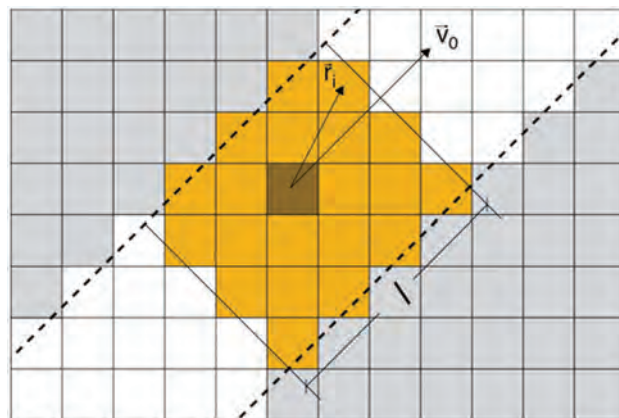


FIG 1. 2D representation of the segmentation procedure. Dashed lines represent the vessel lumen; yellow pixels are the segmentation result. White pixels represent pixel intensity of $\geq 18\%$. Dark pixel is the user-defined reference pixel whose velocity direction was used to label a segment of length l . Segmentation was not updated between cardiac frames. Typical segmentations of the ICA, basilar artery, MCA, and ACA contained 230, 110, 80, and 60 pixels, respectively.

Segmentation

A novel in-house–developed software was used for all 4D PCMRI segmentations. To segment a desired vessel in the 4D PCMRI, a reference pixel was selected by the user in a maximum intensity projection of the time-average complex difference image. A region-growing algorithm included neighboring connected pixels fulfilling 2 conditions: 1) a pixel value of $\geq 18\%$ of the maximum time-averaged complex difference value (observed in the entire $320 \times 320 \times 320$ volume) and 2) the pixel was located within a desired section of the vessel.

The second condition was assessed by means of the relationship:

$$\frac{|\bar{r}_i \cdot \bar{v}_0|}{\|\bar{v}_0\|} \leq \frac{l}{2}$$

where $\bar{r}_i$ is a vector pointing from the reference pixel to the i :th pixel, $\bar{v}_0$ is the vessel direction estimated by the velocity direction in the reference pixel, and l is the desired segment length (Figs 1 and 2). The threshold of 18% was selected because a precalibration series indicated that this value provided complete vessel coverage without inclusion of neighboring static tissue. The segment length l was selected as 5 pixel widths because this distance was similar to the section thickness of the 2D PCMRI scans.

At this processing stage, the flow for each time frame was calculated by use of the spatial average velocity (calculated from the average velocity vector within the segment) of the section multiplied by the area of the vessel, estimated from dividing the segment volume by l . Area overestimations originating from misalignment between $\bar{v}_0$ and the velocity direction of the complete segment were eliminated by use of a correction factor (cosine of misalignment between reference pixel direction and average direction of final segmentation). Interpolated velocity images, perpendicular to the vessel direction, were produced to ensure that no branching occurred within the section of interest. To investigate the reproducibility of the 4D segmentation procedure, the entire dataset was analyzed on 2 occasions. The results from the second occasion were only used in the reproducibility analysis.

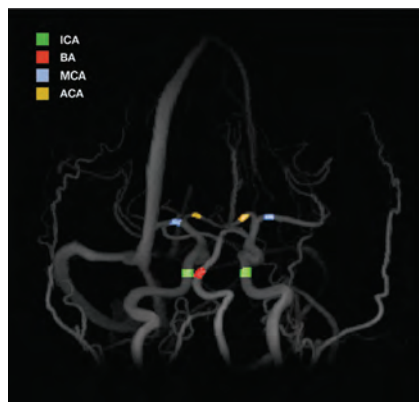


FIG 2. Maximum intensity projection image. Colored sections show segmentations produced for comparison with the 2D PCMRI data.

As a criterion standard reference, the 2D PCMRI data were analyzed by means of Segment v1.8 software (<http://segment.heiberg.se>). The cross-sectional area of the artery was delineated manually by use of the magnitude images, and the size and position of the segmented area were kept constant during the cardiac cycle. The segmented area was drawn generously large to ensure proper capture of the complete vessel. In total, 7 vessels in 10 subjects were assessed, yielding a total of 70 vessels. However, 1 subject lacked a right A1 ACA segment (the right ACA was supplied by the left ACA through the anterior communicating artery). Therefore, all comparisons were based on 69 vessel segments.

Net Flow and Pulsatility

Net flow rates and the volume of ΔV were calculated by use of the same procedure for both 4D and 2D PCMRI waveforms. Net flow was derived as the temporal mean flow rate. On the basis of the assumption that capillary flow is nonpulsatile, the volume variation of the downstream arterial vessel distention, required to dampen the pulsatile arterial flow, can be estimated. This was performed by subtracting the net flow from the flow waveform and then calculating the cumulative integral over the remaining waveform (Fig 3). The difference between the maximum and minimum of this volume variation was defined as ΔV^{4-6} and corresponds to the cyclic distention of downstream arteries required to convert the pulsatile arterial flow to a nonpulsatile capillary flow. Mathematically, this can be expressed as:

$$\Delta V = \int_{\text{systole}} (q(t) - \bar{q}) dt$$

where $q(t)$ is the flow rate and $\bar{q}$ is the net flow rate in the direction of the vessel. Here, systole is defined as the time of the cardiac cycle where the flow rate is higher than the net flow rate (ie, $q(t) > \bar{q}$).

Statistical Analyses

The agreement between 4D and 2D PCMRI was assessed by means of correlation and Bland-Altman plots. The paired-samples t test was used to test systematic differences between the methods. To investigate the influence of physiologic variations,

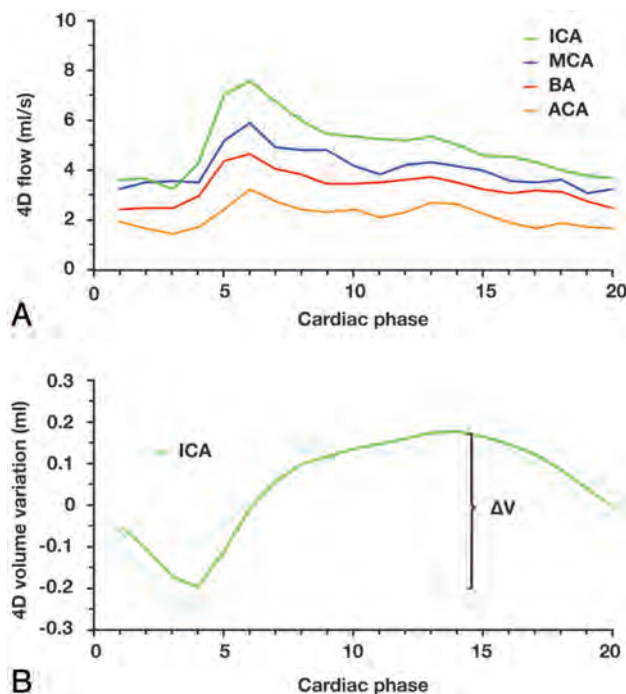


FIG 3. Arterial hemodynamics provided from a 4D PCMRI quantification. A, Flow curves for vessels evaluated in this study. The right ICA, MCA, and ACA are shown. Cardiac phase 1–20 represents the time positions in the cardiac cycle of the reconstructed frames. B, ICA ΔV calculation. Subtraction of net flow and calculation of the cumulative integral on the remaining waveform yield the cyclic volume variation of downstream arteries required to convert the pulsatile right ICA waveform to a nonpulsatile capillary flow. ICA ΔV was defined as the maximum minus minimum of this volume variation.

we also performed all analyses on a subset of measurements in which the difference in heart rate between the 4D and 2D acquisition (ΔHR) was $<5\%$ ($n = 31$). In the complete ensemble of measurements, the heart rate was 64 versus 63 bpm for the 4D and 2D PCMRI acquisitions, respectively, with a standard deviation of the difference of 7 bpm. In the subset of measurements with $\Delta HR < 5\%$, heart rate was 68 versus 68 bpm for the 4D and 2D PCMRI acquisitions, respectively, with a standard deviation of the difference of 2 bpm. The reproducibility of the 4D segmentation procedure was investigated by use of the coefficient of variation of the 2 repeated measurements.

RESULTS

Correlation plots for the net flow and ΔV analysis are provided in Fig 4. When analyzing all vessels simultaneously, the correlations were $r = 0.86$ and $r = 0.95$ for ΔV and net flow, respectively ($n = 69$ vessels). These values increased to $r = 0.93$ and $r = 0.97$, respectively, when investigating only the subset with $\Delta HR < 5\%$ ($n = 31$ vessels).

Corresponding Bland-Altman plots are shown in Fig 5. There were no significant statistical differences between 4D and 2D PCMRI-derived ΔV or net flow when considering the entire ensemble of vessels ($P = .11$ and $P = .98$, respectively). The relative 95% limits of agreement were larger for ΔV than for net flow. The repeated analyses on the subset of measurements with small differences in heart rate had greater influence on the limits of agreement for pulsatility than for net flow.

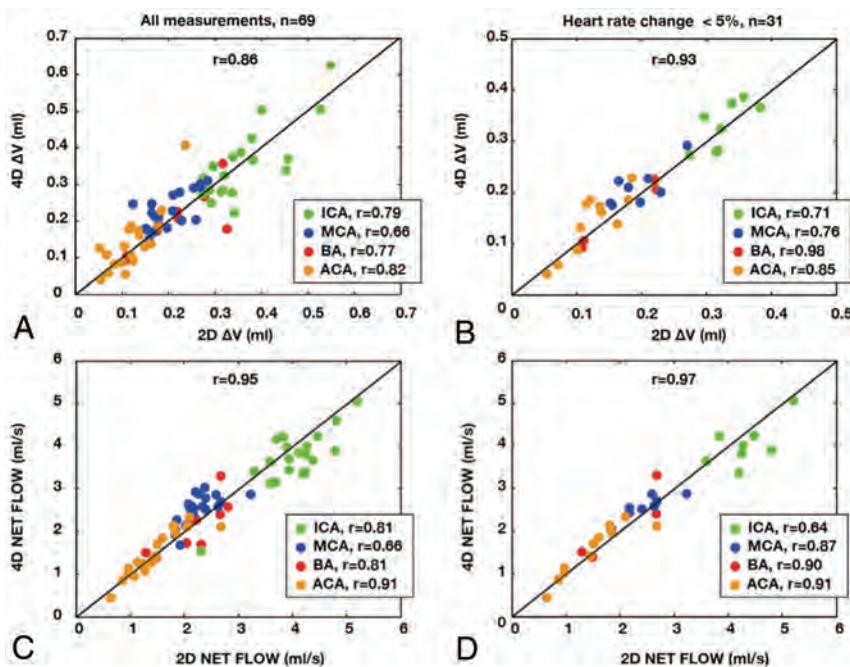


FIG 4. Correlation between 4D and 2D PCMRI quantifications of pulsatility and net flow. *A*, ΔV quantifications for all vessels. *B*, ΔV quantifications, excluding measurements with large differences in heart rate. *C*, Net flow quantifications for all vessels. *D*, Net flow quantifications, excluding measurements with large differences in heart rate.

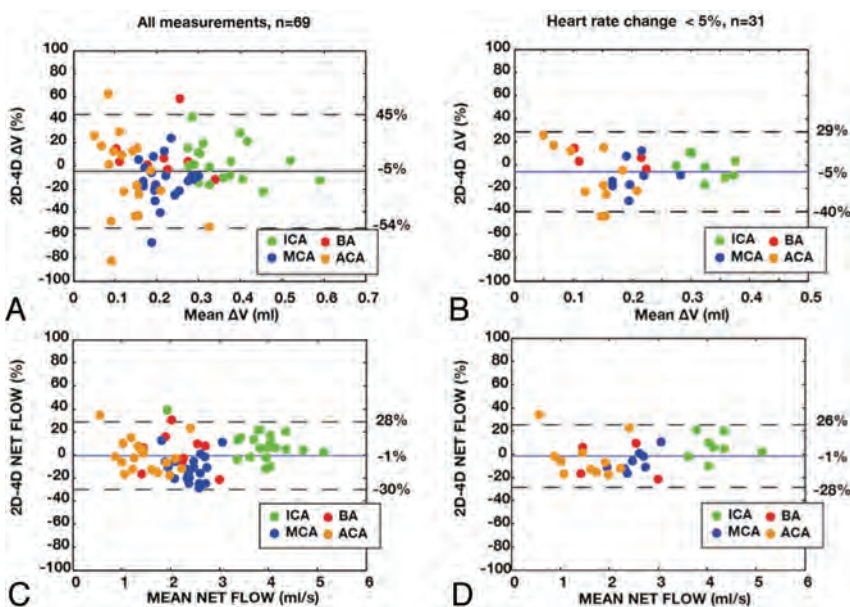


FIG 5. Agreement between 4D and 2D PCMRI quantifications of pulsatility and net flow. Solid lines represent average difference; dashed lines represent 95% limits of agreements. The relative difference was calculated as $(2D - 4D) / [(2D + 4D)/2]$. *A*, ΔV quantifications for all vessels. *B*, ΔV quantifications, excluding measurements with large differences in heart rate. *C*, Net flow quantifications for all vessels. *D*, Net flow quantifications, excluding measurements with large differences in heart rate.

Table 1 and Table 2 show mean values and differences for ΔV and net flow, respectively. Significant differences appeared for the ICA and MCA when all measurements were taken into account in the analysis. These differences were attenuated when considering the stratified subset with $\Delta HR < 5\%$.

The coefficient of variation of the 4D segmentation procedure

was 5% and 3% for ΔV and net flow measurements, respectively. The internal consistency analyses along the ICA showed average differences of 0.000 ± 0.034 mL (mean $\pm$ SD) and 0.090 ± 0.230 mL/s for ICA ΔV and net flow, respectively. These differences were not statistically significant ($P = .83$ and $P = .10$, respectively, $n = 20$). The correlation between the distal and proximal measurements were $r = 0.94$ and $r = 0.94$ for ICA ΔV and net flow, respectively. The typical time required for all 2D PCMRI sequences, including the time-of-flight sequence for vessel localization, was 24 minutes. This was almost 3 times longer than the time required for the 4D PCMRI acquisition.

DISCUSSION

This study evaluated the use of 4D PC-MRI for assessing pulsatile flow in large cerebral arteries. The combination of the PC-VIPR sequence and the proposed segmentation algorithm produced estimations of the volume of arterial pulsatility and net flow consistent with results obtained from 2D PCMRI. These results support the concept of the use of a single 4D PC-VIPR acquisition to effectively assess pulsatility in many intracranial arteries, despite the disadvantage of the use of a single velocity sensitivity setting for all vessels instead of individually optimized sensitivity, as in the 2D PC-MRI approach. The downside of the use of a single velocity sensitivity may be more significant in patients with stenotic arteries and a wider variation in flow velocities. For such investigations, a dual velocity encoding¹⁶ optimization may be warranted. Furthermore, future studies should evaluate 4D PC-VIPR performance in more distal branches, for example, smaller arteries, as such measurements would be of great value when characterizing the cerebral collateral circulation.

There were no obvious qualitative differences between the 4D and 2D PC-MRI images influencing the interpretation of the data. The 4D vessel segmentation algorithm was highly reproducible and did not require demanding calculations, for example, the waveforms appeared instantly as the user selected a reference pixel in the maximum intensity projection (Fig 2).

PC-VIPR net flow quantifications have previously been validated. Phantom measurements have demonstrated high accuracy

Table 1: 4D and 2D PCMRI-based estimation of arterial pulsatility

	Vessel Type	n	ΔV 4D	ΔV 2D	Difference	P Value
			Mean $\pm$ SD (mL)	Mean $\pm$ SD (mL)	Mean $\pm$ SD (mL)	
All	BA	10	0.20 $\pm$ 0.08	0.21 $\pm$ 0.08	0.01 $\pm$ 0.05	.504
	ICA	20	0.35 $\pm$ 0.10	0.36 $\pm$ 0.10	0.01 $\pm$ 0.06	.656
	ICA ^a	20	0.35 $\pm$ 0.10			
	MCA	20	0.23 $\pm$ 0.05	0.20 $\pm$ 0.05	−0.03 $\pm$ 0.04	.006
	ACA	19	0.14 $\pm$ 0.08	0.12 $\pm$ 0.08	−0.02 $\pm$ 0.05	.102
ΔHR <5%	BA	4	0.16 $\pm$ 0.07	0.17 $\pm$ 0.07	0.01 $\pm$ 0.01	.268
	ICA	8	0.33 $\pm$ 0.05	0.33 $\pm$ 0.05	−0.01 $\pm$ 0.03	.668
	MCA	8	0.21 $\pm$ 0.04	0.20 $\pm$ 0.04	−0.02 $\pm$ 0.03	.116
	ACA	11	0.14 $\pm$ 0.06	0.13 $\pm$ 0.06	−0.02 $\pm$ 0.03	.074

Note:—BA indicates basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; ΔHR , difference in heart rate; ΔV , volume of arterial pulsatility.

^aIndicates proximal ICA measurement for internal consistency analyses.

Table 2: 4D and 2D PCMRI-based estimations on arterial net flow

	Vessel Type	n	Net Flow 4D	Net Flow 2D	Difference	P Value
			Mean $\pm$ SD (mL/s)	Mean $\pm$ SD (mL/s)	Mean $\pm$ SD (mL/s)	
All	BA	10	2.15 $\pm$ 0.58	2.18 $\pm$ 0.49	0.03 $\pm$ 0.34	.787
	ICA	20	3.72 $\pm$ 0.70	4.02 $\pm$ 0.62	0.29 $\pm$ 0.40	.004
	ICA ^a	20	3.81 $\pm$ 0.71			
	MCA	20	2.54 $\pm$ 0.36	2.26 $\pm$ 0.34	−0.28 $\pm$ 0.29	<.001
	ACA	19	1.47 $\pm$ 0.52	1.44 $\pm$ 0.49	−0.02 $\pm$ 0.21	.627
ΔHR <5%	BA	4	2.16 $\pm$ 0.89	2.02 $\pm$ 0.74	−0.13 $\pm$ 0.39	.538
	ICA	8	4.04 $\pm$ 0.51	4.32 $\pm$ 0.51	0.28 $\pm$ 0.43	.108
	MCA	8	2.58 $\pm$ 0.27	2.46 $\pm$ 0.42	−0.12 $\pm$ 0.23	.173
	ACA	11	1.55 $\pm$ 0.61	1.49 $\pm$ 0.61	−0.06 $\pm$ 0.26	.427

Note:—BA indicates basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; ΔHR , difference in heart rate; ΔV , volume of arterial pulsatility.

^aIndicates proximal ICA measurement for internal consistency analyses.

of the PC-VIPR sequence,⁸ and results agree with net flow and average velocity measurements by 2D PCMRI^{8,11} and transcranial Doppler.¹¹ For peak systolic and diastolic velocities, previous investigations have displayed a 10% underestimation and a 9% overestimation, respectively, compared with 2D PCMRI.¹¹ Probably, this is an effect from different temporal resolutions. Given the agreement between 4D and 2D PCMRI found in the present study, we hypothesize that ΔV calculations are less influenced by differences in temporal resolution.

In the present study, arterial pulsatility measurements appeared more challenging (ie, wider limits of agreement) compared with net flow measurements. However, the limits of agreement for arterial pulsatility were narrowed by approximately one-third when calculated from measurements with a small difference in recorded heart rate. These data indicate that a large part of the variation between the 2 measurements was a result of physiologic variations, in agreement with previous data.⁵

The standard deviation of the difference between 2D and 4D PCMRI for ICA ΔV and net flow was 0.06 mL and 0.40 mL/s, respectively. A previous study conducted with the use of repeated 2D PCMRI acquisitions showed intrasubject standard deviations of 0.067–0.070 mL and 0.32–0.33 mL for ICA ΔV and net flow, respectively.⁵ This indicated that 2D and 4D PCMRI were associated with the same level of measurement variability, supporting that at least for the ICA, 4D PCMRI can replace 2D PCMRI without compromising measurement performance.

The 4D PCMRI ICA internal consistency analyses demonstrated an internal variance (squared standard deviation of the difference between the 2 measurements) explaining approximately one-third of the variance of differences found between 4D and 2D PCMRI acquisitions, both for ΔV and net flow. The remaining two-thirds of variance found between 2D and 4D PCMRI for the ICA measurements probably represented a mixture of 2D PCMRI internal variance and physiologic fluctuations caused by the separation in time between the 2 acquisitions.

There are several factors that potentially generate differences between 4D and 2D PCMRI measurements. First, the 4D PCMRI acquisitions were significantly longer than a single 2D scan. If the time of peak flow and flow amplitude are unstable between heartbeats, this could generate a more pronounced temporal smoothing in the 4D scan because the reconstructed cardiac cycle represents an average of all acquired heartbeats. Additionally, the resolution differs between the 2 methods. Potentially, this causes some degree of partial volume effects, normally displayed as a flow overestimation in vessels with a

small diameter/pixel size ratio.⁵ In the present study, significant differences between 4D and 2D PCMRI for ICA and MCA flows disappeared when eliminating measurements with large differences in heart rate, but a tendency of 4D PCMRI to underestimate ICA and overestimate MCA flows persisted. However, even if this represented actual offsets, the magnitudes were smaller than 10%, whereby for most applications this will not constitute a limiting factor.

It should be noted that the flow calculation method of the 4D data assumes that the vessel is straight and not curved within the measurement section. This mimics requirements associated with 2D PCMRI acquisitions. In this study, we ensured that flow was captured in straight vessel sections, without branches. Future studies focusing on flow in more complex-shaped arteries may benefit from more sophisticated procedures to characterize flow in the 4D data.

CONCLUSIONS

4D PCMRI provided a practical methodology to estimate pulsatility of large cerebral arteries. The results were consistent with 2D PCMRI estimations. The simple workflow requires minimal prospective planning, and the output allows comprehensive analysis of pulsatile intracranial hemodynamics. Therefore, 4D PCMRI is an important tool for future investigations regarding altered intracranial vascular pulsatility.

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REFERENCES

- Mitchell GF, van Buchem MA, Sigurdsson S, et al. **Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility-Reykjavik study.** *Brain* 2011;134:3398–407
- Michel E, Zernikow B. **Gosling's Doppler pulsatility index revisited.** *Ultrasound Med Biol* 1998;24:597–99
- Bude RO, Rubin JM. **Relationship between the resistive index and vascular compliance and resistance.** *Radiology* 1999;211:411–17
- Wåhlin A, Ambarki K, Birgander R, et al. **Assessment of craniospinal pressure-volume indices.** *AJNR Am J Neuroradiol* 2010;31:1645–50
- Wåhlin A, Ambarki K, Hauksson J, et al. **Phase contrast MRI quantification of pulsatile volumes of brain arteries, veins, and cerebrospinal fluids compartments: repeatability and physiological interactions.** *J Magn Reson Imaging* 2012;35:1055–62
- Bateman GA, Levi CR, Schofield P, et al. **The venous manifestations of pulse wave encephalopathy: Windkessel dysfunction in normal aging and senile dementia.** *Neuroradiology* 2008;50:491–97
- Hsiao A, Lustig M, Alley MT, et al. **Rapid pediatric cardiac assessment of flow and ventricular volume with compressed sensing parallel imaging volumetric cine phase-contrast MRI.** *Am J Roentgenol* 2012;198:W250–59
- Gu T, Korosec FR, Block WF, et al. **PC VIPR: a high-speed 3D phase-contrast method for flow quantification and high-resolution angiography.** *AJNR Am J Neuroradiol* 2005;26:743–49
- Hope MD, Purcell DD, Hope TA, et al. **Complete intracranial arterial and venous blood flow evaluation with 4D flow MR imaging.** *AJNR Am J Neuroradiol* 2008;30:362–66
- Wu Y, Chang W, Johnson KM, et al. **Fast whole-brain 4D contrast-enhanced MR angiography with velocity encoding using undersampled radial acquisition and highly constrained projection reconstruction: image-quality assessment in volunteer subjects.** *AJNR Am J Neuroradiol* 2011;32:E47–50
- Chang W, Landgraf B, Johnson KM, et al. **Velocity measurements in the middle cerebral arteries of healthy volunteers using 3D radial phase-contrast HYPReFlow: comparison with transcranial Doppler sonography and 2D phase-contrast MR imaging.** *AJNR Am J Neuroradiol* 2011;32:54–59
- Frydrychowicz A, Landgraf B, Wieben O, et al. **Scimitar syndrome: added value by isotropic flow-sensitive four-dimensional magnetic resonance imaging with PC-VIPR (phase-contrast vastly undersampled isotropic projection reconstruction).** *Circulation* 2010;121:e434–36
- Johnson KM, Markl M. **Improved SNR in phase contrast velocimetry with five-point balanced flow encoding.** *Magn Reson Med* 2010;63:349–55
- Liu J, Redmond MJ, Brodsky EK, et al. **Generation and visualization of four-dimensional MR angiography data using an undersampled 3-D projection trajectory.** *IEEE Trans Med Imaging* 2006;25:148–57
- Bouthillier A, van Loveren HR, Keller JT. **Segments of the internal carotid artery: a new classification.** *Neurosurgery* 1996;38:425–33
- Nett EJ, Johnson KM, Frydrychowicz, et al. **Four-dimensional phase contrast MRI with accelerated dual velocity encoding.** *J Magn Reson Imaging* 2012;35:1462–71

Hemodynamic Effects of Developmental Venous Anomalies with and without Cavernous Malformations

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ABSTRACT

BACKGROUND AND PURPOSE: Association between developmental venous anomalies is well known, but remains unexplained. Our aim was to study possible hemodynamic differences around developmental venous anomalies with and without cavernous malformations.

MATERIALS AND METHODS: In this prospective study approved by the institutional review board, PWI was performed in 24 patients with 25 DVAs (10 with and 15 without CMs) who consented to participate. We calculated relative cerebral blood volume, relative cerebral blood flow, and relative mean transit time for the brain surrounding the DVA tributaries in reference to contralateral mirror image locations. Corresponding control values (cCBV, cCBF, and cMTT) were generated in a similar fashion for remote ipsilateral regions with normal venous drainage, also in reference to contralateral mirror image locations. Perfusion parameters for DVAs and control regions were tested for differences between groups with the *t* test for independent or paired samples (or the nonparametric equivalents). Similar testing was done for perfusion parameters for DVAs with and without CMs.

RESULTS: Normal-appearing brain surrounding DVAs showed increased rCBV (median = 2.98; range = 1.39–6.61), increased rCBF (median = 2.00, range = 0.79–4.43), and increased rMTT (mean = 1.46; 95% confidence interval, 1.32–1.59). These were significantly higher than median cCBV (0.99; 95% confidence interval, 0.89–1.06; *P* < .01), median cCBF (1.00; 95% confidence interval, 0.94–1.27; *P* < .01), and mean cMTT (1.00; 95% confidence interval, 0.98–1.02; *P* < .01), respectively. Mean rMTT (1.70; 95% confidence interval, 1.46–1.93) for DVAs with CMs was higher than mean rMTT (1.29; 95% confidence interval, 1.19–1.40; *P* < .01) for DVAs without CMs.

CONCLUSIONS: DVAs are strongly associated with altered hemodynamics. Significant differences in these hemodynamic alterations for DVAs with and without CMs suggest their possible role in the formation of CMs.

ABBREVIATIONS: cCBF = relative CBF for control brain parenchyma with normal venous drainage; cCBV = relative CBV for control brain parenchyma with normal venous drainage; CM = cavernous malformation; cMTT = relative MTT for control brain parenchyma with normal venous drainage; DVA = developmental venous anomaly; *r* = relative (for CBV, CBF, MTT)

Developmental venous anomalies are considered developmental variations in the venous drainage pathway for a portion of the brain parenchyma.^{1–4} DVAs are generally discovered incidentally and are considered benign. While there have been some reports of DVAs presenting with hemorrhage or neurologic symptoms,^{4–7} it is unclear and controversial whether this associ-

ation reflects a causal relationship. There is a clear association between DVAs and cavernous malformations, and perhaps hemorrhage, with cavernous malformations found in up to 33%–48% of DVAs in some series.^{3,8}

The reasons behind the tendency of some DVAs to be associated with symptoms or to develop CMs are not fully understood. Various mechanisms have been proposed for clinical manifestations of DVAs, including mechanical compression of the adjacent brain parenchyma, diminished venous outflow across the brain parenchyma drained by the DVA, increased flow related to arterialization of the DVA, stenosis of the draining vein, or the tortuosity of the venous tributaries.^{2,9} While ≥ 1 of these factors may be at play in affecting risk of hemorrhage or CM formation in a given DVA, all these factors are likely to affect the hemodynamics of the blood flow in the brain parenchyma that the DVA is draining. In small case series of 3–4 cases, previous authors have shown that such altered hemodynamics may be manifest in the perfusion

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maps generated from the PWI.^{10,11} A more in-depth study into such perfusion abnormalities may help to better characterize focal hemodynamic alterations in the brain tissue drained by the DVAs and their potential association with hemorrhage/CM formation.

Our purpose was to study the perfusion alteration in the brain parenchyma drained by DVAs by using PWI and to investigate differences in the perfusion parameters around DVAs with and without CMs.

MATERIALS AND METHODS

This prospective study was approved by our institutional review board and conducted in compliance with the Health Insurance Portability and Accountability Act. All patients signed written consent documents to participate.

Patient Selection

The inclusion criteria were the presence of a brain DVA (with or without a CM) diagnosed on prior MR imaging, in the absence of other structural abnormalities of the brain. Potential candidates for the study were identified at our vascular-neurosurgery clinic and by searching the radiology report data base of our institution by using the terms “developmental venous anomaly,” “DVA,” “venous anomaly,” and “venous angioma.” The exclusion criteria were the following: 1) inability to clearly delineate the intraparenchymal course of the venous tributaries of the DVA; 2) midline location of the DVA that precluded a comparison with the contralateral normal brain tissue; 3) claustrophobia, contrast reaction, estimated glomerular filtration rate of <60 mL/min, or any other contraindication to contrast-enhanced MR imaging; and 4) age younger than 18 years.

All qualifying patients were contacted via telephone and invited to participate in the study. A patient who agreed to participate underwent contrast-enhanced MR imaging that included PWI. We were able to identify 66 eligible patients. Of these, 24 (11 men and 13 women) opted to participate and underwent MR imaging between July 2009 and May 2011. The patients ranged from 21 to 75 years of age. At the end of the study, we had 15 DVAs without and 10 with CMs. Eighty-eight percent of DVAs (22/25) were supratentorial, most involving the frontal lobe (6/25, 24%). For DVAs without CMs, the presenting symptoms included headaches in 7 DVAs, and seizures in 1. Seven DVAs without CMs were discovered incidentally. For DVAs with CM, 4 were incidentally discovered, while the presenting symptoms included headaches in 4, seizures in 1, and slurred speech in 1. With the exception of 1 DVA with a CM in a patient who presented with slurred speech related to acute hemorrhage, it was unclear whether any of the symptoms were directly related to DVAs.

Image Acquisition and Postprocessing

MR imaging was performed on a 1.5T scanner (Avanto; Siemens, Erlangen, Germany). The scan included axial T1WI, axial FLAIR imaging, axial SWI, PWI, and postcontrast axial and coronal T1WI. In addition, MR venograms were obtained by using a time-of-flight technique. PWI was performed by using a dynamic susceptibility-weighted imaging technique with intravenous injection of 0.1 mmol/kg of gadoversetamide (OptiMARK; Tyco-Healthcare/Mallinckrodt, St. Louis, Missouri) at a rate of 4 mL/s.

The perfusion data were postprocessed on a postprocessing workstation (Leonardo; Siemens) by one of the authors (A.S. with >10 years of experience in neuroradiology) to generate standard perfusion maps for relative CBV, relative CBF, and relative MTT. The right middle cerebral artery branches within the Sylvian fissure ipsilateral to the DVA were selected to define the arterial input function.

Calculation of Relative Perfusion Values for Brain Parenchyma around the DVAs

For each perfusion map, we selected 3 ROIs in the brain tissue around the DVA tributaries, using the conventional imaging sequences to exclude the venous tributaries or the CM (Fig 1). Each region of interest provided a numeric value (along with an SD, which was not used for analysis) representing the perfusion of the brain in that region (Fig 1C). A corresponding value was calculated by using an identically sized region of interest in a mirror image location in the contralateral brain (Fig 1D). The ratio of these 2 values provided a measure of brain perfusion around a DVA for the given region of interest, relative to the contralateral brain with normal venous drainage. The arithmetic mean of the ratios for the 3 ROIs was used to calculate rCBV, rCBF, and rMTT representing the relative perfusion of brain around the DVA.

Calculation of Relative Perfusion Values for Brain Parenchyma with Normal Venous Drainage

To assure validity of our methods, we also calculated control perfusion values for the brain with normal venous drainage (ipsilateral to the DVA), relative to the contralateral side (Fig 1D). For these, 1-cm² ROIs were drawn on the perfusion maps in the white matter of the frontal lobe, parietal lobe, occipital lobe, and cerebellar hemisphere, unless one of these regions could not be included due to the presence of a large DVA. The arithmetic mean of ratios thus generated was considered to represent control values of relative perfusion for brain parenchyma with normal venous drainage, designated as cCBV, cCBF, and cMTT.

Statistical Analysis

Perfusion parameters around DVAs (rCBV, rCBF, and rMTT) were compared with corresponding control values (cCBV, cCBF, and cMTT, respectively). In addition, rCBV, rCBF, and rMTT for DVAs without CMs were compared with the corresponding values for DVAs with CMs. Normal curves were fitted to data distributions, and the normality of the distributions was tested with the Shapiro-Wilk *W*-test. Ninety-five percent confidence intervals (95% CIs) were calculated for normally distributed data, and medians and ranges were calculated for non-normally distributed data. Equality of variances was tested with the O'Brien, Brown-Forsythe, Levene, and Bartlett tests. Differences between independent group means for normally distributed data with equal variances were tested with the Student *t* test. For non-normally distributed data with equal variances, the nonparametric Wilcoxon rank sum test was used. For data with normal distributions but nonequal variances, the *t* test (assuming unequal variances) was used. For comparisons of paired group means, if the differences were normally distributed, the paired *t* test was used; if the differences were non-normally distributed, the Wilcoxon rank

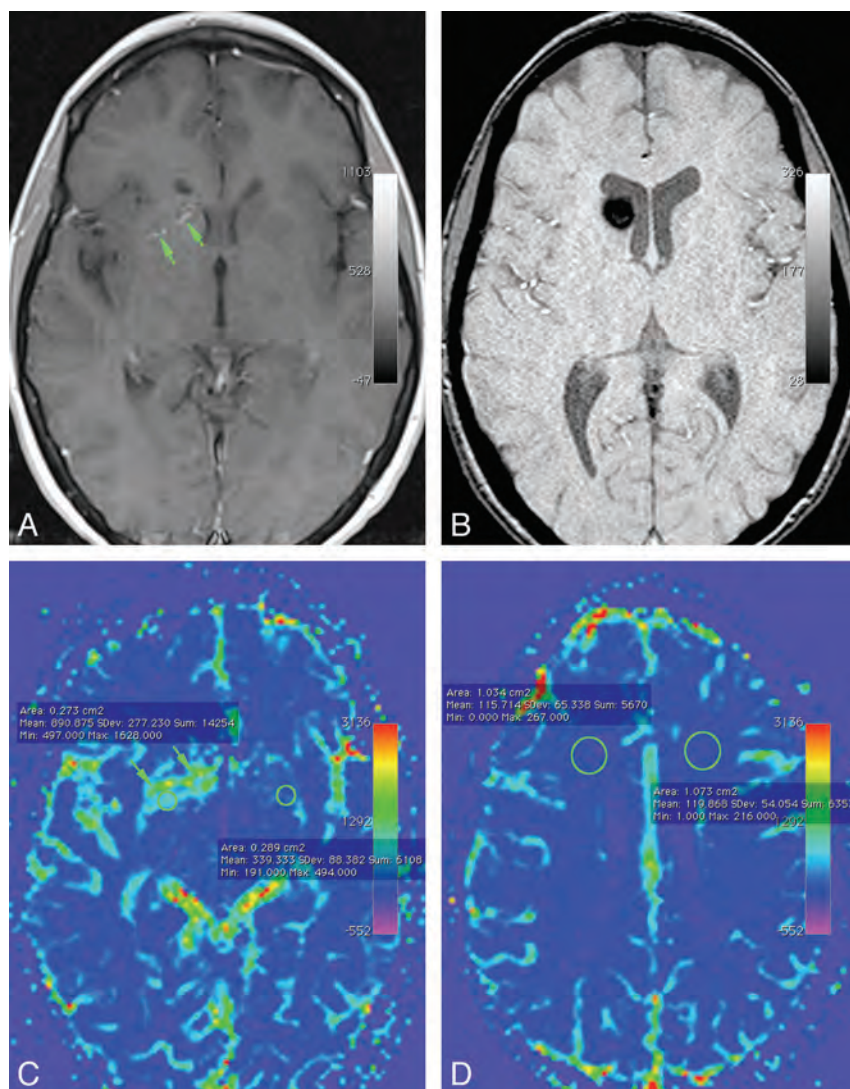


FIG 1. Axial contrast-enhanced T1-weighted (A) and susceptibility-weighted (B) images demonstrate a small developmental venous anomaly (arrows) in the right basal ganglia with a cavernous malformation in the right caudate head (B). Corresponding cerebral blood volume map shows a wide zone of higher cerebral blood volume (indicated by green on this color map) in the brain around the DVA. Note that the elevation of CBV is not restricted to the location of the individual venous channels of the DVA (arrows) but involves a wider confluent zone of brain around the draining vein. Note placement of regions of interest to get the objective parameters for quantification of perfusion around DVAs (C) and for brain with normal venous drainage (D).

Table 1: Descriptive statistics for relative perfusion parameters for brain parenchyma drained by DVAs and for control regions with normal venous drainage

Perfusion Parameter ^a	Mean	95% CI	Median	Minimum	Maximum	P Value ^b
rCBV	3.26	2.61–3.91	2.98	1.39	6.61	.04
rCBF	2.09	1.75–2.43	2.00	0.79	4.43	.19
rMTT	1.46	1.32–1.59	1.44	1.00	2.14	.15
cCBV	1.00	0.98–1.02	0.99	0.89	1.06	.15
cCBF	1.01	0.98–1.04	1.00	0.94	1.27	<.01
cMTT	1.00	0.98–1.02	1.00	0.91	1.15	.11

^a rCBV, rCBF, and rMTT represent relative cerebral blood volume, relative cerebral blood flow, and relative mean transit time respectively, for brain tissue around the DVA. cCBV, cCBF, and cMTT represent corresponding control values as measured in brain tissue with normal venous drainage (ipsilateral to the DVA).

^b P value for Shapiro-Wilk W-test for data distribution normality. A value < .05 indicates a non-normal distribution.

sum was used. For categorical data comparisons, the exact P value for the Fisher exact test was calculated through data permutation. α was set at .05, and 2-tailed tests were used. Statis-

tical analyses were performed with JMP Statistical Software, Release 9.0.0 (SAS Institute, Cary, North Carolina) and StatXact-9 statistical software for exact nonparametric inference (Cytel, Cambridge, Massachusetts).

RESULTS

Perfusion Parameters

For the perfusion parameters studied, Table 1 contains descriptive statistics and the results of testing data-distribution normality with the Shapiro-Wilk W-test. Normal-appearing brain surrounding the DVA showed increased rCBV (median = 2.98, range = 1.39–6.61), increased rCBF (median = 2.00, range = 0.79–4.43), and increased rMTT (mean = 1.46; 95% confidence interval, 1.32–1.59). The differences between rCBV and cCBV (median difference = 1.99, range = 0.34–5.56) were non-normally distributed (Shapiro-Wilk W-test, $P = .04$), with rCBV being higher than cCBV (Wilcoxon signed rank test, $P < .01$). The differences between rCBF and cCBF (mean difference = 1.08; 95% confidence interval, 0.75–1.41) were normally distributed (Shapiro-Wilk W-test, $P = .15$), with rCBF being higher than cCBF (paired t test and Wilcoxon signed rank test, $P < .01$). The differences between rMTT and cMTT (mean difference = 0.46; 95% confidence interval, 0.32–0.59) were normally distributed (Shapiro-Wilk W-test, $P = .10$), with rMTT being higher (paired t test and Wilcoxon signed rank test, $P < .01$).

Comparison of DVAs with and without CMs

For the perfusion parameters in DVAs with and without CMs, Fig 2 contains plots of the values for perfusion parameters and Table 2 contains descriptive statistics and the results of testing data-distribution normality with the Shapiro-Wilk W-test. Data distributions for CBV in DVAs with and without CMs were normally distributed (Shapiro-Wilk W-test, $P \geq .16$) and variances were equal (O'Brien, Brown-Forsythe, Levene, and Bartlett tests, $P \geq .36$). The mean for rCBV in DVAs with CMs was 3.17 (95% confidence interval, 2.01–4.34), and the mean for rCBV in DVAs without CM was 3.32 (95% confidence interval, 2.45–4.20), with no difference between these mean values (Student t test, $P = .82$). The means for cCBV for DVAs with

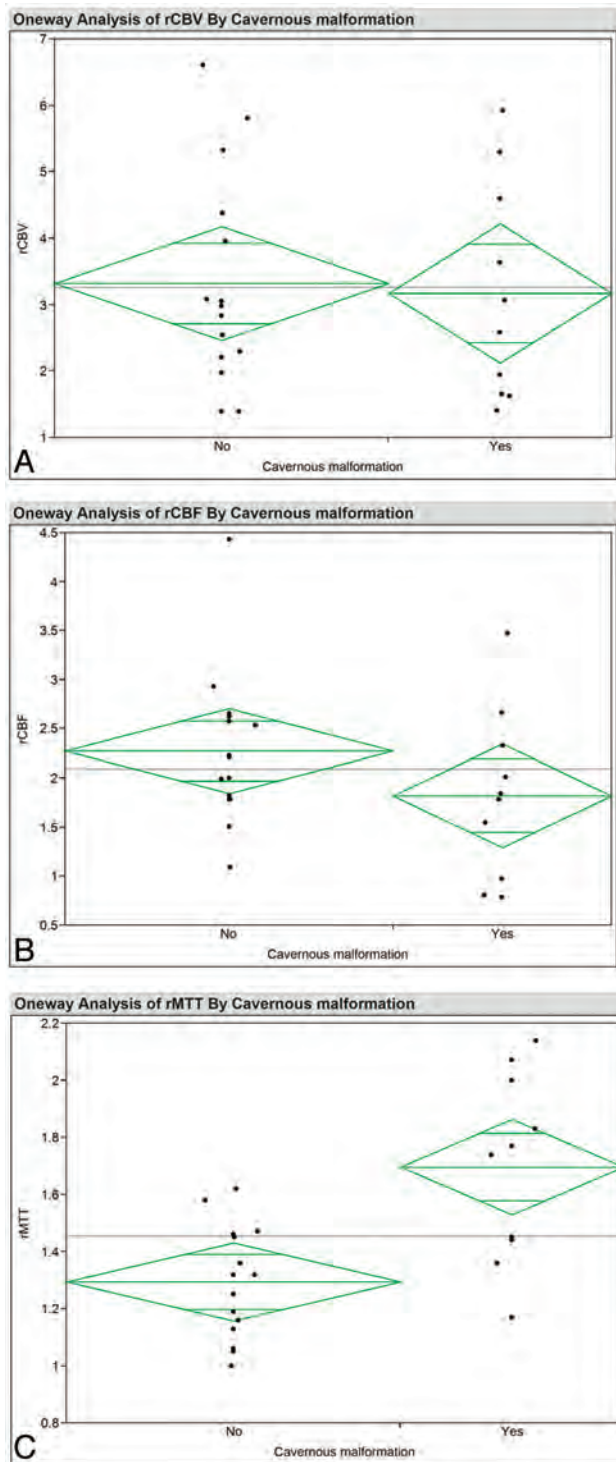


FIG 2. Ninety-five percent mean diamond plots for rCBV (A), rCBF (B), and rMTT (C) for patients with and without cavernous malformations. The horizontal line is the grand mean. The heights of the diamonds represent the 95% confidence intervals, and the widths of the diamonds are proportional to the sample sizes. If the overlap line of one diamond is closer to the mean of another diamond than is the overlap line of that diamond, there is no difference between the groups.

and without CMs were not significantly different (Student *t* test, $P = .08$).

Data distributions for CBF in DVAs with and without CMs were normally distributed (Shapiro-Wilk *W*-test, $P \geq .07$) except

for cCBF in DVAs without CMs (Shapiro-Wilk *W*-test, $P < .01$). Variances were equal (O'Brien, Brown-Forsythe, Levene, and Bartlett tests, $P \geq .15$). The mean for rCBF for DVAs with CMs was 1.82 (95% confidence interval, 1.21–2.43), and the mean for rCBF in DVAs without CMs was 2.28 (95% confidence interval, 1.85–2.70), with no difference between these mean values (Student *t* test, $P = .18$). The means for cCBF in DVAs with and without CMs were not significantly different (Wilcoxon signed rank test, $P = .23$).

Data distributions for MTT in DVAs with and without CMs were normal (Shapiro-Wilk *W*-test, $P \geq .35$), and variances were equal (O'Brien, Brown-Forsythe, Levene, and Bartlett tests, $P \geq .36$). The mean for rMTT in DVAs associated with a CM was 1.70 (95% confidence interval, 1.46–1.93), and the mean for rMTT in DVAs not associated with a CM was 1.29 (95% confidence interval, 1.19–1.40). Variances were not equal (O'Brien and Levene tests, $P \leq .04$). The mean for rMTT in DVAs with a CM was higher than the mean for rMTT in DVAs without an associated CM (*t* test assuming unequal variance, $P < .01$). The means for cMTT in DVAs with and without a CM were not significantly different (Student *t* test, $P = .75$).

The location of DVAs did not differ significantly between the CM and non-CM groups (Fisher exact test, $P = .46$).

DISCUSSION

In view of the presence of some degree of altered perfusion around all the DVAs studied, our results indicate that the presence of a DVA is likely to be inherently associated with altered hemodynamics in the involved brain parenchyma. While supporting previous findings,^{10,11} our results indicate that PWI is able to detect such perfusion alterations around most DVAs, not just anecdotal cases. The pattern of perfusion abnormalities in our study was also similar to that seen previously,^{10,11} with higher relative CBV as well as MTT in the brain around the DVAs. A variable change in relative CBF (Fig 3) is also in accordance with that in previous studies.^{10–12}

The pathogenesis of DVAs is not fully understood. Some investigators consider them to result from in utero thromboses of the developing venous system.^{2,3,13,14} The dilated medullary veins converging onto a prominent collector channel in effect serve as a replacement of the normal venous system that would have otherwise existed in this part of the brain.² Consistent elevation of rMTT and rCBV seen in our study supports this model of DVA pathogenesis of a venous outflow, inherently less robust than normal venous drainage. Similar prolongation of MTT on PWI has been seen in the setting of other conditions affecting venous outflow, such as dural venous thrombosis or patients with Sturge-Weber syndrome.^{15–17} This increase in the MTT for DVAs, however, appears to be due to alterations in the CBV and CBF that follow a pattern distinct from that seen in other restrictive venous pathologies. As per the central volume theorem, MTT is simply a ratio of CBV and CBF.¹⁸ Prolongation of MTT in the presence of venous outflow restriction is usually the result of venous engorgement-induced increase in CBV, along with outflow restriction-induced reduction in CBF, as has been shown in diseases such as Sturge-Weber syndrome.^{16,17}

In contrast, in most of the DVAs studied by us and in previous

Table 2: Descriptive statistics for perfusion parameters in DVAs without and with CMs

Perfusion Parameter ^a	CM	Mean	95% CI	Median	Minimum	Maximum	P Value ^b
rCBV	—	3.32	2.45–4.20	2.98	1.39	6.61	.16
	+	3.17	2.01–4.34	2.83	1.41	5.92	.24
rCBF	—	2.28	1.85–2.70	2.21	1.09	4.43	.07
	+	1.82	1.20–2.43	1.81	0.79	3.47	.60
rMTT	—	1.29	1.19–1.40	1.32	1.00	1.62	.67
	+	1.70	1.46–1.93	1.75	1.17	2.14	.62
cCBV	—	1.01	0.99–1.03	1.01	0.94	1.06	.22
	+	0.98	0.95–1.02	0.98	0.89	1.05	.85
cCBF	—	1.02	0.98–1.06	1.01	0.95	1.27	<.01
	+	0.99	0.96–1.03	0.98	0.94	1.08	.33
cMTT	—	1.00	0.97–1.03	1.00	0.91	1.15	.35
	+	0.99	0.97–1.02	0.99	0.94	1.05	.99

Note: —, +, present; —, absent.

^a rCBV, rCBF, and rMTT represent relative cerebral blood volume, relative cerebral blood flow, and relative mean transit time respectively, as measured in brain tissue around the DVA. cCBV, cCBF, and cMTT represent corresponding control values as measured in brain tissue with normal venous drainage (ipsilateral to the DVA).

^b P value for Shapiro-Wilk W-test for data distribution normality. A value < .05 indicates a non-normal distribution.

reports, the increase in rMTT was seen in the setting of increased rCBV and a less pronounced increase in the rCBF. While the increased rCBV is easy to explain, elevation of rCBF around many DVAs is more difficult to explain solely on the basis of alterations

developmental changes in the arterial inflow that try to minimize stasis of blood in the affected brain by increasing the CBF in the face of increased CBV. A control cerebral blood flow indicator of close to 1 in brain parenchyma with normal venous drainage

in the venous development. Modest reactive vasodilation in arterioles has been demonstrated in response to venous dilation in animal studies.¹⁹ However, it is unlikely that such a reactive change is able to more than overcome the restrictive effects of the outflow restriction in the presence of venous outflow obstruction. The exact explanation for increased rCBF around DVAs remains unclear. However, it is possible that the developmental nature of the venous anomalies (as opposed to the acquired nature of venous obstruction in experimental models/pathologic venous obstruction) is somehow unique in that the etiologic factors responsible for formation of DVAs are also able to induce

developmental changes in the arterial inflow that try to minimize stasis of blood in the affected brain by increasing the CBF in the face of increased CBV. A control cerebral blood flow indicator of close to 1 in brain parenchyma with normal venous drainage would argue against the possibility that these elevated relative CBF values are somehow representing artifacts.

Pathophysiologic implications of these results are also highlighted by the observed differences in the perfusion parameters of DVAs with and without CMs. A greater prolongation of MTT and a trend toward a lesser increase (or even decrease in individual cases) of rCBF in the CM group may be related to greater restrictive effects of DVAs in this group. Significant quantifiable differences in the perfusion parameters around developmental venous anomalies with and without associated cavernous malformations may reflect the role of hemodynamic factors in the development of these malformations. We hypothesize that in a large number of DVAs, the diminished venous capacity still has enough reserves to accommodate the physiologic needs, and such DVAs may remain completely asymptomatic. In other DVAs however, the restrictive effects on the venous drainage may be enough to cause local venous hypertension and thereby the propensity of these vessels to bleed and result in localized hemorrhage and subsequent CM formation. Given that the medullary veins composing the tributaries of the DVA are also known to have thinner walls, such veins may be more prone to bleed with this local venous hypertension.²⁰

DVAs generally fill later in the venous phase on catheter angiography. Our find-

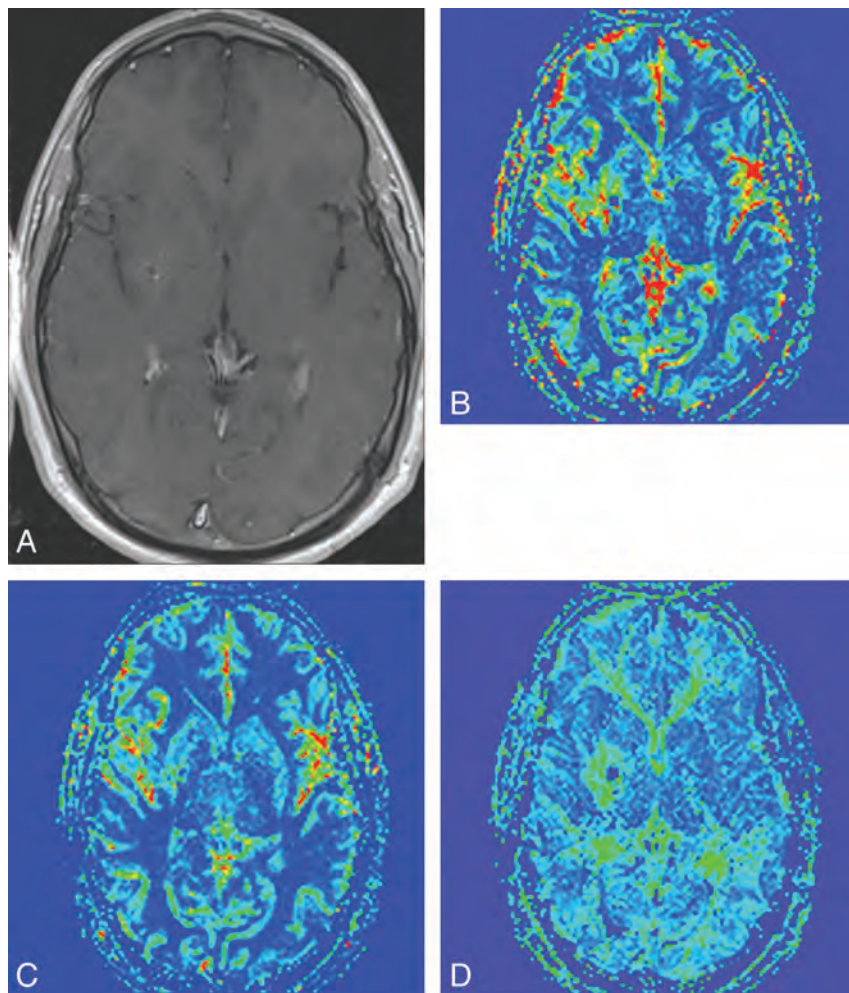


FIG 3. Axial contrast-enhanced T1-weighted image (A) demonstrates tributaries of the DVA in the right lentiform nucleus, seen as punctate enhancing foci. Corresponding rCBV (B), rCBF (C), and rMTT (D) maps demonstrate a zone of perfusion alteration around these tributaries incorporating otherwise normal-appearing brain tissue. Note that in this case, the alteration in rCBV and rMTT maps was more pronounced relative to the rCBF.

ings of prolonged rMTT are consistent with this observation because it has been previously demonstrated that the angiographic circulation time is proportional to the mean transit time.²¹ Previously, authors have also reported some complex DVAs demonstrating early venous drainage, attributing it to microshunts within the DVAs or possibly concomitant DVAs and arteriovenous malformations.^{2,22,23} We did not have any patients with reduced rMTT as could be expected in these patients. While we did not have angiographic correlation for our patients, it is likely that given the rarity of such DVAs with microshunts,² our study failed to include any such patients.

Our study had limitations. The number of patients was relatively small, and our results may not be generalizable to all DVAs. While PWI cannot accurately measure the actual CBV and CBF, it does offer a robust method to evaluate the relative changes in the perfusion of the brain. This is supported by the fact that for brain parenchyma with normal venous drainage, relative perfusion values (cCBV, cCBF, and cMTT) were noted to be close to 1, as would be expected. It is possible that susceptibility effects of CMs can affect the relative perfusion values obtained in the surrounding brain parenchyma. While we cannot be certain of these additional susceptibility effects on the perfusion calculations, none of the ROIs were placed directly in the location of the CMs. In a similar manner, we took precautions not to place the ROIs directly on visible enhancing venous structures. Indeed, the correlation of the perfusions maps and the contrast-enhanced TIWI showed the perfusion alterations not to be restricted to the venous channels themselves but rather extending into the brain parenchyma in between the venous tributaries as well (Figs 1 and 3). However, it is possible that the elevated blood pool in the surrounding brain parenchyma could itself make the quantification of the perfusion parameters in this region less reliable. In a large number of individuals studied, the DVAs were either completely asymptomatic or the patient had symptoms that could not be directly ascribed to them. Similarly, acute hemorrhage was seen in only 1 DVA with an associated CM. It remains unknown whether DVAs with more pronounced symptoms or a greater propensity to bleed are associated with even greater hemodynamic perturbation.

CMs associated with DVAs are sometimes resected surgically. The decision to intervene, however, involves careful assessment of potential benefits and risks, including the risk of future expansion or hemorrhage of the CM. If the extent of altered hemodynamics in the surrounding brain tissue is associated with CM formation as indicated by our study, quantitative evaluation of such altered hemodynamics by using PWI may also provide a means for better assessment of future growth/hemorrhage of the CM. Future longitudinal studies will be needed to test this hypothesis.

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REFERENCES

- Jimenez JL, Lasjaunias P, Terbrugge K, et al. **The trans-cerebral veins: normal and non-pathologic angiographic aspects.** *Surg Radiol Anat* 1989;11:63–72
- Pereira VM, Geibprasert S, Krings T, et al. **Pathomechanisms of symptomatic developmental venous anomalies.** *Stroke* 2008;39:3201–15
- Huber G, Piepgras U, Henkes H, et al. **Venous anomalies of the brain: the clinical significance of the so-called venous angioma** [in German]. *Radiologe* 1991;31:274–82
- Lasjaunias P, Terbrugge K, Rodesch G, et al. **True and false cerebral venous malformations: venous pseudo-angiomas and cavernous hemangiomas** [in French]. *Neurochirurgie* 1989;35:132–39
- Truwit CL. **Venous angioma of the brain: history, significance, and imaging findings.** *AJR Am J Roentgenol* 1992;159:1299–307
- Campeau NG, Lane JL. **De novo development of a lesion with the appearance of a cavernous malformation adjacent to an existing developmental venous anomaly.** *AJNR Am J Neuroradiol* 2005;26:156–59
- Garner TB, Del Curling O Jr, Kelly DL Jr, et al. **The natural history of intracranial venous angiomas.** *J Neurosurg* 1991;75:715–22
- Ostertun B, Solymosi L. **Magnetic resonance angiography of cerebral developmental venous anomalies: its role in differential diagnosis.** *Neuroradiology* 1993;35:97–104
- Hong YJ, Chung TS, Suh SH, et al. **The angioarchitectural factors of the cerebral developmental venous anomaly; can they be the causes of concurrent sporadic cavernous malformation?** *Neuroradiology* 2010;52:883–91
- Camacho DL, Smith JK, Grimme JD, et al. **Atypical MR imaging perfusion in developmental venous anomalies.** *AJNR Am J Neuroradiol* 2004;25:1549–52
- Kroll H, Soares BP, Saloner D, et al. **Perfusion-CT of developmental venous anomalies: typical and atypical hemodynamic patterns.** *J Neuroradiol* 2010;37:239–42
- Matsuda H, Terada T, Katoh M, et al. **Brain perfusion SPECT in a patient with a subtle venous angioma.** *Clin Nucl Med* 1994;19:785–88
- Okudera T, Ohta T, Huang YP, et al. **Developmental and radiological anatomy of the superficial cerebral convexity vessels in the human fetus.** *J Neuroradiol* 1988;15:205–24
- Saito Y, Kobayashi N. **Cerebral venous angiomas: clinical evaluation and possible etiology.** *Radiology* 1981;139:87–94
- Doege CA, Tavakolian R, Kerskens CM, et al. **Perfusion and diffusion magnetic resonance imaging in human cerebral venous thrombosis.** *J Neurol* 2001;248:564–71
- Lin DD, Barker PB, Hatfield LA, et al. **Dynamic MR perfusion and proton MR spectroscopic imaging in Sturge-Weber syndrome: correlation with neurological symptoms.** *J Magn Reson Imaging* 2006;24:274–81
- Lin DD, Barker PB, Kraut MA, et al. **Early characteristics of Sturge-Weber syndrome shown by perfusion MR imaging and proton MR spectroscopic imaging.** *AJNR Am J Neuroradiol* 2003;24:1912–15
- Zierler K. **Indicator dilution methods for measuring blood flow, volume, and other properties of biological systems: a brief history and memoir.** *Ann Biomed Eng* 2000;28:836–48
- Wei EP, Kontos HA. **Responses of cerebral arterioles to increased venous pressure.** *Am J Physiol* 1982;243:H442–47
- Abe M, Hagihara N, Tabuchi K, et al. **Histologically classified venous angiomas of the brain: a controversy.** *Neurol Med Chir (Tokyo)* 2003;43:1–10, discussion 11
- Gado MH, Phelps ME, Hoffman EJ, et al. **Changes in cerebral blood volume and vascular mean transit time during induced cerebral seizures.** *Radiology* 1976;121:105–09
- Awad IA, Robinson JR Jr, Mohanty S, et al. **Mixed vascular malformations of the brain: clinical and pathogenetic considerations.** *Neurosurgery* 1993;33:179–88, discussion 188
- Komiyama M, Mori T, Nakajima H, et al. **Cerebral venous angioma with parenchymal high intensity on T 2-weighted images** [in Japanese]. *No To Shinkei* 2001;53:88–89

Longitudinal Restriction Spectrum Imaging Is Resistant to Pseudoresponse in Patients with High-Grade Gliomas Treated with Bevacizumab

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ABSTRACT

BACKGROUND AND PURPOSE: Antiangiogenic therapies, such as bevacizumab, decrease contrast enhancement and FLAIR hyperintensity in patients with high-grade gliomas in a manner that may not correlate with actual tumor response. This study evaluated the ability of an advanced DWI technique, restriction spectrum imaging, to improve conspicuity within regions of restricted diffusion compared with ADC in patients treated with bevacizumab and to demonstrate that unlike ADC, restriction spectrum imaging is less affected by bevacizumab-induced reductions in FLAIR hyperintensity.

MATERIALS AND METHODS: Restriction spectrum imaging cellularity maps and DWI were available for 12 patients with recurrent high-grade gliomas at baseline and following initiation of bevacizumab. VOIs were drawn for regions of restricted diffusion, surrounding FLAIR hyperintensity, and normal-appearing white matter; and intensity values within regions of restricted diffusion and FLAIR hyperintensity were normalized to normal-appearing white matter. Normalized values were compared between restriction spectrum imaging cellularity maps and ADC at baseline and on treatment by using repeated-measures ANOVA.

RESULTS: All patients exhibited decreases in contrast enhancement and FLAIR hyperintensity following treatment. Normalized intensity values were higher on restriction spectrum imaging cellularity maps compared with ADC in regions of restricted diffusion, whereas intensity values were higher on ADC compared with restriction spectrum imaging cellularity maps in regions of FLAIR hyperintensity. Bevacizumab-induced decreases in FLAIR hyperintensity had a greater effect on ADC than on the restriction spectrum imaging cellularity maps, with the relative sensitivity of ADC to changes in FLAIR hyperintensity being >20 times higher than that on restriction spectrum imaging cellularity maps.

CONCLUSIONS: Restriction spectrum imaging is less influenced by reductions in FLAIR hyperintensity compared with ADC, which may confer an advantage of restriction spectrum imaging over ADC for interpreting tumor response on imaging following antiangiogenic therapy.

ABBREVIATIONS: FLAIR-HI = FLAIR hyperintensity; GBM = glioblastoma multiforme; NAWM = normal-appearing white matter; RD = restricted diffusion; RSI-CMs = restriction spectrum imaging cellularity maps

Current radiographic criteria for monitoring patients with high-grade glioma are heavily dependent on changes in contrast enhancement and FLAIR signal on standard MR images.¹ However, with greater use of antiangiogenic treatments such as

bevacizumab, an anti vascular endothelial growth factor antibody, using contrast enhancement as a surrogate for tumor response has become increasingly challenging.² Patients with recurrent high-grade glioma treated with bevacizumab often exhibit a sharp decrease in contrast enhancement and edema without a corresponding clinical response—a phenomenon called “pseudoresponse”—due to the ability of antiangiogenic agents to normalize hyperpermeable tumor vasculature, thus restoring the blood-brain barrier.^{3,4}

DWI and ADC have been proposed as imaging markers for tumor response in the presence of antiangiogenic agents to ad-

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Demographic and treatment-related characteristics of the patient sample

Patient	Age (yr)/ Sex	Pathology	Initial Therapy	Surgery Prior to Bevacizumab Scan (mo) ^a	Pre and Post- Bavacizumab Scans (day) ^b	Post-Bavacizumab Pathology ^c
1	58/F	GBM WHO IV	XRT + TMZ; TMZ 5/28	GTR, 1	−31, +29	—
2	43/M	AGN/WHO III/IV	XRT + TMZ; TMZ 3/14	GTR, 12	−22, +16	AA/WHO III/IV
3	62/F	GBM / WHO IV	XRT + TMZ; TMZ 3/14	STR, 1+	−3, +112	GBM/WHO IV
4	49/M	GBM/WHO IV	XRT + TMZ; TMZ 3/14	STR, 1	−10, +22	—
5	57/F	GBM/WHO IV	XRT + TMZ; TMZ 5/28, TMZ 3/14	STR, 6+	−13, +49	GBM/WHO IV
6	63/F	GBM/WHO IV	XRT + TMZ; TMZ 5/28	STR, 1	−28, +46	GBM/WHO IV + radiation effect
7	66/M	GBM/WHO IV	XRT + TMZ; TMZ 5/28	STR, 5	−2, +34	GBM/WHO IV + radiation necrosis
8	56/M	AOA/WHO III	XRT + TMZ; TMZ 5/28	RXN, 4+	−15 days, +15	—
9	67/M	GBM/WHO IV	XRT + TMZ; TMZ 5/28	GTR, 7	−7, +29 days	—
10	27/F	AA/WHO III	XRT + TMZ	Bx, 2+	−8, +16	—
11	40/M	GBM/WHO IV	XRT + TMZ; TMZ 5/28	STR, 5+	−37, +35	—
12	56/M	GBM/WHO IV	XRT + TMZ; TMZ 5/28	STR, 7	−49, +27	—

Note:—AOA indicates anaplastic oligoastrocytoma; AA, anaplastic astrocytoma; XRT + TMZ, radiotherapy plus adjuvant temozolomide; TMZ 5/28, temozolomide for 5 days every 28 days; TMZ 3/14, temozolomide for 3 days every 14 days; GTR, gross total resection; STR, subtotal resection; RXN, craniotomy and resection; Bx, biopsy; AGN, anaplastic glioneural neoplasm; WHO = World Health Organization.

^a Months shown indicate the interval between the surgical event and the first scan obtained during bevacizumab treatment.

^b Interval in days between the scan prior to bevacizumab treatment (pre-bevacizumab scan), and initiation of bevacizumab therapy, followed by the interval in days between initiation of bevacizumab therapy and first scan during bevacizumab treatment (post-bevacizumab scan).

^c Pathology after bevacizumab therapy had started.

dress this issue of pseudoresponse.^{5–8} Regions of increased cellularity, such as tumor, restrict water diffusion and decrease ADC values relative to surrounding tissue.^{9,10} However, concomitant edema and tumor-related necrosis increase ADC values, thereby directly opposing the reduction in ADC associated with tumor.^{11,12} This offset may result in diminished conspicuity of tumor on ADC maps and difficulty distinguishing tumor from NAWM. In the setting of antiangiogenic treatments, which can significantly decrease edema, the interpretation of ADC values is further complicated.^{13,14}

To maximize sensitivity to the restricted diffusion signal within tumor cells while excluding the hindered diffusion signal associated with edema, we apply a new, advanced DWI technique called “restriction spectrum imaging.”¹⁵ Whereas ADC reflects both hindered and restricted diffusion pools within a voxel, RSI uses multiple b-values and diffusion times to separate out the spherically restricted water compartment from the hindered water compartment, and it has been previously shown to improve tumor conspicuity relative to high-b-value ADC in patients with primary and metastatic brain tumors.¹⁶ Therefore, RSI may provide a more sensitive and robust biomarker of cellularity compared with conventional DWI and ADC in the context of antiangiogenic treatments that result in significant decreases in edema.

In this study, we evaluated the ability of RSI to improve conspicuity within regions of RD compared with standard ADC in patients with recurrent high-grade glioma treated with bevacizumab. In line with our previous work, we hypothesized that RSI would improve conspicuity within regions of RD over standard ADC, whereas ADC values within regions of RD would approximate those in NAWM. Moreover, we predicted that RSI would be minimally affected by bevacizumab-induced reductions in FLAIR-HI, whereas changes in ADC would be highly influenced by treatment-related reductions in FLAIR-HI due to the sensitivity of ADC to fast hindered diffusion.

MATERIALS AND METHODS

Patients

All patients included in the study signed consent forms approved by the institutional review board. From December 2010 to August 2012, one hundred ninety-three patients with primary and metastatic brain tumors at the UCSD Moores Cancer Center underwent a standardized MR imaging protocol that included the RSI sequence. From this group, 12 patients met the following inclusion criteria to form the final study cohort: 1) recurrent pathologically confirmed high-grade glioma (World Health Organization grade III or IV); 2) at least 1 baseline RSI scan before initiating bevacizumab therapy and a follow-up RSI scan while on bevacizumab; and 3) no significant blood products on susceptibility-weighted images that would confound diffusion signals on the ADC or RSI scans. The average age of the final cohort was 54 years, ranging from 27 to 67 years, with 7 men and 5 women. Nine patients had GBMs, while 3 had grade III gliomas (Table). To further avoid contamination from immediate postsurgical effects such as hemorrhage and cytotoxic edema, we did not perform MRI within the first 2 months following surgery.

MR Imaging

MR imaging was performed on a 3T Signa Excite HDx scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with an 8-channel head coil. Our imaging protocol included pre- and postgadolinium 3D volumetric T1-weighted inversion recovery spoiled gradient-recalled sequences (TE/TR = 2.8/6.5 ms, TI = 450 ms, flip angle = 8°, FOV = 24 cm, matrix = 0.93 × 0.93 × 1.2 mm) and a 3D T2-weighted FLAIR sequence (TE/TR = 126/6000 ms, TI = 1863 ms, FOV = 24 cm, matrix = 0.93 × 0.93 × 1.2 mm). For RSI, a single-shot pulsed gradient spin-echo EPI sequence was used (TE/TR = 96 ms/17 seconds, FOV = 24 cm, matrix = 96 × 96 × 48) with 4 b-values ($b=0, 500, 1500, \text{ and } 4000 \text{ s/mm}^2$) with 6, 6, and 15 unique diffusion directions for each nonzero b-value, respectively (28 total volumes, ~8-minute scanning time).

Preprocessing, ADC Calculation, and RSI Analysis

Before analysis, raw RSI data were corrected for geometric distortions due to susceptibility, gradient nonlinearities, and eddy currents.¹⁷ This was followed by correction of patient motion by using in-house software. ADC values were calculated from a tensor fit to the full dataset (all b-values and diffusion directions).

Details of the RSI model and analysis are given in White et al.¹⁶ Briefly, the diffusion signal in each voxel was fit by using a linear mixture model of restricted and hindered water compartments with spheric and cylindric geometries. For this article, the resulting spherically restricted water fraction formed the basis of our RSI cellularity maps. To maximize sensitivity and specificity to the spherically restricted water fraction, a beam-forming filter was applied to our RSI-CMs to reduce residual signal contamination from cylindrically restricted and hindered water compartments.¹⁶

Longitudinal Registration

For longitudinal measurement of RSI-CMs and ADC in defined regions of FLAIR-HI and NAWM, it was necessary to account for the changes in brain shape caused by tumor growth or surgical resection. A nonlinear registration, as described in McDonald et al.,¹⁸ was used to define a parameterized deformation between the first and second time points (before and after initiation of bevacizumab therapy). The T1-weighted precontrast images, weighted by T2-weighted FLAIR to correct for regions of hypointensity, were used to guide the nonlinear registration, and the computed deformations were then applied to the coregistered RSI-CM and ADC volumes.

Region-of-Interest and Imaging Analysis

Volumetric ROIs were drawn manually on baseline (pre-bevacizumab) scans for the contrast-enhancing region, the FLAIR-HI region surrounding the contrast-enhancing region, and NAWM by using coregistered 3D T1 postcontrast and 3D FLAIR volumes with the Amira software package (Visage Imaging, San Diego, California). NAWM was drawn in isointense white matter contralateral to the tumor on the 3D FLAIR sequence. All manual ROIs were approved by a board-certified neuroradiologist with 3 years of experience before image analysis. An automated region of interest was also generated for the region of RD within the region of contrast enhancement, and this region of interest was used to approximate the actual area of viable tumor within the contrast-enhancing region.¹⁹ Of note, this RD region of interest was generated from the RSI sequence because our prior work has shown improved tumor conspicuity on RSI-CMs compared with ADC.¹⁶ In addition, our prior work has demonstrated that ADC tends to underestimate the area of RD, whereas RSI-CMs are more inclusive of the total area of RD.

Determination of relevant ADC and RSI-CM values was performed in a manner similar to methods described by Gerstner et al.²⁰ Each patient's baseline (pre-bevacizumab) and follow-up (on bevacizumab) scans were used for analysis. The baseline FLAIR region of interest was coregistered with the RSI-CMs and ADC maps from each scan date. This coregistration allowed determination of ADC and RSI-CM values within the region of FLAIR-HI at baseline and determination of ADC and RSI-CM values within the region of RD at baseline.

Statistical Analysis

Intensity values within the RSI-CMs and ADC maps were transformed into z scores on the basis of the mean-intensity values within contralateral NAWM [(Pixel Intensity of RSI-CMs or ADC – Mean Intensity in Contralateral NAWM) / SD in Contralateral NAWM]. The z scores provided a measure of the relative sensitivity of each technique to RD and FLAIR-HI, normalized to NAWM. Z scores were used in all subsequent analyses. Repeated measures ANOVAs were performed within regions of RD and FLAIR-HI with method (RSI-CMs versus ADC) and treatment (baseline versus on treatment) as repeating factors. This procedure allowed us to evaluate the relative sensitivity of each method to RD and FLAIR-HI (main effect of method) and to evaluate whether the relative sensitivity of each method to RD and FLAIR-HI varies as a function of treatment with bevacizumab (method by treatment interaction). The relative sensitivity to change in FLAIR-HI versus RD was also computed for each measure and was defined as follows: Mean z Score Change in FLAIR-HI / Mean z Score in the Region of RD.

RESULTS

In all 12 patients who met the inclusion criteria, a visible decrease in both contrast enhancement and FLAIR-HI was observed following initiation of bevacizumab therapy. Eight patients showed a decrease of $\geq 50\%$ in T1 contrast enhancement, whereas the remaining 4 patients showed a decrease of 25%–50%. Similarly, 2 of the patients showed a corresponding decrease of $\geq 50\%$ in FLAIR-HI surrounding the enhancing region, whereas all 12 patients showed a decrease of at least 25% in FLAIR-HI following treatment with bevacizumab. Figure 1 shows a sample patient at baseline and on treatment with bevacizumab. The decrease in T1 enhancement and FLAIR-HI can be readily appreciated in this patient following initiation of treatment. Areas of RD are more conspicuous on RSI-CMs relative to ADC both at baseline and following treatment, whereas ADC signal intensity following treatment (ie, when not surrounded by FLAIR-HI) appears similar to that in NAWM. Furthermore, the large region of decreased signal intensity on ADC following treatment appears to mirror the decreased signal intensity on the FLAIR image (Fig 1J, -K), whereas RSI-CM intensity changes do not appear similar to decreases in FLAIR hyperintensity (Fig 1K, -L).

Figure 2 shows the normalized values (ie, z scores) for RSI-CMs and ADC in regions of RD and FLAIR-HI before and on treatment with bevacizumab averaged across patients. The repeated measures ANOVA for RD revealed a main effect of method [$F(1,11) = 18.97, P < .01$], indicating that RD intensity values were higher on RSI-CMs relative to ADC both before and on treatment. In fact, mean RSI-CM intensity values were approximately 8 times greater than those in NAWM before and on treatment, whereas mean ADC values were only 0.47 and 1.2 times greater than NAWM at baseline and on treatment, respectively. The repeated measures ANOVA within the region of FLAIR-HI revealed a main effect of method, indicating that FLAIR-HI values were higher on ADC relative to RSI-CMs [$F(1,11) = 88.8, P < .001$]. However, this was qualified by a method by treatment interaction [$F(1,11) = 61.1, P < .001$], which revealed that decreases in FLAIR-HI that occurred on treatment with bevacizumab

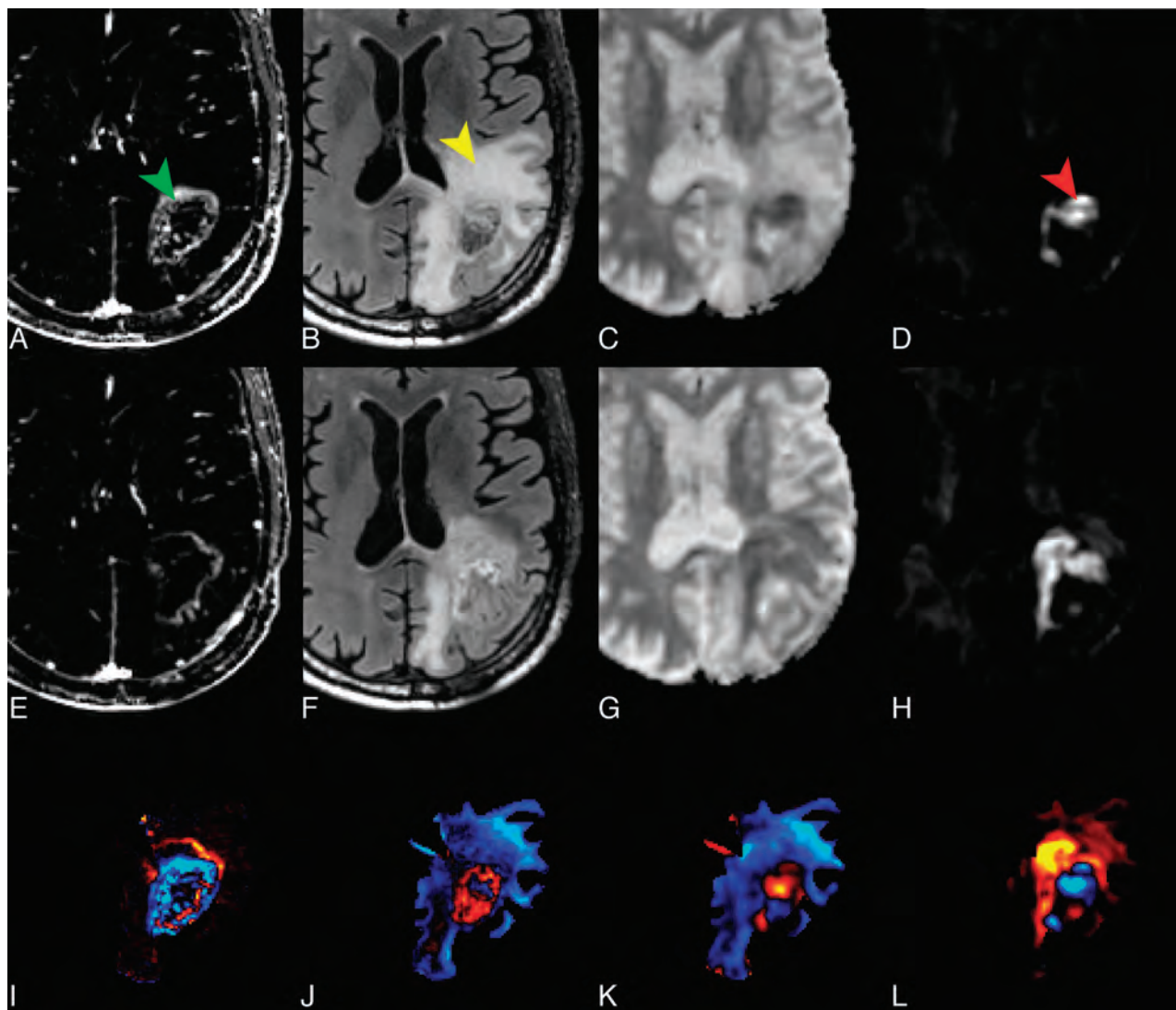


FIG 1. A 67-year-old man with left parietal GBM status after resection and chemoradiation. Top row shows the T1 postcontrast–T1 precontrast (A), FLAIR (B), ADC (C), and RSI-CM (D) images before the start of bevacizumab, while the middle row shows the T1 postcontrast–T1 precontrast (E), FLAIR (F), ADC (G), and RSI-CM (H) images after the initiation of bevacizumab. Arrowheads indicate the contrast-enhancing region (green), the surrounding region of FLAIR-HI (yellow), and the region of RD on RSI-CMs (red). Although there is a decrease in contrast enhancement and surrounding FLAIR-HI after the initiation of bevacizumab, the region of RD increases and becomes more confluent; this change suggests worsening residual/recurrent tumor. Moreover, this increase in the region of RD is much more conspicuous on RSI-CMs compared with the ADC. The bottom row depicts these changes on “change maps” (change in T1 postcontrast–precontrast (I), change in FLAIR (J), change in ADC (K), and change in the RSI-CMs (L), with red-yellow indicating an increase in signal intensity and blue-cyan indicating a decrease in signal intensity. Note that on the ADC change map (K), the area of increased RD is essentially masked by the decreased signal intensity within the region of surrounding FLAIR-HI.

zumab had a greater effect on ADC than on RSI-CM intensity values. As shown in Fig 3, the change in ADC following initiation of bevacizumab was highly correlated with the change in FLAIR-HI ($r = 0.66$, $P < .05$). In addition, the relative sensitivity to the change in FLAIR-HI versus RD on treatment was 23.5 times greater for ADC than for RSI-CMs.

DISCUSSION

Here we demonstrate that RSI, a novel diffusion imaging method, both improves conspicuity within regions of RD relative to ADC and is less influenced by bevacizumab-induced decreases in FLAIR-HI. As shown previously, this effect is because RSI is more sensitive to RD, whereas ADC is more sensitive to hindered diffusion, as seen in areas of FLAIR-HI. In fact, our results suggest that the relative sensitivity of ADC to changes in FLAIR-HI is >20

times greater than that derived from RSI-CMs. Thus, RSI-CMs not only facilitate visualization of areas of true RD associated with tumor cellularity (Fig 1), but they should also provide a more robust biomarker of cellularity relative to ADC in the context of treatment-related decreases in FLAIR-HI.

The utility of ADC for detecting high-grade glioma on the basis of increased RD has been demonstrated in both humans and in animal models.^{9,11} However, concomitant edema and tumor-related necrosis increase ADC values, thereby directly opposing the reduction in ADC associated with tumor. As a result, it can be difficult to discriminate tumor, edema, and NAWM from one another on ADC maps because ADC values in tumor may approximate those of NAWM.^{21–23} Indeed, mouse models and clinical studies of patients with high-grade glioma have demonstrated that ADC is an unreliable

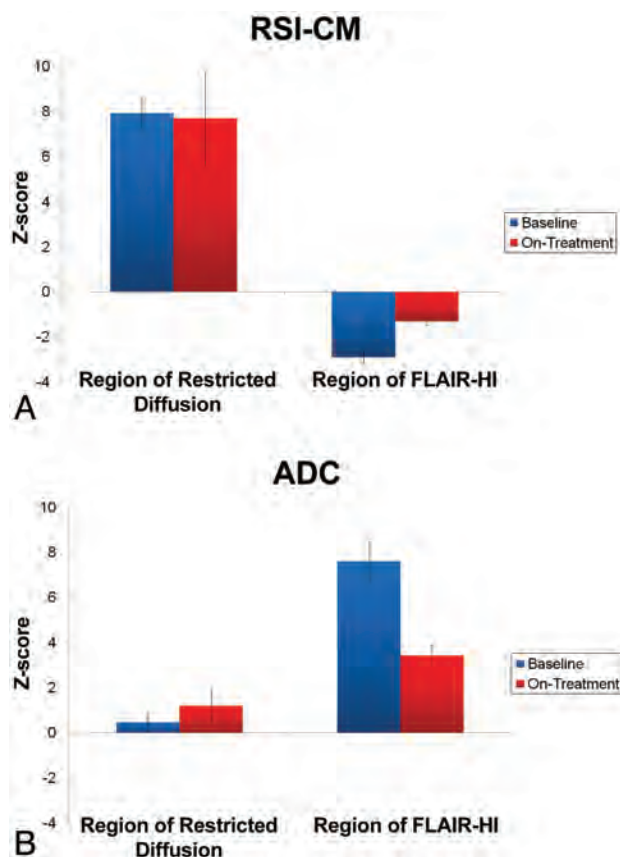


FIG 2. Bar graphs depicting the mean normalized intensity values (z scores) of the RSI-CMs (A) and the ADC (B) in regions of RD and FLAIR-HI before and on treatment with bevacizumab. Error bars reflect the standard error.

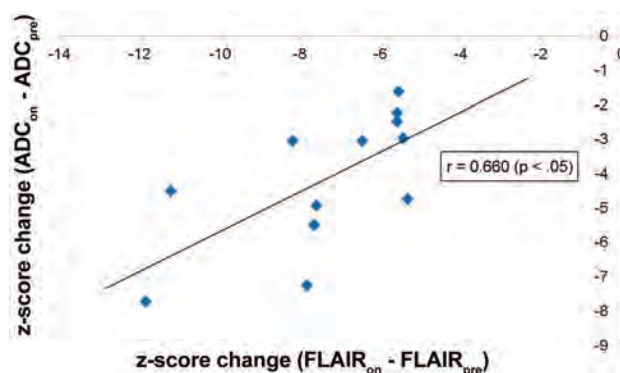


FIG 3. Scatterplot of the relationship between change in ADC z scores (on treatment–pretreatment) and change in FLAIR-HI z scores (on treatment–pretreatment) within the regions of FLAIR-HI. Z scores represent intensity values normalized to NAWM.

tool for differentiating tumor and surrounding edema.^{11,12,23,24} Therefore, when antiangiogenic therapy is administered, subsequent reduction in edema further complicates the interpretation of ADC maps.^{13,14} Although perfusion imaging has been proposed to identify residual or recurrent tumor following antiangiogenic therapy, the results are conflicting. Whereas some studies have shown reduced perfusion following antiangiogenic therapy purportedly due to diminished formation of new blood vessels,^{25,26} other studies have shown elevated perfusion possibly due to vascular normalization.^{3,27}

RSI provides a tool to specifically probe the RD compartment in the brain with minimal influence from the hindered diffusion associated with edema or from changes in vasculature attributable to antiangiogenic agents.

One of the limitations to the approach described in this article is that it requires 3D T1-weighted and FLAIR acquisitions and DWI with multiple b-values, by using a specialized pulse sequence that enables estimation and correction of spatial distortions due to B0 field variation. However, we contend that these sequences are necessary to accurately align images across sequences and with time in patients with high-grade gliomas. In this study, we took several steps to improve image registration across sequences and time in our patients. First, we used a method to correct for spatial distortions in EPI data by combining EPI scans acquired with opposite phase-encoding polarities and thus opposite spatial distortion patterns.¹⁷ Second, we used a nonlinear registration algorithm to improve the alignment of images with time.^{28,29} These methods have been previously applied to serial MRI in large-scale clinical studies^{29,30} and have been shown to have high sensitivity compared with existing methods for measuring brain changes with time.³¹ In addition, our study is limited by a small sample size, heterogeneity of our patient sample, a lack of clinical follow-up, and lack of pathologic confirmation of recurrent tumor in many of our patients. A larger sample size with tissue obtained from targeted biopsies is needed to fully understand the nature of the local RSI signal and to determine its clinical utility. In particular, RSI, like ADC, is not specific to tumor cellularity per se, despite the greater sensitivity of RSI to regions of RD. For example, recent studies have reported regions of marked persistent RD in certain patients following treatment with bevacizumab that do not appear to reflect aggressive tumor.^{26,32} Although the etiology of these strokelike lesions²⁶ on DWI/ADC remains uncertain, pathologic confirmation in a handful of cases has revealed atypical gelatinous necrosis.³² RSI, like ADC, is unable to differentiate these regions of RD caused by bevacizumab-induced hypoxia and radiation necrosis from those that reflect increased cellularity due to recurrent tumor.²⁶

In our study, pathology reports from 5 patients after initiation of bevacizumab therapy revealed that regions of diffusion restriction detected on RSI-CMs and ADC were indeed positive for recurrent high-grade glioma (Table). However, RD secondary to atypical necrosis that arises from bevacizumab-induced hypoxia cannot be ruled out in the remaining patients. Using other advanced imaging modalities, such as PET and perfusion imaging, may be highly beneficial in disambiguating the true nature of regions of persistent RD. Of note, multispectral imaging analysis incorporating PET and perfusion to further probe these regions of persistent RD would require highly precise image registration. In this context, using methods that correct for spatial distortions within each technique and coregistering images by using a nonlinear algorithm, as described above, become paramount. Applying such a multispectral approach to further interrogate regions of RD seen on RSI-CMs and to better ascertain the specificity of the RSI signal is currently underway in our laboratory.

CONCLUSIONS

As the clinical landscape continues to evolve for monitoring response to therapy in patients with high-grade gliomas, new imaging techniques will need to be developed that increase the

sensitivity and specificity to residual/recurrent tumor versus treatment-induced changes. We introduce a new technique, RSI, that increases the sensitivity to areas of RD and is less influenced by changes in FLAIR-HI relative to standard ADC. Future research is needed by using multispectral imaging and targeted biopsies in a large cohort of patients to determine the specificity of RSI to tumor and to evaluate its overall prognostic value.

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REFERENCES

- Macdonald DR, Cascino TL, Schold SC Jr, et al. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;8:1277–80
- Sorensen AG, Batchelor TT, Wen PY, et al. Response criteria for glioma. *Nat Clin Pract Oncol* 2008;5:634–44
- Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;307:58–62
- Hygino da Cruz LC Jr, Rodriguez I, Domingues RC, et al. Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. *AJNR Am J Neuroradiol* 2011;32:1978–85
- Chenevert TL, Stegman LD, Taylor JM, et al. Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. *J Natl Cancer Inst* 2000;92:2029–36
- Pope WB, Kim HJ, Huo J, et al. Recurrent glioblastoma multiforme: ADC histogram analysis predicts response to bevacizumab treatment. *Radiology* 2009;252:182–89
- Gerstner ER, Frosch MP, Batchelor TT. Diffusion magnetic resonance imaging detects pathologically confirmed, nonenhancing tumor progression in a patient with recurrent glioblastoma receiving bevacizumab. *J Clin Oncol* 2010;28:e91–93
- Jain R, Scarpace LM, Ellika S, et al. Imaging response criteria for recurrent gliomas treated with bevacizumab: role of diffusion weighted imaging as an imaging biomarker. *J Neurooncol* 2010;96:423–31
- Sugahara T, Korogi Y, Kochi M, et al. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J Magn Reson Imaging* 1999;9:53–60
- Chenevert TL, Sundgren PC, Ross BD. Diffusion imaging: insight to cell status and cytoarchitecture. *Neuroimaging Clin N Am* 2006;16: 619–32, viii–ix
- Castillo M, Smith JK, Kwok L, et al. Apparent diffusion coefficients in the evaluation of high-grade cerebral gliomas. *AJNR Am J Neuroradiol* 2001;22:60–64
- Stadnik TW, Chaskis C, Michotte A, et al. Diffusion-weighted MR imaging of intracerebral masses: comparison with conventional MR imaging and histologic findings. *AJNR Am J Neuroradiol* 2001;22:969–76
- Batchelor TT, Sorensen AG, di Tomaso E, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell* 2007;11:83–95
- Pope WB, Lai A, Nghiemphu P, et al. MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy. *Neurology* 2006;66:1258–60
- White NS, Leergaard TB, D'Arceuil H, et al. Probing tissue microstructure with restriction spectrum imaging: histological and theoretical validation. *Hum Brain Mapp* 2013;34:327–46
- White NS, McDonald CR, Farid N, et al. Improved conspicuity and delineation of high-grade primary and metastatic brain tumors using “restriction spectrum imaging”: quantitative comparison with high b-value DWI and ADC. *AJNR Am J Neuroradiol* 2013;34: 859–64
- Holland D, Kuperman JM, Dale AM. Efficient correction of inhomogeneous static magnetic field-induced distortion in echo planar imaging. *Neuroimage* 2010;50:175–83
- McDonald CR, White NS, Farid N, et al. Recovery of white matter tracts in regions of peritumoral FLAIR hyperintensity with use of restriction spectrum imaging. *AJNR Am J Neuroradiol* 2013;34: 1157–63
- Holodny AI, Makeyev S, Beattie BJ, et al. Apparent diffusion coefficient of glial neoplasms: correlation with fluorodeoxyglucose-positron-emission tomography and gadolinium-enhanced MR imaging. *AJNR Am J Neuroradiol* 2010;31:1042–48
- Gerstner ER, Chen PJ, Wen PY, et al. Infiltrative patterns of glioblastoma spread detected via diffusion MRI after treatment with cediranib. *Neuro Oncol* 2010;12:466–72
- Yamasaki F, Kurisu K, Satoh K, et al. Apparent diffusion coefficient of human brain tumors at MR imaging. *Radiology* 2005;235:985–91
- Maier SE, Sun Y, Mulkern RV. Diffusion imaging of brain tumors. *NMR Biomed* 2010;23:849–64
- Eis M, Els T, Hoehn-Berlage M. High resolution quantitative relaxation and diffusion MRI of three different experimental brain tumors in rat. *Magn Reson Med* 1995;34:835–44
- Brunberg JA, Chenevert TL, McKeever PE, et al. In vivo MR determination of water diffusion coefficients and diffusion anisotropy: correlation with structural alteration in gliomas of the cerebral hemispheres. *AJNR Am J Neuroradiol* 1995;16:361–71
- Keunen O, Johansson M, Oudin A, et al. Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma. *Proc Natl Acad Sci U S A* 2011;108:3749–54
- Rieger J, Bahr O, Muller K, et al. Bevacizumab-induced diffusion-restricted lesions in malignant glioma patients. *J Neurooncol* 2010;99:49–56
- Sorensen AG, Emblem KE, Polaskova P, et al. Increased survival of glioblastoma patients who respond to antiangiogenic therapy with elevated blood perfusion. *Cancer Res* 2012;72:402–07
- Jovicich J, Czanner S, Greve D, et al. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *Neuroimage* 2006;30:436–43
- Holland D, Dale AM. Nonlinear registration of longitudinal images and measurement of change in regions of interest. *Med Image Anal* 2011;15:489–97
- McDonald CR, Hagler DJ Jr, Girard HM, et al. Changes in fiber tract integrity and visual fields after anterior temporal lobectomy. *Neurology* 2010;75:1631–38
- Holland D, McEvoy LK, Dale AM. Unbiased comparison of sample size estimates from longitudinal structural measures in ADNI. *Hum Brain Mapp* 2012;33:2586–602
- Mong S, Ellingson BM, Nghiemphu PL, et al. Persistent diffusion-restricted lesions in bevacizumab-treated malignant gliomas are associated with improved survival compared with matched controls. *AJNR Am J Neuroradiol* 2012;33:1763–70

Automated Posterior Cranial Fossa Volumetry by MRI: Applications to Chiari Malformation Type I

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ABSTRACT

BACKGROUND AND PURPOSE: Quantification of PCF volume and the degree of PCF crowdedness were found beneficial for differential diagnosis of tonsillar herniation and prediction of surgical outcome in CMI. However, lack of automated methods limits the clinical use of PCF volumetry. An atlas-based method for automated PCF segmentation tailored for CMI is presented. The method performance is assessed in terms of accuracy and spatial overlap with manual segmentation. The degree of association between PCF volumes and the lengths of previously proposed linear landmarks is reported.

MATERIALS AND METHODS: T1-weighted volumetric MR imaging data with 1-mm isotropic resolution obtained with the use of a 3T scanner from 14 patients with CMI and 3 healthy subjects were used for the study. Manually delineated PCF from 9 patients was used to establish a CMI-specific reference for an atlas-based automated PCF parcellation approach. Agreement between manual and automated segmentation of 5 different CMI datasets was verified by means of the *t* test. Measurement reproducibility was established through the use of 2 repeated scans from 3 healthy subjects. Degree of linear association between PCF volume and 6 linear landmarks was determined by means of Pearson correlation.

RESULTS: PCF volumes measured by use of the automated method and with manual delineation were similar, 196.2 ± 8.7 mL versus 196.9 ± 11.0 mL, respectively. The mean relative difference of $-0.3 \pm 1.9\%$ was not statistically significant. Low measurement variability, with a mean absolute percentage value of $0.6 \pm 0.2\%$, was achieved. None of the PCF linear landmarks were significantly associated with PCF volume.

CONCLUSIONS: PCF and tissue content volumes can be reliably measured in patients with CMI by use of an atlas-based automated segmentation method.

ABBREVIATIONS: CMI = Chiari malformation type I; PCF = posterior cranial fossa

The current radiologic definition of CMI is based on the degree of tonsillar herniation below the foramen magnum. However, imaging data with x-ray,¹ CT,² and MR³⁻⁷ gathered over the last several decades documented that CMI is also associated with a smaller than normal PCF. In most studies, length (1D)^{5,6} and area (2D)⁸ measurements of certain PCF landmarks manually delineated on x-ray film¹ or on a midsagittal MR imaging⁶ were used for estimates of the PCF size. Volumetric (3D) assessment of the PCF, either with

CT² or MR imaging,⁴ further confirmed reduced PCF volume in patients with CMI compared with healthy controls. Through the use of manual delineation of the PCF and the brain tissue boundaries, Milhorat et al⁴ reported a smaller PCF volume as well as CSF volume, whereas the hindbrain volume was normal, leading to the notion of an overcrowded PCF. In a more recent study, they reported a small PCF volume only in “classic” CMI but not in “CMI mimicking” etiologies, thereby emphasizing the importance of the PCF volume for differential diagnosis of tonsillar herniation.⁷

Lirng et al⁹ used manual delineation of the PCF in MR imaging followed by image intensity-based segmentation of brain tissue and CSF to assess the effect of age and sex on the PCF volume and crowdedness in healthy subjects. They found that overall, men had a larger PCF and hindbrain volume, whereas women demonstrated a higher degree of crowdedness, which may explain the higher frequency of CMI in women.

Two other studies further suggest that the size of the PCF is also a strong predictor for surgical treatment outcome in CMI. Badie et al³ reported that a smaller ratio of the PCF volume relative to the supra-

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tentorial volume is associated with a better surgical outcome. A more recent study by Noudel et al¹⁰ used a semi-automated method to demonstrate that the response to the PCF decompression surgery is correlated with preoperation volume of PCF and the overall increase in the PCF volume after operation but not with the degree of tonsillar herniation or other tested morphologic measures. These limited data suggest that measurements of the PCF volume are likely to enhance both the diagnostic and prognostic reliability in CMI.

Despite the potential diagnostic and prognostic values of the PCF morphology, volumetric assessments of the PCF size are not commonly used in clinical practice because manual delineation of the PCF on multiple images is time-consuming. Manual length measurements of different landmarks of the PCF are less time-consuming and are more commonly used as surrogate measures of the PCF volume.¹¹ The most common 1D measurements are the lengths of the supraocciput and the clivus bones and the McRae and Twining lines at the midsagittal plane.^{4,6} However, these measurements are highly subjective and are strongly influenced by the MR imaging technique. Furthermore, it is not clear how well these linear (1D) measures correlate with the overall volume of the PCF. With the increasing evidence for the diagnostic potential of PCF measurement, there is a need for a robust automated method for reliable segmentation of the PCF. Moreover, because MR imaging is the primary technique used for diagnosis of CMI, it is important that such a method is available for MR imaging data.

A new approach for automated PCF parcellation is presented. The proposed parcellation uses atlas-guided segmentation, which has been successful in other cerebral regions. In addition to a measurement of the entire PCF volume, the method also provides measurements of the hindbrain tissue and CSF volumes. The robustness of the method is assessed by comparison with manual delineation in CMI data. Additionally, the degree of association between PCF volumes and linear landmarks is assessed.

MATERIALS AND METHODS

Subjects

PCF volumes were measured by use of MR imaging data from 3 healthy subjects who were scanned twice on 2 separate days (1 woman; age range, 29–36 years; mean age, 34 ± 3 years) and 5 symptomatic patients with CMI (3 women; age range, 23–48 years; mean age, 37 ± 10 years). MR imaging data from an additional 9 symptomatic patients with CMI (7 women; age range, 20–68 years; mean age, 37 ± 15 years) were used to create the CMI-specific atlas. All patients had cerebellar tonsillar herniation of at least 5 mm below the foramen magnum and presented with suboccipital headaches and numbness in the upper and/or lower extremities. Six patients had Valsalva-induced headaches. All subjects provided written informed consent, and the study was approved by the institutional review board.

MR Image Acquisition

The MR images used in the study were acquired with a 3T scanner (Magnetom Trio; Siemens, Erlangen, Germany). The structural analysis was performed on 3D T1-weighted image (magnetization prepared rapid acquisition of gradient echo) with the following



FIG 1. The 6 linear landmarks of the PCF superimposed on a midsagittal T1-weighted MR imaging from a patient with CMI: herniation (HR), McRae line (MC), clivus (CL), Twining line (TW), cerebellum (CR), and supraocciput (SO).

acquisition parameters: TR/TE/TI of 1900/2.89/900 ms, flip angle of 9°, FOV of 25.6×25.6 cm, and matrix size of 256×256 , resulting in 1-mm isotropic resolution. Images were acquired in the sagittal orientation.

Linear Measurements of the PCF

Lengths of 6 midsagittal PCF structures were measured on the midsagittal T1-weighted image by a trained expert with 5 years of experience (S.H.L.). These structures were characterized as follows: 1) McRae line measured from the basion and the opisthion, 2) clivus length measured from the basion to the inferior boundary of the dorsum sellae, 3) Twining line measured from the dorsum sellae to the internal occipital protuberance, 4) height of the cerebellum, 5) supraocciput measured from internal occipital protuberance to opisthion, and 6) tonsillar herniation measured from the McRae line to tip of the cerebellar tonsil. An example of these markers overlaid on a midsagittal T1 MR image is shown in Fig 1.

Manual Segmentation of PCF Volume

The PCF was manually outlined on every sagittal section by use of the 3D Slicer software (<http://www.slicer.org>) by a single trained expert (A.M.B.) to avoid interobserver variability. Manual delineations were further reviewed and edited when needed by a neuroradiologist (N.N.). The PCF was anatomically bounded by tentorium cerebelli, occipital bone, clivus, and foramen magnum. The volume of the PCF was calculated by summation of the volume of each voxel within the manually created mask on each sagittal section.

CMI-Specific PCF Atlas

A PCF reference atlas, specific for CMI, was created from T1-weighted images of 9 patients (7 women; age range, 20–68 years; mean age, 37 ± 15 years). PCF labels were manually delineated on each subject image by an expert (A.M.B.) and were reviewed and confirmed for reliability by a neuroradiologist (N.N.). The T1-weighted images were then affine-registered to Montreal Neurological Institute 152 space¹² and averaged to create the atlas template. The delineated PCF region from each of the 9 subjects was

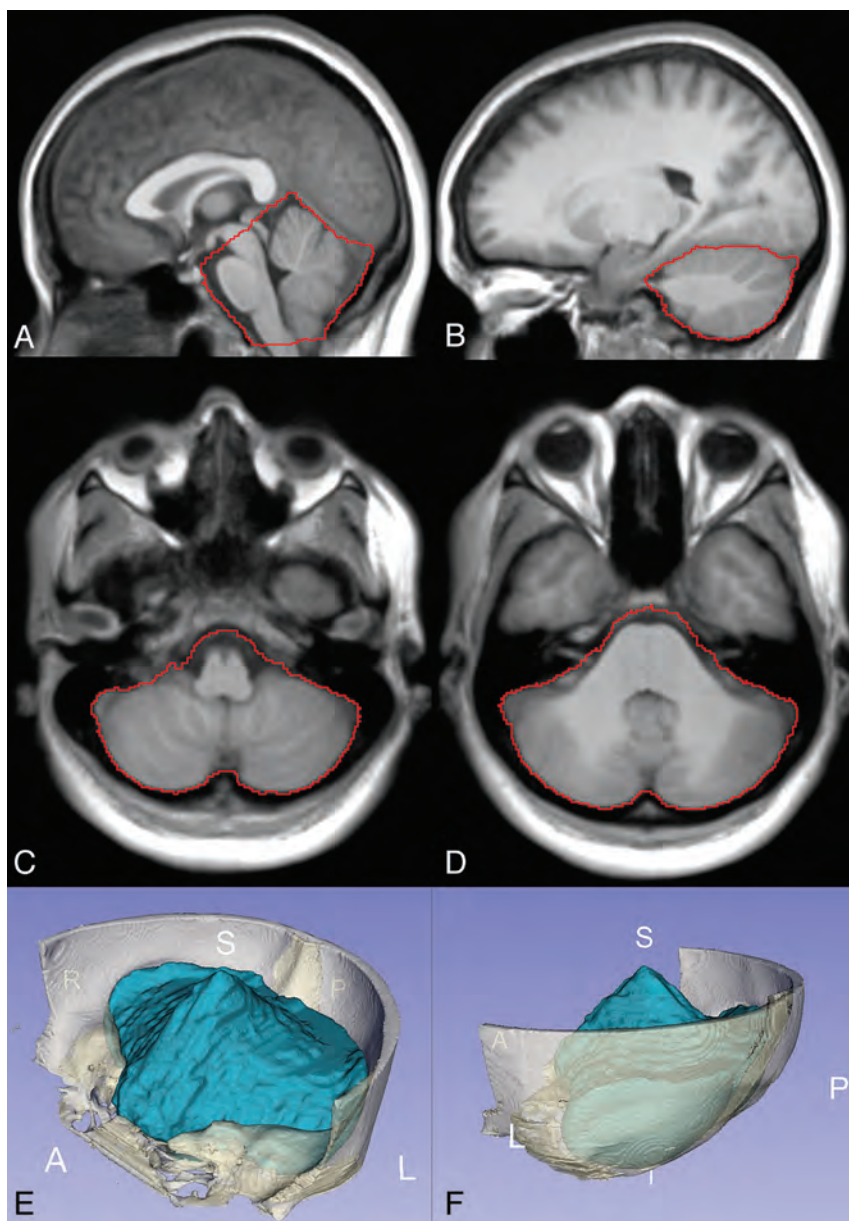


FIG 2. Chiari-specific atlas template and the boundary of the PCF compartment (red outline) shown in sagittal (A and B) and axial (C and D) planes. A 3D volumetric rendering of the PCF mask (blue) generated from the atlas template and surrounding cranium (white) are shown in E and F.

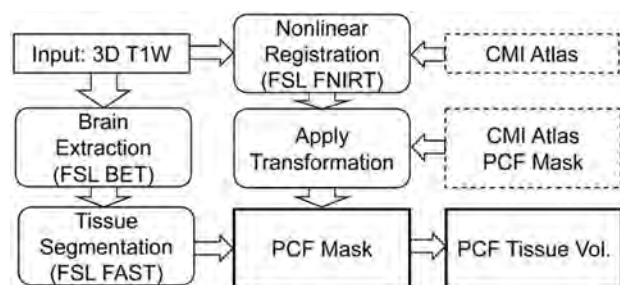


FIG 3. Flow chart illustrating the FSL implementation of the automated process for PCF segmentation and measurement of the PCF tissue volume.

then projected to the atlas space to generate an averaged PCF mask superimposed on the atlas space. The average reference atlas and the superimposed PCF regions are shown in Fig 2.

Automated Segmentation of PCF Volume

Automated segmentation of the PCF volume is achieved by use of the previously described CMI reference atlas. First, a global linear transformation is applied to register the atlas template to the subject dataset by use of the FLIRT tool from FSL software package (<http://www.fmrib.ox.ac.uk/fsl>).¹³ Only the brain region is used for the global registration to avoid adverse effects of cranial and extracranial structures on registration.¹⁴ After the global linear transformation, a more precise local alignment with a nonlinear registration is achieved by use of the FMRIB Nonlinear Image Registration Tool (FNIRT) from FSL,¹⁵ which is based on minimizing a sum-of-squares cost function by use of a Levenberg-Marquardt modification of the Gauss-Newton method. Finally, the PCF mask is mapped to the subject MR imaging through the inverse of the registration to automatically segment the PCF volume.

Automated Segmentation of Brain Tissue

The proposed PCF parcellation method quantifies the volumes of tissue content of the PCF, which include the brain stem, cerebellum, medulla, and pons. Each pixel inside the PCF mask is labeled as gray matter, white matter, or CSF, by use of an algorithm that is based on the hidden Markov random field model and expectation maximization.¹⁶ The cerebellar tonsils extending beyond the foramen magnum are excluded as the result of PCF masking. A flow chart of the FSL implementation of the process for PCF segmentation and measurement of the PCF tissue volume is shown in Fig 3.

The intensity-based segmentation of the PCF tissues was compared with FreeSurfer-based (<http://surfer.nmr.mgh.harvard.edu>) segmentation of the hindbrain. The details of the FreeSurfer segmentation method are provided by Fischl et al.¹⁷ FreeSurfer segmentation is an atlas-based segmentation method, which used both the intensity distribution and the spatial relationships of previously defined brain regions. Labeled brain regions in the brain stem and gray and white matter in left and right cerebellum were combined and used as the hindbrain volume in this study.

Assessment of Automated Segmentation Accuracy and Reliability

The accuracy of the automated segmentation was assessed by comparing the automatically segmented PCF with manual seg-

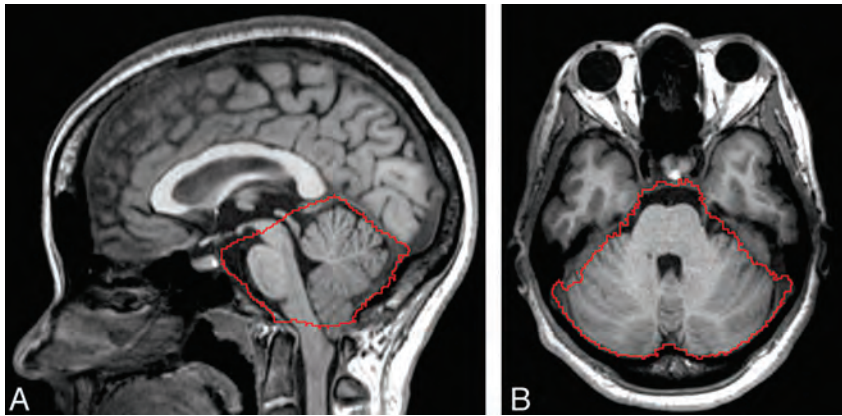


FIG 4. Outline of the PCF mask (red) generated by use of the proposed method on midsagittal (A) and axial (B) planes of T1-weighted MR imaging of a patient with CMI.

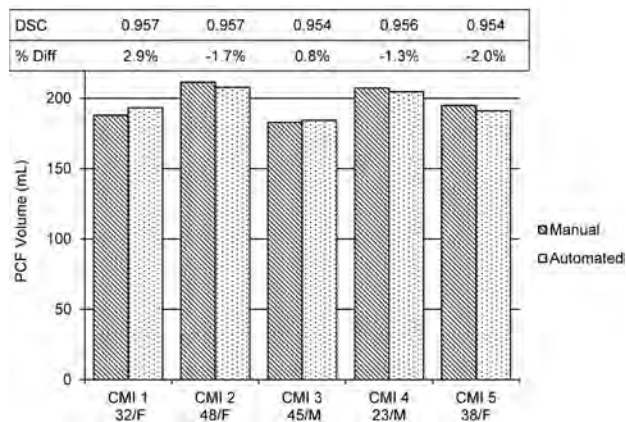


FIG 5. Comparison of PCF volume obtained manually and with the automated segmentation in CMI. The Dice similarity coefficient (DSC) and the relative percent change obtained for each of the 5 patients are shown above the volume bars.

Table 1: Repeated automated PCF volumes measurements

Subject	Age/ Sex	PCF		Relative Percentage Difference
		Volume (mL), Scan 1	Volume (mL), Scan 2	
1	36/M	186.1	186.8	0.4%
2	29/M	207.5	205.9	0.8%
3	36/F	194.7	195.6	0.5%

mentation in 5 patients with CMI. Percentage volume difference between the manual and the automated segmentations were calculated to test for systematic differences. Additionally, the Dice similarity coefficient was used to evaluate the degree of spatial overlap between the automatically and manually segmented PCF. The Dice similarity coefficient is defined as

$$DSC = \frac{2 * V(A \cap M)}{V(A) + V(M)}$$

where A and M denote automated and manual segmentations, and V denotes volume of the region. The value of Dice similarity coefficient ranges between 0–1, representing no overlap to complete spatial overlap, respectively. A Dice similarity coefficient value >0.7 is considered as a good agreement between 2 compared measurements.¹⁸

The reliability of the automated segmentation across scan sessions was tested by means of MR imaging data from the 3 healthy subjects who were scanned twice on 2 separate days. The mean absolute percentage difference of the 2 measurements was calculated by dividing the absolute difference of the 2 measurements by their mean. A paired, 2-tailed t test was applied to determine the significance of differences between volume measurements obtained by use of 2 methods.

The posterior fossa brain tissue volume was measured in 5 patients with CMI by use of the proposed automated method and compared with measurements obtained by means of FreeSurfer.

The mean percentage difference between 2 measurements and degree of spatial overlap was calculated. In addition, the derived crowdedness index, defined as the ratio of the tissue volume and the PCF compartment volume, were compared as well. Finally, linear association between PCF volumes and the length of the 6 different linear PCF markers were assessed by calculating the Pearson correlation coefficient and significance level by use of the data from the 14 patients with CMI. All statistical calculations were performed by use of MedCalc statistical software (MedCalc, Mariakerke, Belgium).

RESULTS

PCF Volumes

Examples of midsagittal and axial images with the identified PCF boundary and the 3D-rendered PCF volume from a representative patient with CMI are shown in Fig 4. The PCF volumes of each of the 5 patients with CMI measured with the 2 methods and the Dice coefficient representing the degree of overlap are shown in Fig 5. The mean and the SD of the manual and the automated segmentations of the PCF volumes in these 5 patients with CMI were similar (197 ± 11 mL and 196 ± 9 mL, respectively). The difference was not significant ($P = .7$). The mean percentage volume difference was $-0.3 \pm 1.9\%$. The mean degree of overlap (Dice coefficient) between the automatically and manually obtained PCF masks was 0.96 ± 0.001 .

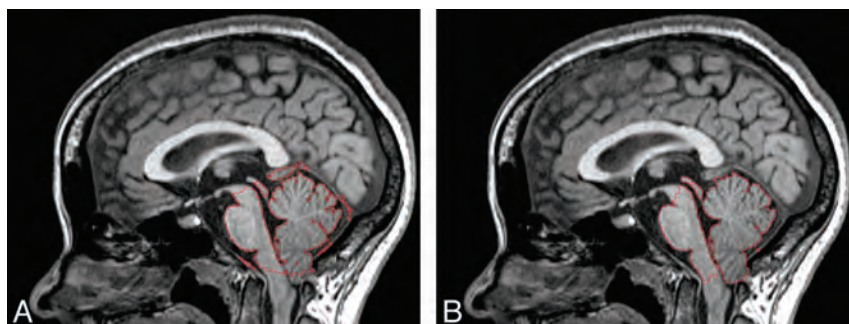
The PCF volumes measured from the 3 healthy subjects who were scanned twice on 2 separate days and the relative percentage difference are listed in Table 1. The mean absolute percentage difference was $0.6 \pm 0.2\%$, with a range of 0.4% to 0.8%; the difference between volume measurements was not statistically significant ($P = .995$).

PCF Crowdedness Indexes

The posterior fossa brain tissue volume, crowdedness indexes of the 5 patients with CMI measured with the proposed method and with FreeSurfer, and the Dice coefficient are listed in Table 2. The mean and SD of the volumes measured with the proposed method and with FreeSurfer were 162 ± 8 mL and 168 ± 9 mL, respectively. The tissue volumes measured by use of FreeSurfer were

Table 2: Comparison of PCF tissue segmentation by means of the proposed method and FreeSurfer

Patient	PCF Tissue Volume (mL) (Proposed Method)	PCF Tissue Volume (mL) (FreeSurfer)	Percentage Volume Difference	Dice Coefficient	Crowdedness Index (Proposed Method)	Crowdedness Index (FreeSurfer)
1	162.8	169.4	4.1%	0.949	0.842	0.876
2	172.1	181.6	5.5%	0.939	0.828	0.874
3	151.9	156.2	2.8%	0.940	0.824	0.847
4	170.1	174.0	2.3%	0.948	0.831	0.850
5	153.9	158.6	3.1%	0.949	0.806	0.830

**FIG 6.** Outline of the PCF tissue masks (red) generated by use of the proposed method (A) and FreeSurfer (B) in 1 of the patients with CMI.

consistently larger in each subject, with a mean percent difference of $3.6 \pm 1.1\%$ ($P = .005$). The mean and SD of the spatial overlap were 0.945 ± 0.004 . Images illustrating the tissue segmentation by the 2 methods are shown in Fig 6A,B, respectively. The corresponding PCF crowdedness indexes were 0.826 ± 0.012 and 0.856 ± 0.017 , respectively. Because FreeSurfer does not provide the PCF volume, the PCF volume obtained by the proposed method was used to estimate the PCF crowdedness obtained by use of the 2 methods.

None of the 6 linear PCF measures were significantly associated with the PCF volume. Five of the linear measures correlated positively with the PCF volume with the following corresponding Pearson correlation coefficients: supraocciput length ($r = 0.38$, $P = .18$), McRae line ($r = 0.37$, $P = .20$), clivus ($r = 0.32$, $P = .27$), Twining line ($r = 0.30$, $P = .30$), and length of cerebellum ($r = 0.29$, $P = .31$). As expected, the herniation length was negatively correlated with the PCF volume, with a Pearson correlation coefficient of -0.17 ($P = .57$).

DISCUSSION

Quantification of the PCF volume and the degree of PCF crowdedness were shown to be beneficial for differential diagnosis of tonsillar herniation^{7,11} and for prediction of surgical outcome.¹⁰ The lack of a reliable automated method for PCF volumetry by use of MR imaging, however, limits the clinical use of these PCF markers. Advanced automated methods for brain parcellation have matured in recent years and are becoming more widely used.^{16,17} This work represents adaptation of established brain segmentation techniques tailored toward PCF volumetry in CMI. The proposed atlas-guided PCF segmentation method is enhanced by the creation of a CMI-specific reference atlas that captures the altered PCF morphology associated with CMI. An excellent agreement between the proposed automated method and manual segmentation by an expert observer is evident by the small relative percentage difference of $-0.3 \pm 1.9\%$ and the very high

mean Dice coefficient of 0.96. The delineation of the PCF obtained by use of the proposed automated method highly agrees with the manual delineation in terms of accuracy and spatial overlap in patients with CMI. Furthermore, a high degree of repeatability is evident from the small absolute percentage difference of $0.6 \pm 0.2\%$ found by use of quantification of the repeated scans in 3 healthy subjects. The automated volume measurement of PCF is minimally affected by the normal variability in patient positioning in the MR imaging scanner.

The mean PCF volume measurement obtained in our small cohort of adult patients with CMI (196 ± 8.7 mL) tends to be larger than previously reported CT and MR-based measurements of 186 mL by Nishikawa et al,¹¹ 174 ± 25 mL by Noudel et al,¹⁰ and 166 ± 8 mL by Milhorat et al.⁷ The bias in the mean volume measurements may be attributed to the differences in the modalities and the possible differences in the segmentation protocols, particularly how the PCF boundaries were defined. Another contributing factor may be related to the difference in the sampling resolution of the volumetric data. In contrast to isotropic 1-mm 3D imaging used in this work, previous reports used 2D-based imaging with thicker sections for the volumetric measurements that can lead to measurement errors caused by large partial volume effect. In addition, the limited number of subjects used in this study to validate the proposed automated method against manual segmentation may not be representative of a CMI population in terms of PCF volume.

The tonsillar herniation in CMI has been attributed to overcrowding of the PCF as a result of a small PCF and normally developed brain tissue volume.^{7,10,11} Therefore, in addition to PCF volume measurement, accurate quantification of brain tissue volume is also critical. Our measurement of mean PCF tissue volume of 162.1 ± 8.2 also tends to be slightly larger than previously reported values of 156 mL by Nishikawa et al¹¹ and 151.8 ± 3.1 mL by Milhorat et al.⁷ However, the measurement of crowdedness, the ratio of PCF tissue volume to PCF volume of 0.826 ± 0.012 , is in good agreement with the mean value of 0.833 reported by Nishikawa et al.¹¹

The comparison of the hindbrain tissue volume measurements between the proposed method and FreeSurfer revealed a statistically significant mean difference of $3.6 \pm 1.1\%$ ($P = .005$). The tissue volumes found through the use of FreeSurfer were consistently larger than volumes obtained by using the proposed method. As demonstrated in Fig 6, this difference is the result of

the exclusion of the tonsillar tissue volume that descends below the foramen magnum. This tissue is excluded because it is outside the PCF and thus does not contribute to the PCF overcrowding.

Assessment of the associations between PCF volumes and the linear PCF markers revealed that none of the 6 measures were significantly associated with the PCF volume. The 5 linear landmarks of the PCF were all modestly positively correlated with the PCF volume. The lack of significance can be explained in part by the small sample. The length of herniation negatively correlated with the PCF volume, which is expected when a normal size cerebellum is compressed inside an increasingly smaller PCF.

The reference atlas used to guide the segmentation was prepared by use of MR images from patients with CMI, all of whom had tonsillar herniation >5 mm. Therefore, this atlas may not be optimal for segmentation of healthy subjects because of morphologic differences. However, for the purpose of reproducibility estimate, data from healthy subjects were used because repeated scans from patients with CMI were not available. Even with this limitation, an excellent reproducibility with an average difference of $0.6 \pm 0.2\%$ is obtained, reflecting the robustness of the proposed method.

CONCLUSIONS

The PCF volume and the degree of crowdedness can be reliably quantified in MR imaging data of patients with CMI by use of an atlas-based approach. Automatically delineated PCF compartments were similar in volume and spatial overlap with those delineated manually by an expert observer. These early results suggest that automated segmentation could substitute for manual delineation of the PCF, thereby advancing the use of PCF parcellation for improved diagnosis and treatment decisions in CMI.

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REFERENCES

1. Nyland H, Krogness KG. Size of posterior fossa in Chiari type I malformation in adults. *Acta Neurochir (Wien)* 1978;40:233–42
2. Vega A, Quintana F, Berciano J. Basichondrocranium anomalies in adult Chiari type I malformation: a morphometric study. *J Neurologic Sci* 1990;99:137–45
3. Badie B, Mendoza D, Batzdorf U. Posterior fossa volume and response to suboccipital decompression in patients with Chiari I malformation. *Neurosurgery* 1995;37:214–18
4. Milhorat TH, Chou MW, Trinidad EM, et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. *Neurosurgery* 1999;44:1005–17
5. Karagoz F, Izgi N, Kapicioglu Sencer S. Morphometric measurements of the cranium in patients with Chiari type I malformation and comparison with the normal population. *Acta Neurochir (Wien)* 2002;144:165–71
6. Sekula RF Jr, Jannetta PJ, Casey KF, et al. Dimensions of the posterior fossa in patients symptomatic for Chiari I malformation but without cerebellar tonsillar descent. *Cerebrospinal Fluid Res* 2005;2:11
7. Milhorat TH, Nishikawa M, Kula RW, et al. Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management. *Acta Neurochir (Wien)* 2010;152:1117–27
8. Krogness KG. Posterior fossa measurements, I: the normal size of the posterior fossa. *Pediatr Radiol* 1978;6:193–97
9. Lirng JF, Fuh JL, Chen YY, et al. Posterior cranial fossa crowdedness is related to age and sex: a magnetic resonance volumetric study. *Acta Radiol* 2005;46:737–42
10. Noudel R, Gomis P, Sotoares G, et al. Posterior fossa volume increase after surgery for Chiari malformation Type I: a quantitative assessment using magnetic resonance imaging and correlations with the treatment response. *J Neurosurg* 2011;115:647–58
11. Nishikawa M, Sakamoto H, Hakuba A, et al. Pathogenesis of Chiari malformation: a morphometric study of the posterior cranial fossa. *J Neurosurg* 1997;86:40–47
12. Mazziotta J, Toga A, Evans A, et al. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos Trans R Soc Lond B Biol Sci* 2001;356:1293–322
13. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Medical Image Analysis* 2001;5:143–56
14. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002;17:143–55
15. Andersson JL, Smith SM, Jenkinson M. FNIRT: FMRIB's non-linear image registration tool. Annual Meeting of the Organization Hum Brain Mapping. Melbourne, Australia, 2008
16. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Medical Imaging* 2001;20:45–57
17. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002;33:341–55
18. Cabezas M, Oliver A, Llado X, et al. A review of atlas-based segmentation for magnetic resonance brain images. *Comput Methods Programs Biomed* 2011;104:e158–e177

Coil Embolization versus Clipping for Ruptured Intracranial Aneurysms: A Meta-Analysis of Prospective Controlled Published Studies

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ABSTRACT

BACKGROUND AND PURPOSE: Coil embolization is an alternative to clipping for intracranial aneurysms. However, controversy exists regarding the best therapeutic strategy in patients with ruptured aneurysms, and there is great center- and country-related variability in the rates of clipping versus coiling. We performed a meta-analysis of prospective controlled trials of clipping versus coil embolization for ruptured aneurysms.

MATERIALS AND METHODS: We performed a search of the English literature for published prospective controlled trials comparing surgical clipping with endovascular coil embolization for ruptured intracranial aneurysms. Data were abstracted from the identified references. Outcomes of interest were the proportion of patients with a poor outcome at 1 year and episodes of rebleeding from the index treated aneurysm after the allocated treatment.

RESULTS: There were 3 prospective controlled trials eligible for inclusion. These studies enrolled 2723 patients. Meta-analysis of these studies showed that the rate of poor outcome at 1 year was significantly lower in patients allocated to coil embolization (risk ratio, 0.75; 95% confidence interval, 0.65–0.87). This relative effect is consistent with an absolute risk reduction of 7.8% and a number needed to treat of 13. The effect on mortality was not statistically different across the 2 treatments. Rebleeding rates within the first month were higher in patients allocated to endovascular coil embolization.

CONCLUSIONS: On the basis of the analysis of the 3 high-quality prospective controlled trials available, there is strong evidence to indicate that endovascular coil embolization is associated with better outcomes compared with surgical clipping in patients amenable to either therapeutic strategy.

ABBREVIATIONS: RCT = randomized clinical trials; GDC = Guglielmi detachable coil; GOS = Glasgow Outcome Scale; ISAT = International Subarachnoid Aneurysm Trial; BRAT = Barrow Ruptured Aneurysm Trial

Rebleeding from a ruptured aneurysm is a deadly complication. Early treatment of the ruptured aneurysm has been proved to reduce the risk of early rebleeding¹ and has been the standard strategy for the treatment of patients with subarachnoid hemorrhage over the past 3 decades.² With the development of neuroendovascular techniques, endovascular coil embolization has become a valid and increasingly used alternative to surgical clip obliteration in patients with ruptured intracranial aneu-

rysms.³ However, the best therapeutic approach in a patient with a ruptured aneurysm continues to be debated, and rates of clipping versus coiling vary greatly across countries and single centers.

Since the approval by the FDA of the GDC in 1995, endovascular coil embolization has been compared with surgical clip occlusion in high-quality prospective controlled studies.^{4–7} We performed a meta-analysis of published prospective controlled studies to evaluate the comparative efficacy of both treatment modalities.

MATERIALS AND METHODS

We searched Medline, Embase, and the Cochrane Library for randomized trials and prospective controlled studies comparing surgical clipping and endovascular coil embolization for ruptured intracranial aneurysms. The electronic databases were searched by use of the OVID interface for trials on human subjects published in English between 2004–2011. A high-quality systematic

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Table 1: Summary of published randomized clinical trials of surgery versus coiling for ruptured aneurysms

	Kuopio	ISAT	BRAT
Period	February 1995 to August 1997	1997 to September 2002	March 2003 to January 2007
Single-center/multicenter	Single	Multicenter	Single
Enrollment	<72 hours	<28 days	<14 days
Total patients screened	242	9559	725
Patients enrolled	109	2143	471
Mean age (years)			
Endovascular	49	52	54
Surgery	50	52	53
No. of patients allocated endovascular	52	1073	233
No. of patients allocated surgery	57	1070	238
Good grade, <i>n</i> (% of total)	93 (85.3)	2018 (94.2)	380 (80.7)
Poor grade, <i>n</i> (% of total)	16 (13.7)	94 (5.8)	91 (19.3)
Crossovers			
From endovascular to surgery	12	9	75
From surgery to endovascular	4	38	4

review previously published provided references before 2004.⁸ Only studies in which patients had been either randomly assigned or prospectively alternatively allocated to surgery and to endovascular treatment were considered. Noncontrolled or retrospective studies comparing clinical results with surgical clipping or endovascular coiling and studies evaluating the effect of drugs or other therapeutic procedures on surgical or endovascular patients were excluded. The key words used, singly or in combination, included aneurysmal subarachnoid hemorrhage, cerebral aneurysm, cerebral aneurysms, clip/clips, coil/coils, clipping, coiling, endovascular, coil embolization, embolization, endovascular coil embolization, endovascular treatment, intracranial aneurysm, intracranial aneurysms, neurosurgical clipping, ruptured aneurysm, ruptured aneurysms, ruptured intracranial aneurysm, ruptured intracranial aneurysms, subarachnoid hemorrhage, and subarachnoid haemorrhage.

One hundred five potentially relevant references were identified on the basis of their titles; 88 were excluded after screening the abstract, and an additional 16 were excluded after reading the full text. The search yielded 1 new prospective controlled study with alternate prospective allocation since 2004.⁷ Eventually, 3 studies were included in the present analysis.

The primary outcome of interest was the percentage of patients with poor outcome at 1 year. The secondary outcome was rebleeding in the first year after treatment.

Data Collection

With the use of a standardized collection data form, data were extracted from all of the eligible trials. These data included:

Descriptive Data. Interval period during which the study was conducted, maximum time allowed from the index SAH, number of patients screened, study size, number of patients in each arm, patient mean age, and completeness of follow-up at 1 year.

Methodologic Data. Single-center or multicenter study, method for outcome assessment at 1 year, and definition of poor outcome.

Outcome Data. Proportion of patients with a poor outcome at 1 year and episodes of rebleeding from the index treated aneurysm during the first year after treatment.

Statistical Analysis. Random effects model was used to pool relative risks (risk ratios) and 95% confidence intervals across studies.⁹ Heterogeneity was evaluated by using the I^2 statistic.¹⁰

RESULTS

Three prospective controlled studies were eligible for inclusion in this analysis. Table 1 summarizes the main study characteristics, methodology, and enrollment. These studies enrolled 2723 patients. Only patients with aneurysms amenable to either surgical or endovascular treatment were enrolled in 2 of the trials,^{4,6} whereas in the remaining trial, all consecutive patients with SAH (including nonaneurysmal SAH) who

agreed to participate in the study were randomly assigned to 1 of the 2 treatment modalities in an alternating fashion.⁷ Functional outcome at 1 year was reported in the 3 studies.

This was performed by use of the GOS (poor outcome defined by GOS 1–3) rated by 1 of the investigators in 1 study^{4,5}; by use of modified Rankin Scale (poor outcome defined by modified Rankin Scale score 3–6) assessed by the patients in a mailed questionnaire (or a caretaker if the patient was unable to complete it) in 1 study⁶; and by use of modified Rankin Scale rated by a research nurse in 1 study.⁷ Methods of assessment of outcome at 1 year, rates of poor outcome according to treatment allocation, and episodes of rebleeding are summarized in Table 2.

Meta-analysis of these studies showed that the rate of poor outcome at 1 year was significantly lower in patients allocated to coil embolization (risk ratio, 0.75; 95% confidence interval, 0.65–0.87) (Fig 1). This difference represents an absolute risk reduction of 7.8% and translates into a number needed to treat of 13 (ie, 13 patients treated by coiling to prevent poor outcome in 1 patient). The effect on mortality was not statistically different across the 2 treatments. Rebleeding rates within the first month were higher in patients allocated to endovascular coil embolization, but the difference was not significant at 1 year (Fig 2). Heterogeneity across studies was minimal (<25%).

DISCUSSION

Since the introduction of GDCs into clinical practice in 1992, 2 randomized trials and 1 prospective controlled clinical trial have been published comparing functional outcome at 1 year after coil embolization versus surgical clip ligation for ruptured intracranial aneurysms. Our meta-analysis of these published trials shows that the odds of poor outcome are higher after surgical treatment than after endovascular treatment, despite a higher early risk of rebleeding from the target aneurysm after coil embolization. Furthermore, subgroup analyses from these clinical trials have indicated that the risks of seizures,¹¹ delayed cerebral ischemia,¹² ischemic lesions on MR imaging,¹³ and in-hospital complications¹⁴ are lower after coil embolization than after surgical clip ligation. A subgroup analysis of patients enrolled in the ISAT also showed improved cognitive outcome after coiling compared with surgery.¹⁵ These observations provide convincing evidence that endovascular coil embolization should be

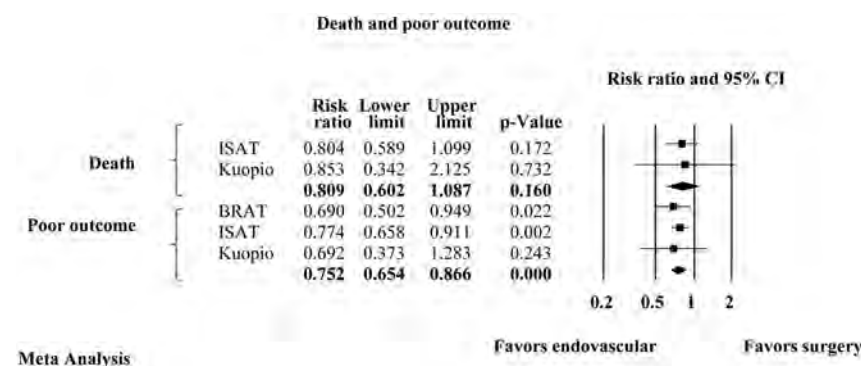
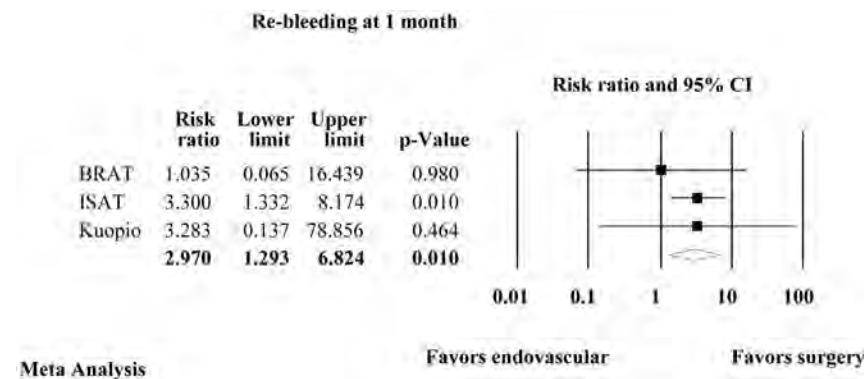
Table 2: Clinical outcome at 1 year (intent-to-treat analysis)

	Kuopio	ISAT	BRAT
Outcome assessment 1 year	Single neurosurgeon	Postal questionnaire filled out by patients	Research nurse
Definition poor outcome	GOS	mRS 3–6	mRS 3–6
Poor outcome			
Endovascular	12/52 (23%)	250/1063 (23.5%)	46/198 (23%)
Surgery	19/57 (33%)	326/1055 (30.9%)	69/205 (34%)
Death			
Endovascular	7/52 (13%)	85/1063 (8.0%)	NA
Surgery	9/57 (16%)	105/1055 (9.9%)	NA
Rebleeding			
Endovascular			
Day 1–30	1	20	1 ^a
Day 31–365	0	6	0
>1 year	0	10	0
Surgery			
Day 1–30	0	6	1
Day 31–365	0	4	0
>1 year	0	3 ^a	0
One-year follow-up complete			
Endovascular	100% ^b	1063/1073 (99%)	198/233 (85%)
Surgery		1055/1070 (98.6%)	205/238 (86%)

Note:—mRS indicates modified Rankin scale; NA, not available.

^a Intent-to-treat analysis;

^b 2 patients excluded after random assignment.

**FIG 1.** Meta-analysis of death and rate of poor functional outcome at 1 year.**FIG 2.** Meta-analysis of rebleeding from the treated aneurysm during the first month after treatment.

strongly considered as the preferred treatment technique for a ruptured aneurysm amenable to either therapeutic technique (surgery or endovascular coiling).

The “Kuopio” study was the first of the 3 published prospective controlled studies of coil embolization versus clip ligation for

ruptured intracranial aneurysms.^{4,5} This trial was a single-center study conducted in Kuopio, Finland, between 1995–1997 shortly after the introduction of endovascular treatment in that center. The study enrolled patients with aneurysms amenable to either surgical or endovascular treatment; patients requiring urgent hematoma evacuation or with a geometry not amenable to coil embolization were excluded.⁵ Overall, 109 patients were randomly assigned to surgery (57 patients) or endovascular treatment (52 patients).^{4,5} Primary clinical outcome at 1 year (measured by the GOS) was not significantly different between the 2 groups (intent-to-treat analysis), though there was a trend toward a lower rate of poor outcome in patients undergoing endovascular treatment (23% versus 33% in those allocated to surgery).⁵ There was 1 episode of early rebleeding after incomplete coil embolization, but no episodes of rebleeding were observed after discharge during a mean follow-up of >4 years.⁵

ISAT was a large, multicenter, randomized trial to assess the effectiveness of coil embolization compared with surgical clip ligation. The study was conducted between 1997–2002, and it was halted prematurely after enrollment of 2143 patients because of a significant outcome difference between the 2 groups favoring endovascular coil embolization.⁶ In ISAT, the proportion of patients with a poor outcome at 1 year (defined as a modified Rankin Scale score of >2) was 23.5% among patients assigned to coil embolization versus 30.9% in those allocated to clip ligation ($P = .0019$). Intrinsic to the ISAT study was the concept of “ equipoise”: to be enrolled into the trial, the ruptured aneurysm had to be judged amenable to either surgical or endovascular treatment by specialists in the 2 disciplines. Therefore, of more than 9000 patients screened at the participating centers during the interval of the study, only 2143 were eventually enrolled in the trial. As a result of the selection criteria,

most patients in ISAT were patients in good clinical grade (94% World Federation of Neurosurgical Societies grades 1–3) with small anterior circulation aneurysms (>90%). The high representation of patients with good grade aneurysmal SAH and anterior circulation aneurysms in ISAT may have been the result of pa-

tients with poor grade SAH and posterior circulation aneurysms being treated preferentially by coil embolization in ISAT centers.

Publication of the results of ISAT changed practice patterns for the treatment of ruptured aneurysms. However, several questions remained unanswered. Given the relatively high number of screened patients who were not considered candidates to participate in ISAT, some questioned the applicability of the ISAT results to patients with aneurysmal SAH at large. Moreover, questions were raised whether the ISAT results could apply to North American centers, where a supposedly higher degree of subspecialization exists among cerebrovascular surgeons dedicated to the care of patients with ruptured intracranial aneurysms.

In response to these concerns, investigators at the Barrow Neurological Institute in Phoenix, Arizona, launched BRAT in 2002.⁷ To assess results in a “real-world” situation, the BRAT investigators randomly assigned in an alternate fashion every patient with SAH admitted to their center during the period of the study who agreed to participate. As a consequence of this design, many patients with nonaneurysmal SAH were entered in the trial. Similarly, a large number of patients allocated to endovascular treatment crossed over to surgical treatment because patients could be enrolled regardless of whether the aneurysm was amenable to both treatment modalities. As a consequence, aneurysms that could not safely be treated with coiling because of technical reasons (ie, very small aneurysms) or clinical considerations (ie, aneurysms associated with intraparenchymal hematomas necessitating surgical evacuation) were originally assigned to embolization. Despite this high rate of crossover, the BRAT study confirmed the ISAT conclusions: outcomes at 1 year were better after coil embolization than after surgical clipping. The proportion of patients with a poor outcome (defined by modified Rankin Scale score >2) was 33.7% in the surgical group versus 23.2% ($P = .02$, intention-to-treat analysis) in the endovascular group. As-treated analysis yielded similar results, with 33.9% of patients in the surgical group and 20.4% in the endovascular group with a poor outcome at 1 year ($P = .01$).

Endovascular coil embolization of ruptured intracranial aneurysms is associated with better outcomes, but the risk of aneurysm recurrence, the need for retreatment, and the risk of rebleeding from the index aneurysm are higher after coil embolization.^{6,7,16} Among patients enrolled in ISAT, 17.4% of those undergoing endovascular treatment required re-treatment because of recurrence/residual aneurysm.¹⁶ Likewise, the risk of rebleeding was higher after endovascular coil embolization. Rates of rebleeding were 3.0% during the first year⁶ and 0.3% per year between post-treatment years 2 and 6, with no episodes of rebleeding after year 6.¹⁷ Despite the higher risk of rebleeding, the initial beneficial effect on functional outcome remained present up to 7 years after treatment,¹⁷ except in the subgroup of very young patients (<40 years).¹⁸

It is possible that the clinical results from endovascular treatment and the degree of long-term protection afforded by coil embolization have improved over the last decade, (ie, since the completion of ISAT) because of increasing operator experience and development of better devices. This argument is supported by the fact that there were no episodes of rebleeding reported in BRAT for up to 2 years after endovascular therapy.⁷ Similarly,

results of prospective studies comparing different coil designs have recently reported better outcomes after coil embolization than those reported in ISAT.¹⁹

Although this meta-analysis of the 3 published randomized clinical trials unequivocally indicates that outcomes at 1 year are better with endovascular treatment, there continue to be patients who are better candidates for surgical clip ligation. Very small aneurysms are often challenging to treat with an endovascular approach.²⁰ Similarly, many middle cerebral artery aneurysms have an unfavorable geometry for primary coiling, and they are often better treated with surgical clipping.²¹ Moreover, very young patients with ruptured anterior circulation aneurysms (especially those who may be noncompliant with follow-up imaging) may also be better candidates for surgical treatment rather than endovascular coil embolization.¹⁸ Despite the evidence from randomized clinical trials, the decision on what is the best treatment for a ruptured aneurysm in a given patient should be individualized by taking into consideration aneurysm-related and patient-specific factors.^{21,22}

We acknowledge that our meta-analysis has limitations. The methodologic quality of the trials included was variable. Only ISAT fulfilled all the criteria of a high-quality randomized controlled trial. Entry criteria and outcome assessment differed across studies. Yet, the finding that all trials produced consistent results favoring the endovascular arm reassures us that these methodologic differences do not negate the validity of the meta-analysis.

CONCLUSIONS

This meta-analysis of published prospective controlled trials of surgical clipping versus endovascular coil embolization for patients with ruptured intracranial aneurysms provides convincing evidence that functional outcome at 1 year is better after endovascular treatment despite a higher risk of rebleeding from the index aneurysm after coil embolization. Hence, when technically feasible, endovascular coil embolization should be the preferred technique for the treatment of ruptured intracranial aneurysms.

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REFERENCES

1. Haley EC Jr, Kassell NF, Torner JC. **The International Cooperative Study on the Timing of Aneurysm Surgery: the North American experience.** *Stroke* 1992;23:205–14
2. Rabinstein AA, Lanzino G, Wijdicks EF. **Multidisciplinary management and emerging therapeutic strategies in aneurysmal subarachnoid haemorrhage.** *Lancet Neurol* 2010;9:504–19
3. Leake CB, Brinjikji W, Kallmes DF, et al. **Increasing treatment of ruptured cerebral aneurysms at high-volume centers in the United States.** *J Neurosurg* 2011;115:1179–83
4. Vanninen R, Koivisto T, Saari T, et al. **Ruptured intracranial aneurysms: acute endovascular treatment with electrolytically detachable coils—a prospective randomized study.** *Radiology* 1999;211:325–36
5. Koivisto T, Vanninen R, Hurskainen H, et al. **Outcomes of early endovascular versus surgical treatment of ruptured cerebral**

- aneurysms: a prospective randomized study. *Stroke* 2000;31:2369–77
6. Molyneux A, Kerr R, Stratton I, et al. **International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.** *Lancet* 2002;360:1267–74
 7. McDougall CG, Spetzler RF, Zabramski JM, et al. **The Barrow Ruptured Aneurysm Trial.** *J Neurosurg* 2012;116:135–44
 8. van der Schaaf I, Algra A, Wermer M, et al. **Endovascular coiling versus neurosurgical clipping for patients with aneurysmal subarachnoid haemorrhage.** *Cochrane Database Syst Rev* 2005; CD003085
 9. DerSimonian R, Laird N. **Meta-analysis in clinical trials.** *Control Clin Trials* 1986;7:177–88
 10. Higgins JP, Thompson SG, Deeks JJ, et al. **Measuring inconsistency in meta-analyses.** *BMJ* 2003;327:557–60
 11. Molyneux AJ, Kerr RS, Yu LM, et al. **International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion.** *Lancet* 2005;366:809–17
 12. Dorhout Mees SM, Kerr RS, Rinkel GJ, et al. **Occurrence and impact of delayed cerebral ischemia after coiling and after clipping in the International Subarachnoid Aneurysm Trial (ISAT).** *J Neurol* 2011;259:679–83
 13. Bendel P, Koivisto T, Kononen M, et al. **MR imaging of the brain 1 year after aneurysmal subarachnoid hemorrhage: randomized study comparing surgical with endovascular treatment.** *Radiology* 2008;246:543–52
 14. Vergouwen MD, Fang J, Casaubon LK, et al. **Higher incidence of in-hospital complications in patients with clipped versus coiled ruptured intracranial aneurysms.** *Stroke* 2011;42:3093–98
 15. Scott RB, Eccles F, Molyneux AJ, et al. **Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: neuropsychological outcomes from the International Subarachnoid Aneurysm Trial (ISAT).** *Stroke* 2010;41:1743–47
 16. Campi A, Ramzi N, Molyneux AJ, et al. **Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT).** *Stroke* 2007;38:1538–44
 17. Molyneux AJ, Kerr RS, Birks J, et al. **Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up.** *Lancet Neurol* 2009;8:427–33
 18. Mitchell P, Kerr R, Mendelow AD, et al. **Could late rebleeding overturn the superiority of cranial aneurysm coil embolization over clip ligation seen in the International Subarachnoid Aneurysm Trial?** *J Neurosurg* 2008;108:437–42
 19. Coley S, Sneade M, Clarke A, et al. **Cerecyte Coil Trial: procedural safety and clinical outcomes in patients with ruptured and unruptured intracranial aneurysms.** *AJNR Am J Neuroradiol* 2012;33:474–80
 20. Brinjikji W, Lanzino G, Cloft HJ, et al. **Endovascular treatment of very small (3 mm or smaller) intracranial aneurysms: report of a consecutive series and a meta-analysis.** *Stroke* 2010;41:116–21
 21. Lanzino G, Fraser K, Kanaan Y, et al. **Treatment of ruptured intracranial aneurysms since the International Subarachnoid Aneurysm Trial: practice utilizing clip ligation and coil embolization as individual or complementary therapies.** *J Neurosurg* 2006;104:344–49
 22. Lanzino G. **The Barrow Ruptured Aneurysm Trial.** *J Neurosurg* 2012;116:133–34

Coil Type Does Not Affect Angiographic Follow-Up Outcomes of Cerebral Aneurysm Coiling: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND AND PURPOSE: Previous studies varied in their conclusions about the superiority of second-generation coils compared with bare platinum. In this systematic review and meta-analysis, we assessed differences in reported unfavorable angiographic outcomes of cerebral aneurysms treated with coil embolization as a function of coil type.

MATERIALS AND METHODS: This systematic review covered 1999–2011 through the use of Ovid MEDLINE and EMBASE. Search terms were “subarachnoid hemorrhage,” “intracranial aneurysms,” “endovascular treatment,” and “coiling.” Inclusion criteria were studies reporting >50 aneurysms with imaging follow-up. We defined “unfavorable angiographic outcome” as either “recanalization,” <90% occlusion, or “incomplete occlusion” at follow-up. Rates of unfavorable outcomes were pooled through the use of random effects models and compared across various coil types. Multivariate random effects meta-regression models were used to further explore the differences in outcomes related to coil type.

RESULTS: We included 82 studies, comprising 90 patient cohorts, among which, 65 (72%) used bare platinum coils, 8 (8.9%) used Matrix, 11 (12%) used HydroCoil, and 6 (6.7%) used Cerecyte. The overall unfavorable outcome rate was 19% (95% CI: 17%, 21%). Unfavorable outcome rates were 20% (95% CI: 17%, 22%) for bare platinum coils, 23% (95% CI: 16%, 29%) for Matrix, 15% (95% CI: 9%, 21%) for HydroCoil, and 15% (95% CI: 7%, 23%) for Cerecyte, respectively. The difference in unfavorable outcome rates among the various coil types was not statistically significant after adjusting for baseline characteristics, including aneurysm size, rupture status, and follow-up duration.

CONCLUSIONS: The rate of unfavorable angiographic outcomes was not statistically different across the major approved coil types. The quality of the evidence, however, remains low because of high heterogeneity, small sample size, and potential publication bias.

ABBREVIATIONS: MeSH = Medical Subject Headings; RCT = randomized, controlled trial; IQR = interquartile range

Despite widespread acceptance of endovascular coil embolization for aneurysms, rates of unfavorable angiographic outcomes remain relatively high. A recent systematic review of coiling literature reported a rate of 18% of such outcomes.¹ In an effort to improve long-term occlusion rates, a number of “modified,” second-generation coil types have been developed and marketed. Numerous single-center case series have been published regarding outcomes for each of these second-generation coil types, including Matrix (Boston Scientific, Natick, Massachusetts),

HydroCoil (MicroVention, Tustin, California),^{2–4} and Cerecyte coils (Codman Neurovascular, Raynham, Massachusetts).^{8,9} In addition, outcomes from several randomized, controlled trials (RCTs) of the major coil types have recently been reported.^{10–12}

To date, relatively few literature reviews of second-generation coils have been published, and such reviews rarely if ever have implemented formal meta-analytic procedures.^{13,14} In this current study, we report results from a systematic review and meta-analysis assessing differences in reported unfavorable angiographic outcomes for cerebral aneurysms treated with coil embolization as a function of coil type.

MATERIALS AND METHODS

The methodology and reporting of this systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.¹⁵

Literature Search

We searched Ovid MEDLINE and EMBASE databases from January 1999 to December 2011. The search was performed by an

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experienced reference librarian. The following key words as Medical Subject Headings (MeSH) terms and text words were used in relevant combinations: “subarachnoid hemorrhage,” “intracranial aneurysm,” “endovascular treatment,” and “coiling” in both “AND” and “OR” combinations. In addition, we reviewed abstracts from selected radiology, neurology, and neurosurgery scientific meetings in the years 2011 and 2012 to identify coil studies (the 2012 annual meeting of the American Society of Neuroradiology, the 2011 annual meeting of the Society of Neurointerventional Surgery, and the 2011 annual meeting of the Congress of Neurologic Surgeons).

Inclusion criteria were 1) >50 aneurysms reported, 2) coil type clearly specified and noted to be either bare platinum, Matrix, HydroCoils, or Cerecyte coils, and 3) available imaging follow-up with DSA or MR angiography. If both MRA and DSA outcomes were available, we included DSA results. If DSA was not available, MR angiography was then used.

Exclusion criteria were 1) traumatic, dissecting, mycotic, or flow-related aneurysms, 2) treatment with other coil types or lack of clarity regarding coil type used, primarily stent-treated aneurysms, or non-coil embolic agents used to perform either aneurysm or parent vessel coil occlusions. When studies had multiple groups comparing different imaging modalities (eg, DSA, MRA), only the groups that were followed with DSA were considered. When the same patient population was the subject of multiple publications, only the study with the largest cohort was included in this analysis.

The primary outcome was “unfavorable” angiographic outcome, defined as any degree of recanalization noted on the follow-up images with comparison to the immediate posttreatment results. Terms such as “aneurysm recurrence,” “new filling of aneurysm lumen,” and “regrowth” were considered synonymous with “recanalization.” If “recanalization” was not reported in a study, then the “unfavorable angiographic outcome” was defined as either <90% degree of occlusion or class 3 on the Raymond scale (incomplete occlusion), which is defined as any opacification of the sac.¹⁶ We considered the longest duration of reported angiographic results for each study when more than 1 phase of follow-up was reported.

Each of 2 reviewers (I.R., G.M.) independently evaluated the articles in the librarian’s primary list and selected studies that fulfilled the inclusion criteria. In the case of a disagreement, D.F.K. reviewed and adjudicated inclusion. For each study, we extracted number of coiled aneurysms, number of aneurysms that had available follow-up, mean aneurysm size, initial rupture status, mean duration of follow-up, use of a core laboratory facility, whether assessed by single or multiple readers, angiographic follow-up outcomes, and coil types.

In this present review, we classified 4 types of coils: bare platinum, Matrix, HydroCoil, and Cerecyte. Guglielmi detachable coils were considered to be equivalent to bare platinum coils. Matrix coils included all Matrix subtypes (Matrix 1, Matrix 2, Matrix ACTIVE, and Matrix POST-ACTIVE). The HydroCoil group included studies that used either HydroCoil or HydroSoft. Cerecyte studies were considered as Cerecyte when their use was clearly stated in the methods.

Statistical Analysis

We used the analysis of variance test to compare baseline group characteristics (mean aneurysm size, proportion of initially rup-

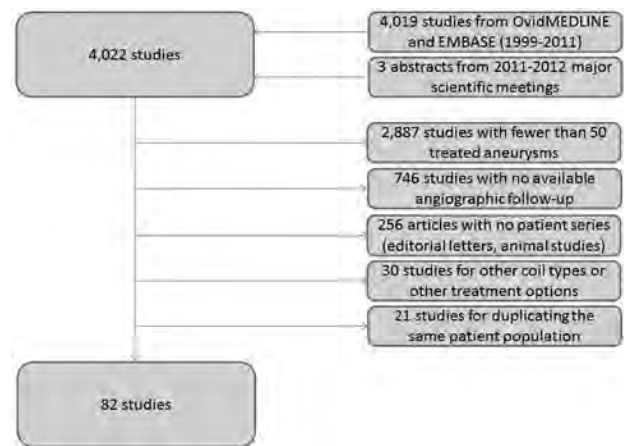


FIG 1. Search strategy in a flow chart along with reasons for exclusion.

tured aneurysms, and mean follow-up duration). We calculated the rates of unfavorable angiographic outcomes from each study. The confidence intervals of the rates were estimated by the Jeffreys method.¹⁷ We used the DerSimonian and Laird random effects method to pool the overall rate of unfavorable outcome as well as the rate of unfavorable outcome for each coil type.^{18,19} To compare rates of unfavorable outcomes among coil types, we used the test of interaction proposed by Altman and Bland.²⁰ We also constructed multivariate nested random effects meta-regression models to further explore the difference of coil types after adjusting for baseline characteristics.¹⁹

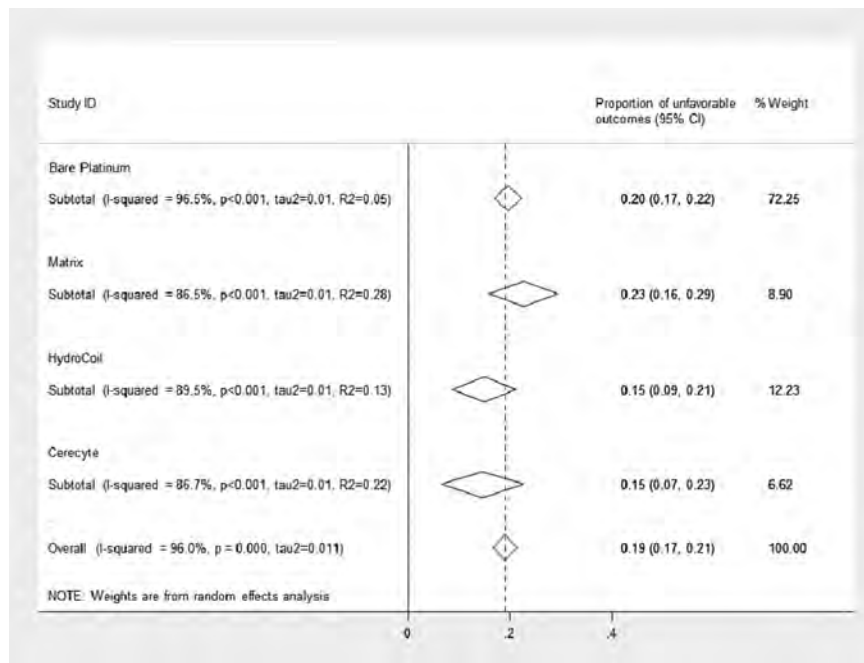
We used the I^2 statistic and the Cochran Q test to measure the overall heterogeneity, which refers to the variations of study outcomes across the studies. $I^2 > 50\%$ and a conservative P value ($P < .10$) suggest high heterogeneity.²¹ The Tau² statistic was adopted to measure the variance across studies. We also used the R^2 statistic to measure the proportion of total variance explained by each coil type. With the use of the Egger regression asymmetry test, we also assessed whether our findings were likely to be biased by the tendency that significant results are more likely to be published, so-called publication bias.²² All statistical analyses were conducted with the use of STATA version 12 (StataCorp, College Station, Texas). We used the GRADE framework to evaluate the overall quality of the evidence (ie, confidence in the estimates).^{23,24}

Study Quality

The quality of the included studies was assessed by use of the New castle–Ottawa Quality Assessment Scale.²⁵ We selected the scale items relevant to uncontrolled studies, such as most the included studies, and therefore quality evaluation focused on the following items: representativeness of the exposed cohort to the population at hand (truly or somewhat representative versus selected groups or no description), selection of the nonexposed cohort (drawn from the same population versus not or no description), ascertainment of exposure (coiling procedure recorded), assessment of the outcome (independent versus self-report), length of follow-up (>6 months or <6 months), and loss to follow-up (>75% of the studied aneurysms were followed versus less).

Table 1: Baseline characteristics of study groups

Coil Group	Number of Studied Groups (%)	Mean Aneurysm Size, mm (SD)	Percentage of Initially Ruptured Aneurysms (SD)	Mean Follow-Up Duration, mo (SD)
Total	90 (100)	8.0 (3.1)	64 (28)	18.9 (19.8)
Bare platinum	65 (72)	8.2 (3.5)	66 (30)	22.2 (22.2)
Matrix	8 (8.9)	7.5 (1.8)	55 (16)	9.4 (3.2)
HydroCoil	11 (12)	7.9 (1.2)	58 (23)	10.3 (4.2)
Cerecyte	6 (6.7)	6.3 (7.9)	72 (22)	11.2 (9.0)

**FIG 2.** Forest plot shows the pooled outcome estimates from random effects analysis.

RESULTS

We identified 4019 potential references published between January 1999 and December 2011 as well as 3 prospective coil studies identified from 2011–2012 conference proceedings^{11,12,26} (Fig 1). There was a disagreement on 8 studies (0.2%) between the 2 reviewers that was resolved by a decision from the senior author. A total of 3940 studies (97%) of 4022 were excluded for the following reasons: <50 treated aneurysms (2887 articles; 72%), no available angiographic follow-up (746 articles; 19%), nonclinical series (editorial letters, nonhuman experimental models for cerebral aneurysms) (256 articles; 6%), utilization of coil types other than the designated included categories or treatment options other than coiling, such as stents alone or parent artery occlusion (30 articles; 0.8%), and duplicate publishing of the same patient population (21 articles; 0.5%). As such, 82 (2%) studies met all inclusion criteria and were included in our analysis (see On-line Appendix for full list of included studies). Seventy-four (90%) of the 82 studies described patients treated with a single coil type. The remaining 8 studies of the included 82 (10%) compared 2 subsets of patient groups that were treated with 2 different coil types. Each subset was considered a separate patient subgroup. In total, there were 90 patient subgroups.

The total number of treated aneurysms was 17,706, of which 12,986 (73%) had available angiographic follow-up outcomes and were included in the final analysis. The overall mean aneurysm size was 8.0 mm (interquartile range [IQR]: 4.6–15 mm).

The average percentage of ruptured aneurysms in the enrolled studies was 64% (IQR: 11–100%). The patients were followed up to 18.9 months (IQR: 4.5–69 months) on average.

Sixty-five (72%) of 90 patient subgroups were treated with bare platinum coils, 8 subgroups (8.9%) were treated with Matrix coils, 11 (12%) were treated with HydroCoils, and 6 (6.7%) were treated with Cerecyte. Table 1 summarizes baseline characteristics of the studied groups. The differences among coil types were not significant regarding mean aneurysm size ($P = .69$), the proportion of initially ruptured aneurysms ($P = .58$), or the mean duration of follow-up ($P = .08$).

The pooled rates of unfavorable outcomes are shown in Fig 2. Overall, the rate of unfavorable outcomes from all studies was 19% (95% CI: 17%, 21%) (2452 of 12,986 aneurysms). For bare platinum coils, the rate was 20% (95%

CI: 17%, 22%) (1907 of 10,370 aneurysms), for Matrix it was 23% (95% CI: 16%, 29%) (279 of 1128 aneurysms), for HydroCoil it was 15% (95% CI: 8.7%, 21%) (175 of 977 aneurysms), and for Cerecyte it was 15% (95% CI: 6.6%, 23%) (91 of 511 aneurysms). The difference in rates across various coil types was not statistically significant ($P = .32$). Even after adjusting for baseline rupture, aneurysm size, follow-up time, core laboratory, and multiple-reader interpretation effect, we found no significant differences in the reported unfavorable outcomes rates between coil types (Table 2).

Across studies, substantial heterogeneity was observed in all pooled outcome estimates ($I^2 > 50\%$, $P < .001$) (Fig 2). The Egger regression asymmetry test suggested potential publication bias ($P < .001$). The quality of the included studies is summarized in Fig 3. Only 3 (3.7%) of 82 studies were RCTs.^{10,12} The remaining studies were observational cohort studies with or without a control group. Fig 3 summarizes the quality of the included studies. Selection of nonexposed cohorts was not adequate because most of the studies described a single-center series of patients with no control group. The assessment of outcome was self-reported except for 8 (9.8%) of 82 studies in which an independent core laboratory reported the angiographic outcomes. The other items were found to be adequate in the included studies. The overall quality of the current evidence (ie, confidence in the estimates) is

low, considering the observational nature of most of the studies, heterogeneity, and the likelihood of publication bias.

DISCUSSION

In the current study, with the use of formal meta-analytic tools, we found that reported rates of unfavorable angiographic outcomes were not significantly different among the various leading types of endovascular coils for aneurysm therapy. Overall, approximately 1 in 5 aneurysms showed unfavorable outcome at follow-up. At first glance, both HydroCoil and Cerecyte rates appear to be superior to bare platinum and Matrix, with the former coil types showing 15% and the latter coil types showing 20% unfavorable outcome rates. However, given the relatively small numbers of aneurysms, even when pooling studies, the confidence intervals for all reported proportions were wide and thus significant differences were not shown. The results from this current study were further compromised by substantial heterogeneity among studies as well as by signals of potential publication bias. Taken together, these results suggest that clear differences among coil type have yet to be manifest and that implementation of future, high-quality, prospective studies remains of paramount importance.

Previous studies have failed to demonstrate consensus regarding the relative advantages of second-generation coils compared with bare platinum coils. Whereas some previous studies were encouraging for improved outcomes,^{7,27-30} others were not as promising.^{13,31,32} Three recent RCTs compared

bare platinum coils with each of the leading modified coils, including HydroCoil,¹⁰ Matrix,¹¹ and Cerecyte coils.¹² The HELPS trial found a slight improvement in major recurrences among aneurysms that were treated with HydroCoils. However, the MAPS and Cerecyte trials found no significant advantages of newer devices over bare platinum.

Previous reviews of the literature have assessed possible advantages of Matrix coils¹³ and other second-generation coils.¹⁴ The results of our current study are relatively consistent with previous studies, in that none has found significant differences between coil types on angiographic follow-up. However, our current study improves on this prior literature in several ways. First, previous studies comprised studies up to the year 2005¹³ or 2007¹⁴; therefore, our results bring the evidence base up to date. Furthermore, with the use of formal meta-analytic techniques, we accounted for potential confounding variables such as aneurysm size, baseline rupture status, and duration of follow-up, all of which can impact rates of unfavorable angiographic outcome. Finally, our data point to substantial heterogeneity as well as potential publication bias, which mandate that all of these results should undergo careful scrutiny by practitioners.

Our study has many limitations. The heterogeneity of the studies in the literature forced us to combine patients that were followed by either DSA or MR angiography despite possible technique-related variations and combine multiple types of unfavorable results, including incomplete occlusion and Raymond class 3, with recanalization. Also, most studies were excluded for incomplete reporting of outcomes. We did not consider other variables that would potentially affect outcomes, including proportion of wide-necked aneurysms and anatomic location. The lack of statistical significance may also be due underpowered subgroup analyses and should not be interpreted as equivalence of the different coil types. Finally, in this systematic review, we found only 3 RCTs. Observational studies are subject to high risk of bias be-

Table 2: Multivariate random effects meta-regression

Variable	Odds Ratio	95% Confidence Interval	P Value
Bare platinum	Reference		
Matrix	0.93	0.30, 2.89	.90
HydroCoil	0.46	0.17, 1.25	.13
Cerecyte	0.58	0.17, 1.99	.38

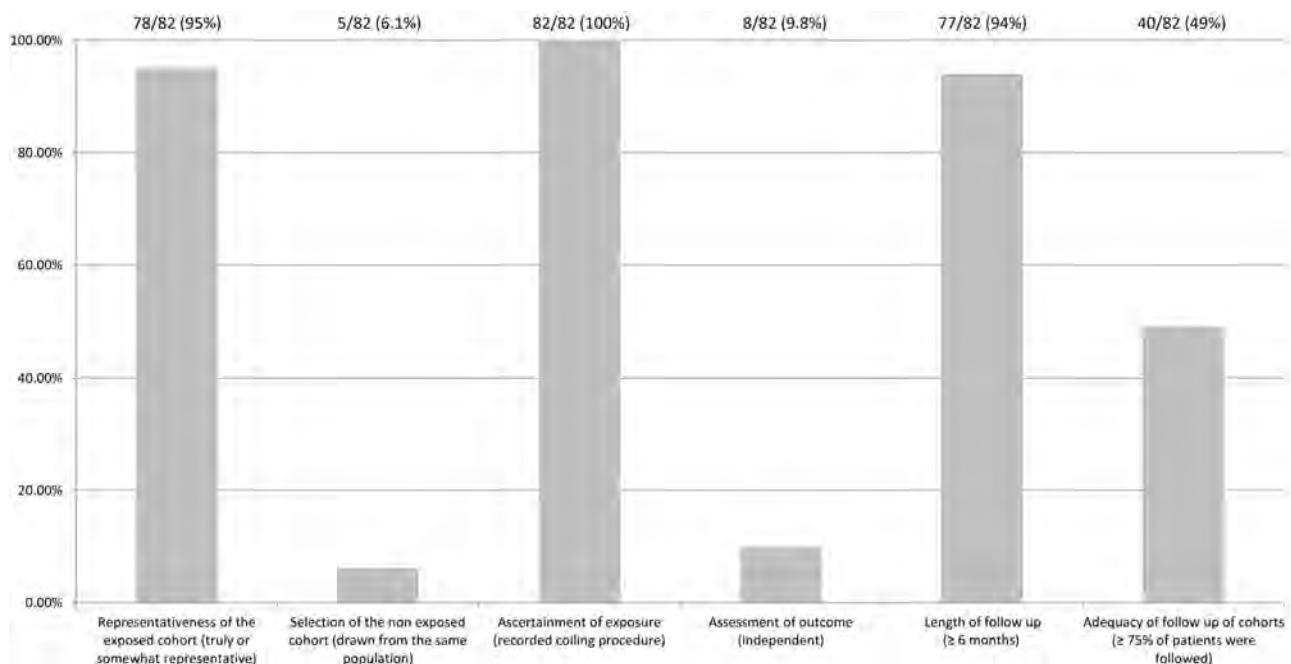


FIG 3. Quality assessment of the included studies.

cause of baseline imbalance and potential outcome confounding. By pooling results from observational studies and RCTs, ecological bias may have affected our results. Further studies are clearly needed to provide higher quality evidence.

CONCLUSIONS

The rate of unfavorable angiographic outcomes of cerebral aneurysms treated with coil embolization was not statistically different across the major approved coil types.

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REFERENCES

- Rezek I, Mousan G, Wang Z, et al. Effect of core laboratory and multiple-reader interpretation of angiographic images on follow-up outcomes of coiled cerebral aneurysms: a systematic review and meta-analysis. *AJNR Am J Neuroradiol* 2013;34:1380–84
- Linfante I, Akkawi NM, Perlow A, et al. Polyglycolide/polylactide-coated platinum coils for patients with ruptured and unruptured cerebral aneurysms: a single-center experience. *Stroke* 2005;36:1948–53
- Mitra D, Herwadkar A, Soh C, et al. Follow-up of intracranial aneurysms treated with Matrix detachable coils: a single-center experience. *AJNR Am J Neuroradiol* 2007;28:362–67
- Ishii A, Murayama Y, Nien YL, et al. Immediate and midterm outcomes of patients with cerebral aneurysms treated with Matrix1 and Matrix2 coils: a comparative analysis based on a single-center experience in 250 consecutive cases. *Neurosurgery* 2008;63:1071–79
- Berenstein A, Song JK, Niimi Y, et al. Treatment of cerebral aneurysms with hydrogel-coated platinum coils (HydroCoil): early single-center experience. *AJNR Am J Neuroradiol* 2006;27:1834–40
- Deshaias EM, Adamo MA, Boulos AS. A prospective single-center analysis of the safety and efficacy of the Hydrocoil embolization system for the treatment of intracranial aneurysms. *J Neurosurg* 2007;106:226–33
- Gunnarsson T, Tong FC, Klurfan P, et al. Angiographic and clinical outcomes in 200 consecutive patients with cerebral aneurysm treated with hydrogel-coated coils. *AJNR Am J Neuroradiol* 2009;30:1657–64
- Butteriss D, Gholkar A, Mitra D, et al. Single-center experience of Cerecyte coils in the treatment of intracranial aneurysms: initial experience and early follow-up results. *AJNR Am J Neuroradiol* 2008;29:53–56
- Geyik S, Yavuz K, Ergun O, et al. Endovascular treatment of intracranial aneurysms with bioactive Cerecyte coils: effects on treatment stability. *Neuroradiology* 2008;50:787–93
- White PM, Lewis SC, Gholkar A, et al. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomized controlled trial. *Lancet* 2011;377:1655–62
- Claiborne Johnson S, McDougal C, Gholkar A. The MAPS (Matrix and Platinum Science) Trial: primary results. In: Proceedings of the Eighth Annual Meeting of the Society of Neurointerventional Surgery, Colorado Springs, Colorado: July 25–28, 2011
- Molyneaux AJ, Fox A, Sneade M, et al. Cerecyte Coil Trial: angiographic and clinical outcomes of endovascular coiling in patients with ruptured and unruptured intracranial aneurysms treated with Cerecyte coils compared with bare platinum coils: final results of a prospective randomized trial. In: *Proceedings of the American Society of Neuroradiology 50th Annual Meeting and the Foundation of the ASNR Symposium*, New York: April 21–26, 2012
- Smith MJ, Mascitelli J, Santillan A, et al. Bare platinum vs Matrix detachable coils for the endovascular treatment of intracranial aneurysms: a multivariate logistic regression analysis and review of the literature. *Neurosurgery* 2011;69:557–65
- White PM, Raymond J. Endovascular coiling of cerebral aneurysms using “bioactive” or coated-coil technologies: a systematic review of the literature. *AJNR Am J Neuroradiol* 2009;30:219–26
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–69
- Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. *Stroke* 2001;32:1998–2004
- Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26:404–13
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;7:177–88
- Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;318:1730–37
- Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326:219
- Julian PTH, Simon GT, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60
- Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34
- Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3, rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–06
- Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4, rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407–15
- Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Third Symposium on Systematic Reviews: Beyond the Basics*. 2000 July; Oxford, UK.
- Pierot L, Cognard C, Ricolfi F, et al. Mid-term anatomic results after endovascular treatment of ruptured intracranial aneurysms with GDC and Matrix coils: analysis of the CLARITY series. *AJNR Am J Neuroradiol* 2012;33:469–73
- Murayama Y, Viñuela F, Ishii A, et al. Initial clinical experience with Matrix detachable coils for the treatment of intracranial aneurysms. *J Neurosurg* 2006;105:192–99
- Park JH, Kang HS, Han MH, et al. Embolization of intracranial aneurysms with HydroSoft coils: results of the Korean multicenter study. *AJNR Am J Neuroradiol* 2011;32:1756–61
- Cloft HJ, Kallmes DF. Aneurysm packing with HydroCoil embolic system versus platinum coils: initial clinical experience. *AJNR Am J Neuroradiol* 2004;25:60–62
- O’Hare AM, Fanning NF, Ti JP, et al. HydroCoils, occlusion rates, and outcomes: a large single-center study. *AJNR Am J Neuroradiol* 2010;31:1917–22
- Roth C, Struffert T, Grunwald IQ, et al. Long-term results with Matrix coils vs GDC: an angiographic and histopathological comparison. *Neuroradiology* 2008;50:693–99
- Piotin M, Spelle L, Mounayer C, et al. Intracranial aneurysms coiling with Matrix: immediate results in 152 patients and midterm anatomic follow-up from 115 patients. *Stroke* 2009;40:321–23

Use of CT Angiography and Digital Subtraction Angiography in Patients with Ruptured Cerebral Aneurysm: Evaluation of a Large Multihospital Data Base

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ABSTRACT

BACKGROUND AND PURPOSE: Both CT angiography and digital subtraction angiography are used to detect aneurysms in patients with subarachnoid hemorrhage. We examined a large multihospital data base to determine how practice is evolving with regard to the use of CT angiography and DSA in patients with ruptured cerebral aneurysm.

MATERIALS AND METHODS: The Premier Perspective data base was used to identify hospitalizations of patients treated with clipping or coiling of ruptured cerebral aneurysms from 2006–2011. Billing information was used to determine pretreatment and posttreatment use of DSA and CT angiography during hospitalization.

RESULTS: A total of 4972 patients (1022 clipping, 3950 coiling) at 116 hospitals were identified. The percentage of patients with SAH who underwent pretreatment CT angiography significantly increased from 20% in 2006 to 44% in 2011 ($P < .0001$), whereas the percentage of patients who underwent DSA remained unchanged from 96–94% ($P = .28$). This CT angiography trend was observed in coiling patients (17–42%, $P < .0001$) and clipping patients (32–54%, $P < .0001$). There was a significant increase in the percentage of patients who underwent posttreatment imaging from 41% in 2006 to 48% in 2011 ($P = .0037$). This trend was observed in clipping patients (33–65%, $P < .0001$) but not coiling patients (43–45%, $P = .62$).

CONCLUSIONS: For the pretreatment evaluation of ruptured aneurysms, the use of CT angiography increased from 2006–2011 without a corresponding decrease in the use of DSA. These results raise the question of potential redundancy without added clinical value of the second test.

The standard examination to evaluate for a source of subarachnoid hemorrhage for decades has been conventional angiography, which has now evolved into digital subtraction angiography. This is reflected in the American Heart Association/American Stroke Association guidelines for the management of aneurysmal SAH, which strongly recommend DSA in their class I recommendations.¹ In recent years, however, surgery without DSA on the basis of CT angiography has been advocated.^{2–5} A recent meta-analysis concluded that CT angiography can be used as a primary examination tool in the diagnostic work-up of patients with SAH,⁶ but that conclusion has been questioned because of weaknesses of CT angiography in the detection of small aneurysms and aneurysms adjacent to the skull base.^{7–9} Whether the imaging method used is DSA or CT angiography, the imaging

must identify the source of bleeding, most commonly an aneurysm. We evaluated a large, multihospital data base to determine how practice is evolving with regard to the use of CT angiography and DSA in patients with ruptured cerebral aneurysm.

MATERIALS AND METHODS

Study Population and Data Retrieval

The Perspective data base is a voluntary, fee-supported collection of data developed by Premier, Inc, to assess quality and resource use.¹⁰ As of 2011, the Perspective data base contained information from more than 600 US hospitals and consisted of approximately 15% of hospitalizations nationwide. This data base contains detailed hospitalization information, including patient and hospital demographics, diagnoses, and all billed items including procedures and diagnostic tests administered in relation to the day of admission. Because the Perspective data base consists of only de-identified patient and hospital data, our institutional review board deemed this study exempt from review and patient consent.

Patients who presented with subarachnoid hemorrhage (ICD-9-CM diagnostic code 430) from 2006–2011 were identified. Pa-

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Patient and hospital demographics

	Clipping	Coiling
Patient		
Number of patients	1022	3950
Age, y, median (interquartile range)	53 (45–61)	55 (46–65)
Female sex, <i>n</i> (%)	667 (65%)	2800 (71%)
Hospital		
Region, <i>n</i> (%)		
Midwest	156 (15%)	447 (11%)
South	436 (43%)	1666 (42%)
Northeast	273 (27%)	1290 (33%)
West	157 (15%)	547 (14%)
Median number of beds (range)	623 (447–725)	623 (442–683)
Urban location, <i>n</i> (versus rural)	1011 (99%)	3857 (98%)
Teaching, <i>n</i> (versus nonteaching)	699 (68%)	2684 (68%)

tients were included if they underwent aneurysmal clipping (ICD-9 procedural code 39.51, “clipping of aneurysm”) or coiling (ICD-9 procedural codes 39.52, [“other repair of aneurysm”], 39.72 [“endovascular repair of occlusion of head and neck vessels”], 39.75 [“endovascular embolization or occlusion of vessel[s] of head or neck by using bare coils”], 39.76 [“endovascular embolization or occlusion of vessel[s] of head or neck by using bioactive coils”], and 39.79 [“other endovascular repair [of aneurysm] of other vessels”]) during hospitalization. Patient billing information was used to confirm clipping patients by the presence of an aneurysm clip and to confirm coiling patients by the presence of endovascular coil(s).

Hospitals were defined as clipping or coiling centers if they performed clipping or coiling procedures at a rate of at least 5:1 over the 2006–2011 timeframe compared with coiling or clipping, respectively. Hospitals that performed both clipping and coiling at <5:1 ratio were defined as performing both procedures.

Billing information was used to retrieve use of DSA or CT angiography during hospitalization. Day of DSA or CT angiography in relation to the day of admission was retrieved. Patients were included if they had DSA of the carotid or vertebral arteries or CT angiography of the head before clipping or coiling, defined as the day before or day of the procedure. The use of CT angiography and DSA at any point after clipping or coiling to discharge was also retrieved.

Statistics

Data were extracted from the Perspective data base by use of SAS (SAS, version 9.3; SAS Institute, Cary, North Carolina) and analyzed by use of JMP (version 9, SAS Institute). Continuous results are presented as median and interquartile range to account for nonparametric data distributions. Categorical results are presented as percentages. Differences in imaging use in 2006 and 2011 were compared by use of Fisher exact test.

RESULTS

Study Population

A total of 4972 patients were identified, of which 1022 were clipping cases and 3950 were coiling cases. Patient demographic characteristics are shown in the Table. A total of 116 hospitals were represented in the 2006–2011 timeframe. Most hospitals were urban, and more than half were teaching hospitals.

Pretreatment Imaging

Trends in pretreatment imaging from 2006–2011 are shown in Fig 1. A wide variation in use of imaging was observed. Overall,

65% (3216/4972) of patients with SAH underwent DSA only, 6% (301/4972) underwent CT angiography only, and 29% (1455/4972) underwent both DSA and CT angiography before clipping or coiling. The use of CT angiography was almost twice as high in hospitals that predominantly performed clipping (61%, 150/247) compared with hospitals that predominantly performed coiling (34%, 765/2251, $P < .0001$) or hospitals that performed both procedures (34%, 841/2474, $P < .0001$). For clipping patients, 56% (570/1022) underwent DSA only, 20% (210/1022) underwent CT angiography only, and 24% (242/1022) underwent both DSA and CT angiography. For coiling patients, 67% (2646/3950) underwent DSA alone and 33% (1304/3950) underwent both DSA and CT angiography.

The use of pretreatment CT angiography and DSA varied, depending on the hospital. Teaching hospitals had significantly higher rates for the use of CT angiography (40% [1362/3383] versus 25% [391/1589], $P < .0001$) and lower rates for the use of DSA (93% [3145/3383] versus 96% [1521/1589], $P < .0001$) compared with nonteaching hospitals. High-volume centers (≥ 20 cases/year) had higher rates for the use of DSA (96% [2844/2962] versus 91% [1822/2010]), $P < .0001$ and lower rates for the use of CT angiography (33% [990/2962] versus 38% [763/2010], $P = .0011$) compared with low-volume centers. Rates for the use of DSA were higher in the Northeast (95% [1477/1563]), South (94% [1977/2102]), and West (92% [643/704]) hospitals compared with Midwest hospitals (89% [569/603]). Rates for the use of CT angiography were higher in Northeast hospitals (43% [672/1563]), compared with South (32% [676/2102]), West (33% [220/704]), and Midwest (31% [185/603]) hospitals.

The percentage of patients with SAH who underwent pretreatment CT angiography significantly increased from 20% (157/771) in 2006 to 44% (377/852) in 2011 ($P < .0001$), whereas the percentage of patients who underwent DSA remained unchanged from 96% (734/771) to 94% (800/852) ($P = .28$). The fraction of patients who underwent pretreatment CT angiography increased from 2006–2011 in patients undergoing coiling (17% [104/604] to 42% [296/702], $P < .0001$) and in patients undergoing clipping (32% [53/167] to 54% [81/150], $P < .0001$). The fraction of patients who underwent DSA decreased from 84% (140/167) to 77% (115/150) ($P = .12$) for patients treated with clipping. All coiling patients underwent DSA.

Posttreatment Imaging

Trends in posttreatment imaging are shown in Fig 2. Overall, 43% (2162/4972) of patients who received treatment for SAH underwent imaging after clipping or coiling, with 22% (1096/4972) receiving DSA only, 12% (575/4972) receiving CT angiography only, and 10% (491/4972) receiving both DSA and CT angiography. Rates for the use of posttreatment imaging were higher in hospitals that predominantly performed coiling (52% [1180/2251]) compared with hospitals that predominantly performed clipping (34% [85/247], $P < .0001$) or hospitals that performed both procedures (36%, [897/2474], $P < .0001$).

Rates for the use of posttreatment CT angiography and DSA varied, depending on the hospital. Teaching hospitals had a similar rate for the use of DSA (31% [1057/3383] versus 33% [530/1589], $P = .14$) but a higher rate for the use of CT angiography (22% [761/3383] versus 19% [305/1589], $P = .0085$) compared

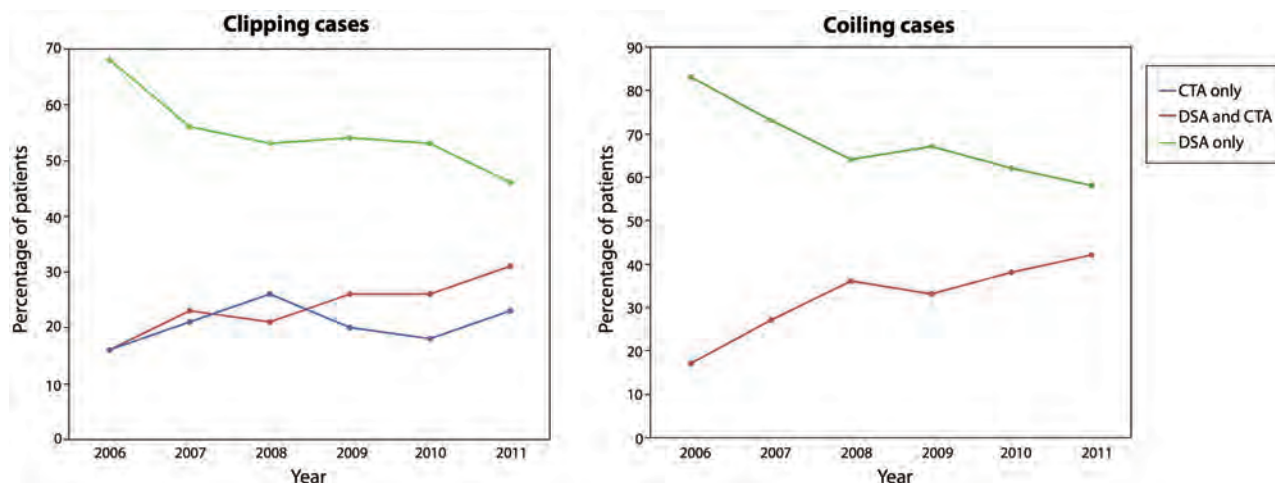


FIG 1. Trends in CT angiography and DSA use before clipping or coiling of ruptured aneurysms. Percentages of patients who underwent CT angiography only (blue line), DSA only (green line), or both CT angiography and DSA (red line) before clipping (left graph) or coiling (right graph) procedures from 2006–2011 are shown.

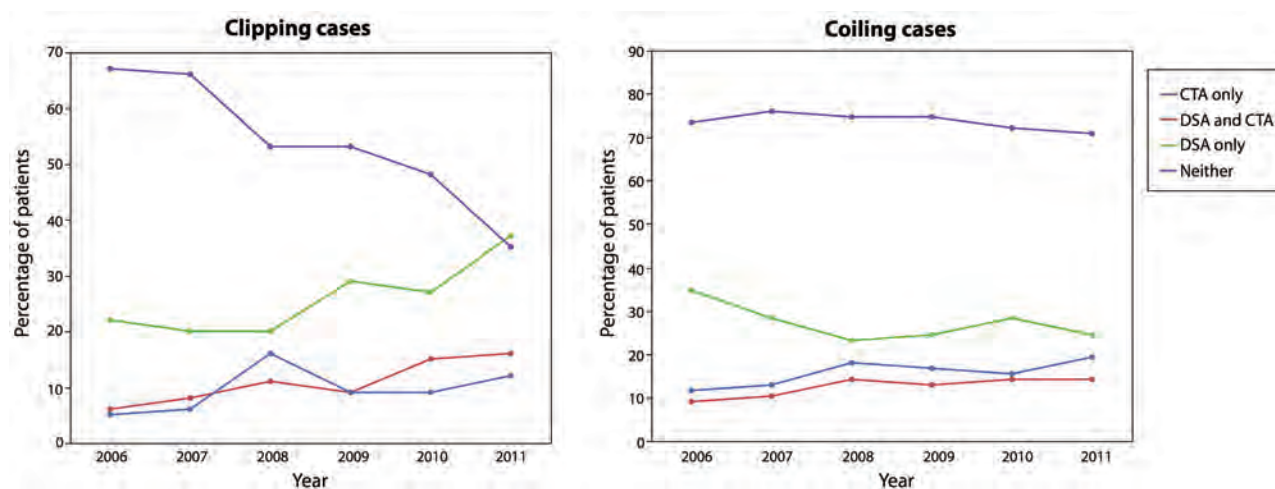


FIG 2. Trends in CT angiography and DSA use after clipping or coiling of ruptured aneurysms. Percentages of patients who underwent CT angiography only (blue line), DSA only (green line), both CT angiography and DSA (red line), or neither (purple line) after clipping (left graph) or coiling (right graph) procedures from 2006–2011 are shown.

with nonteaching hospitals. High-volume centers (≥ 20 cases/year) also had similar rates for the use of DSA (31% [920/2962] versus 33% [667/2010], $P = .12$) but higher rates for the use of CT angiography (23% [684/2962] versus 19% [382/2010], $P = .0011$) compared with low-volume centers. Rates for the use of DSA were higher in West hospitals (40% [282/704]) compared with South (29% [609/2102]), Northeast (31% [491/1563]), and Midwest (34% [205/603]) hospitals. Rates for the use of CT angiography were higher in Midwest hospitals (30% [180/603]) compared with Northeast (22% [348/1563]), South (19% [391/2102]), and West (21% [147/704]) hospitals.

There was a significant increase in the percentage of patients who underwent posttreatment imaging from 41% (317/771) in 2006 to 48% (412/852) in 2011 ($P = .0037$). This increase was attributable to the increase in the rate for the use of CT angiography from 15% (117/771) to 26% (221/852, $P < .0001$). Patients treated with clipping were increasingly subjected to posttreatment imaging from 2006–2011. The fraction of clipping patients who underwent posttreatment imaging significantly increased from 33% (55/167) in 2006

to 65% (97/150) in 2011 ($P < .0001$), with increases in the rate for the use of DSA alone (from 22% [36/167] to 37% [55/150], $P = .0041$), CT angiography alone (from 5% [9/167] to 12% [18/150], $P = .0436$), and both DSA and CT angiography (from 6% [10/167] to 16% [24/150], $P = .0058$). Conversely, the fraction of coiling patients who underwent posttreatment imaging increased minimally from 43% [262/604] to 45% [315/702], $P = .62$).

DISCUSSION

Our study demonstrates that most patients continue to undergo DSA before clipping or coiling treatment of a ruptured aneurysm, but 20% of patients treated with clipping were imaged with CT angiography only. Rates for the use of CT angiography were higher in teaching and high-volume medical centers compared with nonteaching and low-volume medical centers. We also found higher rates for the use of CT angiography at centers that predominantly perform clipping compared with centers that predominantly perform coiling. DSA has historically been used to diagnose aneurysms in the setting of SAH, and the use of CT angiography in this context is a recent

phenomenon. Rates for the use of DSA did not decrease substantially from 2006–2011, indicating that CT angiography tends to be used in most cases as a study in addition to DSA rather than as a replacement of DSA. Performance of both CT angiography and DSA before treatment of an aneurysm can increase the cost of treatment and the risk of contrast-induced nephropathy relative to the use of either technique alone, with unclear clinical benefit in many cases.

Although every patient who is treated with coiling undergoes DSA of the aneurysm being treated, it may not be a complete, 4-vessel DSA if a CT angiogram is deemed adequate for evaluation of the remaining blood vessels. We are not able to determine the degree of completeness of the DSA in this study; therefore we cannot ascertain how often CT angiography led to an abbreviated DSA.

Because of the noninvasive nature of CT angiography relative to DSA, an argument might be made that the use of CT angiography might be safer than the use of DSA. Through the use of the data base in this study, we cannot accurately assess complications of cerebral angiography to determine whether avoiding DSA by performing CT angiography resulted in better patient outcomes. Because the risk of permanent sequelae from DSA performed in patients with SAH is very low,¹¹ an improvement in safety resulting from avoidance of DSA would be difficult to confirm. Even at centers that generally use DSA as the primary imaging, CT angiography might occasionally be used in the situation of an aneurysm causing parenchymal hematoma requiring urgent surgery, which occurs most commonly with middle cerebral artery aneurysms.

Patients treated with clipping were increasingly subjected to post-treatment CT angiography and/or DSA imaging from 2006–2011, whereas posttreatment imaging of patients undergoing coiling remained fairly constant. The use of more imaging after clipping compared with coiling might be at least partly because all patients undergoing coiling receive angiographic assessment at the end of the procedure, but patients undergoing clipping often do not receive angiographic assessment. We are not able to identify intraoperative DSA in the clipping cohort. This increasing trend may suggest an increasing desire by surgeons to get confirmation of adequate clipping with DSA. CT angiography and DSA in the days after clipping or coiling might be performed to evaluate the treatment result or to evaluate vasospasm. Vasospasm and delayed ischemic deficits occur less frequently in patients treated with coiling relative to those treated with clipping,¹² which might contribute to less DSA and CT angiography after the aneurysm is treated by coiling.

This study has several limitations. First, this study is retrospective, and the decision of whether to perform CT angiography or DSA is ultimately made by the provider. Second, indications for imaging are not available in the Perspective data base; therefore, the clinical decision-making process for each hospitalization and the reasons that providers chose CT angiography, DSA, or both modalities are unknown. The implications of our findings may be different for pretreatment and posttreatment imaging because they have different indications. Third, the Perspective data base only captures imaging that was performed during hospitalization. Imaging that may have been performed immediately before or after hospitalization would therefore have been missed. Fourth, the data base is not a random sampling of hospitals, and therefore results may not be representative of all hospitals or hospitalizations. Fifth, some coding inaccuracies undoubtedly occur that can affect the retrospective evaluation of an

administrative data base. Such coding inaccuracies are unlikely to lead to misrepresentation of overall trends in the use of imaging. Sixth, whereas our study shows an increasing trend in the use of CT angiography, the level of use of DSA and CT angiography considered optimal or appropriate is unknown. Finally, the findings of our study are only applicable to ruptured aneurysms. The use of DSA and CT angiography may be different with unruptured aneurysms or SAH from other causes.

CONCLUSIONS

For the pretreatment evaluation of ruptured aneurysms, the use of CT angiography increased from 2006–2011, but without a corresponding decrease in the use of DSA. The increased use of CT angiography without a corresponding decrease in DSA use raises the question of potential redundancy in the diagnostic tests without added clinical value of the second test.

Disclosures: Jennifer McDonald—UNRELATED: Grants/Grants Pending: GE Healthcare.* David Kallmes—UNRELATED: Consultancy: ev3,* Medtronic,* Codman,* Grants/Grants Pending: MicroVention,* ev3,* Sequent,* Benvenue Medical,* Micrus,* Codman,* Royalties: UVA Patent Foundation; Payment for Development of Educational Presentations: ev3,* Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: MicroVention.* Giuseppe Lanzino—UNRELATED: Consultancy: ev3/Covidien,* Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: ev3/Covidien,* Comments: FDA panel. Harry Cloft—UNRELATED: Grants/Grants Pending: Cordis Endovascular.* (*Money paid to institution.)

REFERENCES

1. Bederson JB, Connolly ES Jr, Batjer HH, et al. **Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the stroke council, American Heart Association.** *Stroke* 2009;40:994–1025
2. Agid R, Lee SK, Willinsky RA, et al. **Acute subarachnoid hemorrhage: using 64-slice multidetector CT angiography to “triage” patients’ treatment.** *Neuroradiology* 2006;48:787–94
3. Agid R, Willinsky RA, Farb RI, et al. **Life at the end of the tunnel: why emergent CT angiography should be done for patients with acute subarachnoid hemorrhage.** *AJNR Am J Neuroradiol* 2008;29:e45
4. Fox AJ, Symons SP, Aviv RI. **CT angiography is state-of-the-art first vascular imaging for subarachnoid hemorrhage.** *AJNR Am J Neuroradiol* 2008;29:e41–42
5. Gonzalez-Darder JM, Pseudo-Martinez JV, Feliu-Tatay RA. **Microsurgical management of cerebral aneurysms based in CT angiography with three-dimensional reconstruction (3D-CT angiography) and without preoperative cerebral angiography.** *Acta Neurochirurgica* 2001;143:673–79
6. Westerlaan HE, van Dijk JM, Jansen-van der Weide MC, et al. **Intracranial aneurysms in patients with subarachnoid hemorrhage: CT angiography as a primary examination tool for diagnosis—systematic review and meta-analysis.** *Radiology* 2011;258:134–45
7. Jayaraman MV, Haas RA, Do HM, et al. **Should CT angiography be routinely used in patients suspected of having aneurysmal subarachnoid hemorrhage? No!** *Radiology* 2010;254:314–15
8. Kallmes DF, Layton K, Marx WF, et al. **Death by nondiagnosis: why emergent CT angiography should not be done for patients with subarachnoid hemorrhage.** *AJNR Am J Neuroradiol* 2007;28:1837–38
9. Moran CJ. **Aneurysmal subarachnoid hemorrhage: DSA versus CT angiography—is the answer available?** *Radiology* 2011;258:15–17
10. **Premier Perspective Database.** Charlotte, North Carolina: Premier Research Services. 2012
11. Cloft HJ, Joseph GJ, Dion JE. **Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis.** *Stroke* 1999;30:317–20
12. Dumont AS, Crowley RW, Monteith SJ, et al. **Endovascular treatment or neurosurgical clipping of ruptured intracranial aneurysms: effect on angiographic vasospasm, delayed ischemic neurological deficit, cerebral infarction, and clinical outcome.** *Stroke* 2010;41:2519–24

Double Stent–Assisted Coil Embolization Treatment for Bifurcation Aneurysms: Immediate Treatment Results and Long-Term Angiographic Outcome

K. Yavuz, S. Geyik, S. Cekirge, and I. Saatci

ABSTRACT

BACKGROUND AND PURPOSE: The goal of endovascular treatment of cerebral bifurcation aneurysms is to achieve safe coiling of the sac along with preserving patency of the diverging branches. Our purpose was evaluate procedural safety and efficacy as well as the long-term durability of endovascular treatment of bifurcation aneurysms with double stent–assisted coiling.

MATERIALS AND METHODS: One hundred ninety-one consecutive patients with bifurcation aneurysms were included in this series. Technical failure occurred in 3 aneurysms (1.5%); 188 patients with 193 aneurysms treated with double stent–assisted coiling were retrospectively evaluated; 113 aneurysms were located at middle cerebral artery bifurcation, 42 at the anterior communicating artery, 22 at the basilar artery bifurcation, and the remaining 16 at the internal carotid artery bifurcation; 132 were small (<10 mm), 56 were large (10–25 mm), and 5 were giant (>25 mm).

RESULTS: The technical success rate of double-stent application was 98.5% (193 aneurysms). In total, there were 5 procedural complications with an associated rate of 2.7%, one of which led to death (0.5%). Delayed ischemic stroke occurred in 2 patients (1.1%). Overall, permanent morbidity occurred in 2 patients, with associated rate of 1.1%. Follow-up was obtained in 186 aneurysms (96.4%), and recanalization occurred in 4 aneurysms (2.2%). In subgroup analysis, the recanalization rate was 3.8% for large aneurysms and 40% for giant aneurysms. No recanalization occurred in small aneurysms.

CONCLUSIONS: Dual stent–assisted coiling of cerebral aneurysms is a feasible and safe procedure. It may offer a curative solution with long-term durability for treatment of wide-neck small and large aneurysms.

ABBREVIATIONS: DSAC = double-stent assisted coil; AcomA = anterior communicating artery

In early practice, the application and technical success of endovascular treatment of cerebral aneurysms with detachable coils were widely affected by morphologic factors, including shape and dome-to-neck ratio.¹ Nevertheless, the use of adjunctive materials such as remodeling balloons,² the neck-bridge device,³ and, thereafter, self-expanding stents,⁴ has resulted in significant expansion of patient selection criteria.

Easy and safe navigation, mostly through a microcatheter without a need for an exchange procedure, is the most important feature of the self-expanding stents currently in use, compared with the balloon-expandable coronary stents. Although the initial idea behind the use of a stent was to obtain a mechanical scaffold across the neck of the broad-based aneurysms, subsequent laboratory data have

shown the benefit of hemodynamic alterations in the aneurysm sac before and after stent deployment.^{5,6}

Bifurcation aneurysms may present a therapeutic challenge with unfavorable geometric configurations. The double stent–assisted coiling technique, defined by Chow et al,⁷ offers maintenance of patency of involved branches with deployment of stents in each particular vessel, along with creation of a new bifurcation point across the neck of the related aneurysm. Likewise, in sidewall aneurysms, laboratory data revealed flow alterations after placement of stents in the Y-configuration at the neck of a bifurcating aneurysm model.⁸ Moreover, double-stent placement in Y-configuration may provide sufficient flow reduction even without endosaccular coiling and may result in aneurysm thrombosis in selected situations, as reported in a recently published series.⁹

Herein, we report our immediate treatment results and long-term clinical and angiographic follow-up data on 183 bifurcation aneurysms treated with the double stent–assisted coil embolization technique.

MATERIALS AND METHODS

This retrospective case series included 188 consecutive patients with 193 intracranial bifurcation aneurysms treated with the

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Table 1: Patient and aneurysm characteristics

No of Patients	188
Sex	
Female	111
Male	77
Age, y	
Mean	50.3
Minimum	15
Maximum	72
No. of treated aneurysms	193
Aneurysm location (%)	
Anterior	171 (88.6)
MCA	113
AcomA	42
ICA bifurcation	16
Posterior	22 (11.4)
Basilar bifurcation	22
Aneurysm size (%)	
Small, <100 mm	132 (68.4)
Large	56 (29)
Giant	5 (2.6)

double stent–assisted coil embolization technique between September 2006 and August 2011 (Table 1). DSAC was deemed necessary in bifurcation aneurysms 1) when the origins of the branching arteries could not be preserved otherwise (including balloon assistance or single-stent placement); 2) when there was no identifiable aneurysm neck and therefore it was necessary to create a barrier for neck construction; and 3) when the aneurysm could not be packed fully otherwise and was likely to recur, particularly those of large size. Twenty-one patients had prior treatment or failed attempts; 167 patients received double stent–assisted coiling as the ini-

tial treatment. Of these 21 patients, 19 had recanalized aneurysms after balloon remodeling–assisted and/or single stent–assisted coiling; 1 patient had a clip remnant and the other had a failed surgical clipping attempt. Most of the patients presented with headache. Only 3 patients who presented with subarachnoid hemorrhage were included in this series; 1 of these patients were treated within the acute phase of SAH caused by coil protrusion into the parent artery, and the remaining 2 were treated in the subacute phase after appropriate premedication with antiplatelet (anti-aggregating) agents.

One hundred thirteen aneurysms were located at middle cerebral artery bifurcation; 42 at the anterior communicating artery; 22 at the basilar artery bifurcation; and remaining 16 at the internal carotid artery bifurcation. Of the 193 aneurysms, 132 were small, 56 were large, and 5 were giant. Two of the giant aneurysms showed partial thrombosis. All giant and large aneurysms had neck size wider than 4 mm. All small aneurysms had dome-to-neck ratio ≤ 1.5 (Fig 1–3).

Five patients with AcomA aneurysms, treated with X-configured DSAC embolization, had been reported previously in a technical note.¹⁰ According to the configuration or shape of the 2 stents, 183 aneurysms were treated with Y-configuration; 8 with AcomA aneurysms and 1 with fenestrated basilar artery aneurysms treated with X-configuration. One internal carotid artery bifurcation had T-configured double stents, one of which was deployed horizontally from the contralateral side.

Strict anti-aggregation and intraprocedural anticoagulation protocols were administered in all but 1 case that had an unplanned DSAC in the acute phase of SAH. Accordingly, double antiplatelet therapy with acetylsalicylic acid (300 mg per day) and

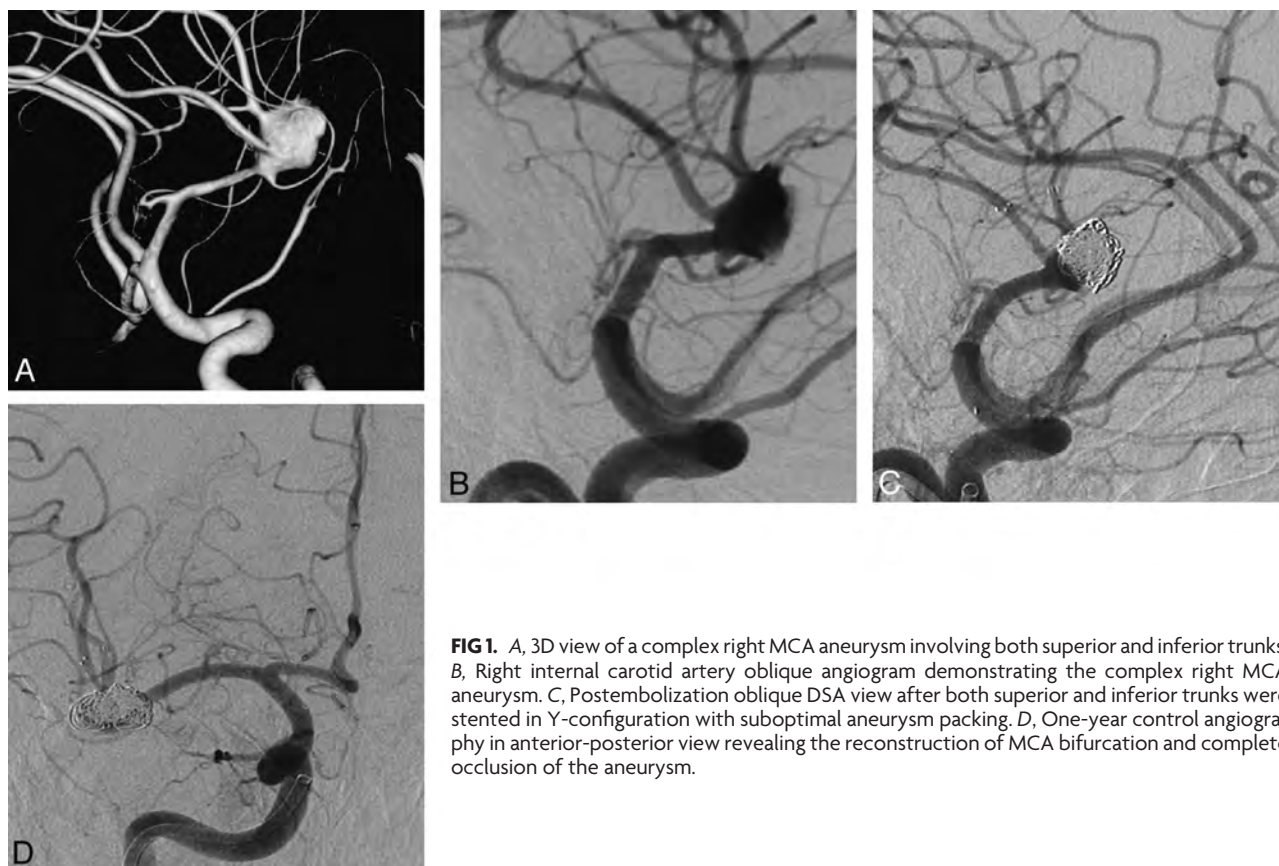


FIG 1. A, 3D view of a complex right MCA aneurysm involving both superior and inferior trunks. B, Right internal carotid artery oblique angiogram demonstrating the complex right MCA aneurysm. C, Postembolization oblique DSA view after both superior and inferior trunks were stented in Y-configuration with suboptimal aneurysm packing. D, One-year control angiography in anterior-posterior view revealing the reconstruction of MCA bifurcation and complete occlusion of the aneurysm.

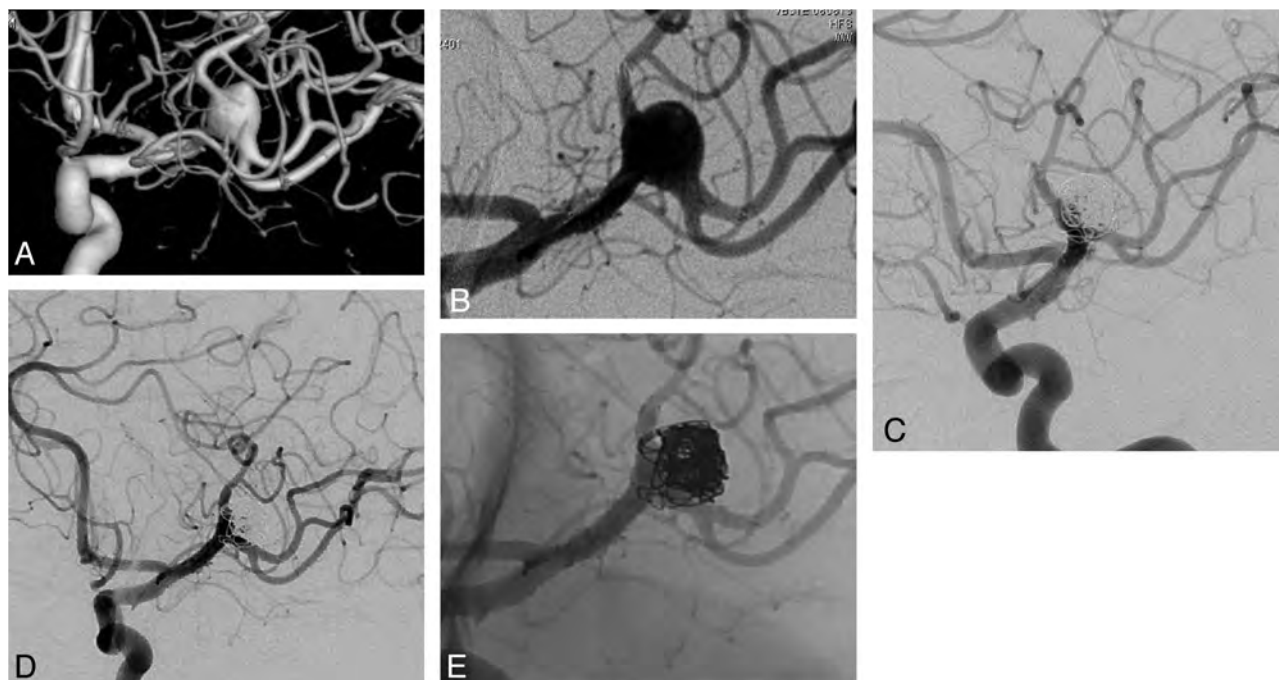


FIG 2. A, 3D view of a complex left MCA aneurysm with both superior and inferior trunks of MCA originating from the aneurysm sac. B, Preoperative DSA revealing both trunks of left MCA stented in Y-configuration, creating a neck. C, Six-month control DSA showing stable aneurysm occlusion. D and E, Two-year control angiography with subtracted (D) and nonsubtracted (E) views confirming long-term aneurysm occlusion and MCA bifurcation reconstruction.



FIG 3. A, 3D view of wide-neck right middle cerebral artery aneurysm. B, Flat-panel CT angiography showing the alignment of Enterprise and Solitaire stents in Y-configuration. C, Postembolization oblique DSA view with total packing of the aneurysm with coils.

clopidogrel were initiated 1 week before the procedure with a loading dose of 300–600 mg clopidogrel, followed by 75 mg daily. Thrombocyte inhibition levels were confirmed by means of VerifyNow (Accumetrics, San Diego, California) and a standard thrombocyte aggregation test. The procedure was not performed if the patient did not have a platelet inhibition level of 30% at minimum. If the patient had resistance to clopidogrel after use for 1 week or the second test showed that the patient was still a low responder, the anti-aggregation medicine was switched to ticlopidine. After the control angiogram was obtained at the sixth month, clopidogrel was discontinued and acetylsalicylic acid was to be taken life-long. Anticoagulation protocol during the procedure consisted of intravenous administration of heparin with close monitoring of blood activated clotting time levels.

Technique

All procedures were performed under general anesthesia with bi-plane flat-panel angiography; a 90-cm 6F introducer sheath was used in combination with 6F guiding catheters. DSAC consists of deployment of 2 self-expanding stents; the second is placed to pass through the interstices of the first stent, 1 in each branch coming off from the sac or neck of the broad-based bifurcation aneurysm. In this technique, with the crossing stent wires, a new bifurcation point is created below the neck of the aneurysm (redirecting the blood flow toward the relevant branches) for safe coiling of the sac, obviating the risk of coil protrusion to the parent artery. Selection of the branch to be catheterized first is extremely important for the success of the technique; that is, the angle between the proximal vessel and the diverging branch is the most important

Table 2: Stent types used in dual-stent reconstruction

Type of Stent	Total (%)	MCA	AcomA	Basilar	ICA
Double Neuroform	6 (3.1)	2	0	2	2
Double Enterprise	126 (65.3)	79	30	11	6
Double Solitaire	32 (16.6)	12	7	7	6
Enterprise + Solitaire	29 (15.1)	20	5	2	2
Total	193	113	42	22	16

factor for decision-making—the one that has a sharper angle must be stented before the one with a wider angle. The second criterion is the orientation of the aneurysm neck; that is, the side involved by the aneurysm neck for a wider segment should be stented first.

According to our technique, a microcatheter (Prowler Select Plus, Codman & Shurtleff, Raynham, Massachusetts; Rebar, ev3, Irvine, California) with an inner size of 0.021 inches was used in combination with various guidewires. Afterward, a 0.010-inch microcatheter (SL 10, Boston Scientific, Fremont, California; Echelon 10, ev3) was placed into the aneurysm sac over various guidewires before deployment of the first stent. The first stent was then deployed within the branch to extend to the main vessel, covering the neck of the aneurysm partially. The microcatheter was passed through one of the struts of the first stent, and the second stent was placed to extend from the other branch to the main artery to cover the remaining neck segment.

The stents used for double-stent placement in this series are given in Table 2. In the beginning of our experience, only the commercially available Neuroform stents (Boston Scientific), which had an open-cell design, were used in the first 6 cases, as in the technique first described by Chow et al.⁷ Since then, with the introduction of the self-expanding stents that could be navigated through a microcatheter and after we succeeded in *in vitro* testing of Enterprise (Cordis Neurovascular) and Solitaire (ev3) stents for the technique of dual-stent placement in an intersecting configuration, we modified the double-stent application technique. These stents were preferred to augment flow redirection. In this series, double Enterprise stents of 4.5-mm diameter with combinations of variable lengths (ie, 22, 28, or 37 mm) were used in 126 aneurysms. Double Solitaire stents with different combinations of 4 × 20 mm and 3 × 30 mm were used in 32 aneurysms; Enterprise and Solitaire stents were combined in 29 aneurysms.

The aneurysms were coiled with a variety of bare platinum coils; however, softer coils were preferred to avoid kick-back of the microcatheter, which would result in recatheterization of the aneurysm sac. We did not suggest dense packing of the aneurysm sac because we thought that dual-stent placement would create a flow-diverging effect.

RESULTS

DSAC was attempted in 196 aneurysms, and technical failure occurred in 3 aneurysms (1.5%), resulting in a technical success rate of 98.5%. The first stent was deployed in these 3 patients uneventfully; however, the second stent could not be placed, but we were able to complete the endovascular treatment with coiling successfully with no complication, and the control angiography revealed stable complete occlusion of the relevant aneurysms despite the first stent partly covering the neck initially. No problems were encountered regarding stent opening within the bifurcation

branches despite the mismatch between stent and artery diameters.

There were 5 procedural complications (5/188; 2.7%), 1 of which led to death resulting from intraprocedural rupture, with an associated mortality rate of 0.5%. Aneurysm rupture occurred in 2 other patients during coiling,

but these patients were discharged without clinical consequences. Acute in-stent thrombus was observed in 1 patient and resolved completely with intravenous tirofiban injection. In the remaining patient, loss of consciousness developed with sudden onset 12 hours after the uneventful embolization procedure of an unruptured aneurysm, and the immediate CT scan revealed SAH of unknown origin. This patient was discharged with left-side moderate paresis and became independent the sixth month after the initial treatment (modified Rankin Scale 1).

Transient ischemic symptoms occurred in 2 patients within 30 days; diffusion-weighted MR imaging revealed small diffusion lesions, and their symptoms resolved with the addition of low-molecular-weight heparin to anti-aggregation therapy. Delayed ischemic stroke occurred in 2 patients (1.1%) as the result of unauthorized early cessation of clopidogrel. Overall, cumulative, procedure-related hemorrhagic, and delayed ischemic complications occurred in 9 (4.8%) patients, of which death occurred in 1 patient (0.5%) and permanent morbidity in 2 patients (1.1%).

According to the immediate posttreatment angiograms, 49 of 193 (25.4%) aneurysms were completely obliterated (Raymond class I); 63 of 193 (32.6%) had a neck remnant (Raymond class II), and the remaining 81 of 193 (42%) aneurysms had incomplete obliteration (Raymond class III).

Until August 2011, 186 of 193 aneurysms were out of at least 6 months for follow-up, and control angiography was performed in all, at 6 months to 2 years; the results were evaluated with respect to initial occlusion grade and aneurysm size. According to the latest follow-up, 152 aneurysms had initial control angiography at the sixth month; 34 aneurysms had initial control angiography at the first year. Of those that had initial follow-up, 87 aneurysms had an additional 2-year control. In these 186 aneurysms, recurrence was noted in 4 aneurysms, with an overall recanalization rate of 2.2%. All 4 of these aneurysms received the dual stent–assisted coiling as a retreatment after the initial treatment with the balloon–remodeling technique or single stent–assisted coiling. In this series, there was no recanalization seen in aneurysms in which DSAC was performed as the initial treatment.

The follow-up results of 186 aneurysms with respect to immediate postoperative angiography results are shown in Table 3. There was no recanalization in the group, which had had class I occlusion initially. All aneurysms that had had class III occlusion in the immediate postoperative angiography showed further occlusion to class I at control angiography. The 4 aneurysms that showed recanalization had class II occlusion initially.

In regard to the aneurysm size, follow-up data revealed the following results.

1) One hundred twenty-eight of 132 of the small aneurysms had control angiography; no recanalization occurred. 2) Control angiography was available in 53 of 56 large aneurysms; recanalization

Table 3: Angiographic occlusion rates at 6-month follow-up

Occlusion Rate	Angiographic Occlusion at Initial Control Angiography				
	No. of Initial Occlusions	No. of Follow-Up	Class I	Class II	Class III
Class I	49 (25.4)	46	46	0	0
Class II	63 (32.6)	60	52	4	4
Class III	81 (42)	80	80	0	0
Total	193 (100)	186	178	4	4

zation occurred in 2 aneurysms (3.8%). 3) In 5 giant aneurysms, all with follow-up, 2 had recanalization (40%).

DISCUSSION

To preserve the patency of the branching arteries while achieving a complete occlusion of bifurcation aneurysms, devices such as remodeling balloons,² the neck-bridge device,³ and stents⁴ have been used adjunctively for endovascular treatment.

Having the capability of adapting their shape to the anatomy of arterial bifurcation, supercompliant balloons may provide safer and denser packing because they secure the neck and enable better coil conformation compared with conventional coiling.³ However, with aneurysms having too wide a neck, a single balloon may not be sufficient to protect from coil herniation, even when a round balloon is positioned at the neck instead of the balloon catheter with its tip positioned in one particular branch. A double balloon, placed in each branch, crossing the neck of the aneurysm, may be a solution, but, this technique has the disadvantage of having 3 microcatheters in the same artery simultaneously.

The TriSpan neck-bridge device (Boston Scientific) is an important tool that was used to achieve safe coil occlusion of bifurcation aneurysms while preserving the parent artery.² The device had the advantages of easy placement through a microcatheter, single material remained within the sac, and it did not require the use of antiplatelet agents. However, TriSpan is not commercially available presently, and the published data are limited to the series about the initial experience without any data regarding the long-term efficacy.¹¹

More recently, self-expanding stents have come into clinical use; well-defined advantages of these devices are improvement of packing densities while preserving coil protrusion into the parent artery¹² and alteration of intra-aneurysmal hemodynamics.^{6,8} Likewise, the flow alterations obtained with sidewall aneurysms in laboratory investments after stent placement⁵ and the magnitude of the velocity of the jet entering the sac, has been reduced after placement of 2 Neuroform stents at the aneurysm neck in Y-configuration in the bifurcating aneurysm model.⁸ The effects of stents were shown to be more apparent at the end of the cardiac cycle by reducing shear stress in the sac almost by 40%.⁸ Furthermore, stents act as a biologic system by inducing endothelialization over the struts, which leads to healing of the vessel wall also at the segment of broad-based aneurysm location.¹³ Placement of 2 intersecting stents across the aneurysm neck, even without additional coiling, may result in complete occlusion or reduction in filling of the aneurysms in some cases.⁹ Thus, the flow diversion effect of double-stent placement in Y-configuration is confirmed in vivo as well.

Dual stent-supported, or so-called “Y-configured” stent-assisted coil embolization of bifurcation aneurysms, was first defined by Chow et al⁷ and Perez-Arjona et al¹⁴ for treatment of

wide-neck basilar artery bifurcation aneurysms, which then was followed by the application of a technique for treatment of an MCA aneurysm by Sani et al.¹⁵

These reports have pointed out the advantage of reconstruction of the bifurcation with deployment of double stents in each diverging branch, when a single

stent does not adequately bridge the aneurysm neck, enabling the safe coiling of the sac without a risk of coil protrusion. The open-cell design of the stents leads to relatively easy passage through the struts of the deployed stent and almost fully opens the second stent at the cross-section of 2 stents taking Y-configuration.⁷ However, in our practice, with the introduction of closed-cell stents, the technique for DSAC evolved, and we began to use 2 closed-cell stents passing between the struts and through the cell of the stent. Although not proved with laboratory investigation on flow models, the idea behind the use of 2 closed-cell stents was that the intersection of stents, taking an hour-glass shape at the aneurysm neck when crossing each other, would act like a separator, diverting the flow streamlines into branches below the initial apex of the bifurcation and thus potentially decreasing the wall shear stress at the aneurysm neck. On the other hand, closed-cell design may have the disadvantage of kinking at the bifurcation point where the branches are diverging with acute angles, and this may make the passage of the microcatheter through the particular cell difficult. We failed to pass through the struts of the first stent to place the second stent in 3 cases, which may be explained by this issue. Moreover, central crimping and ovalization with luminal loss leading to incomplete stent apposition to the vessel have been documented with Enterprise stents, depending on the curvature.¹⁶

Technically, the Enterprise stent offers the advantage of having a distal wire, so that the microcatheter can be advanced over the wire after the first stent is placed. This eliminates the need to catheterize the former stent and therefore increases the safety of the technique while the risk of the microcatheter passing between the wall of the artery and stent is excluded. A second advantage is the anchoring flared (ie, 0.5 mm larger than the stent diameter) ends, which reduce the risk of stent migration during the passage of the microcatheter for deployment of the second one. On the other hand, major advantages of the Solitaire are: 1) It is fully retrievable, allowing precise placement. 2) It does not have a distal wire, that is, it can be deployed exactly at the tip of the microcatheter. Therefore, there is no need to navigate the microcatheter further for the purpose of purchasing the vessel segment for the distal wire, especially when there is a second tight curve at the diverging branch after bifurcation, which is not an infrequent anatomic feature, especially of MCAs. 3) It has a relatively larger cell size compared with the Enterprise, which eases passage of the microcatheter. However, the latter may sometimes be disadvantageous when struts do not secure the neck well. Thus, clinical practitioners should take these features into consideration when choosing the appropriate stent that would work best with the particular anatomic features.

A meta-analysis of the literature, concerning the safety and efficacy of endovascular treatment of unruptured aneurysms, re-

vealed 4.8% unfavorable procedural outcome.¹⁷ Furthermore, it has been shown that in-hospital outcomes, regarding procedural mortality and morbidity, do not increase by the adjunctive use of stents compared with procedures performed without the use of a stent.¹⁸ A literature survey including 37 articles with 1510 aneurysms treated with stent-supported coiling revealed almost 10% thromboembolic complication rate, with an associated mortality rate of 0.6%.¹⁹ Learning curve analysis obtained in this study showed that the complication rate is affected by the operator's experience with the procedure.¹⁹

The cumulative complication rate observed in this study was not higher than the previous series. The only death included in this series (0.5%) occurred as the result of aneurysm rupture during coiling procedure, which is not uncommon with endovascular therapy. Relatively less occurrence of periprocedural ischemic complications (ie, 2 patients; 1.1%) would be attributable to strict anti-aggregation protocol that is checked twice with 2 different methods before the procedure. Nevertheless, delayed ischemic complications were observed in 2 patients (1.1%) who ceased usage of clopidogrel prematurely, implicating the importance of the drug compliance in the long term.

In this series, we had a recanalization rate of 2.2% and total occlusion rate of 97.8% at 6 months among those with follow-up (note that follow-up rate was 186/193; 96.4%) despite a relatively low level of initial total occlusion (25.4%) in the immediate post-operative angiography. Although no control group or matching series exist in the literature, dual-stent support appears to have an impact on the durability of the endosaccular packing. A literature survey revealed a recanalization rate of 14% after single stent-assisted coiling.¹⁹ Although this series is matchless for further discussion and may provoke controversy, our results inspire the augmented effect of intersecting dual-stent support resulting from flow changes. Of the 128 small wide-neck aneurysms, follow-up revealed no recanalization regardless of initial occlusion rates. Of the 53 large aneurysms, which had follow-up, recanalization was seen in 2 aneurysms, resulting in a rate of 3.8%. With conventional coiling, the recanalization rate is reported to be 20% and 35.3% for wide-neck small aneurysms and large aneurysms, respectively.²⁰ In a large series consisting of 864 aneurysms located in the MCA bifurcation and the AcomA, the authors reported an overall recanalization rate of 12% with the adjunctive use of remodeling balloons, regardless of the aneurysm size.²¹ In a series consisting of 174 MCA aneurysms, a 27.2% recanalization rate was reported of the 114 aneurysms that had follow-up with angiography.²² From this perspective, the 2.2% recanalization rate that was achieved with DSAC seems promising.

Throughout the time of this study, a wide variety of other methods have been defined for stent application in bifurcation aneurysm treatment such as linear stent placement,²³ nonoverlapping Y-stent placement,²⁴ the waffle-cone technique,²⁵ and so forth, which are mostly limited to anecdotal case series or a single case report. However, as explained above, our hypothesis was that crossing points of 2 closed-cell stents creates a point located below the initial apex of the bifurcation, which acts as a flow diverter and potentially induces further aneurysm thrombosis by reducing the flow. Recent work by Baharoglu et al²⁶ and Gao et al,²⁷ pointing out the contribution of vessel angle with respect to inflow of the

aneurysm, claims that the angular configuration change after stent placement is an effective factor to reduce wall shear stress. Their work encourages our theoretic hypothesis as well. Accordingly, linear or nonoverlapping or kissing-stent techniques probably would lack this effect, and the waffle-cone technique may increase the flow toward the aneurysm sac.

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REFERENCES

- Debrun GM, Aletich VA, Kehrli P, et al. **Selection of cerebral aneurysms for treatment using Guglielmi detachable coils: the preliminary University of Illinois at Chicago experience.** *Neurosurgery* 1998;6:1281–97
- Moret J, Cognard C, Weill A, et al. **Reconstruction technique in the treatment of wide-neck intracranial aneurysms: long-term angiographic and clinical results-apropos of 56 cases.** *J Neuroradiol* 1997;24:30–44
- Raymond J, Guilbert F, Roy D. **Neck-bridge device for endovascular treatment of wide-neck bifurcation aneurysms: initial experience.** *Radiology* 2001;221:318–26
- Fiorella D, Albuquerque FC, Deshmukh VR, et al. **Usefulness of the Neuroform stent for the treatment of cerebral aneurysms: results at initial (3–6 mo) follow-up.** *Neurosurgery* 2005;56:1191–201
- Tateshima S, Tanishita K, Hakata Y, et al. **Alteration of intraaneurysmal hemodynamics by placement of a self-expandable stent: laboratory investigation.** *J Neurosurg* 2009;111:22–27
- Canton G, Levy DI, Lasheras JC, et al. **Flow changes caused by the sequential placement of stents across the neck of sidewall cerebral aneurysms.** *J Neurosurg* 2005;103:891–902
- Chow MM, Woo HH, Masaryk TJ, et al. **A novel endovascular treatment of a wide-necked basilar apex aneurysm by using a Y-configuration, double-stent technique.** *AJNR Am J Neuroradiol* 2004;25:509–12
- Canton G, Levy DI, Lasheras JC. **Hemodynamic changes due to stent placement in bifurcating intracranial aneurysms.** *J Neurosurg* 2005;103:146–55
- Cekirge HS, Yavuz K, Geyik S, et al. **A novel 'Y' stent flow diversion technique for the treatment of bifurcation aneurysms without endosaccular coiling.** *AJNR Am J Neuroradiol* 2011;32:1262–68
- Saatci I, Geyik S, Yavuz K, et al. **X-configured stent-assisted coiling in the endovascular treatment of complex anterior communicating artery aneurysms: a novel reconstructive technique.** *AJNR Am J Neuroradiol* 2011;32:113–17
- Keukeleire DK, Vanlangenhove P, Defreyne L. **Evaluation of a neck-bridge device to assist endovascular treatment of wide-neck aneurysms of the anterior circulation.** *AJNR Am J Neuroradiol* 2008;29:73–78
- Bendok BR, Parkinson RJ, Hage ZA, et al. **The effect of vascular reconstruction device-assisted coiling on packing density, effective neck coverage, and angiographic outcome: an in vitro study.** *Neurosurgery* 2007;61:835–41
- Wanke I, Forsting M. **Stents for intracranial wide-necked aneurysms: more than mechanical protection.** *Neuroradiology* 2008;50:991–98
- Perez-Arjona E, Fessler RD. **Basilar artery to bilateral posterior cerebral artery Y stenting for endovascular reconstruction of wide-necked basilar apex aneurysms: report of three cases.** *Neurol Res* 2004;26:276–81
- Sani S, Lopes DK. **Treatment of a middle cerebral artery bifurcation aneurysm using a double Neuroform stent Y configuration and coil embolization: technical case report.** *Neurosurgery* 2005;57(1 Suppl):E209

16. Heller RS, Malek AM. Parent vessel size and curvature strongly influence risk of incomplete stent apposition in Enterprise intracranial aneurysm stent coiling. *AJNR Am J Neuroradiol* 2011;32:1714–20
17. Naggara ON, White PM, Guilbert F, et al. Endovascular treatment of unruptured intracranial aneurysms: systematic review and meta-analysis of the literature on safety and efficacy. *Radiology* 2010;256:887–97
18. McDonald JS, Norgan AP, McDonald RJ, et al. In-hospital outcomes associated with stent-assisted endovascular treatment of unruptured cerebral aneurysms in the USA. *J Neurointerv Surg* 2012; May 5, Epub ahead of print
19. Shapiro M, Becske T, Sahlein D, et al. Stent-supported aneurysm coiling: a literature survey of treatment and follow-up. *AJNR Am J Neuroradiol* 2012;33:159–63
20. Murayama Y, Nien YL, Duckwiler G, et al. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg* 2003;98:959–66
21. Cekirge HS, Yavuz K, Geyik S, et al. HyperForm balloon remodeling in the endovascular treatment of anterior cerebral, middle cerebral, and anterior communicating artery aneurysm: clinical and angiographic follow-up results in 800 consecutive patients. *J Neurosurg* 2011;114:944–53
22. Vendrell JF, Menjot N, Costalat V, et al. Endovascular treatment of 174 middle cerebral artery aneurysms: clinical outcome and radiologic results at long-term follow-up. *Radiology* 2009;253:191–98
23. Lubicz B. Linear stent-assisted coiling: another way to treat very wide-necked intracranial aneurysms. *Neuroradiology* 2011;53:457–59
24. Cho YD, Park SW, Lee JY, et al. Non-overlapping Y-configuration stenting technique with dual closed cell stents in wide-neck basilar tip aneurysms. *Neurosurgery* 2011, Epub ahead of print
25. Horowitz M, Levy E, Sauvageau E, et al. Intra/extra-aneurysmal stent placement for management of complex and wide-necked-bifurcation aneurysms: eight cases using the waffle cone technique. *Neurosurgery* 2006;58(4 Suppl 2):ONS258–262
26. Baharoglu MI, Schirmer CM, Hoit DA, et al. Aneurysm inflow-angle as a discriminant for rupture in sidewall cerebral aneurysms: morphometric and computational fluid dynamic analysis. *Stroke* 2010;41:1423–30
27. Gao B, Baharoglu MI, Cohen AD, et al. Stent-assisted coiling of intracranial bifurcation aneurysms leads to immediate and delayed intracranial vascular angle remodeling. *AJNR Am J Neuroradiol* 2012;33:649–54

3D Cine Phase-Contrast MRI at 3T in Intracranial Aneurysms Compared with Patient-Specific Computational Fluid Dynamics

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ABSTRACT

BACKGROUND AND PURPOSE: CFD has been proved valuable for simulating blood flow in intracranial aneurysms, which may add to better rupture risk assessment. However, CFD has drawbacks such as the sensitivity to assumptions needed for the model, which may hinder its clinical implementation. 3D PC-MR imaging is a technique that enables measurements of blood flow. The purpose of this study was to compare flow patterns on the basis of 3D PC-MR imaging with CFD estimates.

MATERIALS AND METHODS: 3D PC-MR imaging was performed in 8 intracranial aneurysms. Two sets of patient-specific inflow boundaries for CFD were obtained from a separate 2D PC-MR imaging sequence (2D CFD) and from the 3D PC-MR imaging (3D CFD) data. 3D PC-MR imaging and CFD were compared by calculation of the differences between velocity vector magnitudes and angles. Differences in flow patterns expressed as the presence and strengths of vortices were determined by calculation of singular flow energy.

RESULTS: In systole, flow features such as vortex patterns were similar. In diastole, 3D PC-MR imaging measurements appeared inconsistent due to low velocity-to-noise ratios. The relative difference in velocity magnitude was $67.6 \pm 51.4\%$ and $27.1 \pm 24.9\%$ in systole and $33.7 \pm 21.5\%$ and $17.7 \pm 10.2\%$ in diastole for 2D CFD and 3D CFD, respectively. For singular energy, this was reduced to $15.5 \pm 13.9\%$ at systole and $19.4 \pm 17.6\%$ at diastole (2D CFD).

CONCLUSIONS: In systole, good agreement between 3D PC-MR imaging and CFD on flow-pattern visualization and singular-energy calculation was found. In diastole, flow patterns of 3D PC-MR imaging differed from those obtained from CFD due to low velocity-to-noise ratios.

ABBREVIATIONS: CFD = computational fluid dynamics; PC-MRI = cine phase-contrast MR imaging; RA = rotational angiography; VNR = velocity-to noise ratio

Despite a decrease in fatalities of subarachnoid hemorrhage caused by intracranial aneurysm rupture in recent years,¹ this devastating event is lethal in one-third² to 50%³ of patients. Treatment of incidentally found unruptured aneurysms consists of endovascular coiling or surgical clipping, with procedure-related morbidity and mortality rates slightly in favor of the for-

mer.⁴ Because the risk of treatment potentially outweighs the risk of rupture,⁵ treatment decisions should be based on as much available information on the individual aneurysm as possible. It is widely believed that intra-aneurysmal hemodynamics contributes substantially to rupture risk assessment and treatment-planning assistance.⁶⁻⁹ Many studies showed promising results when conducting assessment of risk factors such as intra-aneurysmal flow patterns and wall shear stress by using patient-specific CFD.¹⁰⁻¹² A drawback of performing CFD is the difficulty in converting large amounts of patient-specific data into workable models.⁹ Without patient-specific data for inflow and outflow boundary conditions, assumptions have to be made regarding heart rate and blood flow, the shape of the inlet-velocity profile, and flow-division ratios in the outflow branches.¹⁴ Further drawbacks are the need for large computational power and extensive calculation time. Despite these drawbacks, CFD has recently been used to associate intra-aneurysmal hemodynamics with rupture.¹⁵

The enormous advancements in MR imaging technology in the past decade now allow direct measurement of intra-aneurys-

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mal flow by using 3D PC-MR imaging.¹⁹ Moreover, the technique was validated against CFD in a real-size phantom.¹⁶ However, clinical application of 3D PC-MR imaging in intracranial aneurysms is complicated by the requirements for high-resolution, high SNR, and patient-tolerable scanning times. In this study, a 3D PC-MR imaging sequence with a scanning duration of approximately 10 minutes, therefore clinically feasible, was applied to 8 intracranial aneurysms. The results were compared with patient-specific CFD simulations in which spatial and temporal boundary conditions obtained from a separate 2D PC-MR imaging and from the 3D PC-MR imaging acquisition were applied. Comparison was performed on a voxel-by-voxel basis by calculating the mean and SD of the paired differences of velocity magnitude and singular energy. The purpose of this study was to assess whether the results of 3D PC-MR imaging and patient-specific CFD are comparable and whether 3D PC-MR imaging can measure important quantitative and qualitative features of intra-aneurysmal flow.

MATERIALS AND METHODS

Population

The patients were included in a larger study on intra-aneurysmal hemodynamics. Inclusion criteria for that study were a minimal aneurysm size of approximately 3 mm, adult age (18–75 years), and a requirement that patients be enrolled in a diagnostic aneurysm work-up with at least 3D rotational angiography. The patients met a Glasgow Outcome Scale score of ≥ 4 .¹⁷ Patients were excluded if they had contraindications for either 3D-RA or MR imaging. Further inclusion requirement for this study was a successful 3D PC-MR imaging measurement in an unruptured intracranial aneurysm. The local ethics committee approved the study protocol, and written informed consent was obtained from all participating patients. The age of the patients ranged between 44 and 65 years with a mean of 51 ± 7.7 years. Five patients were female; 3 patients were male. The dimensions of the aneurysms were determined on the 3D-RA data by using 3D Slicer (www.slicer.org) and are listed in On-line Table 1.

MR Imaging

The protocol consisted of 3 MR imaging sequences that were conducted on a 3T scanner (Intera; Philips Healthcare, Best, the Netherlands) by using an 8-channel head coil.

First, a high-resolution time-of-flight sequence was performed with a scan resolution of $0.39 \times 0.6 \times 1$ mm, interpolated to $0.39 \times 0.39 \times 0.5$ mm. Imaging parameters were the following: TE/TR/flip angle, 4.2/21.4 ms/20°; receiver bandwidth, 32 kHz; imaging volume, $200 \times 200 \times 92$ mm; parallel imaging factor, 2.5; scanning time, 6.16 minutes.

Second, to acquire 2D PC-MR imaging data that served as inflow boundary conditions for CFD, we placed a section perpendicular to the parent artery proximal to the aneurysm. The acquisition was retrospectively gated by using either an electrocardiogram or peripheral pulse unit. Scan resolution was $0.64 \times 0.65 \times 3$ mm. Further imaging parameters were the following: TE/TR/flip angle, 5.7/8.5 ms/10°; receiver bandwidth, 172 kHz; imaging volume, $200 \times 200 \times 3$ mm in 1 section; parallel imaging factor, 2. For aneurysm 5, the velocity encoding was 70 cm/s in all direc-

tions; for the others, 100 cm/s in all directions. The number of measured cardiac phases (ie, temporal resolution) depended on the heart rate and ranged between 23 and 36 cardiac phases, to keep the scanning time close to 3 minutes and 30 seconds. The view-sharing factor for the retrospective sorting of acquired k-lines was set to 1.8.¹⁸

Third, the 3D PC-MR imaging acquisition was retrospectively gated by using either an electrocardiogram or peripheral pulse unit at an acquired resolution of $0.8 \times 0.8 \times 0.8$ mm. Further imaging parameters were the following: TE/TR/flip angle: 3.0/5.8 ms/15°; receiver bandwidth, 54 kHz; imaging volume, $200 \times 200 \times 20$ mm in 25 transversal sections; parallel imaging factor, 3. The velocity encoding was 70 cm/s in all directions for aneurysm 5 and 100 cm/s in all directions for the others; scanning time was 10.22 minutes at 60 beats/min. The number of acquired cardiac phases was 10.

MR Imaging Postprocessing

Phase images were corrected for background phase offset errors by subtracting the average phase in a static region of interest near the aneurysm for every velocity-encoding direction and cardiac phase individually.¹⁹ The segmentation of the vessel and aneurysms was performed with the use of a level set evolution algorithm²⁰ applied in the phase-contrast magnitude images. This was done for every cardiac phase separately. Velocity values in pixels that were located outside the segmentation or had partial voluming were set to zero. Pixels in the regions of interest that had velocity aliasing were manually corrected in all 3 directions. The cardiac cycles were reordered so that the systolic phase occurred at the end of the cardiac cycle. These postprocessing steps were performed with custom-built software in Matlab (MathWorks, Natick, Massachusetts) and took approximately 4 hours to conduct. To calculate the flow ratios of the outflow branches, we imported the data into GTFlow (Gyrotools, Zürich, Switzerland).

CFD Setup

The geometric vascular models used for CFD simulations were created from 3D rotational angiography. Images were acquired with a single-plane angiographic unit (Integris Allura and Neuro; Philips Healthcare). For more detail see Geers et al.⁶ The voxel size of the measurement is given in On-line Table 1. There was no difference in the 3D rotational angiography acquisition for the patients. All imaging parameters were constant with an image intensifier FOV of 22 cm for all cases. 3D-RA images were imported into the Vascular Modeling Tool Kit (<http://www.vmtk.org/>).²¹ With the use of a level set algorithm, isosurfaces were created that were subsequently meshed by using an average edge length of 0.1 mm, with a minimum of 0.1 μ m and a maximum 0.4 mm.

Meshes were created consisting of 1,168,002 to 2,608,270 tetrahedral elements with a mesh density of at least 3000 elements per cubic millimeter. The sizes of the meshes are listed in On-line Table 1. All CFD simulations were performed in FLUENT 6.3 (ANSYS, Canonsburg, Pennsylvania). Blood density was set to 1060 kg/m³; and dynamic viscosity, to 0.004 kg/ms.

To study the influence of inflow boundary conditions, we performed 2 different series of simulations: 1) CFD with spatial and temporal inflow boundary conditions obtained from 2D PC-MR

imaging and 2) CFD with spatial and temporal inflow boundary conditions obtained from 3D PC-MR imaging.

The pipeline for imposing velocity-inlet boundary conditions in the CFD simulations obtained from 2D PC-MR imaging was as follows: First, the aneurysm in the time-of-flight measurement and the proximal vessel in the 2D PC-MR imaging section were manually selected. Subsequently, the 2D PC-MR imaging data were positioned on the time-of-flight data by using rotation and translation matrices extracted from DICOM headers. The CFD mesh was constructed, and a rigid registration of the time-of-flight measurement on the CFD mesh was conducted with the fMRI of the Brain Linear Image Registration Tool (<http://www.fmrib.ox.ac.uk/analysis/research/flirt/>).²² The velocities measured with 2D PC-MR imaging were rotated and translated likewise and interpolated onto the nodes of the CFD inflow boundary. The velocity at the nodes at the edge of the vessel was set to zero. These last steps were performed for every measured cardiac phase in 2D PC-MR imaging.

Imposing inflow boundary conditions obtained from 3D PC-MR imaging were realized by rigid registration of the 3D PC-MR imaging segmentation to the CFD geometry and subsequent interpolation of the velocity values of the 3D PC-MR imaging measurement found at the CFD inflow boundary to the nodes at this location. These steps were performed with custom-built software in Matlab.

CFD iterations were continued until the residual of the continuity equation was below 0.001. The CFD estimates were resolved at fixed time intervals equal to the measured RR interval divided by the number of cardiac phases used for the 2D PC-MR imaging. Three heart cycles were simulated to eliminate transient effects. The third of these cycles was used in the comparison with the PC-MR imaging results.

Flow through the outflow vessels of the CFD model was prescribed according to outflow measurements at every cardiac phase of the 3D PC-MR imaging data averaged with time. If an outflow vessel was too small to quantify flow, a combination of measured flow and Murray's law²³ was applied. The average simulation time was 36 hours per aneurysm.

Data Quantification and Visualization

Calculations of the SNR of the phase-contrast magnitude images at peak systole and end diastole of the 3D PC-MR imaging measurements were performed as described by Price et al.²⁴ S_1 and S_2 represent phase-contrast magnitude signals in a region of interest during different cardiac phases of similar mean velocity magnitude. By subtracting these images, an image containing minimum signal and maximum noise is obtained. SNR is then calculated by

$$1) \quad SNR = \frac{\text{mean}(S_1 + S_2)_{ROI}}{\sqrt{2SD(S_1 - S_2)_{ROI}}}.$$

As the region of interest for the SNR calculation, the total aneurysm with inflow and outflow vessels was taken. VNR equals the product of SNR and velocity divided by the velocity encoding. VNR is not calculated separately.

During postprocessing, the number of cardiac phases of CFD was reduced to equal the number of cardiac phases of the 3D PC-MR imaging measurement.

To quantify differences between 3D PC-MR imaging and CFD, we registered the CFD data and linearly interpolated them to the 3D PC-MR imaging data. To take aneurysm pulsatility in the 3D PC-MR imaging data into account, we conducted registration for every cardiac phase separately. Peak systole and end diastole were defined as the cardiac phase in which the spatially averaged velocity magnitude was maximal and minimal, respectively.

Further comparison consisted of quantification of the location and magnitude of vortices, by calculation of singular energy, as developed by Liu and Ribeiro,²⁵ of the intra-aneurysmal flow.²⁶ Multiple vortices or vortices fluctuating with time are thought to be an indicator of rupture.²⁷ Quantification of vortices by calculating singular energy may therefore be useful in rupture-risk assessment in aneurysms. In this study, the magnitude and location of singular energy was used for comparison of the velocity fields between 3D PC-MR imaging and CFD.

The technique used in the current study extended the original 2D approach to 3D by including the singular energy for the transverse, sagittal, and coronal 2D sections. For further details, see Marquering et al.²⁶ A scale σ of 4 voxels (3.2 mm) was used.

All quantification and visualization were performed with custom-built software in Matlab. Pathline images were created, and flow quantification in the inflow vessel of the 2D and 3D PC-MR imaging was performed in GTFlow. The input flow, inflow vessel area, mean velocity magnitude, and peak systolic velocity magnitude values for the aneurysms are given in On-line Table 1.

For both CFD with inflow boundaries from 2D and 3D PC-MR imaging, Bland-Altman plots analyzing velocity magnitude and singular energy differences over the entire heart cycle on a per-aneurysm level are shown in On-line Figs 1–4, as well as Bland-Altman plots showing the spatially averaged differences in velocity magnitude and singular energy at systole and diastole (On-line Figs 5 and 6).

A supplemental analysis was performed for the differences between 3D PC-MR imaging and CFD, with inflow boundary conditions obtained from 2D PC-MR imaging consisting of partitioning the aneurysm in an inflow region and a dome region. The results are shown in On-line Table 2.

Statistics

The difference in velocity magnitude and singular energy between CFD and 3D PC-MR imaging was determined for every voxel and subsequently averaged over space to yield a mean paired difference (*MDif*) at every cardiac phase:

$$2) \quad MDif = \frac{\sum_{n=1}^N MRI_n - CFD_n}{N},$$

where N is the number of voxels. Its significance was tested with a paired t test; $P < .05$ was considered statistically significantly different. The SD of the paired difference (*SDif*) was calculated as

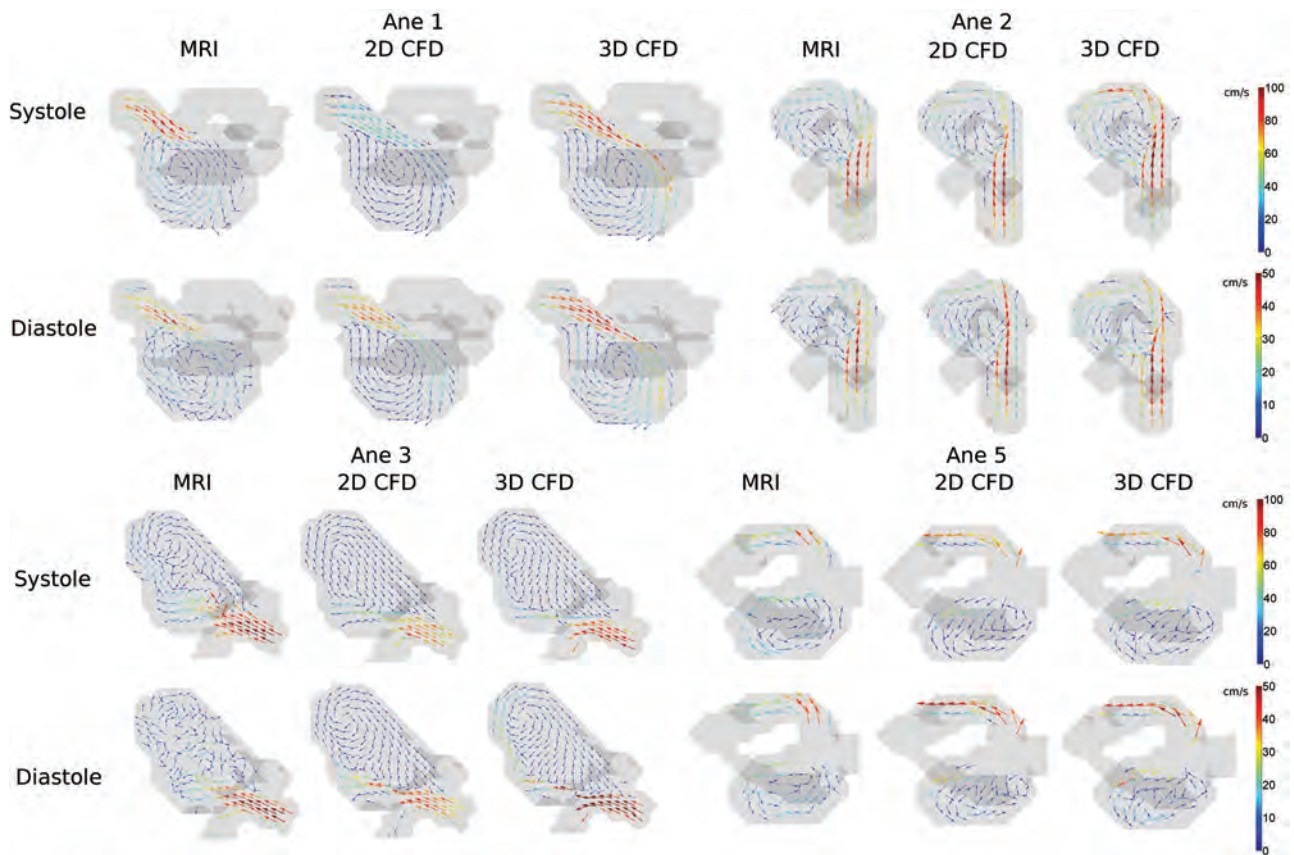


FIG 1. Velocity vector images in a characteristic section depicting the main vortex in 4 aneurysms and the inflow jet in 3 of the aneurysms. The images depict the aneurysms at peak systole and diastole in isosurfaces (gray) for 3D PC-MR imaging, CFD with inflow boundary conditions obtained from 2D PC-MR imaging, and CFD with inflow boundary conditions obtained from 3D PC-MR imaging.

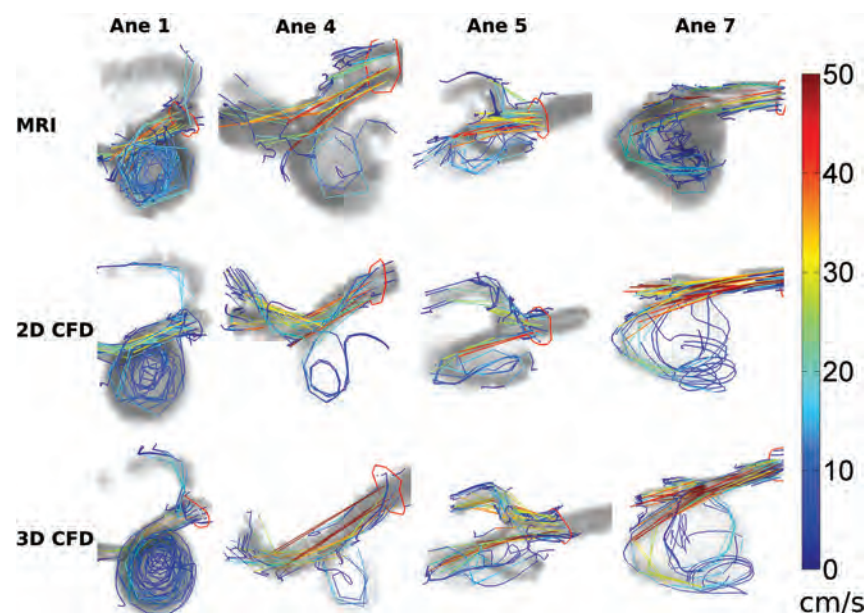


FIG 2. Pathlines over the entire cardiac cycle depicting similar complex flow in aneurysm volumes (gray background) of aneurysms 1, 4, 5, and 7 for 3D PC-MR imaging; CFD with inflow boundary conditions obtained from 2D PC-MR imaging; and CFD with inflow boundary conditions obtained from 3D PC-MR imaging.

well. A relative difference in velocity magnitude between both methods was based on the mean CFD velocity magnitude per subject:

$$3) \quad RDif = \frac{MDif}{\left(\frac{\sum_{n=1}^N CFD_n}{N} \right)}$$

Differences in flow direction were calculated from the angle difference between corresponding velocity vectors. Because the distribution of the angle difference was not normal, median rather than mean values were calculated.

RESULTS

The SNR of the 3D PC-MR imaging velocity measurements was 19.5 ± 3.4 .

Figure 1 shows intra-aneurysmal flow patterns in 4 aneurysms. In systole, the circular motion in the vortices and the direction of inflow jets were qualitatively similar for the 3 methods. This finding can further be appreciated from the pathlines in Fig 2. In Fig 1 for diastole, the vortices of the 3D PC-MR imaging measurement appeared disrupted

and irregular in most aneurysms.

For most aneurysms, the 3D PC-MR imaging measurements resulted in higher velocity magnitude values than CFD with in-

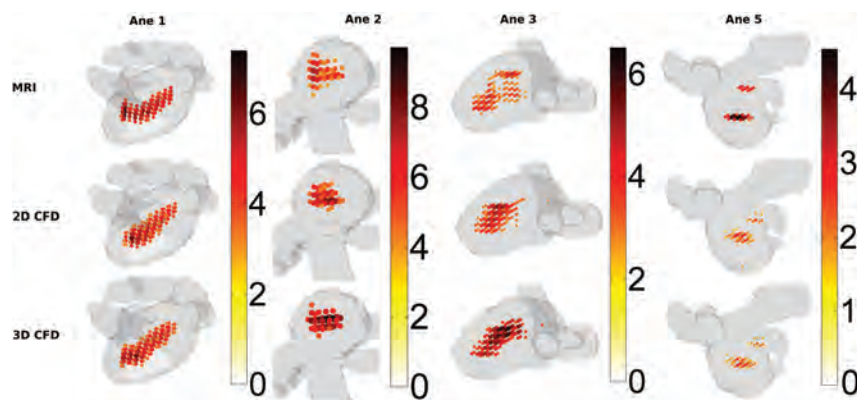


FIG 3. Singular-energy magnitude and location at peak systole in aneurysm volumes (gray) of aneurysm 1, 2, 3, and 5 for 3D PC-MR imaging; CFD with inflow boundary conditions obtained from 2D PC-MR imaging; and CFD with inflow boundary conditions obtained from 3D PC-MR imaging. For visualization purposes, only the areas with singular energy above half the maximum value are indicated.

flow boundary conditions obtained from 2D PC-MR imaging (On-line Table 3). When inflow boundary conditions from 3D PC-MR imaging were used, the velocity magnitude values were higher for CFD than for 3D PC-MR imaging in a few simulations. For both CFD methods, the *SDif* and the *RDif* were higher in systole than in diastole and differences in estimated local flow direction were found primarily in diastole.

The Bland-Altman plots in On-line Figs 1–4 show similar behavior for the difference in velocity magnitude and singular energy between 3D PC-MR imaging and both CFD methods

In Fig 3, the locations with singular energy magnitude higher than half the maximum are displayed for 4 aneurysms. For aneurysms 1, 2, and 3, the locations and magnitudes of the maximum singular energy were similar. For aneurysm 5, the magnitude of the singular energy was approximately twice as low for both CFD methods. *RDif* averaged over all aneurysms in systole was a factor of 3 smaller for singular energy than for velocity magnitude (On-line Table 4).

On-line Fig 5A shows that in systole an offset in velocity magnitude was found for the difference between 3D PC-MR imaging and CFD with 2D PC-MR imaging inflow boundary conditions. For velocity magnitude at diastole and singular energy at both systole and diastole, the Bland-Altman plots (On-line Figs 5 and 6) were similar for the difference between 3D PC-MR imaging and CFD with 2D PC-MR imaging and 3D PC-MR imaging inflow boundary conditions.

In On-line Table 2, *MDif*, *SDif*, and *RDif* are given for the separated inflow vessel and dome of the aneurysms. At systole, *MDif* was generally higher for the inflow region than for the dome, while *RDif* was lower for the inflow region than the dome. Further differences were similar to the analysis of the total geometry.

DISCUSSION

Studies comparing 3D PC-MR imaging with CFD on a voxel-by-voxel basis in human aneurysms at 3T are not available in the literature, to our knowledge. One study compared 3D PC-MR imaging with CFD in the aorta,²⁸ and 1 study in 5 intracranial aneurysms at 1.5T at relatively low spatial resolution.²⁹ Another

study compared 3D PC-MR imaging with CFD in canine aneurysm models.³⁰ All studies found a good qualitative agreement between both techniques and a moderate quantitative agreement. Note that the purpose of the CFD simulations in this study was to compare the results with the 3D PC-MR imaging measurements. To compare the modalities on a voxel basis, we downsized the flow fields obtained from CFD simulations to the voxel size of 3D PC-MR imaging. The original CFD data were therefore not displayed.

The need for reliable patient-specific CFD simulations has been described by many authors. However, the prescription of inflow boundary conditions that produce accurate CFD results is still a

matter of debate. Several studies used flow rates that were measured with 2D PC-MR imaging in separate healthy volunteers.^{9,31} Patient-specific spatial and temporal velocity vector values as measured with 3D PC-MR imaging at each node of the inflow boundary and subsequent comparison with 3D PC-MR imaging have been applied at relatively low resolution in only 2 studies.^{28,29} This is the first study to perform this comparison in intracranial aneurysms at 3T, to our knowledge.

To be able to prescribe boundary conditions with high spatial and temporal resolution, we performed a 2D PC-MR imaging measurement to obtain inflow profiles. Furthermore, the difference with inflow boundary conditions obtained at lower spatial and temporal resolution was investigated by prescribing inflow boundary conditions obtained from 3D PC-MR imaging. It was shown that different inflow boundary conditions produce different results in terms of velocity magnitude. However, the differences in the direction of the velocity vectors, expressed as the angle between vortices or as locations of vortices by singular energy, were found to be small when using inflow boundary conditions obtained from different techniques.

On average, the 3D PC-MR imaging measurements resulted in 30% higher flow estimates than the 2D PC-MR imaging ones. Discrepancies between flow measurements from 2D and 3D PC-MR imaging ($\pm 18\%$)³² or 2D and endovascular sonography ($\pm 15\%$)³³ have been reported in the literature earlier. Wentland et al³⁴ concluded that flow measurements in healthy volunteers in the renal vasculature revealed that 3D measurements tended to be more internally consistent than 2D measurements.

In On-line Table 1, it can be seen that segmentation of the sections obtained by 3D PC-MR imaging resulted in larger areas than for the 2D PC-MR imaging sections. A slightly smaller segmentation can result in the discarding of many voxels around the circumference of the vessel and therefore in severe area underestimation. Despite the lower mean velocities in the 3D PC-MR imaging measurement, the larger vessel area resulted in larger flow values than 2D PC-MR imaging.

A consequence of the smaller vessel segmentation in 2D PC-MR imaging was that velocities at nodes at the edges of the

inflow boundary in CFD were interpolated toward zero. The wider segmentation in 3D PC-MR imaging led to higher input velocities at the edges of the inflow boundary in the CFD simulation. Therefore 3D PC-MR imaging corresponded better with CFD simulations with inflow boundary conditions obtained from 3D PC-MR imaging than the simulations by using inflow boundary conditions obtained from 2D PC-MR imaging.

Six simulations with boundary conditions obtained from 3D PC-MR imaging were performed; in 2 cases, the inflow of the CFD was located outside the imaging volume of the PC-MR imaging sequence.

The systematic differences in local velocity were reduced 5-fold for *MDif* and 2-fold for *RDif* by using inflow boundary conditions from 3D PC-MR imaging instead of 2D PC-MR imaging. The fan-shaped profiles of the Bland-Altman plots in On-line Figs 1–4 reveal that the discrepancies between 3D-PC-MR imaging and both CFD methods are proportional with the mean of 3D PC-MR imaging and CFD. Random differences (*SDif*) were similar for both inflow boundary conditions. The results for the singular energy and the median angle were similar. We therefore conclude that different inflow boundary conditions have a large influence on magnitude of velocity values. However, velocity vector directions and locations and magnitude of vortices are fairly independent of inflow boundary conditions.

The singular energy measure as presented in this study is introduced to facilitate the comparison between 3D PC-MR imaging and CFD. Singular energy provides a quantitative measure of flow patterns. It is unclear whether it may lead to more insight into the nature of the aneurysm with respect to rupture, as has been discussed in the literature recently.^{35,36} While this is an intriguing possibility, it was not the purpose of the current work to address the predictive value of this quantity.

Another limitation is the semiautomatic segmentation of the 3D rotational angiography dataset, resulting in possible under- or overestimation of neck width.³⁷ Also limitations with regard to the 3D PC-MR imaging setup may contribute to the found discrepancies between both techniques. In our study, SNR values within aneurysms were relatively low due to small voxel sizes and the use of parallel imaging.³⁸ Therefore, at low velocities during diastole, the velocity may be overestimated due to noise. Furthermore, the temporal resolution of the 3D PC-MR imaging was relatively low, resulting in temporal low-pass filtering (ie, underestimation of velocities in the systolic phase).

It is clear that more accurate estimation of intracranial aneurysm hemodynamics from PC-MR imaging requires improved technology. Higher field strengths can improve SNR.³⁹ One recently developed promising technique to improve PC-MR imaging measurement is divergence-reduction processing.⁴⁰

CONCLUSIONS

In this study, high-resolution 3D PC-MR imaging was compared with patient-specific CFD on a voxel-by-voxel basis in 8 aneurysms. In peak systole, qualitative similarities in flow features such as vortical flow patterns and inflow behavior were evident. In end diastole, the flow patterns of the 3D PC-MR imaging measurements were different compared with those generated with CFD due to the low velocity-to-noise ratio of the 3D PC-MR imaging

measurements. Singular energy calculation revealed quantitative agreement between 3D PC-MR imaging and CFD in systole.

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REFERENCES

1. Nieuwkamp DJ, Setz LE, Algra A, et al. **Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis.** *Lancet Neurol* 2009;8:635–42
2. Greebe P, Rinkel GJ, Hop JW, et al. **Functional outcome and quality of life 5 and 12.5 years after aneurysmal subarachnoid haemorrhage.** *J Neurol* 2010;257:2059–64
3. Vega C, Kwoon JV, Lavine SD. **Intracranial aneurysms: current evidence and clinical practice.** *Am Fam Physician* 2002;66:601–08
4. Wiebers DO, Whisnant JP, Huston J, 3rd, et al. **Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment.** *Lancet* 2003;362:103–10
5. Ford MD, Nikolov HN, Milner JS, et al. **PIV-measured versus CFD-predicted flow dynamics in anatomically realistic cerebral aneurysm models.** *J Biomech Eng* 2008;130:021015
6. Geers AJ, Larrabide I, Radaelli AG, et al. **Patient-specific computational hemodynamics of intracranial aneurysms from 3D rotational angiography and CT angiography: an in vivo reproducibility study.** *AJNR Am J Neuroradiol* 2011;32:581–86
7. Ford MD, Lee SW, Lownie SP, et al. **On the effect of parent-aneurysm angle on flow patterns in basilar tip aneurysms: towards a surrogate geometric marker of intra-aneurysmal hemodynamics.** *J Biomech* 2008;41:241–48
8. Rayz VL, Boussel L, Lawton MT, et al. **Numerical modeling of the flow in intracranial aneurysms: prediction of regions prone to thrombus formation.** *Ann Biomed Eng* 2008;36:1793–1804
9. Cebal JR, Castro MA, Burgess JE, et al. **Characterization of cerebral aneurysms for assessing risk of rupture by using patient-specific computational hemodynamics models.** *AJNR Am J Neuroradiol* 2005;26:2550–59
10. Boussel L, Rayz V, Martin A, et al. **Phase-contrast magnetic resonance imaging measurements in intracranial aneurysms in vivo of flow patterns, velocity fields, and wall shear stress: comparison with computational fluid dynamics.** *Magn Reson Med* 2009;61:409–17
11. Cebal JR, Castro MA, Appanaboyina S, et al. **Efficient pipeline for image-based patient-specific analysis of cerebral aneurysm hemodynamics: technique and sensitivity.** *IEEE Trans Med Imaging* 2005;24:457–67
12. Chien A, Castro MA, Tateshima S, et al. **Quantitative hemodynamic analysis of brain aneurysms at different locations.** *AJNR Am J Neuroradiol* 2009;30:1507–12
13. Sforza DM, Putman CM, Cebal JR. **Hemodynamics of cerebral aneurysms.** *Annu Rev Fluid Mech* 2009;41:91–107
14. Venugopal P, Valentino D, Schmitt H, et al. **Sensitivity of patient-specific numerical simulation of cerebral aneurysm hemodynamics to inflow boundary conditions.** *J Neurosurg* 2007;106:1051–60
15. Mut F, Lohner R, Chien A, et al. **Computational hemodynamics framework for the analysis of cerebral aneurysms.** *Int J Numer Method Biomed Eng* 2011;27:822–39
16. van Ooij P, Guédon A, Poelma C, et al. **Complex flow patterns in a real-size intracranial aneurysm phantom: phase contrast MRI compared with particle image velocimetry and computational fluid dynamics.** *NMR in Biomed* 2012;25:14–26
17. Wilson JT, Pettigrew LE, Teasdale GM. **Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use.** *J Neurotrauma* 1998;15:573–85
18. Slavin GS, Bluemke DA. **Spatial and temporal resolution in cardio-**

- vascular MR imaging: review and recommendations. *Radiology* 2005;234:330–38
19. Lotz J, Meier C, Leppert A, et al. Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation. *Radiographics* 2002;22:651–71
20. Li C, Xu C, Gui C, et al. Level set evolution without re-initialization: a new variational formulation. In: *Proceedings of the 2005 IEEE Computer Society Conference on Computer Vision and Pattern Recognition*, San Diego, California. June 20–25, 2005:430–36
21. Antiga L, Piccinelli M, Botti L, et al. An image-based modeling framework for patient-specific computational hemodynamics. *Med Biol Eng Comput* 2008;46:1097–112
22. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal* 2001;5:143–56
23. Murray CD. The physiological principle of minimum work: I. The vascular system and the cost of blood volume. *Proc Natl Acad Sci U S A* 1926;12:207–14
24. Price RR, Axel L, Morgan T, et al. Quality assurance methods and phantoms for magnetic resonance imaging: report of AAPM Nuclear Magnetic Resonance Task Group No. 1. *Med Phys* 1990;17:287–95
25. Liu W, Ribeiro E. Scale and rotation invariant detection of singular patterns in vector flow fields. In: Hancock E, Wilson R, Windeatt T, et al, eds. *SSPR & SPR Proceedings of the 2010 Joint IAPR International Conference on Structural, Syntactic, and Statistical Pattern Recognition, LNCS No, 6218*. Berlin: Springer-Verlag; 2010:522–31
26. Marquering HA, van Ooij P, Streekstra GJ, et al. Multiscale flow patterns within an intracranial aneurysm phantom. *IEEE Trans Biomed Eng* 2011;58:3447–50
27. Cebal JR, Mut F, Weir J, et al. Association of hemodynamic characteristics and cerebral aneurysm rupture. *AJNR Am J Neuroradiol* 2011;32:264–70
28. Stalder AF, Liu Z, Hennig J, et al. Patient specific hemodynamics: combined 4D flow-sensitive MRI and CFD. In: Wittek A, Nielsen PMF, Miller K, eds. *Computational Biomechanics for Medicine*. New York: Springer-Verlag; 2011:27–38
29. Isoda H, Ohkura Y, Kosugi T, et al. Comparison of hemodynamics of intracranial aneurysms between MR fluid dynamics using 3D cine phase-contrast MRI and MR-based computational fluid dynamics. *Neuroradiology* 2010;52:913–20
30. Jiang J, Johnson K, Valen-Sendstad K, et al. Flow characteristics in a canine aneurysm model: a comparison of 4D accelerated phase-contrast MR measurements and computational fluid dynamics simulations. *Med Phys* 2011;38:6300–12
31. Castro MA, Putman CM, Cebal JR. Computational fluid dynamics modeling of intracranial aneurysms: effects of parent artery segmentation on intra-aneurysmal hemodynamics. *AJNR Am J Neuroradiol* 2006;27:1703–09
32. Stalder A, Russe M, Frydrychowicz A, et al. Quantitative 2D and 3D phase contrast MRI: optimized analysis of blood flow and vessel wall parameters. *Magn Reson Med* 2008;60:1218–31
33. Schneiders JJ, Ferns SP, van Ooij P, et al. Comparison of phase-contrast MR imaging and endovascular sonography for intracranial blood flow velocity measurements. *AJNR Am J Neuroradiol* 2012;33:1786–90
34. Wentland A, Grist TM, Wieben O. Repeatability and internal consistency of abdominal 2D and 4D PC MR flow measurements. *J Cardiovasc Magn Reson* 2012;14(Suppl 1):W13
35. Kallmes DF. Point: CFD—computational fluid dynamics or confounding factor dissemination. *AJNR Am J Neuroradiol* 2012;33:395–96
36. Cebal JR, Meng H. Counterpoint: realizing the clinical utility of computational fluid dynamics—closing the gap. *AJNR Am J Neuroradiol* 2012;33:396–98
37. Schneiders JJ, Marquering HA, Antiga L, et al. Intracranial aneurysm neck size overestimation with 3D rotational angiography: an exploratory study on the impact on intra-aneurysmal hemodynamics simulated with computational fluid dynamics. *AJNR Am J Neuroradiol* 2013;34:121–28
38. Thunberg P, Karlsson M, Wigstrom L. Accuracy and reproducibility in phase contrast imaging using SENSE. *Magn Reson Med* 2003;50:1061–68
39. van Ooij P, Zwanenburg JJM, Visser F, et al. Quantification and visualization of flow in the circle of Willis: time-resolved three-dimensional phase contrast MRI at 7 T compared with 3 T. *Magn Reson Med* 2013;69:868–76
40. Busch J, Giese D, Wissmann L, et al. Construction of divergence-free velocity fields from cine 3D phase-contrast flow measurements. *Magn Reson Med* 2013;69:200–10

What Is Meant by “TICI”?

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ABSTRACT

BACKGROUND: In 2003, Higashida et al proposed the Thrombolysis In Cerebral Infarction scale to evaluate angiographic intracranial flow. Our aim is to review how subsequently published studies define TICI.

MATERIALS AND METHODS: We used the ISI Web of Knowledge and SciVerse Scopus databases to search for “TICI” and “thrombolysis in cerebral infarction” and for articles that cited the original TICI paper from January 2004 through May 2012. Articles were categorized according to their definition of the TICI categories, typically grades 0–4, with grade 2 (partial reperfusion) subdivided into 2a and 2b, and rate of contrast entry to the perfused area. In addition, we catalogued the type of redefinitions of TICI subcategory 2 and additions of new categories.

RESULTS: Of 236 articles screened, 74 were included. Eight (11%) explicitly followed the TICI scale as originally defined. Thirty-seven (50%) cited Higashida but did not define their scale. Fifteen (21%) used and explained modified scales. Thirteen (18%) used the term TICI, but did not define the scale and did not cite Higashida. Eighteen (24%) specified a 2a subcategory. Nine defined grade 2a as <67% filling, 6 defined it as <50%, and 3 did not offer a percentage. Two studies added a 2c subcategory. Fifty-two (70%) used a cutoff level to define “successful reperfusion.” Of these, 65% used $TICI \geq 2$, 33% used $TICI \geq 2b$, and 2% used $TICI = 3$.

CONCLUSIONS: There is substantial variability in the definition and/or application of the TICI scale in the literature. This variability could considerably impact our understanding of results of revascularization studies.

ABBREVIATIONS: TICI = Thrombolysis in Cerebral Infarction; TIMI = Thrombolysis in Myocardial Infarction

The Thrombolysis in Myocardial Infarction scale is a widely applied, graded response scale for assessment of treatment outcome in the coronary arteries.¹ In 2003, Higashida et al² proposed a seemingly simple modification of the TIMI scale to evaluate intracranial perfusion assessed in cerebral angiography. This new scale, the Thrombolysis in Cerebral Infarction scale, was intended to standardize the grading of angiographic outcomes, particularly for trials of endovascular treatment of acute ischemic stroke (Table 1). As originally described, TICI categories span from no perfusion (grade 0) to complete perfusion (grade 3). The “partial perfusion” category (grade 2) is defined as cases in which contrast passes the obstruction but with rates of entry and wash-out slower than normal and is subdivided into 2 subcategories, 2a

and 2b. Although the TICI scale has achieved fairly rapid acceptance into the medical literature, the scale was somewhat arbitrarily created and has not been validated or tested systematically.

Although the TICI scale has been criticized because of confusing internal inconsistencies,³ it is still widely used in the literature.⁴ Modifications of the TICI scale have been subsequently proposed, such as a change in the definition of the 2a subcategory (to indicate <50% filling of the vascular territory) or by the addition of a 2c subcategory.⁵ Our current aim is to review published studies that use the TICI scale to describe how the TICI scale is defined and utilized across studies.

MATERIALS AND METHODS

We performed a search of the medical literature by using the ISI Web of Knowledge and SciVerse Scopus databases. We searched for the terms “TICI” and “thrombolysis in cerebral infarction.” We also used these databases to search for all articles from January 2004 through May 2012 that cited the original TICI paper. In addition, we reviewed the reference list from all identified articles to identify other papers by using graded response scales for cere-

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Table 1: The original Thrombolysis in Cerebral Infarction perfusion scale²

Category	Title	Description
Grade 0	No Perfusion	No antegrade flow beyond the point of occlusion.
Grade 1	Penetration with Minimal Perfusion	The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction.
Grade 2	Partial Perfusion	The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel.
Grade 2a	Complete Perfusion	Only partial filling (less than two-thirds) of the entire vascular territory is visualized.
Grade 2b		Complete filling of all of the expected vascular territory is visualized but the filling is slower than normal.
Grade 3	Complete Perfusion	Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

bral perfusion, whether or not these papers referenced or utilized the original TICI paper.

In the initial description of the TICI scale in 2003, grade 0 indicates no perfusion as evidenced by no antegrade flow beyond the point of arterial occlusion.² Grade 1 is defined as penetration with minimal perfusion” and applies when the “contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction.” Grade 2 is broadly defined as partial perfusion, which occurs when the contrast material passes beyond the obstruction, opacifies the distal arterial bed, but the rate of entry of contrast and/or its rate of clearance from the vascular bed are slower than comparable areas not perfused by the previously occluded vessel. The opposite cerebral artery or the arterial bed proximal to the occlusion can be used for comparison rates. Grade 2 is subdivided into 2a and 2b. A grade of 2a indicates partial filling (less than two-thirds) of the entire vascular territory and 2b indicates complete filling of the expected vascular territory, but with a perceptibly slower filling rate than normal. Finally, grade 3 is defined as complete perfusion and applies when “antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of the contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.”²

With our literature search, we identified a total of 236 articles. We excluded articles that did not relate to the TICI scale (115 articles) and articles that were in languages other than English or that were not accessible in full length (49 articles). We qualitatively assessed whether the definition of TICI in each article adhered to the original definition of the TICI scale and evaluated the articles that were cited when TICI was described. We then accordingly categorized the articles into 4 groups: 1) articles that explicitly stated the scale and followed the original TICI scale completely, 2) articles that did not explicitly define the scale but cited the original TICI paper, 3) articles that defined a modified scale, and 4) articles that used TICI but did not define the scale and did not cite the original TICI paper. We also catalogued the type and number of definitions of subcategory 2a and noted if a subcategory of TICI was used as a threshold for “successful revascularization.” This study was exempt from institutional review board review.

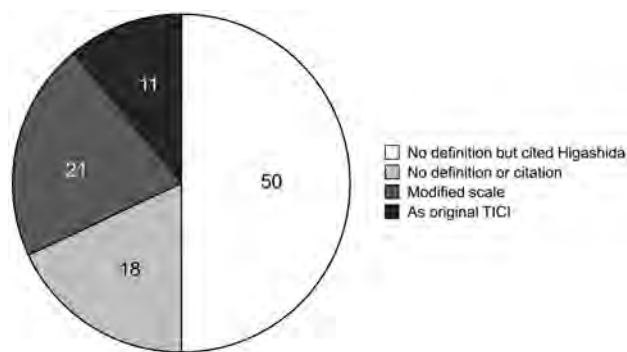


FIG 1. Distribution of definition and citation of the TICI scale in the literature. Articles in the English literature that use the TICI (Thrombolysis in Cerebral Infarction) grading scale, distributed according to definition and citation of TICI.

RESULTS

Of 74 total included articles, 8 (11%) followed the original TICI scale completely and explicitly stated the categories.⁶⁻¹³ One article claimed to have followed the scale completely but did not state the categories.¹⁴ Thirty-seven (50%) articles did not explicitly define the scale but still cited the original paper by Higashida et al.¹⁵⁻⁵¹ Modifications of the TICI scale were used in 15 (20%) articles.^{4,5,52-65} Of these, 8 cited only the original TICI paper, 4 cited the original TICI paper and other papers, and 3 cited only other papers. Thirteen (18%) articles used TICI but did not define the scale and did not cite the original TICI paper.^{13,30,56,66-75} These results are depicted in Fig 1.

Eighteen (24%) of articles mentioned the rate of contrast filling in their use of TICI. Most modifications of TICI eliminated the subcategories of 2a and 2b. Only 18 (24%) articles specified a 2a subcategory. Of these, 9 defined 2a as filling of <67% of the affected vascular territory (compatible with the original TICI) and 6 defined 2a as filling of <50% of the affected vascular territory. A 2c subcategory was added in 2 articles, and a category 4 was added in 1 article. Examples of the variability in definitions of TICI categories are detailed in Table 2.

Most articles ($n = 52$, 70%) defined a threshold within the TICI scale that indicated “successful revascularization” as one of the study end points. Of these, 34 (65%) used TICI ≥ 2 , 17 (33%) used TICI $\geq 2b$ (although only 1 of these studies defined a precise

Table 2: Varying definitions of TICI grades in the literature

Category	Definition
Grade 0	No flow No canalization Complete occlusion No recanalization/reperfusion
Grade 1	Minimal recanalization (<20%) Minimal flow (very slow) without significant flow distal to the occlusion site Limited or no reperfusion Distal movement of thrombus without reperfusion Perfusion past initial occlusion, but limited distal branch filling
Grade 2	Partial recanalization—recanalization of some but not all of the occluded arteries Incomplete recanalization/reperfusion Near-normal flow, with flow distal to the occlusion but not filling the distal branches normally
Grade 2a	Perfusion of <50% of the MCA distribution Partial filling of the entire vascular territory Partial perfusion with incomplete distal filling of <50% of expected territory
Grade 2b	Partial filling of the entire vascular territory Partial perfusion with incomplete distal branch filling of ≥50–99% of the expected territory Complete filling, but the filling is slower than normal
Grade 2c	Perfusion of half or greater of the vascular distribution of the occluded artery Near-complete perfusion without clearly visible thrombus but with delay in contrast run-off
Grade 3	Full perfusion with filling of all distal branches, including M3, M4 Normal flow Partial recanalization with >50% reperfusion
Grade 4	Full perfusion with normal filling of distal branches in a normal hemodynamic fashion Complete recanalization/reperfusion

cutoff for 2b; 67% filling of the vascular territory), and 1 used TICI = 3. These thresholds for successful angiographic revascularization were prespecified in the methods in 40 (77%) of these articles.

DISCUSSION

The term “TICI” connotes a standard and widely accepted metric of revascularization, analogous to the ubiquitous TIMI outcome for coronary revascularization. In the current study, we found substantial variability in how the term “TICI” scale is both defined and used in the recent English literature. Far from being a consistent and universal scale, we noted that only a small minority of studies, by use of the term “TICI” when reporting outcomes after revascularization, actually used the original TICI scale. Furthermore, many studies failed to provide sufficient detail to allow the reader to understand exactly what categories were used. Finally, the definition of successful revascularization varied widely among studies. These current findings are relevant for several reasons.

First, our understanding of the current literature has the potential to be greatly affected by these findings. The modification that changed the cutoff point between TICI subcategories 2a and 2b has particular relevance because a grade on the TICI scale ≥2b was used as an end point to define successful reperfusion in one-third of the articles that specified this end point in our study. Second, the definition of TICI will affect study design for future trials of endovascular therapy for acute ischemic stroke. The TICI

grading scale is increasingly used to define end points of revascularization success in studies. If we define success as achieving a certain grade of TICI (eg, TICI 2b) but we do not have consistent grading systems, we cannot compare or combine results of clinical studies. To achieve enough patients for studies to be powered adequately, it is necessary for investigators from different centers to collaborate together. Without a standardized grading scale, this will not be possible. It is essential that we communicate clearly with consistent terminology.

To our knowledge, our study is the first to specifically describe the varying definitions of the TICI scale as it is reported in the literature. Others, however, have previously called attention to the confusion surrounding the TICI scale.^{3,76} In 2007, Tom-sick⁷⁶ acknowledged confusion about the different revascularization scales. He noted the inconsistent descriptions and applications in the literature; some focus on recanalization, some focus on reperfusion, and others confusingly (and erroneously) use the terms interchangeably. Letters denoting acronyms for different scales are littered throughout the literature and include the TICI, TIMI, TIBI (Thrombolysis in Brain Ischemia), and AOL (Arterial Occlusive Lesion) scales. In a previous review of the

TICI scale, the inherent inconsistencies within the original TICI scale itself were identified.³ For example, there is no applicable TICI grade for a case in which greater than two-thirds but less than “complete” filling of the vascular territory is visualized. In addition, there is no applicable TICI grade for a partially revascularized territory with normal rate of distal opacification, a scenario not uncommonly encountered.³

The TIMI scale—unlike the TICI scale—has not been the subject of frequent modifications. The definition of the TIMI scale throughout the abundant cardiology literature has not been systematically evaluated, but there is general consensus that when used for the evaluation of myocardial perfusion before and after coronary reperfusion therapies, it is used consistently. In the mid1990s, a quantitative assessment of coronary flow called the corrected TIMI Frame Count (CTFC) was reported in an attempt to standardize the scale,⁷⁷ but the original semiquantitative TIMI scale has continued to be the standard used by interventional cardiologists. However, the TIMI scale cannot be easily applied to the more complex cerebral arteries. One review found that 7 different operationalized versions of the TIMI scale have been used in major stroke trials, emphasizing again the need for a single, uniform, consistent scale for grading of perfusion in cerebral arteries.⁷⁸

This study has several limitations. Some articles from our literature search were not reviewed because of a lack of accessibility of full-length articles or because they were written in languages

other than English, creating a selection bias. However, increasing the number of studies we reviewed may have increased the observed variability in TICI definitions. Also, the categories into which articles were divided were subjectively chosen and were evaluated by only 2 investigators.

Further opportunities to refine our grading scales and further our understanding of brain reperfusion abound. Weaknesses in current grading scales for cerebral perfusion are not limited to confusing terminology. Vessel recanalization in the treatment of acute ischemic stroke has been shown to be associated with favorable clinical functional outcomes, but when reperfusion is only partial, the clinical relevance of the use of different TICI grade 2 subdivisions is not known. Furthermore, there are few data regarding the intra-observer and interobserver variability when applying the TICI scale to angiography results. It also remains unclear whether it is appropriate to apply TICI to the posterior circulation and whether the degree of collateral flow—particularly in cases with distal M3–4 occlusions—modifies the effect of revascularization (as measured by TICI) on clinical outcomes.

Scales are designed to aid in the objective description of angiographic results, standardize data for research studies, and assist in outcome prediction.⁷⁹ We hope that by clarifying what we mean by “TICI,” we will be better able to evaluate the efficacy of revascularization therapies for acute ischemic stroke in the future.

CONCLUSIONS

There is substantial variability in how the TICI scale is defined and applied in the cerebrovascular literature. Few studies provide sufficient detail for readers to understand what is meant by each TICI grade. Because TICI score is increasingly used as an outcome measure in studies of revascularization therapies in acute ischemic stroke, this variability has the potential to considerably impact results and our understanding of these therapies.

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REFERENCES

1. TIMI Study Group. **The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings.** *N Engl J Med* 1985;312:932–36
2. Higashida RT, Furlan AJ, Roberts H, et al. **Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke.** *Stroke* 2003;34:e109–137
3. Kallmes DF. **TICI: if you are not confused, then you are not paying attention.** *AJNR Am J Neuroradiol* 2012;33:975–76
4. **The Interventional Management of Stroke (IMS) II Study.** *Stroke* 2007;38:2127–35
5. Noser EA, Shaltoni HM, Hall CE, et al. **Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke?** *Stroke* 2005;36:292–96
6. Kim EY, Heo JH, Lee SK, et al. **Prediction of thrombolytic efficacy in acute ischemic stroke using thin-section noncontrast CT.** *Neurology* 2006;67:1846–48
7. Kulcsar Z, Bonvin C, Pereira VM, et al. **Penumbra system: a novel mechanical thrombectomy device for large-vessel occlusions in acute stroke.** *AJNR Am J Neuroradiol* 2010;31:628–33
8. Lee KY, Han SW, Kim SH, et al. **Early recanalization after intravenous administration of recombinant tissue plasminogen activator as assessed by pre- and post-thrombolytic angiography in acute ischemic stroke patients.** *Stroke* 2007;38:192–93
9. Schumacher HC, Meyers PM, Higashida RT, et al. **Reporting standards for angioplasty and stent-assisted angioplasty for intracranial atherosclerosis.** *J Vasc Interv Radiol* 2009;20:S451–73
10. Suh DC, Kim JK, Choi CG, et al. **Prognostic factors for neurologic outcome after endovascular revascularization of acute symptomatic occlusion of the internal carotid artery.** *AJNR Am J Neuroradiol* 2007;28:1167–71
11. Lau AY, Wong EH, Wong A, et al. **Significance of good collateral compensation in symptomatic intracranial atherosclerosis.** *Cerebrovasc Dis* 2012;33:517–24
12. Liebeskind DS, Cotsonis GA, Saver JL, et al. **Collateral circulation in symptomatic intracranial atherosclerosis.** *J Cereb Blood Flow Metab* 2011;31:1293–301
13. Roth C, Papanagiotou P, Behnke S, et al. **Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions.** *Stroke* 2010;41:2559–67
14. Liebeskind DS, Cotsonis GA, Saver JL, et al. **Collaterals dramatically alter stroke risk in intracranial atherosclerosis.** *Ann Neurol* 2011;69:963–74
15. Almekhlafi MA, Hu WY, Hill MD, et al. **Calcification and endothelialization of thrombi in acute stroke.** *Ann Neurol* 2008;64:344–48
16. Imai K, Mori T, Izumoto H, et al. **MR imaging-based localized intra-arterial thrombolysis assisted by mechanical clot disruption for acute ischemic stroke due to middle cerebral artery occlusion.** *AJNR Am J Neuroradiol* 2011;32:748–52
17. Kole M, Amin B, Marin H, et al. **Intracranial angioplasty and stent placement for direct cerebral revascularization of nonacute intracranial occlusions and near occlusions.** *Neurosurg Focus* 2009;26:E3
18. Mordasini P, Frabetti N, Gralla J, et al. **In vivo evaluation of the first dedicated combined flow-restoration and mechanical thrombectomy device in a swine model of acute vessel occlusion.** *AJNR Am J Neuroradiol* 2011;32:294–300
19. Nogueira RG, Schwamm LH, Buonanno FS, et al. **Low-pressure balloon angioplasty with adjuvant pharmacological therapy in patients with acute ischemic stroke caused by intracranial arterial occlusions.** *Neuroradiology* 2008;50:331–40
20. Raychev R, Ovbiagele B. **Endovascular therapy of acute ischemic stroke.** *Exp Opin Pharmacother* 2011;12:913–30
21. Sugg RM, Noser EA, Shaltoni HM, et al. **Intra-arterial reteplase compared to urokinase for thrombolytic recanalization in acute ischemic stroke.** *AJNR Am J Neuroradiol* 2006;27:769–73
22. Castano C, Dorado L, Guerrero C, et al. **Mechanical thrombectomy with the Solitaire AB device in large artery occlusions of the anterior circulation: a pilot study.** *Stroke* 2010;41:1836–40
23. Deguchi I, Dembo T, Fukuoka T, et al. **Usefulness of MRA-DWI mismatch in neuroendovascular therapy for acute cerebral infarction.** *Eur J Neurol* 2012;19:114–20
24. Deshmukh VR, Fiorella DJ, Albuquerque FC, et al. **Intra-arterial thrombolysis for acute ischemic stroke: preliminary experience with platelet glycoprotein IIb/IIIa inhibitors as adjunctive therapy.** *Neurosurgery* 2005;56:46–54
25. Fesl G, Patzig M, Holtmannspoepter M, et al. **Endovascular mechanical recanalisation after intravenous thrombolysis in acute anterior circulation stroke: the impact of a new temporary stent.** *Cardiovasc Intervent Radiol* 2012;35:1326–31
26. Froehler MT, Tateshima S, Duckwiler G, et al. **The hyperdense vessel sign on CT predicts successful recanalization with the Merci device in acute ischemic stroke.** *J Neurointervent Surg* 2013;5:289–93
27. Hauck EF, Ogilvy CS, Siddiqui AH, et al. **Direct endovascular recanalization of chronic carotid occlusion: should we do it? Case report.** *Neurosurgery* 2010;67:E1152–59
28. Sandhu GS, Parikh PT, Hsu DP, et al. **Outcomes of intra-arterial thrombolytic treatment in acute ischemic stroke patients with a matched defect on diffusion and perfusion MR images.** *J Neurointervent Surg* 2012;4:105–09
29. Jankowitz B, Aghaebrahim A, Zirra A, et al. **Manual aspiration**

thrombectomy: adjunctive endovascular recanalization technique in acute stroke interventions. *Stroke* 2012;43:1408–11

30. Kang DH, Hwang YH, Kim YS, et al. Direct thrombus retrieval using the reperfusion catheter of the Penumbra system: forced-suction thrombectomy in acute ischemic stroke. *AJNR Am J Neuroradiol* 2011;32:283–87
31. Kim SJ, Ha YS, Ryoo S, et al. Sulcal effacement on fluid attenuation inversion recovery magnetic resonance imaging in hyperacute stroke: association with collateral flow and clinical outcomes. *Stroke* 2012;43:386–92
32. Kwon TH, Kim BM, Nam HS, et al. Carotid stenting in acute ischemic stroke patients with intraluminal thrombus. *Neuroradiology* 2011;53:773–78
33. Liebeskind DS, Sanossian N, Yong WH, et al. CT and MRI early vessel signs reflect clot composition in acute stroke. *Stroke* 2011;42:1237–43
34. Loh Y, Liebeskind DS, Shi ZS, et al. Partial recanalization of concomitant internal carotid-middle cerebral arterial occlusions promotes distal recanalization of residual thrombus within 24 h. *J Neurointerv Surg* 2011;3:38–42
35. Machi P, Costalat V, Lobotesis K, et al. Solitaire FR thrombectomy system: immediate results in 56 consecutive acute ischemic stroke patients. *J Neuroint Surg* 2012;4:62–66
36. Machi P, Lobotesis K, Maldonado IL, et al. Endovascular treatment of tandem occlusions of the anterior cerebral circulation with Solitaire FR thrombectomy system: initial experience. *Eur J Radiol* 2012;81:3479–84
37. Mordasini P, Hiller M, Brekenfeld C, et al. In vivo evaluation of the Phenox CRC mechanical thrombectomy device in a swine model of acute vessel occlusion. *AJNR Am J Neuroradiol* 2010;31:972–78
38. Park MS, Kim JT, Yoon W, et al. Intra-arterial thrombolysis after full-dose intravenous tPA via the “Drip and Ship” approach in patients with acute ischemic stroke: preliminary report. *Chonnam Med J* 2011;47:99–103
39. Parrilla G, Garcia-Villalba B, Espinosa de Rueda M, et al. Hemorrhage/contrast staining areas after mechanical intra-arterial thrombectomy in acute ischemic stroke: imaging findings and clinical significance. *AJNR Am J Neuroradiol* 2012;33:1791–96
40. Prothmann S, Lockau H, Dorn F, et al. The Phenox clot retriever as part of a multimodal mechanical thrombectomy approach in acute ischemic stroke: single center experience in 56 patients. *Sci World J* [Epub ahead of print 24 April 2012]
41. Psychogios MN, Kreusch A, Wasser K, et al. Recanalization of large intracranial vessels using the Penumbra system: a single center experience. *AJNR Am J Neuroradiol* 2012;33:1488–93
42. Roth C, Junk D, Papanagiotou P, et al. A comparison of 2 stroke devices: the new Aperio clot-removal device and the Solitaire AB/FR. *AJNR Am J Neuroradiol* 2012;33:1317–20
43. Siemonsen S, Lobel U, Sedlacik J, et al. Elevated T2-values in MRI of stroke patients shortly after symptom onset do not predict irreversible tissue infarction. *Brain* 2012;135:1981–89
44. Sauvageau E, Levy EI. Self-expanding stent-assisted middle cerebral artery recanalization: technical note. *Neuroradiology* 2006;48:405–08
45. Stampfl S, Hartmann M, Ringleb PA, et al. Stent placement for flow restoration in acute ischemic stroke: a single-center experience with the Solitaire stent system. *AJNR Am J Neuroradiol* 2011;32:1245–48
46. Tatum J, Farid H, Cooke D, et al. Mechanical embolectomy for treatment of large vessel acute ischemic stroke in children. *J Neurointerv Surg* 2013;5:128–34
47. Alhazzaa M, Murphy A, Lum C, et al. Angioplasty as an adjuvant therapy for the treatment of acute ischemic stroke. *Can J Neurol Sci* 2011;38:593–99
48. Yin NS, Benavides S, Starkman S, et al. Autopsy findings after intracranial thrombectomy for acute ischemic stroke: a clinicopathologic study of 5 patients. *Stroke* 2010;41:938–47
49. Zhu L, Liebeskind DS, Jahan R, et al. Thrombus branching and vessel curvature are important determinants of middle cerebral artery trunk recanalization with Merci thrombectomy devices. *Stroke* 2012;43:787–92
50. Ribo M, Molina CA, Alvarez B, et al. Intra-arterial administration of microbubbles and continuous 2-MHz ultrasound insonation to enhance intra-arterial thrombolysis. *J Neuroimaging* 2010;20:224–27
51. Kulcsar Z, Bonvin C, Lovblad KO, et al. Use of the Enterprise intracranial stent for revascularization of large vessel occlusions in acute stroke. *Klinische Neuroradiologie* [Epub ahead of print 28 Feb 2010]
52. Belisle JG, McCollom VE, Tytle TL, et al. Intraarterial therapy for acute ischemic strokes. *J Vasc Interv Radiol* 2009;20:327–33
53. King S, Khatri P, Carrozella J, et al. Anterior cerebral artery emboli in combined intravenous and intra-arterial rtPA treatment of acute ischemic stroke in the IMS I and II trials. *AJNR Am J Neuroradiol* 2007;28:1890–94
54. Levy EI, Mehta R, Gupta R, et al. Self-expanding stents for recanalization of acute cerebrovascular occlusions. *AJNR Am J Neuroradiol* 2007;28:816–22
55. Seifert M, Ahlbrecht A, Dohmen C, et al. Combined interventional stroke therapy using intracranial stent and local intraarterial thrombolysis (LIT). *Neuroradiology* 2011;53:273–82
56. Ribo M, Molina C, Alvarez B, et al. Buying time for recanalization in acute stroke: arterial blood infusion beyond the occluding clot as a neuroprotective strategy. *J Neuroimaging* 2009;19:188–90
57. Tomsick T, Broderick J, Carrozella J, et al. Revascularization results in the Interventional Management of Stroke II trial. *AJNR Am J Neuroradiol* 2008;29:582–87
58. Watanabe M, Mori T, Imai K, et al. Endovascular interventions for patients with serious symptoms caused by embolic carotid T occlusion. *Neurol Med Chir (Tokyo)* 2011;51:282–88
59. Yoo AJ, Verduzco LA, Schaefer PW, et al. MRI-based selection for intra-arterial stroke therapy: value of pretreatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization. *Stroke* 2009;40:2046–54
60. Ikushima I, Ohta H, Hirai T, et al. Balloon catheter disruption of middle cerebral artery thrombus in conjunction with thrombolysis for the treatment of acute middle cerebral artery embolism. *AJNR Am J Neuroradiol* 2007;28:513–17
61. Khatri P, Abruzzo T, Yeatts SD, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology* 2009;73:1066–72
62. Lee JS, Hong JM, Kim EJ, et al. Comparison of the incidence of parenchymal hematoma and poor outcome in patients with carotid terminus occlusion treated with intra-arterial urokinase alone or with combined IV rtPA and intra-arterial urokinase. *AJNR Am J Neuroradiol* 2012;33:175–79
63. Li YH, Li MH, Zhao ZG, et al. Comparison of MRI-based thrombolysis for patients with middle cerebral artery occlusion <or =3 h and 3–6 h. *Neurology India* 2009;57:426–33
64. Liu W, Yin Q, Yao L, et al. Decreased hyperintense vessels on FLAIR images after endovascular recanalization of symptomatic internal carotid artery occlusion. *Eur J Radiol* 2012;81:1595–600
65. Gandini R, Pampana E, Del Giudice C, et al. Acute stroke treatment using the Penumbra endovascular mechanical thrombolysis device: a single-centre experience. *La Radiologia Medica* 2012;117:1199–214
66. Bang JS, Oh CW, Jung C, et al. Intracranial stent placement for recanalization of acute cerebrovascular occlusion in 32 patients. *AJNR Am J Neuroradiol* 2010;31:1222–25
67. Halleivi H, Barreto AD, Liebeskind DS, et al. Identifying patients at high risk for poor outcome after intra-arterial therapy for acute ischemic stroke. *Stroke* 2009;40:1780–85
68. Costalat V, Machi P, Lobotesis K, et al. Rescue, combined, and stand-alone thrombectomy in the management of large vessel occlusion stroke using the Solitaire device: a prospective 50-patient single-center study: timing, safety, and efficacy. *Stroke* 2011;42:1929–35
69. Dababneh H, Guerrero WR, Khanna A, et al. Management of tandem

- occlusion stroke with endovascular therapy. *Neurosurg Focus* 2012;32:E16
70. Khatri P, Broderick JP, Khoury JC, et al. **Microcatheter contrast injections during intra-arterial thrombolysis may increase intracranial hemorrhage risk.** *Stroke* 2008;39:3283–87
 71. Kwon JH, Shin SH, Weon YC, et al. **Intra-arterial adjuvant tirofiban after unsuccessful intra-arterial thrombolysis of acute ischemic stroke: preliminary experience in 16 patients.** *Neuroradiology* 2011;53:779–85
 72. Rohde S, Haehnel S, Herweh C, et al. **Mechanical thrombectomy in acute embolic stroke: preliminary results with the Revive device.** *Stroke* 2011;42:2954–56
 73. San Roman L, Obach V, Blasco J, et al. **Single-center experience of cerebral artery thrombectomy using the TREVO device in 60 patients with acute ischemic stroke.** *Stroke* 2012;43:1657–59
 74. Wehrschoetz M, Wehrschoetz E, Augustin M, et al. **Early single center experience with the Solitaire thrombectomy device for the treatment of acute ischemic stroke.** *Intervent Neuroradiol* 2011;17:235–40
 75. Yoo AJ, Chaudhry ZA, Nogueira RG, et al. **Infarct volume is a pivotal biomarker after intra-arterial stroke therapy.** *Stroke* 2012;43:1323–30
 76. Tomsick T. **TIMI, TIBI, TICI: I came, I saw, I got confused.** *AJNR Am J Neuroradiol* 2007;28:382–84
 77. Gibson CM, Cannon CP, Daley WL, et al. **TIMI frame count: a quantitative method of assessing coronary artery flow.** *Circulation* 1996;93:879–88
 78. Soares BP, Chien JD, Wintermark M. **MR and CT monitoring of recanalization, reperfusion, and penumbra salvage: everything that recanalizes does not necessarily reperfuse!** *Stroke* 2009;40:S24–27
 79. Cloft HJ, Kallmes DF. **Scaling back on scales with a scale of scales.** *AJNR Am J Neuroradiol* 2011;32:219–20

Tentorial Dural Fistulas: Endovascular Management and Description of the Medial Dural-Tentorial Branch of the Superior Cerebellar Artery

J.V. Byrne and M. Garcia

ABSTRACT

BACKGROUND AND PURPOSE: TDAVFs are uncommon causes of spontaneous intracranial hemorrhage. A retrospective review of their management was performed after repeatedly observing a previously under-recognized medial dural-tentorial branch of the SCA.

MATERIALS AND METHODS: Thirteen patients were diagnosed with TDAVFs by CT/MR imaging and DSA during a 5.8-year period. Seven patients presented after intracranial hemorrhage. Twelve patients were treated endovascularly, and one, surgically.

RESULTS: Eleven TDAVFs were located in the midline (7 at the falx cerebelli and 4 at the torcular), and 2 were petrotentorial. All torcular TDAVFs were associated with sinus thrombosis and showed bidirectional drainage relative to the tentorium. No sinus thrombosis was seen in the falx cerebelli subtype, which drained infratentorially only, except in 1 patient who had had unrelated surgery previously. Venous drainage was directly to cortical veins except for 1 petrotentorial and 2 torcular TDAVFs. A branch of the SCA, the medial dural-tentorial artery, was observed in 5 midline TDAVFs. Its anatomy was defined with selective angiography. Endovascular therapy resulted in a cure in 5 and subtotal occlusion in 6, and staged treatment is ongoing in 1 patient. One patient was cured after surgery.

CONCLUSIONS: TDAVFs frequently cause intracranial hemorrhage and therefore warrant treatment. Endovascular therapy proved effective in this series, and arteriography was essential for understanding the various fistula subtypes and for treatment planning. We emphasize the importance of recognizing the medial dural-tentorial artery of the SCA with its characteristic course along the tentorium on angiography. This artery should be included in future anatomic descriptions of the cranial blood supply.

ABBREVIATIONS: AICA = anterior inferior cerebellar artery; ADS = artery of Davidoff and Schechter; DAVF = dural arteriovenous fistula; SCA = superior cerebellar artery; TDAVF = tentorial dural arteriovenous fistula

Dural arteriovenous fistulas account for 10%–15% of all intracranial vascular shunts.^{1,2} The TDAVF is a rare subgroup, constituting <4% of DAVFs.^{1,3–6} TDAVFs are most frequently diagnosed in middle-aged men,^{2,4,5,7} unlike DAVFs elsewhere, which are more frequent in elderly women.^{8,9} Spontaneous intracranial hemorrhage is the usual presenting symptom because cortical venous reflux is common.^{4,6,7,10} Otherwise, diagnosis relies on imaging because neurologic symptoms are nonspecific and nonlocalizing.^{6,11–16}

TDAVFs are generally considered separate from DAVFs located along the transverse and sigmoid sinuses despite their proximity. This distinction appears to be historic and is based on anatomic, symptomatic, and therapeutic differences. Anatomically,

DAVFs primarily involve the single-layer dura of the calvaria, while TDAVFs occur in the reflected (double-layer) dura of the tentorium and its attachments. Because TDAVFs usually drain to cortical veins, invasive treatment is recommended, irrespective of presentation.^{4,6,7,10} Treatment is traditionally by surgical resection but access is often difficult,¹⁰ and endovascular therapy is a recognized and increasingly used alternative, either alone or in combination with surgery.¹⁷ Another alternative is stereotactic radiosurgery, which has been reported in feasibility studies^{18,19} and may be a useful adjunct to endovascular treatment.

Due to their rarity, the number of reports describing TDAVFs and their management is limited. Nevertheless, several classification systems have been proposed on the basis of location and venous drainage patterns.^{5,7} The arterial supply is not an important feature in these descriptions, but with the increasing use of endovascular treatment, it is clearly important and may be helpful in classification and distinguishing TDAVFs from DAVFs located at the tentorial margins.

We present 13 TDAVFs and classify them according to location and overall vascular supply. Special attention is drawn to an

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Table 1: Patient details and presenting symptoms

No.	Age (yr)	Sex	Clinical Presentation	Initial CT/MR
1	45	M	Collapse, headache	CT/CTA: ICH posterior fossa, developing hydrocephalus
2	64	M	Unrelated stroke, incidental finding on imaging	CT/CTA: small subacute ischemic area supratentorially, dilated abnormal vessels in the posterior fossa
3	56	M	Collapse, vomiting, dysarthria, blurred vision	CT/CTA: ICH posterior fossa, developing hydrocephalus
4	65	F	Transient arm weakness	MRI: abnormal vessels with venous engorgement
5	65	M	Acute-onset headache	CT/CTA: SAH in the posterior fossa with ventricular spread, hydrocephalus
6	64	F	Hearing loss, tinnitus, diplopia	MRI: abnormal vascular structures in the right-side posterior fossa
7	64	F	Headache, progressive mental confusion, dysphasia	CT/CTV: engorged leptomeningeal veins
8	66	M	Visual disturbance and hemianopia	MRI: multiple congested intracranial veins
9	58	M	Acute-onset headache	CT/CTA: posterior fossa SAH
10	60	F	Severe headache, vertigo	CT/CTA: perimesencephalic SAH
11	64	M	Collapse, vomiting, aphasia	CT: posterior fossa SAH with intraventricular spread
12	56	F	Pulsatile tinnitus	MRI/MRA: abnormal vessels
13	60	M	Acute-onset headache	CT: cerebellar ICH

Note:—CTV indicates venous phase CTA.

under-recognized medial dural-tentorial branch of the superior cerebellar artery, which has not been previously demonstrated by selective arteriography, to our knowledge. We describe the main features of this artery to emphasize its importance in future anatomic descriptions of TDAVFs.

PATIENTS AND METHODS

Patients

A search of our institutional data base identified 13 patients with TDAVFs presenting between January 2007 and September 2012. DAVFs of the transverse or sigmoid sinuses and other posterior fossa locations not supplied by tentorial arteries were excluded. All patients underwent initial CT/CTA and/or MR imaging/MRA, as well as subsequent DSA before treatment. The mean age was 59.8 years (age range, 45–66 years) with a male/female ratio of 8:5 (Table 1).

Presentation

Symptoms were the following: headache ($n = 7$), tinnitus ($n = 2$), visual disturbances ($n = 3$), transient weakness ($n = 1$), and progressive confusion ($n = 1$). One patient presented after imaging for coincidental stroke. Seven patients presented after spontaneous intracranial hemorrhage; 3 were initially unconscious, requiring mechanical ventilation. Imaging showed posterior fossa hemorrhage; principally subarachnoid in 4, cerebellar in 3, with intraventricular hemorrhage in 4 patients (Table 1).

Angiographic Findings

TDAVFs were classified by the arteriovenous shunt location (Fig 1). Most were midline and could be separated into torcular ($n = 4$) (Figs 2 and 3) and falx cerebelli ($n = 7$) (Figs 4 and 5). The remaining 2 fistulas were at lateral petrotentorial locations along the petrous attachment of the tentorium. All drained to subarachnoid/cortical veins and were classified as type III or IV fistulas, except 1 petrotentorial and 2 torcular fistulas that were graded type II a + b according to Cognard et al.²⁰ In 2 of the torcular fistulas, bilateral occlusion of the lateral/sigmoid sinuses was present, and in the other 2, complete or partial thrombosis of 1 lateral sinus was evident (Table 2).

The arterial supply demonstrated on DSA is detailed in Table 2. This arose from tentorial branches of the ICA in 8 cases, specifically the meningohypophyseal trunk ($n = 7$) and the inferolateral

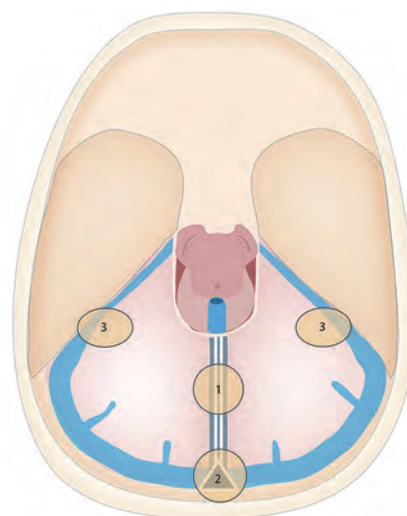


FIG 1. Sites of TDAVFs: 1 = falx cerebelli, 2 = torcular, and 3 = petrotentorial locations.

trunk ($n = 1$); from branches of the external carotid artery in 10 cases, specifically the middle meningeal ($n = 8$), the occipital ($n = 9$), and the ascending pharyngeal ($n = 3$) arteries; from branches of the vertebral artery in 8 cases, specifically the musculospiral (extradural) branches ($n = 3$) and the posterior meningeal artery ($n = 7$); from branches of the basilar artery, specifically the posterior inferior cerebellar artery ($n = 3$), AICA ($n = 2$), a previously under-recognized medial dural-tentorial branch of the SCA ($n = 5$), and the tentorial branch of the posterior cerebral artery ($n = 4$). In patient 11, a flow aneurysm arose from a feeding PICA. There was bilateral fistulous supply in 7 patients, principally involving the posterior division of the middle meningeal and occipital arteries.

The tentorial arteries arising from the meningohypophyseal trunk supplied both median and medial-laterally located fistulas. However, the tentorial branch of the posterior cerebral artery, also known as the artery of Davidoff and Schechter,²¹ and the medial dural-tentorial branch of the SCA only supplied fistulas located at the midline and showed the same characteristic courses on lateral DSA projections. The ADS makes a gentle curve, concave

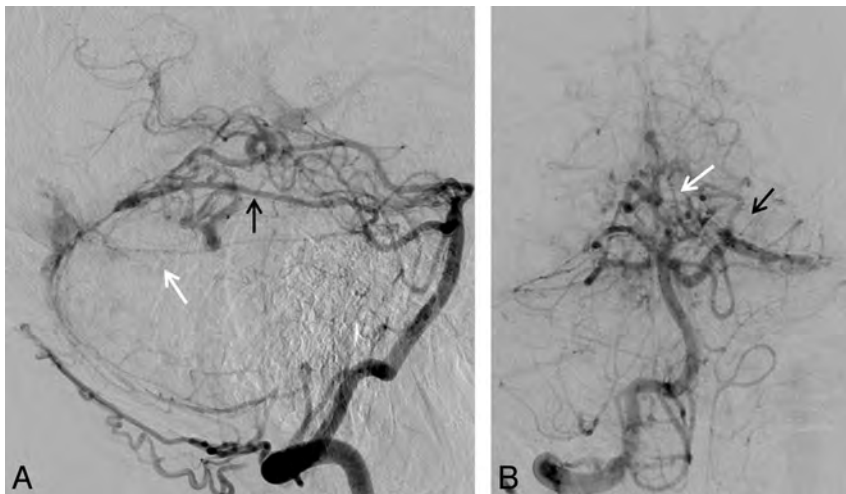


FIG 2. Torcular TDAVF (patient 8). Injections of the right vertebral artery in the lateral (A) and anteroposterior (B) views. Note the medial dural-tentorial branch of the left SCA (white arrow) running below the ADS (black arrow); both arteries are supplying the fistula. Additional supply is seen from the posterior meningeal artery and muscular branches of the extracranial vertebral artery.

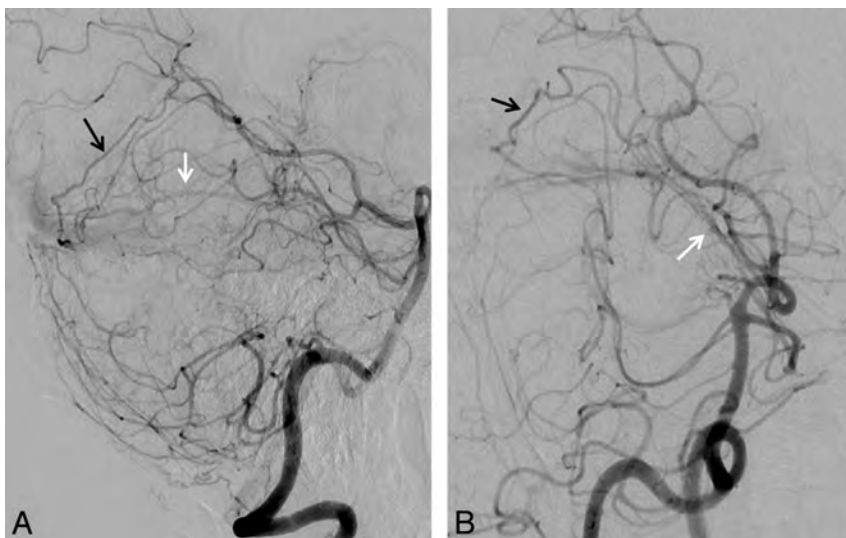


FIG 3. Torcular TDAVF (patient 7). Injections into the left vertebral artery in lateral (A) and the right vertebral artery in lateral-oblique (B) views show the supply to the fistula from the left ADS (black arrows) and the left medial dural-tentorial branch of the SCA (white arrows). There was additional arterial supply from branches of the external carotid artery (not shown).

inferiorly, from anterior to posterior, while the more inferiorly lying medial dural-tentorial artery of the SCA has a more horizontal posterior course toward the midpoint of the inferior surface of the straight sinus. Both arteries turn medially posterior to the tentorial hiatus and run toward the midline (Figs 2–5).

None of the fistulas showed supratentorial venous drainage only. The fistulas at the falx cerebelli drained inferiorly to the posterior fossa veins in all cases and additionally to the supratentorial cortical veins in 1 patient. The 4 lesions at the torcular drained to tentorial veins and then to both infra- and supratentorial cortical veins. The petrotentorial fistulas drained to cortical veins above and below the tentorial attachment in 1 patient and only infratentorially in 1 patient (Table 2).

Endovascular Treatments

Endovascular therapy was performed in 12 patients (1 after fistula recurrence following surgery), and 1 patient was treated by surgery after failed endovascular therapy. Endovascular therapy was performed as single treatments (7 patients) or staged (3 patients underwent 2, and 2 patients 3) treatments. Access was transarterial in 10 or transvenous and transarterial in 2 patients. Embolization was performed with either ethylene-vinyl alcohol, formulated as Onyx (ev3, Irvine, California) or *n*-butyl cyanoacrylate formulated as Glubran (GEM, Viareggio, Italy). Onyx was used alone in 5, in combination with Glubran in 3, and with coils in 2 patients. Adjuvant coils were used transarterially to reduce blood flow and transvenously to occlude a large venous pouch in treatments of torcular and petrotentorial TDAVFs, respectively. Glubran was used alone to occlude an arterial aneurysm after SAH in 1 patient.

Procedural complications occurred during 4 endovascular treatments, without causing new symptoms or disability. They comprised 1 arterial dissection, 1 perforation (managed by sealing with Glubran), and 2 microcatheter ruptures (1 without vessel damage and 1 causing Onyx efflux and occlusion of the distal occipital artery) (Table 3).

Treatment Results

Anatomic. Endovascular therapy achieved complete occlusion of the fistula in 5 and subtotal occlusion in 6 patients. One patient is still in treatment, and the remaining patient (who was treated surgically) was cured (Table 4).

Clinical. Symptoms resolved completely in 3, improved in 6, and are unchanged in 1 patient. Two patients died due to other complications. One patient died 2 weeks after complete occlusion of the fistula due to malignant cerebellar swelling causing brain stem compression despite decompression occipital craniectomy to remove the presenting hematoma. The other patient died 6 months after endovascular treatment due to pulmonary edema. The last patient is still recovering after emergency treatment of a ruptured flow-related PICA aneurysm. The patient who remains symptomatic showed temporary improvement after successful surgery but subsequently developed headache without evidence of hydrocephalus or recurrence on imaging (Table 4).

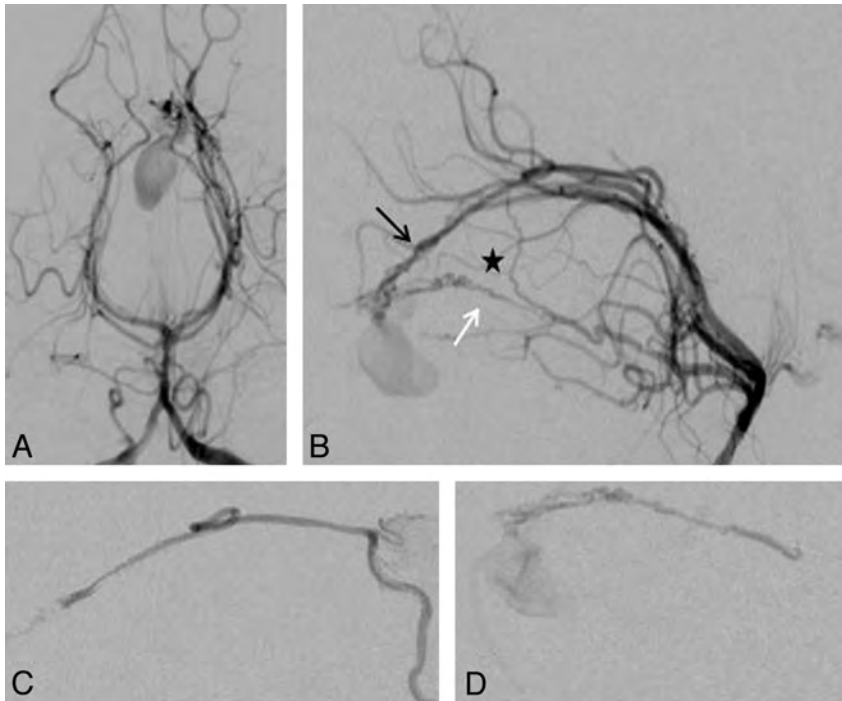


FIG 4. Falx cerebelli TDAVF (patient 1). Injections of the left vertebral artery in anteroposterior (A) and lateral (B) views and supraselective injection of the ADS (C) and medial dural-tentorial branch of the SCA (D). The fistula supply arises from the left ADS (black arrow) and left medial dural-tentorial branch of the SCA (white arrow). The asterisk marks a connection between these 2 arteries within the tentorium.

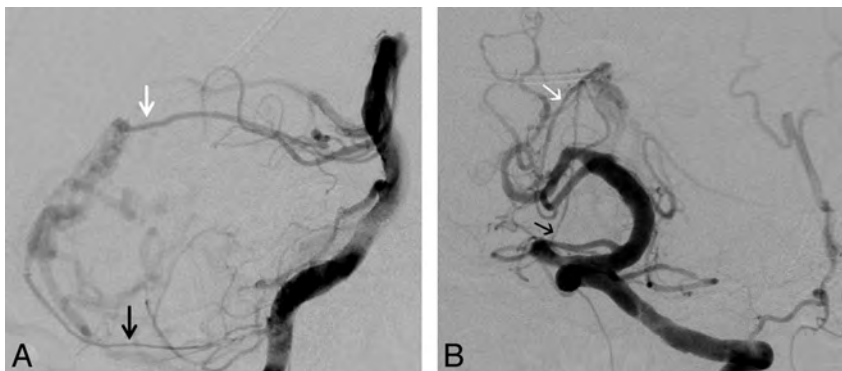


FIG 5. Falx cerebelli TDAVF (patient 2). Injections of the left vertebral artery in lateral (A) and anteroposterior (B) views. Arterial supply to the fistula arises, among others, from the medial dural-tentorial branch of the right SCA (white arrows) and the right posterior meningeal artery (black arrows). Additional supply from branches of the external carotid artery and the marginal tentorial artery are not shown.

DISCUSSION

Classification and Venous Features

In descriptions of TDAVFs, the term “incisura” is used ambiguously. For example, Ono et al²² called it “tentorial edge” and Wollschlaeger and Wollschlaeger,²¹ “free margin of the tentorium.” Literally it means “opening,” which would restrict the term to the hiatus and not the adjacent tentorium or its anterior free edge.⁷ To avoid confusion, we have simply divided TDAVFs into midline and mediolateral lesions and used conventional anatomic landmarks to separate the former.

In contrast to the more frequent DAVF of the lateral sinus

located within the sinus wall^{2,5} and associated with sinus thrombosis,^{4,8} TDAVFs are typically located in the dura not directly connected to major sinuses.^{2,5} However, among our patients, all 4 torcular TDAVFs showed some degree of major sinus thrombosis. This observation may indicate that they had or have direct connections with the sinus and explain their more benign angioarchitecture, with 2 of the 4 being classified as Cognard type II a + b. It may also be a clue to their etiology, because prior sinus thrombosis is a probable cause for the development of lateral and sigmoid sinus DAVFs.⁸ Torcular TDAVFs could thus represent an intermediate entity between sinus and purely tentorial fistulas. Two torcular TDAVFs were graded as Cognard type IV, which may indicate a stage in the development of the fistula with extension into the reflected dural layers of the tentorium. In any event, all the torcular TDAVFs drained both infra- and supratentorially, so the location appears to act as an anatomic venous epicenter connecting both supra- and infratentorial compartments.

In this series, TDAVFs of the falx cerebelli were remote from a major sinus, consistently drained infratentorially, and were graded Cognard type III or IV. The extent of the falx cerebelli varies from a midline thickening of the dura to a septum extending from the inferior surface of the straight sinus to the foramen magnum. In its more complete form, it rarely extends farther anteriorly than the midpoint of the straight sinus, which is often the site of cerebellar veins connecting to the sinus (eg, declival veins). This variability could explain overlap with torcular-located lesions at 1 extreme and the solely infratentorial drainage of TDAVFs when the falx cerebelli is fully formed. It also explains the frequency of hemorrhage at presentation in the latter situation. Furthermore, because

TDAVFs of the falx cerebelli were not associated with major sinus thrombosis, their etiology may differ from that of torcular and petrotentorial TDAVFs.^{5,19} One possible cause is trauma, because one of our patients had had an occipital craniotomy. One can speculate that the superior attachment of the falx cerebelli could act as a stress point for traumatic vessel injury.

Our observed venous drainage routes support the classification of TDAVFs proposed by Picard et al,⁵ who divided TDAVFs into 3 groups: 1) the tentorial marginal type with the fistulas located along the free edge of the tentorial hiatus and draining both

Table 2: Anatomic and angiographic findings

No.	Site	Location	Drainage	Grade ^a	Arterial Feeders
1	Falx cerebelli	Midline	Infratentorially	IV	Meningohypophyseal trunk, ADS, SCA
2 ^b	Falx cerebelli	Midline	Infra- and supratentorially	IV	Occipital, middle meningeal, posterior meningeal arteries, meningohypophyseal trunk, SCA
3	Falx cerebelli	Midline	Infratentorially	IV	Occipital, middle meningeal, posterior meningeal arteries
4	Torcular	Midline	Supra- and infratentorially	II a + b	Occipital, middle meningeal, posterior meningeal, ascending pharyngeal, arteries, meningohypophyseal trunk, vertebral artery branches
5	Falx cerebelli	Midline	Infratentorially	IV	PICA, posterior meningeal artery
6	Petrotentorial right	Right	Infratentorially	IV	Middle meningeal, ascending pharyngeal arteries, meningohypophyseal trunk, AICA
7	Torcular	Midline	Supra- and infratentorially	II a + b	Occipital, middle meningeal arteries, ADS, SCA
8	Torcular	Midline	Infra- and supratentorially	IV	Occipital, posterior meningeal arteries, meningohypophyseal trunk, ADS, SCA vertebral artery branches
9	Falx cerebelli	Midline	Infratentorially	IV	Occipital middle meningeal, falcine arteries
10	Falx cerebelli	Midline	Infratentorially	III	Vertebral artery branches, PICA, SCA
11	Falx cerebelli	Midline	Infratentorially	IV	Occipital, middle meningeal, posterior meningeal arteries, PICA, ADS
12	Petrotentorial left	Left	Infra- and supratentorially	II a + b	Occipital, middle meningeal, falcine, ascending pharyngeal arteries, meningohypophyseal trunk, inferolateral trunk, AICA
13	Torcular	Midline	Supra- and infratentorially	IV	Occipital, middle meningeal, posterior meningeal arteries, meningohypophyseal trunk

^a According to Cognard et al.²⁰

^b Previous surgery.

Table 3: Treatments

No.	Method of Treatment	Embolitic Material	No. of Embolized Arterial Feeders	Route	EVT Sessions	Complications
1	EVT	Glubran, Onyx	2	Transarterial	1	None
2	EVT	Onyx	1	Transarterial	1	None
3	EVT	Onyx	1	Transarterial	1	None
4	EVT	Coils, Onyx	1	Coils, transvenous; Onyx, transarterial	2	Dissection
5	EVT	3 Coils	1	Transarterial	1	None
6	EVT	Glubran, Onyx	2	Transarterial	1	Perforation
7	EVT	Onyx	1	Transarterial	1	None
8	EVT	Onyx	2	Transarterial	2	None
9	1) Surgery 2) EVT after recurrence	Glubran, Onyx	6	Transarterial	3	Microcatheter rupture
10	Surgery after failed EVT	None	N/A	N/A	1	None
11	EVT	Glubran to flow aneurysm	1	Transarterial	2 ^a	None
12	EVT	Onyx, coils	2	Both	3	Microcatheter rupture
13	EVT	Onyx	1	Transarterial	1	None

Note:—N/A indicates not applicable; EVT, endovascular treatment.

^a Incomplete Onyx embolization 4 years previously at another hospital; fistula then already present.

supra- and infratentorially, 2) the tentorial lateral type adjacent to the lateral sinus and draining to supratentorial veins, and 3) the tentorial medial type with fistulas sited adjacent to the torcular and straight sinuses draining to the infratentorial draining system. Lawton et al⁷ proposed a classification with 6 anatomic locations and venous drainage patterns. This classification was based on a larger series of 31 patients and separates midline lesions into Galenic, straight sinus, and torcular. The last 2 have drainage patterns similar to those of our falx cerebelli and torcular subtypes.

Arterial Characteristics

The tentorium derives its principal arterial blood supply from tentorial branches of the ICA and dural branches of the vertebral artery and external carotid artery. These arterial systems are men-

ingeal or dural and are usually identifiable on angiography in the nonpathologic state. Additional transsarachnoid supply from the primarily pial arteries, such as the cortical branches of the PICA and contributions to the subarcuate plexus at the internal acoustic meatus from the AICA,⁹ is less evident, unless abnormally hypertrophied. Whether such transsarachnoid arterial traffic is “normal” or only develops in response to the development of a DAVF is difficult to establish in vivo, and we generally rely on postmortem descriptions. The identification of a tentorial branch of the posterior cerebral artery, the ADS, was only after its enlargement in response to pathology.²¹ We assume that this explains the development of the medial dural-tentorial branch of the SCA identified in our patients. Both arteries appear to supply medially sited

Table 4: Clinical and anatomic outcomes

No.	Clinical Result	Anatomic Result
1	Died 2 weeks later due to edema with brain stem compression	Cure
2	Cure	Cure
3	Improved	Cure
4	Improved	Subtotal occlusion
5	Died due to pulmonary edema 8 months later	Subtotal occlusion
6	Improved	Subtotal occlusion
7	Cure	Cure
8	Improved	Subtotal occlusion
9	Improved	Subtotal occlusion
10	Unchanged	Cure (surgery)
11	Residual symptoms (treatment ongoing)	PICA aneurysm occluded
12	Improved	Subtotal occlusion
13	Cure	Cure

DAVFs. The characteristics of the arterial supply to DAVFs in this study helped to define both midline and mediolateral fistulas as tentorial and proved crucial for endovascular therapy planning. Thus, we suggest that the type of feeding artery and the venous drainage should be used to categorize subtypes of TDAVF.

Medial Dural-Tentorial Branch of the SCA

The course and cerebral structures supplied by the SCA are described in standard anatomic texts and comprehensive reviews, but these do not include a supply to the tentorial dura.^{19–22} Although a transcisternal branch to the dura of the tentorial hiatus has been inconsistently described in anatomic studies,^{22–25} this vessel has been mentioned in case reports of TDAVFs without being fully characterized.^{2,4,7,19,26} Recently, a branch from the SCA was observed during surgery for a TDAVF but could not be identified on angiography.²⁷

Various names being given to this poorly defined medial dural-tentorial artery of the SCA include “meningeal artery” or “tentorial artery” of the SCA,^{2,4,7,19,26} and some authors appear to have confused this artery with the ADS.⁷ The ADS is described as arising from the posterior cerebral artery¹⁹ and, therefore, runs above the tentorium, so it should be easily differentiated from the medial dural-tentorial branch of the SCA. However, artery-to-artery anastomoses can develop between these arteries within the tentorium (Fig 4) due to the rich dural arterial network.²⁸ Such connections are common in this vascular network, and in 2 patients, we further observed connecting branches between the marginal tentorial artery and the medial dural-tentorial branch of the SCA.

The medial dural-tentorial branch of the SCA was a common feature of midline TDAVFs. It is surprising that it has not found its own nomenclature in anatomic descriptions of the blood supply to the tentorium. Its omission from reviews focusing on the anatomic organization of the dura^{19,23} may be due to its absence or small size in the nonpathologic state. It arises from the superior or rostral trunk of the SCA and traverses the ambiens cistern under the tentorium, which it enters in the posterior half of the incisura. In our patients, it showed a characteristic course on lateral DSA, running in an almost straight or only slightly concave downwards curve from anterior to posterior, and on anteropos-

terior DSA, it curves medially to reach the midline posterior to the incisura. Its course thus parallels that of the marginal tentorial artery. Fistulous contributions by transarachnoid anastomoses from primarily cerebral arteries are well-recognized,⁵ and we considered whether these might occur superficial to the tentorium (ie, that the artery runs inferior to the tentorium directly to the fistula site, but the observed anastomosis with the ADS [Fig 4] demonstrates a substantial transdural course).

Regardless of the explanation for its under-recognition, this study suggests that the medial dural-tentorial branch of the SCA should be expected to supply midline TDAVFs posterior to the incisura. Selective angiography may be necessary for confirmation of its origin from the SCA and, as in one of our patients, can be used for embolization (Fig 4). Thus, recognition of its contribution is essential for diagnosis, endovascular treatment planning, and possibly in posterior fossa surgery.²⁷

CONCLUSIONS

Endovascular therapy was effective in this series, and arteriography was essential for diagnosis and planning. The medial dural-tentorial artery of SCA supplies midline TDAVFs, has a characteristic course along the tentorium, and should be included in future descriptions of tentorial blood supply.

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REFERENCES

- Kajita Y, Miyachi S, Wakabayashi T, et al. A dural arteriovenous fistula of the tentorium successfully treated by intravascular embolization. *Surg Neurol* 1999;52:294–98
- Zhou LF, Chen L, Song DL, et al. Tentorial dural arteriovenous fistulas. *Surg Neurol* 2007;67:472–81
- Wajnberg E, Spilberg G, Rezende MT, et al. Endovascular treatment of tentorial dural arteriovenous fistulae. *Interv Neuroradiol* 2012;18:60–68
- van Lindert E, Hassler W, Kühne D, et al. Combined endovascular-microsurgical treatment of tentorial-incisural dural arteriovenous malformations: report of five cases. *Minim Invasive Neurosurg* 2000;43:138–43
- Picard L, Bracard S, Islak C, et al. Dural fistulae of the tentorium cerebelli: radioanatomical, clinical and therapeutic considerations. *J Neuroradiol* 1990;17:161–81
- Tomak PR, Cloft HJ, Kaga A, et al. Evolution of the management of tentorial dural arteriovenous malformations. *Neurosurgery* 2003 52: 750–60, discussion 760–62
- Lawton MT, Sanchez-Mejia RO, Pham D, et al. Tentorial dural arteriovenous fistulae: operative strategies and microsurgical results for six types. *Neurosurgery* 2008;62(suppl 1):110–24
- Harrigan MR, Deveikis JP. *Handbook of Cerebrovascular Disease and Neurointerventional Technique*. New York: Humana Press; 2009
- Byrne JV. *Tutorials in Endovascular Neurosurgery and Interventional Neuroradiology*. Berlin: Springer-Verlag; 2012
- Davies MA, ter Brugge K, Willinsky R, et al. The natural history and

- management of intracranial dural arteriovenous fistulae. Part 2. Aggressive lesion. *Interv Neuroradiol* 1997;3:303–11
11. Biondi A, Ricciardi GK, Clemenceau S, et al. **Dural arteriovenous fistulas of the tentorial margin: angiographic aspects and endovascular treatment.** In: *Proceedings of the 41st Meeting of the American Society of Neuroradiology, Washington, DC. April 28-May 2, 2003*
 12. Grigorian IA, Stepanian MA. **Trigeminal neuralgia and tentorial dural arteriovenous malformation** [in Russian]. *Zh Vopr Neirokhir Im N N Burdenko* 2010;46–51
 13. Mariniello G, Briganti F, Vergara P, et al. **Dural tentorial arteriovenous fistula causing isolated trochlear nerve palsy: remission after endovascular embolization.** *J Neurointerv Surg* 2012;4:e5
 14. Matsushige T, Nakaoka M, Ohta K, et al. **Tentorial dural arteriovenous malformation manifesting as trigeminal neuralgia treated by stereotactic radiosurgery: a case report.** *Surg Neurol* 2006;66:519–23
 15. Rahme R, Ali Y, Slaba S, et al. **Dural arteriovenous malformation: an unusual cause of trigeminal neuralgia.** *Acta Neurochir (Wien)* 2007;149:937–41, discussion 941
 16. Takeshita T, Toyoda K, So G, et al. **A tentorial dural arteriovenous fistula presenting progressive myelopathy: a case report** [in Japanese]. *Brain Nerve* 2011;63:611–15
 17. Tubbs RS, Nguyen HS, Shojja MM, et al. **The medial tentorial artery of Bernasconi-Cassinari: a comprehensive review of its anatomy and neurosurgical importance.** *Acta Neurochir (Wien)* 2011;153:2485–90
 18. Shin M, Kurita H, Tago M, et al. **Stereotactic radiosurgery for tentorial dural arteriovenous fistulae draining into the vein of Galen: report of two cases.** *Neurosurgery* 2000;46:730–33
 19. Lewis AI, Tomsick TA, Tew JM Jr. **Management of tentorial dural arteriovenous malformations: transarterial embolization combined with stereotactic radiation or surgery.** *J Neurosurg* 1994;81:851–59
 20. Cognard C, Gobin YP, Pierot L, et al. **Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage.** *Radiology* 1995;194:671–80
 21. Wollschlaeger PB, Wollschlaeger G. **An infratentorial meningeal artery** [in German]. *Radiologe* 1965;5:451–52
 22. Ono M, Rhoton AL Jr., Barry M. **Microsurgical anatomy of the region of the tentorial incisura.** *J Neurosurg* 1984;60:365–99
 23. Hardy DG, Peace DA, Rhoton AL Jr. **Microsurgical anatomy of the superior cerebellar artery.** *Neurosurgery* 1980;6:10–28
 24. Martins C, Yasuda A, Campero A, et al. **Microsurgical anatomy of the dural arteries.** *Neurosurgery* 2005;56(suppl 2):211–51
 25. Stranding S. *Gray's Anatomy: The Anatomical Basis of Clinical Practice*, London, UK: Churchill Livingstone; 2008
 26. Miyagi K, Iwasa H, Yoshimizu N, et al. **Tentorial dural arteriovenous malformation: a case report (author's transl)** [in Japanese]. *No Shinkei Geka* 1976;4:1185–91
 27. Weil AG, McLaughlin N, Denis D, et al. **Tentorial branch of the superior cerebellar artery.** *Surg Neurol Int* 2011;2:71
 28. Newton TH, Cronqvist S. **Involvement of dural arteries in intracranial arteriovenous malformations.** *Radiology* 1969;93:1071–78

Endovascular Treatment of Deep Hemorrhagic Brain Arteriovenous Malformations with Transvenous Onyx Embolization

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ABSTRACT

SUMMARY: Brain AVMs are a rare cause of cerebral hemorrhage and SAH, and their treatment is still debated. The aim of this study was to describe a novel endovascular approach with transvenous embolization of deep hemorrhagic brain AVMs. Five patients (3 females, 2 males; mean age, 33.2 years) underwent a transvenous embolization of a deep hemorrhagic brain AVM at our institution between February and April 2012. Clinical and angiographic data at the end of the procedure and after 6 months are reported. All the AVMs were completely obliterated, and no intra- or postprocedural complications occurred. The clinical outcome was unchanged or improved in all patients. Transvenous endovascular treatment may be considered in small, hemorrhagic, and deep AVMs with single deep drainage in those cases in which neurosurgical and radiosurgical treatment might not be indicated.

ABBREVIATIONS: ACA = anterior cerebral artery; AChA = anterior choroidal artery; bAVMs = brain AVM; mRS = modified Rankin Scale; PCA = posterior cerebral artery

Brain AVMs are a rare cause of cerebral hemorrhage or SAH, and the therapeutic strategy is still debated. Several studies reported in the literature compared the results of endovascular, neurosurgical, and radiosurgical series, considering both single or associated treatments.¹⁻⁴ Concerning the embolization of bAVMs, the conventional transarterial treatment showed encouraging results in terms of safety and effectiveness, even if the results are less satisfactory than the surgical ones.⁵⁻⁸ However, in those cases in which the surgical approach may expose the patient to high risk, such as in deep localizations or eloquent areas, the endovascular and/or radiosurgical treatment may provide better clinical results.⁹ Furthermore, the slow effects of radiosurgery may be considered a limitation in hemorrhagic bAVMs because the risk of an early rebleeding would not be reduced. The evolution of endovascular treatment with the introduction of embolizing agents that progressively occlude the lumen of arteries and veins (Onyx 18; ev3-Covidien, Irvine, California) and detachable-tip microcatheters has allowed interventional neuroradiologists

to plan different strategies to obtain safe curative embolizations of bAVMs. The aim of this work was to describe a preliminary experience with transvenous embolization in a small series of patients with deep hemorrhagic bAVMs.

MATERIALS AND METHODS

Five patients (3 females, 2 males; mean age, 33.2 years) with deep hemorrhagic bAVMs underwent endovascular treatment with Onyx 18 by using a transvenous approach at our institution between February and April 2012. Patient characteristics are summarized in the Table. All patients were admitted or referred to our Interventional Neuroradiology Unit after a CT scan showed an SAH or parenchymal hematoma in atypical locations and a DSA examination documented the presence of a bAVM with deep venous drainage (the size of the nidus was evaluated in centimeters: height $\times$ length $\times$ width). In 4 patients, the AVMs had never been treated, and in 1 patient, the residual nidus of a previously subtotally occluded AVM was responsible for a late bleeding 3 years later.

Our interventional neuroradiology and neurosurgical teams discussed each case, and the endovascular treatment was preferred. Endovascular treatment was chosen after considering the risks of the surgical approach and the transvenous approach because of the presence of arterial feeders made up of short perforator branches arising from functional arteries (AChA and the P2 segment of PCA in 3 cases, the posterolateral choroidal artery in 1 case, and the antero-inferior cerebellar artery in 1 case). The treatment was scheduled at least 3 weeks after the hemorrhage (average latency was 61.8 days). All the endovascular procedures were performed with the patient under general anesthesia, without systemic heparinization (heparin was ad-

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Patient characteristics

Patient No.	Age (yr), Sex	First Treatment/Residual	Localization, Side	Venous Drainage	Vascular Approach	Nidus Size (cm)	Angiographic Result	Intra- or Post procedural Complications
1	36, F	First treatment	Paraventricular, left	Deep, single	Transvenous	<3	Complete occlusion	None
2	23, F	First treatment	Thalamomesencephalic, left	Deep, single	Transvenous	<3	Complete occlusion	None
3	11 F	First treatment	Pontocerebellar angle, left	Deep, single	Combined	<3	Complete occlusion	None
4	36, M	First treatment	Paraventricular, left	Deep, single	Combined	<3	Complete occlusion	None
5	61, M	Residual	Medial temporopolar, left	Deep (single) and superficial (single)	Combined	<3	Complete occlusion	None

ministered only in the perfusion sac). All arterial and venous accesses were performed from the femoral artery and vein. A triaxial system was used in the transvenous approach: a 6F guide catheter (Envoy; Codman Neurovascular, Raynham, Massachusetts), an intermediate catheter (DAC 0.044; Concentric Medical, Mountain View, California), and a 3-cm detachable-tip microcatheter (Apollo; ev3-Covidien). A second microcatheter (Apollo) was positioned in all cases in the direct main arterial feeder to the AVM to obtain a selective study of the nidus and its venous drainage without the overlap with other vascular structures and to perform intraprocedural controls during the transvenous embolization.

In 3 cases, a combined embolization (transvenous + transarterial) was performed, and in the other 2 cases, Onyx was injected only from the venous side. The “plug and push” technique was used to inject Onyx retrogradely from the origin of the intranidal portion of the draining vein into the nidus and subsequently into the arterial feeders by using a roadmap view. The fractionated injection of Onyx (average volume injected, 2.5 mL) was performed in 60–90 minutes. The procedure was considered completed when arteriovenous shunts were no longer recognizable during the angiographic controls, the draining vein was completely occluded, and a reflux within the arterial feeders direct to the nidus was obtained. The final phases of the embolizations, when the proximal segment of the draining vein was occluded, were performed under controlled hypotension. All patients underwent CT immediately after the procedure, and a delayed awakening was performed in the Neurosurgical Intensive Care Unit approximately 6–12 hours later. A clinical neurologic examination was performed in all cases at discharge; at 6 months, angiographic follow-up was performed in 4/5 patients. IV dexamethasone, 8 mg/day, was administered for 1 week after the procedure to prevent possible postoperative focal brain edema and perilesional swelling.

RESULTS

In all 5 cases, complete occlusion of the AVM was obtained without intra- or postprocedural complications and the CT performed at the end of the procedures showed no hemorrhage. The clinical status of all patients was unchanged or improved at discharge and after 6 months. A brief description of each case is reported below.

Case 1

A 36-year-old woman was admitted to our institution after the onset of acute headache, aphasia, and severe hemiparesis. A CT scan showed a 5 × 4 cm, deep, left temporoparietal hematoma

with perilesional edema. The patient immediately underwent a DSA evaluation, which documented a small (2.5 × 2 × 1.5 cm), deep, retroinsular, thalamic-pulvinar, periventricular, left-sided bAVM. The arterial feeders originated from the distal segment of the AChA, from the MCA (insular perforating arteries), and from the ACA (artery of the splenium of the corpus callosum); the AVM was drained through the deep venous system (single drainage: superior choroidal vein toward the internal cerebral vein). The case was discussed with our neurosurgical team, and we decided to proceed with the evacuation of the hematoma, which was considered life-threatening, and the removal of the AVM. After the operation, DSA evaluation showed that the superficial part of the AVM, fed from branches originating from the MCA and the ACA, was removed and a deep residual portion of the AVM was still present (Fig 1A, -B). The endovascular treatment was scheduled when the patient was clinically stable. A microcatheter was positioned through the straight sinus and the internal cerebral vein within the intranidal segment of the superior choroidal vein. A second microcatheter was positioned within the AChA to perform a superselective study of the AVM and further controls during the procedure (Fig 1C, -D). The AVM was completely obliterated, and the transvenous injection of 1.5 mL of Onyx (Fig 1E, -F) was necessary to obtain the retrograde filling of the arterial feeders at the end of the procedure. The final angiograms, the postprocedural CT scan, the MRI-MRA (1 week later), and the 6-month DSA follow-up confirmed the complete obliteration of the AVM without complications (Fig 2). The patient was discharged with a slight dysarthria (mRS score, 1) and, after 6 months, was asymptomatic (mRS score, 0).

Case 2

A 23-year-old female patient was referred to our institution after a previous hemorrhage (1 year before) from a small (2 × 1.5 × 1.5 cm), left, subthalamomesencephalic AVM occurred a few days after the positioning of ventriculo-peritoneal drainage in a third-ventricular cyst. Several radiosurgical opinions were sought with negative responses. The neurologic examination at admission documented a moderate right hemiparesis, a slight left seventh cranial nerve palsy, left ptosis, and a partial deficit of the homolateral cranial nerve III with left mydriasis. Distal branches of the AChA and small thalamogeniculate perforators from the P2 segment of the posterior cerebral artery fed the AVM with a single, deep venous drainage through the left peduncular vein, a tribu-

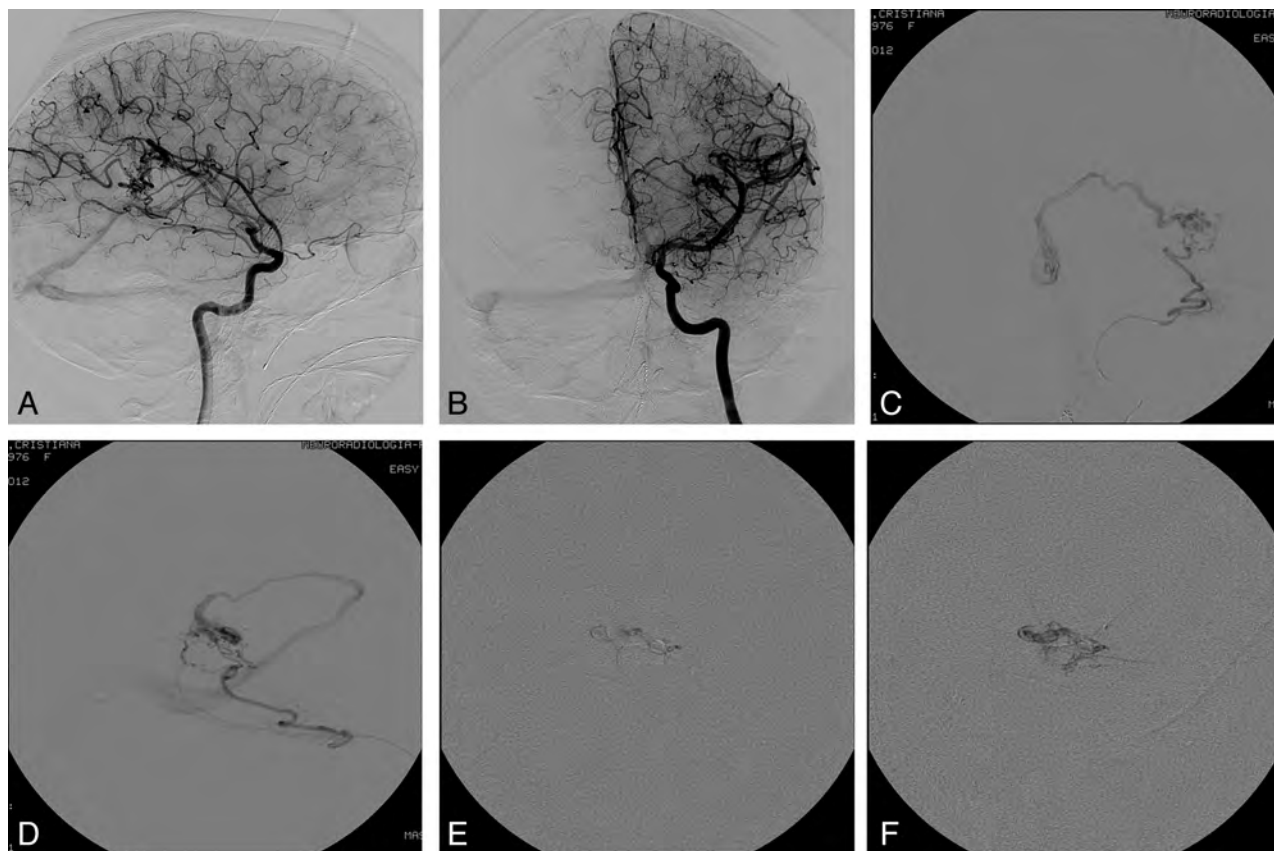


FIG 1. Case 1. Pretreatment DSA examination in anteroposterior (AP; A) and lateral (B) views. Visualization of the angioarchitecture of the AVM through a superselective injection within the AchoA in AP (C) and lateral (D) projections. Intracranial progression of Onyx during transvenous injection from the intranidal portion of the main draining vein (E and F).

tary of the basal vein of Rosenthal. A bifemoral arterial access was used. A microcatheter was placed within the AchoA, at the level of the plexal point and immediately after the origin of perforators, directed toward the internal capsule (visualized with injections within the AchoA), to have direct control of the nidus. A balloon (HyperGlide 4 × 15; ev3-Covidien) was positioned within the PCA and inflated each time Onyx penetrated the nidus to avoid retrograde filling of the artery through the perforators. A venous femoral access was used to reach the intranidal segment of the draining vein. The AVM, the draining vein, and the arterial feeders were occluded, preserving the PCA and the AchoA, with the injection of 1.8 mL of Onyx. A postprocedural CT scan showed no new ischemic or hemorrhagic lesions, and MR imaging performed 1 week later was negative for recent cerebral thalamopuncuncular ischemic lesions. A 6-month DSA follow-up showed stable occlusion of the nidus. The patient was discharged with unchanged neurologic examination findings (mRS score, 3), with a slight motor improvement after 6 months.

Case 3

An 11-year-old girl was referred to our interventional neuro-radiology unit after a hemorrhage in the posterior cranial fossa secondary to a small AVM (1 × 1 × 1.5 cm) of the left pontocerebellar angle fed by the rostralateral branch of the antero-inferior cerebellar artery and drained through a cortical ectatic cerebellar vein toward the superior petrous sinus. The case was discussed with our pediatric neurosurgical team, and the en-

dovascular approach was chosen. At admission, the patient was asymptomatic. A combined treatment was performed: The nidus was subtotally obliterated with 1 mL of Onyx from the venous side; and the injection of 0.3 mL of Glubran (GEM, Viareggio, Italy) at 20% dilution from the arterial feeder completed the embolization. The AVM was also completely occluded after 6 months, and the patient was asymptomatic at discharge and during the clinical follow-up (mRS score, 0).

Case 4

A 36-year-old male patient was referred to our center after a CT scan and DSA detected a small (1.5 × 2 × 2.5 cm), hemorrhagic, left retrothalamal parasplenic AVM that caused a severe SAH with ventricular inundation. The patient was comatose and an external ventricular drainage was immediately positioned. On awakening, he was in a vegetative status, which slightly improved during the 7 following months (mRS score, 5). The multiple arterial feeders originated from the left posterior choroid plexus, and the single venous drainage was observed through a homolateral subependymal parachoroidal vein tributary of the atrial vein toward the basal vein of Rosenthal. The left posterolateral choroidal artery and the draining vein were catheterized; and combined alternate injections of Onyx (1.4 mL from the venous side and 0.8 mL from the posterolateral choroidal artery) were performed, obtaining the complete exclusion of the AVM (Figs 3 and 4). A postprocedural CT scan was negative for new ischemic or hemorrhagic lesions. In this patient, it was not possible to perform DSA control

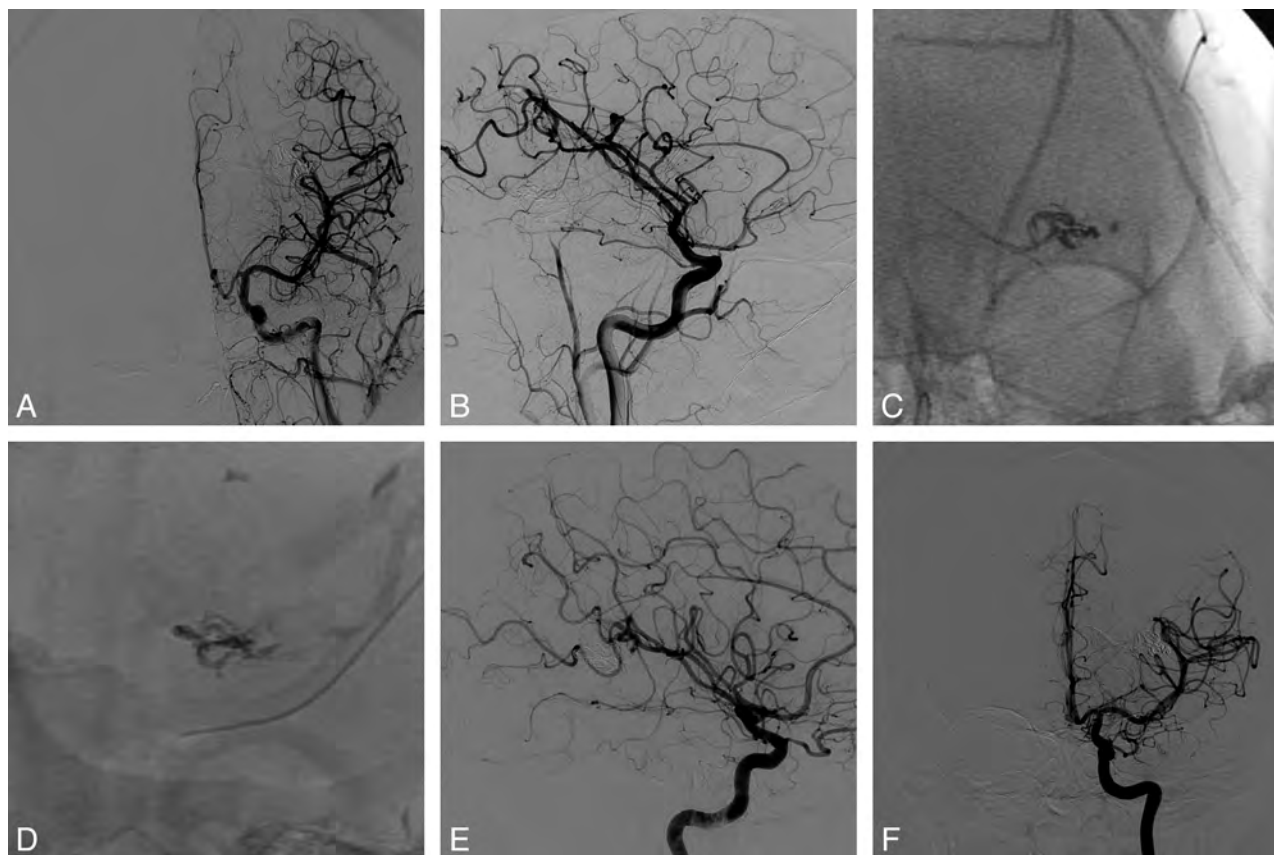


FIG 2. Case 1. Final angiograms at the end of the procedure in anteroposterior (AP; A) and lateral (B) views. Onyx cast at the end of the procedure (DSA unsubtracted images) in AP (C) and lateral (D) views. Six-month DSA follow-up in AP (E) and lateral (F) projections confirming the complete and persistent occlusion of the AVM.

because his clinical condition was unchanged at discharge and after the 6-month clinical follow-up (mRS score, 5).

Case 5

A 61-year-old man with type 1 neurofibromatosis and Crohn disease was referred to our institution in 2009 after a brain MR imaging and MR angiography revealed the presence of a left, medium ($2 \times 3 \times 2.5$ cm), medial temporobasal AVM fed by the AchoA, middle meningeal artery, and MCA (temporal branches), drained through a temporobasal cortical vein and the anterior insular vein, a tributary of the first segment of the basal vein of Rosenthal. The AVM was treated with transarterial embolization, obtaining the subtotal exclusion of the nidus with a small remnant portion ($1.5 \times 1 \times 1$ cm), and radiosurgical completion was recommended. The patient did not undergo radiosurgery for personal reasons and because of the surgical removal of a mediastinal neurofibroma. In March 2012, he was admitted to our center because of a left temporal hemorrhage, which was detected with CT. At admission, the patient was in a stupor, aphasic, and severely hemiparetic (mRS score, 4). DSA evaluation was immediately performed and documented an increased volume of the remnant portion of the AVM ($3 \times 2 \times 2$ cm) with arterial feeders arising from the cisternal segment and from the plexal point of the left AchoA, from small perforators of the MCA (anterior temporal artery), from the PCA (anterior temporal branches), and minimally from the accessory meningeal artery. The plexiform nidus

was drained predominantly through the deep venous system (basal vein of Rosenthal), and a small superficial drainage was observed through a temporal cortical vein tributary of the vein of Labbé. Endovascular treatment was preferred, and a combined approach was chosen. The accessory meningeal artery and the basal vein of Rosenthal were catheterized; after the occlusion of the minimal meningeal feeders, the nidus and the draining vein were completely obliterated with a transvenous intranidal injection of 6 mL of Onyx and retrograde filling of all the arterial feeders. The patient was discharged without neurologic deficits (mRS score, 0) and was asymptomatic even after 6 months. The DSA follow-up confirmed the complete obliteration of the AVM.

DISCUSSION

The results obtained in this small series raised some questions about critical issues that still remain debated, because to our knowledge, no series of patients with deep bAVMs treated with transvenous embolization has been reported in literature, though Massoud and Hademenos¹⁰ had previously proposed a very similar concept. The only case previously reported by Nguyen et al¹¹ described a transvenous embolization of a hemorrhagic bAVM supplied by an en-passant arterial feeder. In this case, an intranidal pseudoaneurysm was angiographically detected and occluded with transvenous injections of Onyx 34 and Onyx 18, resulting in bAVM cure. The transvenous approach was chosen

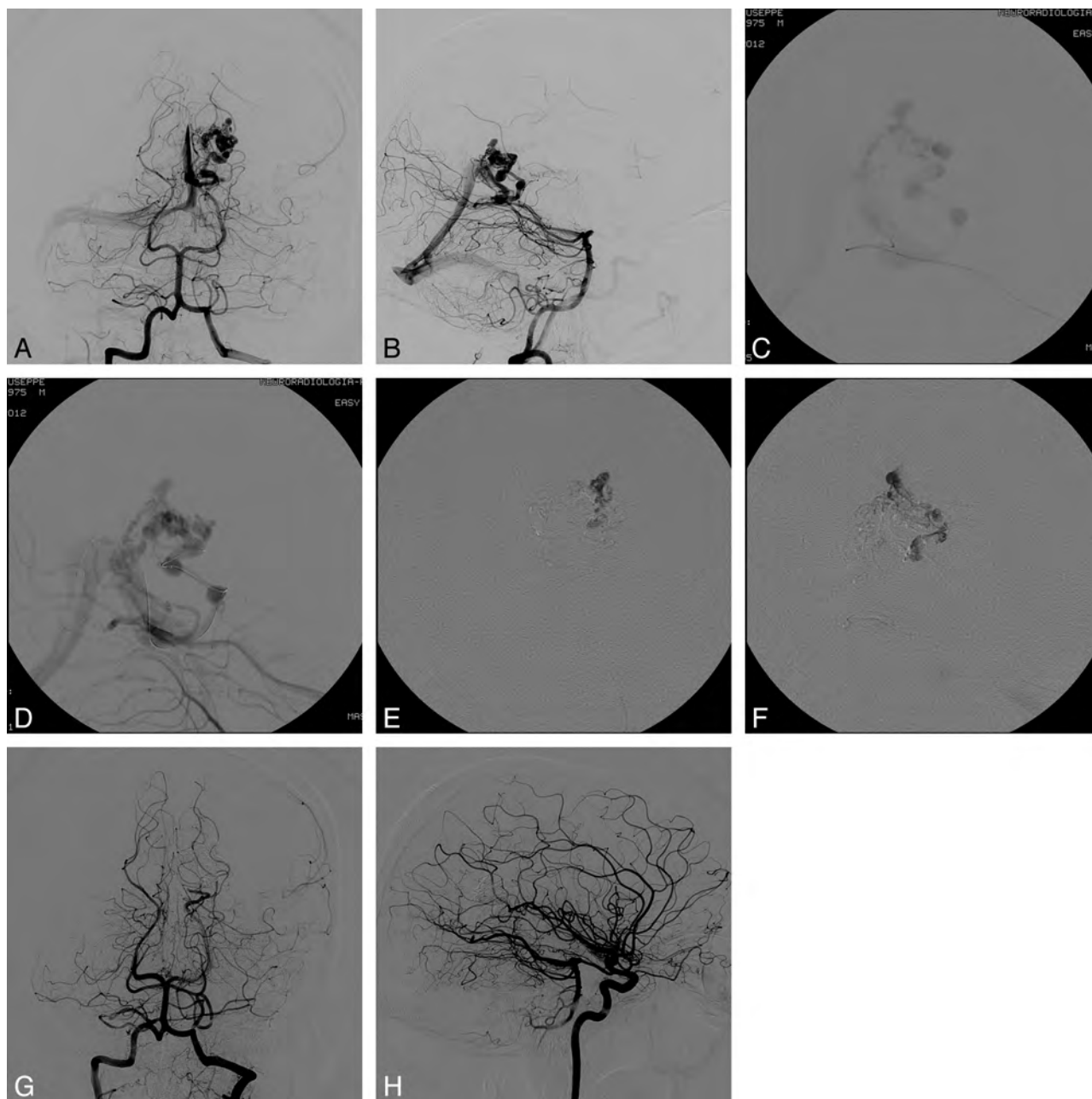


FIG 3. Case 4. Pretreatment DSA evaluation in anteroposterior (AP; A) and lateral (B) views. Visualization of the nidus and the draining venous system with transvenous injection through the microcatheter positioned at the origin of the draining vein (C) and the intermediate catheter positioned within the straight sinus (D). Intracranial penetration of Onyx through transvenous injection from the main venous drainage (E and F). DSA evaluation at the end of the procedure in AP (G) and lateral (H) views: The AVM is completely obliterated.

after an unsuccessful attempt of catheterization of the arterial feeder complicated by a branch occlusion secondary to a spasm. In our series, all the AVMs we treated with this approach were small (<3 cm), hemorrhagic, localized in deep territories with high risk for the surgical approach (1 in the pontocerebellar angle, 1 in the subthalamus and mesencephalon, 2 paraventricular thalamic-pulvinar AVMs, and 1 in the choroid fissure) and in eloquent areas. Furthermore, 4/5 AVMs had a single, deep drainage (only in case 5 was a superficial drainage present). Therefore, we considered these cases to be good targets for the transvenous approach.

The timing of treatment after the hemorrhage remains contro-

versial. Although no evidence is reported in literature, to our knowledge, the presence of an intranidal pseudoaneurysm may be a reasonable indication for immediate endovascular treatment (target embolization). In our series, the aim of the transvenous approach was curative. A partial transvenous embolization would result in the occlusion of the venous outlet and in a potentially high risk of rebleeding from the residual nidus. The reason to wait for at least 3 weeks was to obtain the spontaneous reabsorption of the hematoma, which could compress and hide some portions of the nidus, and to encourage the healing of the bleeding point. Furthermore, no intra- or paranidal aneurysms were observed in our series after the DSA evaluation performed in the acute phase



FIG 4. Case 4. Onyx cast at the end of the procedure (DSA unsubtracted image, lateral view).

of hemorrhage. The venous access was performed from the femoral vein and intracranially through the straight sinus in 4/5 cases; the nidus was reached through basal vein of Rosenthal in 3 cases (cases 2, 4, and 5) and in 1 case from the superior choroidal vein (case 1). In the other case, the superior petrous sinus was used for the venous access and the nidus was reached through the vein of the great horizontal fissure of the cerebellum (case 3).

No technical difficulties were observed and no access-related complications occurred. In all the cases, the injection of Onyx was performed from the intranidal segment of the draining vein, adjacent to the nidus. We always decided to catheterize both the draining vein and the main arterial feeder for 2 reasons: to have a pure view of the nidus and, when possible, to perform superselective intraprocedural controls without overlapping vascular structures, though complete angiographic series were also obtained when injecting from the guiding catheter. A simultaneous injection in the carotid and vertebral territories from the guiding catheters was performed in 1 case, because the arterial feeders originated from the both the anterior and posterior circulation (case 2). In 3/5 cases, transvenous embolization was associated with transarterial injection of Onyx to obliterate the peripheral parts of the nidus (cases 3, 4, and 5). However, when combined injections were performed, the nidus was predominantly occluded from the venous side. The decision to perform intra-arterial injections was case-dependent: In case of nonfunctional arteries (eg, the accessory meningeal artery or the distal posterolateral choroidal artery), the combined embolization with Onyx 18 (transarterial and transvenous, cases 4 and 5) was performed alternately to occlude the most peripheral portions of the nidus during the early phases of the procedure. In 1 case (case 3), the transarterial embolization was performed with 0.3 mL of Glubran exclusively during the final stages to achieve a rapid occlusion of residual peripheral portions of the bAVM. The transvenous injection of Onyx was used with the rationale of determining the retrograde occlusion of the nidus starting from the intranidal portion of the draining vein, where the dysplastic plexal venous shunts converge.

The transvenous embolization may be considered “centrifugal” because it determines the progression of Onyx from the central portions of the nidus toward the peripheral ones. The Onyx penetration through the intranidal dysplastic venous shunts, which are interposed between the draining vein and the periph-

eral arterial feeders, occurs extensively when a stable plug is obtained within the origin of the draining vein. Onyx spreads toward the peripheral portions of the nidus until complete obliteration of the whole bAVM and its arterial feeders is achieved. During all the phases of the transvenous embolization, it is mandatory to have good control of the reflux along the draining vein. Onyx initially laminates along the venous wall without causing an immediate occlusion of the vessel. In this way, we were able to obtain a progressive reduction of the venous caliber and of the blood outflow, to determine a slow alteration of the hemodynamic balance during all the phases of the procedure.

We also persisted in injecting Onyx in roadmap view when the arteriovenous shunt was completely occluded during the angiographic controls, to obliterate all the small perinidal vessels that would not be recognizable at DSA evaluation. The venous reflux was 1–3 cm. In all cases, it did not exceed the distal marker of the microcatheter and no difficulties were observed at retrieval. We were careful not to occlude the confluent veins into the main draining vein to avoid venous infarctions or bleeding secondary to hemodynamic alterations in the functional cerebral veins close to the bAVM. In all cases, the occlusion of a 1- to 3-cm segment of the draining vein did not result in venous hemodynamic alterations, so we considered the deep occluded vein as functionally excluded from the cerebral circulation. That was confirmed in those patients who underwent MR imaging during the postprocedural hospitalization, because no perilesional edema was recognizable.

We considered the following as key points of this technique: the progressive and controlled lamination of Onyx within the draining vein; the transvenous rapid nidal occlusion and the retrograde filling of all the arterial feeders, which may prevent hemorrhagic complications. These complications may be secondary to hemodynamic imbalance due either to the restriction of the venous outlet caused by an early and uncontrolled obliteration of the distal part of the draining vein in the presence of a subtotal occlusion of the nidus, or because of the residual filling of portions of the nidus still fed by small feeders when the draining vein is already occluded. For this reason, we believe that the transvenous embolization may provide good control of the nidal occlusion and of the retrograde filling of all the arterial feeders. From this point of view, the mechanism of obliteration of a brain AVM may be similar to that occurring in dural arteriovenous fistulas: When the vein is occluded, retrograde occlusion of the arterial feeders is observed. Only in the presence of multiple, short, “comb” perforators supplying the AVM (case 2) was a balloon positioned within the PCA at the P2-P3 segment and inflated during the injections of Onyx to prevent reflux into the parent vessel. In the other cases, the perforators feeding the AVM were single and longer, and we had sufficient control of their retrograde filling.

The transvenous approach might not be indicated in medium and large AVMs with multiple venous drainage. Indeed, in these cases, the penetration of Onyx within the nidus would be slower with a venous outlet restriction when the main draining vein is occluded, with higher risk of venous hypertension within the accessory venous drainage and consequent possible venous bleeding.

The main limitation of this series is the small number of patients, though we consider this study to represent only a preliminary experience. The possible indications, the operators' experience, and the selection of the patients represent some of many critical issues. However, further studies with larger populations are necessary to demonstrate the safety of this approach.

CONCLUSIONS

The transvenous embolization of deep bAVMs should still be described as an "experimental" treatment in small, hemorrhagic AVMs, when the surgical approach may be considered high risk and radiosurgery is not indicated. The feasibility of the technique and the possibility to achieve complete occlusion of the nidus with a single procedure, in those cases in which a conventional endovascular treatment is also challenging or not safe, may suggest that the transvenous approach is a further alternative therapeutic strategy in these types of bAVMs.

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REFERENCES

1. Fleetwood IG, Steinberg GK. **Arteriovenous malformations.** *Lancet* 2002;359:863–73
2. Mattle HP, Schroth G, Seiler RW. **Dilemmas in the management of patients with arteriovenous malformations.** *J Neurol* 2000;247:917–28
3. Richling B, Killer M, Al-Schameri AR, et al. **Therapy of brain arteriovenous malformations: multimodality treatment from a balanced standpoint.** *Neurosurgery* 2006;59:S148–57
4. Söderman M, Andersson T, Karlsson B, et al. **Management of patients with brain arteriovenous malformations.** *Eur J Radiol* 2003;46:195–205
5. Hamilton MG, Spetzler RF. **The prospective application of a grading system for arteriovenous malformations.** *Neurosurgery* 1994;34:2–7, discussion 6–7
6. Lundqvist C, Wihkolm G, Svendsen P. **Embolization of cerebral arteriovenous malformations. Part II. Aspects of complications and late outcome.** *Neurosurgery* 1996;39:460–467
7. Weber W, Kis B, Siekmann R, et al. **Preoperative embolization of intracranial arteriovenous malformations with Onyx.** *Neurosurgery* 2007;61:244–54, discussion 252–54
8. Natarajan SK, Ghodke B, Britz GW, et al. **Multimodality treatment of brain arteriovenous malformations with microsurgery after embolization with Onyx: single-center experience and technical nuances.** *Neurosurgery* 2008;62:1213–25, discussion 1225–26
9. Hurst RW, Berenstein A, Kupersmith MJ, et al. **Deep central arteriovenous malformations of the brain: the role of endovascular treatment.** *J Neurosurg* 1995;82:190–95
10. Massoud TF, Hademenos GJ. **Transvenous retrograde nidus sclerotherapy under controlled hypotension (TRENTH): a newly proposed treatment for brain arteriovenous malformations—concepts and rationale.** *Neurosurgery* 1999;45:351–63, discussion 363–65
11. Nguyen TN, Chin LS, Souza R, et al. **Transvenous embolization of a ruptured cerebral arteriovenous malformation with en-passage arterial supply: initial case report.** *J Neurointerv Surg* 2010;2:150–52

Incidental Thyroid Nodules on CT: Evaluation of 2 Risk-Categorization Methods for Work-Up of Nodules

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ABSTRACT

BACKGROUND AND PURPOSE: Thyroid nodules are common incidental findings on CT, but there are no clear guidelines regarding their further diagnostic work-up. This study compares the performance of 2 risk-categorization methods of selecting CT-detected incidental thyroid nodules for work-up.

MATERIALS AND METHODS: The 2 categorization methods were method A, based on nodule size ≥ 10 mm, and method B, a 3-tiered system based on aggressive imaging features, patient age younger than 35 years or nodule size of ≥ 15 mm. In part 1, the 2 categorization methods were applied to thyroid cancers in the SEER data base of the National Cancer Institute to compare the cancer capture rates and survival. In part two, 755 CT neck scans at our institution were retrospectively reviewed for the presence of ITNs of ≥ 5 mm, and the same 2 categorization methods were applied to the CT cases to compare the number of patients who would theoretically meet the criteria for work-up. Comparisons of proportions of subjects captured under methods A and B were made by using the McNemar test.

RESULTS: For 84,720 subjects in the SEER data base, methods A and B each captured 74% (62,708/84,720 and 62,586/84,720, respectively) of malignancies. SEER subjects who would not have met the criteria for further work-up by both methods had equally excellent 10-year cause-specific and relative survival of $> 99\%$. For part 2, the prevalence of ITNs of ≥ 5 mm at our institution was 133/755 (18%). The number of ITNs that would be recommended for work-up by method A was 57/133 (43%) compared with 31/133 (23%) for method B ($P < .0005$).

CONCLUSIONS: Compared with using a 10-mm cutoff, the 3-tiered risk-stratification method identified fewer ITNs for work-up but captured the same proportion of cancers in a national data base and showed no difference in missing high-mortality cancers.

ABBREVIATIONS: CI = confidence interval; ITN = incidental thyroid nodule; OR = odds ratio; SEER = Surveillance, Epidemiology, and End Results

An incidental thyroid nodule is defined as a thyroid nodule detected in studies performed for indications not specific to the thyroid in a patient without known thyroid disease. An ITN is a common finding seen in 1 in 6 contrast-enhanced neck CT scans and also frequently seen on cervical spine CT and chest CT scans.¹ ITNs pose a difficult problem for radiologists and clinicians because despite favorable features of the low malignancy rate in ITN of 0.5%–9%^{2,3} and excellent survival for most thyroid cancers, many radiologists feel compelled to recommend work-up of ITNs seen on CT for fear of missing a malignancy. The decision to

further evaluate such incidental nodules can start a cascade of sonographic imaging, biopsy, and even surgery for nodules that are commonly discovered to be benign. The cost of routinely pursuing work-up of ITNs includes unneeded patient anxiety and a substantial health care economic burden.¹

Additionally, the radiologist's approach to reporting ITNs on CT can vary widely because of a lack of clear guidelines.^{4,5} In practice, the most common method for selecting a CT-detected ITN for sonography is to use a 10-mm-size cutoff.⁵ This size has been arbitrarily chosen on the basis of extrapolation from sonographic recommendations, but unlike sonography, CT has no signs that help to further differentiate malignant from benign nodules.^{4,6} If ≥ 10 mm is the only criterion for selection, then $\leq 78\%$ of ITNs on CT could require sonography.³ Thus, there is a need for a more effective method of managing CT-detected ITNs.

A recently proposed strategy for reporting ITNs seen on cross-sectional imaging is based on prioritizing subsets of patients who are more likely to have malignant nodules.⁷ Each of the risk

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categories in this 3-tiered system is intended to help the radiologist communicate the risk of malignancy in a CT-detected ITN and the need for work-up with sonography. We modified the 3-tiered system for this study: Risk category 1 is a nodule of any size with aggressive imaging features of invasive or metastatic disease, risk category 2 is a nodule of any size in a patient younger than 35 years of age, and risk category 3 is a nodule at or above a cutoff of 15 mm and not meeting criteria for categories 1 and 2. The ideal categorization method for reporting nodules should increase the detection of malignancy while also reducing the number of nodules requiring work-up. Although this tiered risk system could potentially perform better than a method based solely on size, it requires validation.

This study aimed to compare the performance of 2 risk-categorization methods of selecting CT-detected ITNs for work-up. These aims were evaluated by an analysis of the Surveillance, Epidemiology, and End Results data base of the US National Cancer Institute (<http://seer.cancer.gov>) to determine the malignancy capture rate and a retrospective review of ITNs on neck CT studies at our institution to determine the number of ITNs that would potentially require work-up. Our hypothesis was that the 3-tiered system, compared with size cutoff alone, would capture clinically important cancers that confer the greatest risk of mortality while reducing the number of nodules that would be referred to sonography for work-up.

MATERIALS AND METHODS

In part 1, we evaluated the performance of these 2 categorization methods by using the SEER cancer registry to compare capture of thyroid cancer and survival. In part 2, we applied the categorization methods to a retrospective cohort of ITNs seen on CT at our institution to compare the proportion of patients that would be recommended for sonographic work-up. Part 2 also served as an additional check to ensure that the methods worked in a real-world population of patients.

Categorization Methods

Method A was based simply on nodule size. When applied to tumors in part 1, nodule size refers to the recorded maximum tumor diameter in the SEER data base, obtained from pathology or imaging reports. When applied to nodules on CT in part 2, nodule size refers to the largest diameter on axial CT images in the region of focal attenuation abnormality. In addition to the cutoff of ≥ 10 mm, we also evaluated sizes of 15 and 20 mm to consider alternate size cutoffs that other groups or practices may adopt.

Method B used a 3-tiered system based on the aggressiveness of imaging features, patient age, and nodule size.⁸ In this system, 3 subcategories were created on the basis of the risk of malignancy as described below.

Risk category 1 (highest risk) denotes patients with concerning CT findings such as local invasion, suspicious lymphadenopathy, or systemic metastatic disease. Risk category 2 is patients younger than 35 years of age and not meeting the criteria for risk category 1. This group was selected because of their higher ratio of malignant-to-benign nodules.^{6,9-13} Risk category 3 is nodule size ≥ 15 mm and not meeting the criteria for risk category 1 or 2. The 15-mm cutoff for risk category 3 is higher than that in method A

and is intended to reflect a higher size threshold for work-up of nodules that lack aggressive imaging findings or demographic risk factors. This cutoff has also been used in sonographic evaluation of thyroid nodules by several groups.^{2,14}

The purpose of having 3 risk categories is to help the radiologist communicate the risk of malignancy in a CT-detected ITN and the need for work-up with sonography. For example, for risk category 1 the radiologist would strongly recommend work-up, while for risk category 3, the radiologist could report the finding in the impressions without specific mention of work-up, leaving more flexibility for the clinician's input.

For purposes of this study, patients meeting the criteria for any of the 3 risk categories were considered to be receiving work-up under method B. We evaluated the performance of method B overall and the performance of each risk category.

Of note, clinical risk factors such as family history, childhood radiation exposure, and endocrine syndromes were not included in our risk assessment because this information is not available in the SEER data base and radiologists' access to this information may be limited in practice. In the original description of the 3-tier system, patients with these risk factors were assigned to risk category 2.⁸

Uncategorized subjects not meeting the size criteria for method A or B would compose the subgroup for which work-up with sonography and biopsy would have theoretically not been pursued if the nodule was seen on CT.

Part 1: SEER Data Base of Thyroid Malignancy

Subjects. The SEER Program collects cancer data from 18 population-based registries representing 28% of the US population.¹⁵

Cases were selected on the basis of a diagnosis of thyroid carcinoma. Although this data base only contained cancers and not benign ITNs, this part of the study served as a model to compare the number of cancers that would potentially be captured or missed with the categorization methods. The purpose of using these data was to compare the capture rate and not the diagnostic ability (sensitivity, specificity, and accuracy) of the 2 methods because calculating these latter statistics would require inclusion of benign cases.

Subjects were excluded if they were coded as any of the following: not the first malignant primary, not actively followed, alive with no survival time, missing or unknown cause of death (for the cause-specific survival analysis only), not in the research data base, or missing data regarding age or nodule size. The SEER data base provided the sex and age of each patient at diagnosis, follow-up time, vital status at follow-up, tumor size, and staging information. Recorded tumor sizes are intended to reflect sizes at initial staging. Because tumor size was not recorded in the SEER data base before 1983, the dataset used in this study included only cases diagnosed from January 1983 through December 2009.¹⁵

Application of Categorization Methods. The SEER data on tumor size and stage were based on a combination of pathology and imaging, but for the purposes of this study, we assumed that this information could be obtained on CT. SEER subjects were stratified by methods A and B by using data on age; size of the cancer;

and initial staging designation of localized, regional, or distant metastatic disease.

Outcome Measure. We calculated the proportion of patients in the SEER data base that would have been captured with method A compared with B. This indicated the number of cancers that would have met the criteria for undergoing work-up and thus would have been potentially diagnosed if they had presented initially as ITNs on CT. We compared the relative survival and cause-specific survival for patients that were uncategorized by methods A and B. This was a way of determining whether the cancers missed (uncategorized) by method A differed from those in method B.

Part 2: CT Cohort of Incidental Thyroid Nodules

Subjects. We retrospectively reviewed all (consecutive) subjects with contrast-enhanced neck CT and CTA examinations performed at a single institution in a 12-month period from July 1, 2002, to June 30, 2003. We chose the first year in which an electronic PACS was available at our institution to maximize the duration of clinical follow-up. Although thyroid nodules may also be seen on cervical spine and chest CT and MR images of the neck and chest, we have not examined these studies because the protocols are less likely to consistently include the entire thyroid gland (smaller FOV, saturation bands, or artifacts). Of 1127 contrast-enhanced neck CT or CTA examinations performed in the target time interval, 266 were excluded because they were not the patient's first neck cross-sectional study during the target time, 13 were not available for review due to technical reasons, 22 were excluded due to incomplete visualization of the thyroid, and 71 were excluded due to a thyroid-specific indication or known history of thyroid cancer or thyroid surgery. The final study group consisted of 755 patients with 549 soft-tissue neck CT scans (section thickness, 3 mm; interval, 3 mm) and 206 neck CTA examinations (section thickness, 1.25 mm; interval, 0.5 mm). During the period, imaging was performed with 120–150 mL of iopamidol (Isovue-300; Bristol-Meyers Squibb, Princeton, New Jersey) with an injection rate of 3 mL/s on 16-row multidetector CT scanners (LightSpeed; GE Healthcare; Milwaukee, Wisconsin).

The study was approved by the institutional review board at our institution, with waivers of informed consent and authorization of the Health Insurance Portability and Accountability Act.

Application of Categorization Methods. Two fellowship-trained neuroradiologists with 5 years' experience in interpreting neck CT examinations retrospectively reviewed axial CT images for thyroid nodules measuring at least 5 mm in diameter by using electronic calipers. A nodule is defined as a focal region of attenuation distinct from the remainder of the thyroid parenchyma. They recorded the following findings: number of nodules in the thyroid, maximal dimension of the largest nodule, calcification or simple cystic composition, and aggressive features. Aggressive features fulfilling the criteria for risk category 1 for method B were extrathyroid invasion and distant or nodal metastases. Data were recorded independently, with observers blinded to any follow-up information. Nodules meeting the criteria for category 1 (invasive or lymphadenopathy) were reviewed by a third neuroradiology fellowship-trained radiologist with 10 years' experience reading

neck CT scans. Any potentially ambiguous cases were also flagged for consensus review. Medical records of subjects with ITN were reviewed to determine age, sex, clinical follow-up, and pathology if available.

Outcome Measure. We compared the proportion of nodules that would meet the criteria for methods A and B. This was an indication of the work-up rate for ITNs detected on CT.

Statistical Analysis

For part 1, relative survival and cause-specific survival analyses were performed by using Seer*Stat 7.0.9 (National Cancer Institute; <http://seer.cancer.gov/seerstat/releasesnotes.html>) and the R package (www.r-project.org). Relative survival was calculated on the basis of observed survival of the cohort relative to expected survival, where expected survival is determined from census population survival data, adjusting for age, sex, race, and year. The mean survival and 95% confidence intervals for the 3 size-cutoff values of method A and the 3-tiered system of method B were calculated and compared. Comparison of survival was performed by using Cox regression to yield hazard odds ratios for the variables in the categorization methods.

For part 2, comparisons of proportions of patients captured under methods A and B were made by using the McNemar test. Statistical significance was determined by P value $< .05$.

RESULTS

Part 1: SEER Data Base of Thyroid Malignancy

Subjects and Survival. We recorded 107,466 cases of thyroid carcinoma as the patient's first or only malignant primary. After exclusion criteria were applied, there were 84,720 subjects for relative survival and 84,439 subjects for cause-specific survival analysis. The histologic types were papillary (86% [72,582/84,720]), follicular (10% [8721/84,720]), medullary (2.1% [1777/84,720]), and anaplastic (0.6% [508/84,720]) carcinomas. Table 1 shows the characteristics of the subjects and the thyroid cancers.

Overall, there were 2697 deaths attributed to thyroid cancer that occurred within 10 years of diagnosis, representing 3.2% of the cohort of 84,439 subjects and yielding a 10-year cause-specific survival of 95.7% (80,840/84,439). Overall relative survival in the cohort at 10 years was 97.4% (89.4/91.7). Relative and thyroid cancer-specific survival by age, sex, and tumor characteristics is presented in Table 1.

Categorization Methods: Effect on Cancer Capture. Table 2 shows the cancers captured with each method for the thyroid cancer population. The size cutoff of ≥ 10 -mm of method A captured 74% of cancers, compared with 59% with a 15-mm threshold and 46% with a 20-mm threshold. The 3-tiered system of method B captured 74% of the thyroid cancer population.

Categorization Methods: Effect on Survival. Table 2 shows the survival of subsets of the thyroid cancer population classified by the categorization methods. Regarding method A, relative survival estimates show no evidence of excess mortality for thyroid cancer subgroups with tumor sizes < 10 mm, 15 mm, or 20 mm. The thyroid cancer-specific 10-year survival rates for tumor sizes < 10 mm, 15 mm, and 20 mm were greater than 99% and are

Table 1: Survival of patients with thyroid carcinoma by patient demographics and tumor characteristics

	Percentage Total	10-Year Relative Survival (%)	95% CI	10-Year Thyroid Cancer-Specific Survival (%)	95% CI
Total	100%	97.4	97.0–97.7	95.7	95.5–95.9
Sex					
Male	23%	93.8	92.9–94.7	92.0	91.4–92.5
Female	77%	98.4	98.0–98.6	96.8	96.6–97.0
Age (yr)					
0–19	2.2%	99.1	98.3–99.5	99.3	98.7–99.6
20–34	21%	99.3	98.9–99.5	99.7	99.5–99.8
35–49	36%	99.3	98.9–99.5	98.9	98.7–99.0
50–64	27%	96.2	95.3–96.9	94.6	94.1–95.1
≥65	15%	90.3	88.1–92.1	81.0	79.9–82.0
SEER summary stage					
Localized or unstaged	61%	99.9	99.8–99.9	99.0	98.9–99.1
Regional	35%	95.6	95.0–96.2	94.4	94.0–94.8
Distant	4.1%	56.1	53.5–58.5	58.2	56.0–60.4
Tumor size (mm)					
<5	12%	99.9	99.7–99.9	99.4	99.0–99.6
5–10	14%	99.8	99.6–99.9	98.9	98.6–99.2
10–14	15%	99.8	99.5–99.9	99.0	98.7–99.2
15–19	13%	99.8	99.5–99.9	98.3	97.9–98.6
20–29	20%	99.4	98.3–99.8	97.0	96.7–97.4
30–39	11%	96.6	95.5–97.4	95.2	94.6–95.7
≥40	14%	84.0	82.7–85.2	83.3	82.4–84.2

Table 2: Survival in patients with thyroid malignancy in the SEER data base using risk-categorization methods of size cutoff (method A) and the 3-tiered system (method B)^a

	Percentage Total	10-Year Relative Survival (%)	95% CI	10-Year Thyroid Cancer-Specific Survival (%)	95% CI
Method A (size cutoff)					
≥10 mm	74%	96.4	96.0–96.7	94.7	94.4–94.9
<10 mm	26%	99.8	99.7–99.9	99.1	98.9–99.3
≥15 mm	59%	95.4	94.9–95.8	93.7	93.4–94.0
<15 mm	41%	99.8	99.8–99.9	99.1	98.9–99.2
≥20 mm	46%	94.1	93.5–94.6	92.4	92.0–92.7
<20 mm	54%	99.9	99.8–99.9	98.9	98.7–99.0
Method B (3-tiered risk categories)					
Categories 1, 2, and 3	74%	96.0	95.6–96.3	94.6	94.3–94.8
Category 1	39%	91.5	90.9–92.1	90.7	90.3–91.1
Category 2	13%	99.7	99.2–99.9	99.9	99.7–99.9
Category 3	23%	99.8	99.7–99.9	98.0	97.7–98.3
Not categorized	26%	99.9	99.8–99.9	99.5	99.3–99.7

^a Nodules smaller than the size cutoff and in the “not categorized” group for method B would represent nodules that would not receive work-up if the methods were applied.

significantly different for tumors above the size cutoffs ($P < .0001$). The cause-specific survival curves as a function of tumor size are shown in Fig 1.

Under method B, the 26% unassigned subjects had a 99.9% relative survival and 99.5% cause-specific survival. Cause-specific survival among cancers not captured under method B was not significantly different from that of method A ($P = .26$). Compared with the uncategorized subset, the 39% of cancer subjects identified as risk category 1 had a markedly worse 10-year cause-specific survival with an OR of 22.07 (95% CI, 17.11–28.47; P value $< .0001$). The OR for risk category 2, relative to the uncategorized group was 0.43 (95% CI, 0.25–0.75; P value = .003), indicating that it had a significantly better survival rate than the uncategorized group. Risk category 3 had a moderately worse 10-year cause-specific survival rate than the unassigned group (OR, 4.90; 95% CI, 3.73–6.47; P value $< .0001$). The thyroid cancer-specific survival curves stratified by method B are shown in Fig 2.

Part 2: CT Cohort of Incidental Thyroid Nodules

Subjects and Prevalence of Incidental Thyroid Nodules. Among 755 subjects (mean age, 50.2 ± 20.8 years; 52% male), there were 133 patients with thyroid nodules of ≥ 5 mm (mean age, 60.7 ± 16.5 years; 32% male), resulting in an ITN prevalence of 18%. Mean nodule size was 11 ± 6.9 mm. The characteristics of these patients and their CT findings are shown in the On-line Table.

Categorization Methods: Effect on Work-Up Rate. One hundred thirty-three patients with ITNs were included in the cohort for evaluation of categorization methods (Table 3). Method A captured 54 patients (43%) with the ≥ 10 -mm threshold. Alternative size thresholds of ≥ 15 and ≥ 20 mm captured 22 (17%) and 12 (9%) patients, respectively.

The 3-tiered system of method B captured 31 patients (23%) (Table 3), significantly less than those captured with

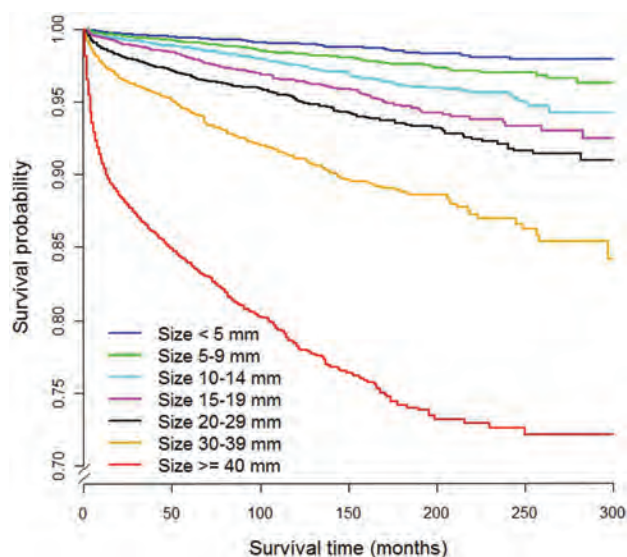


FIG 1. Cause-specific survival curves as a function of tumor size for thyroid cancers in the SEER data base. This represents method A of risk categorization.

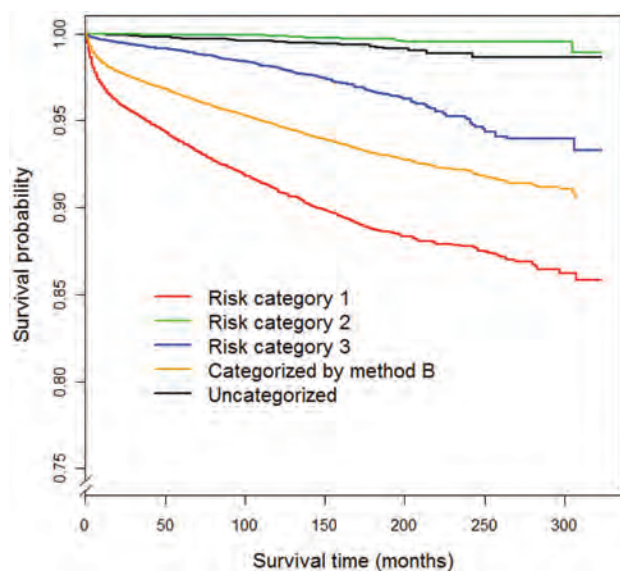


FIG 2. Cause-specific survival curves of thyroid cancers in SEER stratified by the 3-tiered system (method B).

method A (P value $< .0005$). All nodules in category 2 were < 10 mm.

Review of medical records found that a small number of nodules underwent further evaluation. Biopsy performed in 14 patients revealed 12 benign nodules and 2 cases of thyroid lymphoma. There were no cases of papillary thyroid cancers. Both cases of lymphoma met the criteria for category 1; one measured 1.5 cm and the other measured 2 cm in the maximal axial dimension on CT. Patients without pathology had a median follow-up time of 24 months (interquartile range, 6–105 months). No additional thyroid cancers were diagnosed during that time.

DISCUSSION

ITNs are very common on CT, but malignancy in the ITN is uncommon. While it would be ideal for a categorization method

Table 3: Comparison of capture rates of incidental thyroid nodules by methods A and B^a

Categorization Method	Patients	Total
Method A (size cutoff)		
≥10 mm	57	43%
<10 mm	76	57%
≥15 mm	22	17%
<15 mm	111	83%
≥20 mm	12	9%
<20 mm	121	91%
Method B (3-tiered system)		
Category 1, 2, or 3	31	23%
Category 1	2	2%
Category 2	9	7%
Category 3	20	15%
Not categorized	102	77%
Total	133	

^aIncidental thyroid nodules from retrospective CT review were stratified by size cutoff (method A) and the 3-tiered system (method B). The nodules smaller than the size cutoff and in the “not categorized” group for method B would represent nodules that would not receive work-up if the methods were applied.

to capture all incidental thyroid malignancies, it may be more rational and cost-effective to capture all malignancies associated with poor outcome. Our 3-tiered system improved on a size-only method by capturing the same proportion of cancers as in the SEER data base while almost halving the number of nodules targeted for work-up. Although interpretation of these findings is subject to the limitations discussed below, the clinical implication is that a larger proportion of ITNs detected on CT can be managed more conservatively without missing high-mortality cancers.

To date, a size of 10 mm is the most common method of triaging CT-detected nodules for work-up,^{4,5} despite there being no guidelines and no evidence to support this cutoff size. While increasing the cutoff size for work-up would obviously reduce the number of patients having work-ups, there should be a balance so as not to increase the proportion of missed malignancies. Our retrospective review of ITNs on CT in 1 year at our institution shows that if we considered size alone, using a 15-mm cutoff compared with a 10-mm cutoff could more than halve the number of patients requiring work-up, but the disadvantage is that with SEER data, nearly half the number of cancers would be missed.

The rationale for developing method B was to improve on a size-based categorization by taking into consideration additional features that either increase the risk for malignancy in an ITN or are associated with higher mortality. The performance of method B in capturing cancers with poorer survival in the SEER data base is largely the result of including aggressive imaging features or suspicious lymphadenopathy in risk category 1. The other subgroup highlighted by method B was young subjects because this group has a higher malignant-to-benign ratio in a given thyroid nodule.^{6,9-13} We found that the age group younger than 35 years had a discordant proportion of ITNs versus thyroid cancer: Younger than 35 years represented 7% of ITNs by CT review, but 23% of thyroid cancers recorded in SEER. Thus, the additional burden associated with working up young patients may be justified by the greater yield of detecting malignancy.

There are additional clinical risk factors such as family history of malignancy, childhood radiation, and endocrine syndromes that increase the malignancy risk.⁴ In the original description of the 3-tiered system, patients with these risk factors were assigned

to risk category 2.⁸ In our modified 3-tiered system (method B), we did not include clinical risk factors because this clinical information was not available from the SEER data base and, in practice, the radiologist's access to this information may be limited. Radiologists reporting ITNs should be aware of the clinical risk factors and modify their recommendations when these factors are present.

There are several limitations to this study. In part 1, a major limitation was the assumption that the data in SEER correspond to information seen on imaging. In practice, early tumor with microscopic local invasion and nodal metastases may have been missed on CT. This study may, therefore, overestimate the relative performance of method B in capturing malignancies on CT. It is also possible that some cancers between 10 and 15 mm were not seen on CT and we have overestimated the performance of method A. The second limitation of part 1 is that survival for most cases in the SEER data base was based on diagnosed and treated tumors. The uncategorized patients by our 2 methods could have had worse survival had they not been diagnosed and treated. However, the main purpose of evaluating survival was to compare the biology of the tumors between the 2 categorization methods. The data show that the tumors uncategorized by both methods are equally less aggressive than the tumors that met the criteria for work-up. Furthermore, survival in small tumors is likely to be excellent because epidemiologic trends show the absence of a survival improvement despite increased diagnosis of small thyroid cancers and a Japanese study showed no deaths during 10 years in nonaggressive small thyroid carcinomas that did not receive treatment.^{16,17}

There are also limitations for our CT retrospective review. It would have been interesting and ideal to have histology of the thyroid nodules to determine the number of missed cancers with each categorization method. However, the purpose of using the cohort was to determine the potential work-up rate and not the accuracy of the methods. The work-up rate in a future study could be improved with uniform radiology-report recommendations based on our proposed stratification system. In the present study, we did not address other risk factors that are known to affect the risk of thyroid malignancy, such as radiation exposure and family history.

CONCLUSIONS

A stratification approach to ITN that incorporates aggressive imaging findings, age younger than 35 years, and a 15-mm cutoff for triaging work-up has several advantages. Compared with the common practice of a 10-mm-size cutoff, the 3-tiered system reduces excess work-up of benign ITNs while capturing the same proportion of thyroid malignancies and is no more likely to miss high-mortality malignancies.

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REFERENCES

1. Yousem DM, Huang T, Loevner LA, et al. **Clinical and economic impact of incidental thyroid lesions found with CT and MR.** *AJNR Am J Neuroradiol* 1997;18:1423–28
2. Tan GH, Gharib H. **Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging.** *Ann Intern Med* 1997;126:226–31
3. Yoon DY, Chang SK, Choi CS, et al. **The prevalence and significance of incidental thyroid nodules identified on computed tomography.** *J Comput Assist Tomogr* 2008;32:810–15
4. Cooper DS, Doherty GM, Haugen BR, et al. **Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer.** *Thyroid* 2009;19:1167–214
5. Johnson PT, Horton KM, Megibow AJ, et al. **Common incidental findings on MDCT: survey of radiologist recommendations for patient management.** *J Am Coll Radiol* 2011;8:762–67
6. Shetty SK, Maher MM, Hahn PF, et al. **Significance of incidental thyroid lesions detected on CT: correlation among CT, sonography, and pathology.** *AJR Am J Roentgenol* 2006;187:1349–56
7. Hoang JK, Lee WK, Lee M, et al. **US Features of thyroid malignancy: pearls and pitfalls.** *Radiographics* 2007;27:847–60, discussion 861–65
8. Hoang JK, Raduazo P, Yousem DM, et al. **What to do with incidental thyroid nodules on imaging? An approach for the radiologist.** *Semin Ultrasound CT MR* 2012;33:150–57
9. Belfiore A, La Rosa GL, La Porta GA, et al. **Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity.** *Am J Med* 1992;93:363–69
10. Fowler CL, Pokorny WJ, Harberg FJ. **Thyroid nodules in children: current profile of a changing disease.** *South Med J* 1989;82:1472–78
11. Kirkland RT, Kirkland JL, Rosenberg HS, et al. **Solitary thyroid nodules in 30 children and report of a child with a thyroid abscess.** *Pediatrics* 1973;51:85–90
12. Machens A, Holzhausen HJ, Dralle H. **The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma.** *Cancer* 2005;103:2269–73
13. Rago T, Fiore E, Scutari M, et al. **Male sex, single nodularity, and young age are associated with the risk of finding a papillary thyroid cancer on fine-needle aspiration cytology in a large series of patients with nodular thyroid disease.** *Eur J Endocrinol* 2010;162:763–70
14. Frates MC, Benson CB, Charboneau JW, et al. **Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement.** *Radiology* 2005;237:794–800
15. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973–2009 varying)—linked to County Attributes—Total US, 1969–2010 Counties, National Cancer Institute, Division of Cancer Control & Population Sciences, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission; 2012. <http://seer.cancer.gov/data/seerstat/nov2011>. Accessed May 28, 2012
16. Davies L, Welch HG. **Increasing incidence of thyroid cancer in the United States, 1973–2002.** *JAMA* 2006;295:2164–67
17. Ito Y, Miyauchi A, Inoue H, et al. **An observational trial for papillary thyroid microcarcinoma in Japanese patients.** *World J Surg* 2010;34:28–35

CT Imaging Correlates of Genomic Expression for Oral Cavity Squamous Cell Carcinoma

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ABSTRACT

BACKGROUND AND PURPOSE: Imaging correlates of genetic expression have been found for prognostic and predictive biomarkers of some malignant diseases, including breast and brain tumors. This study tests the hypothesis that imaging findings correlate with relevant genomic biomarkers in oral cavity squamous cell carcinoma.

MATERIALS AND METHODS: Surplus frozen tissue from 27 untreated patients with oral cavity squamous cell carcinoma who underwent preoperative CT imaging was analyzed for gene expression. A team of neuroradiologists blinded to the genomic analysis results reviewed an extensive list of CT findings. The imaging correlated with genomic expression for cyclin D1, angiogenesis-related genes (vascular endothelial growth factor receptors and ligands), which relate to enhancement on the basis of other tumor types; and epidermal growth factor receptor, which may relate to proliferation and mass effect.

RESULTS: Expression of vascular endothelial growth factor receptors 1 and 2 correlated with the enhancement of the primary tumor ($P = .018$ and $P = .025$, respectively), whereas the epidermal growth factor receptor correlated with mass effect ($P = .03$). Other exploratory correlations included epidermal growth factor receptor to perineural invasion ($P = .05$), and certain vascular endothelial growth factor receptors and ligands to mass effect ($P = .03$) and increased ($P = .01$) or decreased ($P = .02$) primary tumor size.

CONCLUSIONS: We report that CT imaging correlates with gene expression in untreated oral cavity squamous cell carcinoma. Enhancement of the primary tumor and degree of mass effect correlate with relevant genomic biomarkers, which are also potential drug targets. Eventually, treatment decisions may be aided by combining imaging findings into meaningful phenotypes that relate directly to genomic biomarkers.

ABBREVIATIONS: ECS = extracapsular spread; EGFR = epidermal growth factor receptor; HPV = human papillomavirus; HU = Hounsfield unit; OSCC = oral cavity squamous cell carcinoma; VEGF = vascular endothelial growth factor

Head and neck squamous cell carcinoma is the sixth most common cancer with approximately 600,000 cases per year worldwide and approximately 50,000 cases per year in the United States.^{1,2} Despite advances in treatment, the 5-year survival rate of patients with squamous cell carcinoma remains at 40%–50%.³ The most common site involved is the oral cavity.¹ Known risk factors include alcohol; tobacco; and, to a lesser degree, human

papillomavirus (HPV).⁴ As in most solid tumors, squamous cell carcinoma is usually caused by genetic alterations. Tumors in tobacco users tend to have more genomic alterations than in HPV-associated disease,⁵ and these alterations may contribute to treatment resistance.

Treatment failure most frequently takes the form of local and regional recurrences, but as disease control in these areas improves, treatment failures are more often a result of distant metastasis. The presence of cervical lymph node metastases, especially extracapsular spread (ECS), is a reliable adverse prognostic factor.⁶ The promise of basing treatment decisions on specific driver gene mutations or changes in expression, known as genomic biomarkers, has yet to be fully realized because of our poor understanding of the mechanisms of regional and distant metastases of squamous cell carcinoma.

Imaging phenotypes may convey relevant genomic information. Correlation of imaging morphologic features to the genotype and gene expression have already been made in other tumor

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sites, such as the breast, liver, or brain.⁷⁻¹⁵ Advantages of imaging include a larger area of coverage than pathologic specimens, which extends evaluation to tissue beyond the surgical resection margins, and less expense than combinations of multiple genomic tests, especially if obtained anyway as routine practice. If imaging findings can correlate with clinically useful molecular or genomic biomarkers, then a potential exists for improved tissue sample targeting,⁸ clinical decision making, response monitoring,¹⁶ and discovering and validating molecular targets.¹⁷ For example, higher expression of a gene correlated with invasion in glioblastoma by MR imaging and was subsequently found to be a prognostic biomarker of survival.¹⁷ However, imaging-to-genetic correlations have yet to be demonstrated for squamous cell carcinoma of the oral cavity (OSCC).

Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor on the cell surface related to cell growth that is both a predictive biomarker in head and neck squamous cell carcinoma^{18,19} and a chemotherapy target.^{3,20} EGFR expression has been related to the ratio of contrast-enhanced tumor and necrosis in brain tumors⁹ and primary tumor size and nodal metastasis for breast cancer.²¹ Vascular endothelial growth factor (VEGF) ligands and receptors are signaling proteins involved in angiogenesis and are targets for chemotherapy.⁹ VEGF expression has been related to brain and liver tumor enhancement and elevated perfusion.^{10,11,15} Cyclin D protein alters cell cycle progression and interacts with several proteins and receptors, including tumor necrosis factor alpha and retinoblastoma protein. Cyclin D1 may be a marker of poor prognosis and higher recurrence rates in OSCC, especially of the tongue,^{22,23} and has been associated with smaller, well-defined breast cancers.²⁴ We tested the hypothesis that CT imaging findings correlate with selected genomic biomarkers in patients with OSCC.^{5,25}

MATERIALS AND METHODS

Genomics

After institutional review board approval, untreated patients with OSCC underwent extensive genomic evaluation of surplus frozen tissue removed during a clinically indicated surgical procedure. A total of 27 of these patients had good-quality pathology specimens that underwent genomic analysis and also preoperative contrast-enhanced CT examinations for retrospective review. Exome sequencing for some of these patients has been published previously.⁵ Only gene expression was examined for this analysis. Total RNA was isolated by using Tri Reagent (Sigma-Aldrich, St. Louis, Missouri) according to the manufacturer's instructions. RNA was hybridized to the Human Exon 1.0ST expression array platform (Affymetrix, Santa Clara, California) according to the manufacturer's instructions. Data were background-corrected with robust multiarray average and quantile normalized in R (R statistical computing software; <http://www.r-project.org/>) with the *aroma.affymetrix* library. Probes were averaged across each gene. The groups of genes assessed in this preliminary study included cyclin D1 protein, EGFR, and VEGF ligands (VEGF-A, -B, and -C) and receptors including VEGF-r1 (also known as FMS-like tyrosine kinase receptor 1), VEGF r2 (kinase insert domain receptor or fetal liver kinase 1), and VEGF-r3 (FMS-like tyrosine kinase re-

Table 1: Patient demographics

Patient No.	Age (y)	Sex	Stage	Subsite
1	62	M	T2 N0	OT
2	66	M	T3 N2	OT
3	62	M	T3 N0	OT
4	75	F	T4 N2c	OT/FOM
5	23	M	T3 N2b	OT
6	40	M	T3 N1	OT
7	50	M	T4 N2b	OT
8	69	M	T4 N2c	OT/FOM
9	61	M	T2 N1	OT
10	62	F	T3 N0	OT
11	60	F	T2 N2b	OT/BOT
12	40	M	T4 N2c	OT
13	60	M	T4 N0	OT/FOM
14	50	M	T4a N2c	OT
15	85	F	T2 N0	OT
16	56	M	T4 N2c	FOM
17	50	F	T2 N0	OT
18	74	M	T4 N2b	OT
19	53	M	T3 N0	OT
20	61	F	T2 N2b	OT
21	76	F	T2 N0	OT
22	56	M	T3 N2b	Bucca
23	48	M	T2 N1	FOM
24	74	M	T4 N0	Gingiva
25	64	M	T2 N1	FOM
26	62	M	T1 N0	Bucca
27	67	M	T4 N2c	FOM

Note:—BOT indicates base of tongue; F, female; FOM, floor of mouth; M, male; N, nodal stage; OT, oral tongue; T, tumor stage.

ceptor 4). Additional demographic, pathology, and follow-up data were gathered. HPV status was noted if available.

Imaging

Imaging analysis was done by consensus of 2 board-certified neuroradiologists. A third reader was used to resolve discrepancies. All readers were blinded to genetic results.

The CT technique changed during the course of the study. Most patients underwent imaging on a 16-detector LightSpeed CT scanner (GE Healthcare, Milwaukee, Wisconsin) with axial 1.25- to 2.5-mm collimation at 120 kVp and 200–240 mA, after injection of 120 mL of Omniscan (GE Healthcare) at 3 mL/s with a 90-second delay. A second angled acquisition was performed as necessary to eliminate dental artifacts.

Bidimensional measurements of the primary tumor and, if present, the largest metastatic lymph node were made on axial images. The cross-sectional area [for an ellipse = π ($\frac{1}{2}$ long axis $\times$ $\frac{1}{2}$ short axis)] and the ratio of the long axis over the short axis were calculated. Enhancement of the primary site and of the largest solid component of lymph nodes was measured by a representative region of interest in Hounsfield units (HU). The enhancement of the submandibular gland was used as a positive control to normalize the values among patients (lesion HU/submandibular gland HU). For the primary tumor, borders were judged as ill- vs well-defined and as regular vs irregular. Invasion into adjacent structures was noted. Mass effect was graded as none, mild if there was < 1 cm displacement of airway or other adjacent structures, moderate for 1–2 cm displacement and marked if > 2 cm. Perineural extension of the primary tumor or ECS from lymph nodes was assessed both by imaging and subsequent pathologic

examination. Necrosis was estimated by fifths (0%–20%, 20%–40%, etc) for both primary and lymph nodes. The presence of calcification or ulceration was also noted.

Statistics

Associations between gene expression and imaging variables were assessed by use of Pearson correlation and ordinal regression for contiguous and categoric imaging features, respectively. Bonferroni correction set the adjusted significant level at a P value $\leq$

.00036 for an unadjusted P value $\leq$.05. Specific hypotheses to be tested based on other tumor types included 1) positive correlations between VEGF expression and enhancement^{10,11}; 2) EGFR expression with necrosis, tumor size, and presence of nodal metastasis^{9,21}; and 3) a negative correlation with cyclin D1 expression and tumor size and invasion.²⁴ We also hypothesized that because EGFR relates to growth and proliferation, it would have a positive correlation to mass effect,⁸ though this trend has not been reported previously. To check for confounding factors and groups of imaging features, we also assessed the associations among imaging features themselves by using ordinal regression (categoric vs continuous), Pearson correlation (continuous vs continuous), or the Fisher exact test (categoric vs categoric).

RESULTS

Images were available from 2001–2010. The average age of the patients was 59 ± 13 years; of 27 patients, 20 (74%) were men (Table 1). Most tumors were located in the oral tongue (19/27, or 59%), with 4 tumors involving the floor of the mouth, 3 tumors involving the bucca or gingiva, and 4 tumors involving a combination of sites. Primary tumors were staged pathologically as T1 in 1 patient, T2 in 9 patients, T3 in 6 patients, and T4 in 11 patients. Nodal staging was N0 in 10 patients, N1 in 4 patients, N2 in 13 patients, and N3 in no patients. Only 1 patient with a T4 N2b cancer of the oral tongue was found to test positive for HPV.

Imaging results revealed a spectrum of findings. The average size of the primary tumor was 3.6 ± 1.2 cm in the long axis with an elliptic cross-sectional area of 6.1 ± 5.8 cm². All primary tumors enhanced to some degree with either avid enhancement (absolute 119 ± 29 HU or normalized ratio 1.2 ± 0.3), minimal enhancement (3 patients: absolute 89 ± 16 HU or normalized ratio 1.2 ± 0.2), or in 1 case rim enhancement with a primarily necrotic tumor. A total of 9 patients had invasion deep into the muscle, 3 had invasion into the bone, and the remaining patients did not have deep invasion. Although no gross perineural extension was seen on imaging, 8 patients had perineural invasion by pathologic examination. Most tumors were irregular ($n = 22$), ill defined ($n = 21$), and partially necrotic ($n = 21$), and had mild to moderate mass effect ($n = 19$) with few ulcers ($n = 9$) and no calcifications. Of the 17 patients with pathologic nodal disease, 2 had tumors that were not readily detected on CT scanning. Of the affected largest lymph nodes, the average size was 1.4 ± 0.4 cm in the long

axis. Most lymph nodes enhanced ($n = 12$) and were necrotic ($n = 10$), with 8 patients having ECS on pathologic examination (only one of which was identified on imaging). In these presurgical patients, no nodal calcification was seen and distant metastatic disease was not found.

Expression of VEGF receptors 1 and 2 correlated with enhancement of the primary tumor ($P = .018$ and $P = .025$, respectively; Fig 1), whereas EGFR correlated with mass effect ($P = .03$; Fig 2). The hypothesis that EGFR would corre-

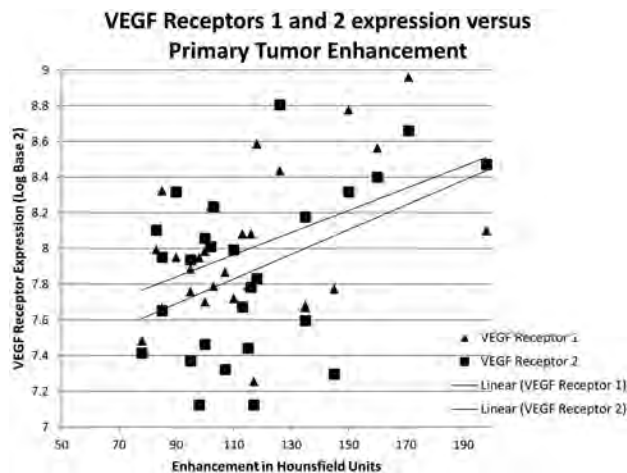


FIG 1. Scatterplot showing relationship of increased enhancement and VEGF receptors 1 and 2 expression. The linear fitting demonstrates that as the absolute enhancement in HU increases, the receptor expression (in log base 2) also increases.

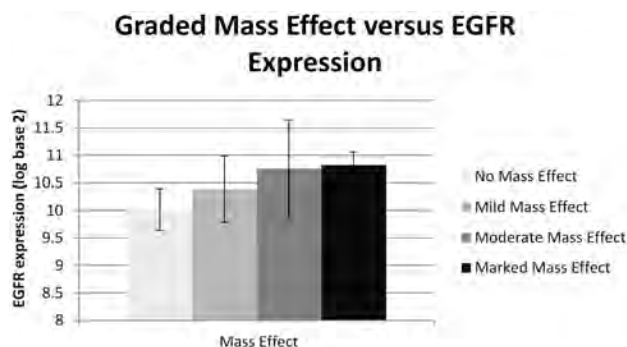


FIG 2. Bar graph reflecting positive correlation between the grading of mass effect and the expression of EGFR (in log base 2) with standard deviation bars.

Table 2: Correlations of gene expression to maximal axial cross-sectional area

Imaging Finding	Gene Expressed	Coefficient Value	Significance (P Value)
Mass effect	EGFR	OR: +1.2	.032 ^a
Perineural invasion	EGFR	OR: +3.1	.047
Axial cross-sectional area (cm ²)	VEGF ligand A	PC: +0.49	.014
Axial orthogonal distance (cm)	VEGF ligand A	PC: +0.47	.010
Mass effect	VEGF ligand B	OR: +2.8	.026
Enhancement of primary tumor (HU)	VEGF receptor 1	PC: +0.45	.018 ^a
Axial maximal diameter (cm)	VEGF receptor 2	PC: −0.44	.023
Axial cross-sectional area (cm ²)	VEGF receptor 2	PC: −0.42	.029
Enhancement of primary tumor (HU)	VEGF receptor 2	PC: +0.43	.025 ^a
Enhancement of submandibular gland (HU)	VEGF receptor 2	PC: +0.43	.026

Note:—cm indicates centimeter; OR, ordinal regression; PC, Pearson correlation.

^a Denotes confirmation of a priori hypothesis.

late with necrosis, primary tumor size, or lymph node metastases was not supported. No significant correlations were found for cyclin D protein, VEGF ligand C, or VEGF receptor 3. However, a trend was observed toward cyclin D1 expression and decreased orthogonal primary tumor size ($P = .11$). Additional exploratory correlations that did not survive correction of significance values for multiple correlations are given in Table 2. As demonstrated in Fig 3, when the estimated cross-sectional area of the primary tumor increased, the expression of VEGF ligand A increased ($P = .01$) but expression of VEGF receptor 2 decreased ($P = .03$).

We also tested associations among imaging characteristics to look for confounding variables and groups of imaging characteristics. Larger tumors (maximal diameter, orthogonal, and cross-sectional area) tended to have more mass effect ($P = .0018$ – $P = .0035$). The largest-diameter tumors correlated with invasion into muscle or bone ($P = .04$). The patients who had moderate to marked mass effect or perineural invasion on pathologic examination had higher EGFR expression compared with those patients with neither moderate to marked mass effect nor perineural invasion (10.7 ± 0.7 vs 10.2 ± 0.4 , respectively; $P = .05$ by unpaired t test). Furthermore, 4 (50%) of 8 patients with moderate to marked mass effect had perineural invasion, but 4 (33%) of 12 patients with mild mass effect and none (0%) of 7 patients with no

mass effect had perineural invasion. This trend was not quite statistically significant ($P = .08$; Fisher exact test between marked-mass-effect group and no-mass-effect group). Also, enhancement tended to correlate with both the tumor and the submandibular gland as a regional control ($P = .00005$), possibly because of contrast bolus differences among patients.

DISCUSSION

We tested correlates of the CT imaging appearance with genomic expression in a group of patients with previously untreated OSCC. Initial results suggest that degree of enhancement and mass effect indicate particular genetic alterations, similar to associations in other tumor types and related to drug targets. Limitations to this study included the small population, small number of genes tested, the relatively long period during which patients underwent imaging with varying imaging techniques, and the general nature of the retrospective review. None of the image-to-gene associations survived correction for the multiple correlations and, therefore, must be viewed with some skepticism. However, the associations demonstrated by other tumor types (eg, enhancement and VEGF receptors 1 and 2) are more likely to be true according to Bayesian probability. These simple correlations between a single imaging measurement and single gene expression are reductions of the complex interactions between the host stroma and the tumor.

Despite these limitations, the correlations suggest that grouping imaging findings into imaging phenotypes may further correlate with specific driver genes. Increased EGFR has correlated previously with worse stage and prognosis with treatment resistance.^{18,19,26} The association between size with mass effect and invasion, which also correlated with EGFR expression, may help to elucidate the association with tumor grade. The grouping of clinical and imaging findings into representative phenotypes could not only help in understanding and predicting genomic expression but also reinforce imagers' search patterns and the risk for invasion, which may not be directly visualized on imaging.

Smaller tumors had increased expression of different genes (VEGF receptor 2) than larger tumors (EGFR, VEGF ligand A), suggesting that tumor size and growth pattern are governed by underlying genomic expression and not solely by the time until diagnosis (Fig 3). Thus, a large tumor with invasion could suggest

EGFR predominant expression, whereas a small tumor with avid enhancement could suggest increased VEGF receptor 2 expression (Fig 4). The differential expression of VEGF ligands and receptors with varying imaging features indicates that further work is needed to understand the reported association between high VEGF expression and increased recurrence rates with poor survival outcome, which did not clarify the subtypes of the receptor or ligand.²⁷

CONCLUSIONS

In summary, we demonstrated correlations between CT findings and OSCC

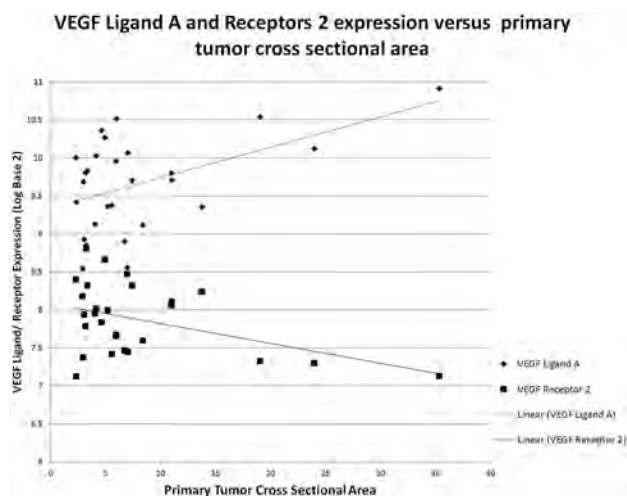


FIG 3. Scatterplot showing relationship of increasing primary tumor ellipsoid estimated cross-sectional area with increasing VEGF ligand A and decreased receptor 2 expression (in log base 2) with linear fitting.

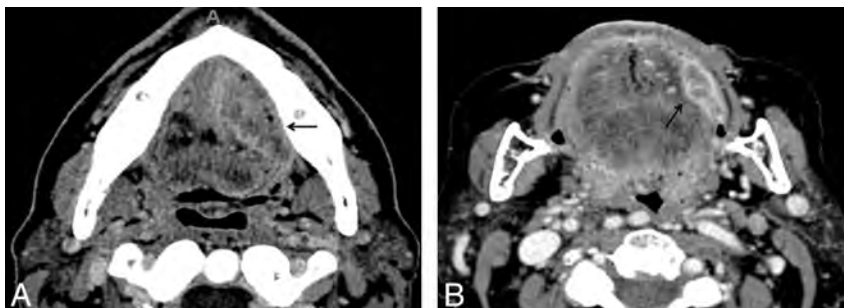


FIG 4. Example cases of highest expression for specific genes by use of contrast-enhanced axial CT images in different patients. A, Large OSCC located in the left tongue and at the floor of the mouth OSCC (arrow) with intrinsic tongue and perineural invasion (on histologic examination) and mass effect narrowing the airway. This tumor has the highest EGFR expression. B, Small left buccal tumor with avid enhancement with the highest VEGF receptor 1 and 2 expression.

gene expression. The size and invasion of the tumor (and therefore stage and prognosis) may relate to specific driver gene expression. Further studies are needed with a greater number of patients, additional imaging modalities, additional tumor sites, and other potentially relevant genes to determine if grouping imaging features related to gene expression into imaging phenotypes is useful in the management of head and neck squamous cell carcinoma.

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REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. **Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.** *Int J Cancer* 2010;127:2893–917
2. Jemal A, Siegel R, Xu J, et al. **Cancer statistics, 2010.** *CA Cancer J Clin* 2010;60:277–300
3. Leemans CR, Braakhuis BJ, Brakenhoff RH. **The molecular biology of head and neck cancer.** *Nat Rev Cancer* 2011;11:9–22
4. Argiris A, Karamouzis MV, Raben D, et al. **Head and neck cancer.** *Lancet* 2008;371:1695–709
5. Agrawal N, Frederick MJ, Pickering CR, et al. **Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1.** *Science* 2011;333:1154–57
6. Spector ME, Gallagher KK, Light E, et al. **Matted nodes: poor prognostic marker in oropharyngeal squamous cell carcinoma independent of HPV and EGFR status.** *Head Neck* 2012;34:1727–33
7. Makkat S, Luytbaert R, Stadnik T, et al. **Deconvolution-based dynamic contrast-enhanced MR imaging of breast tumors: correlation of tumor blood flow with human epidermal growth factor receptor 2 status and clinicopathologic findings—preliminary results.** *Radiology* 2008;249:471–82
8. Diehn M, Nardini C, Wang DS, et al. **Identification of noninvasive imaging surrogates for brain tumor gene-expression modules.** *Proc Natl Acad Sci U S A* 2008;105:5213–18
9. Furnari FB, Fenton T, Bachoo RM, et al. **Malignant astrocytic glioma: genetics, biology, and paths to treatment.** *Genes Dev* 2007;21:2683–710
10. Leo C, Giaccia AJ, Denko NC. **The hypoxic tumor microenvironment and gene expression.** *Semin Radiat Oncol* 2004;14:207–14
11. Maia AC, Jr., Malheiros SM, da Rocha AJ, et al. **MR cerebral blood volume maps correlated with vascular endothelial growth factor expression and tumor grade in nonenhancing gliomas.** *AJNR Am J Neuroradiol* 2005;26:777–83
12. Shimizu H, Kumabe T, Shirane R, et al. **Correlation between choline level measured by proton MR spectroscopy and Ki-67 labeling index in gliomas.** *AJNR Am J Neuroradiol* 2000;21:659–65
13. Emblem KE, Scheie D, Due-Tønnessen P, et al. **Histogram analysis of MR imaging-derived cerebral blood volume maps: combined glioma grading and identification of low-grade oligodendroglial subtypes.** *AJNR Am J Neuroradiol* 2008;29:1664–70
14. Jenkinson MD, du Plessis DG, Smith TS, et al. **Histological growth patterns and genotype in oligodendroglial tumours: correlation with MRI features.** *Brain* 2006;129:1884–91
15. Kanematsu M, Osada S, Amaoka N, et al. **Expression of vascular endothelial growth factor in hepatocellular carcinoma and the surrounding liver: correlation with angiographically assisted CT.** *AJR Am J Roentgenol* 2004;183:1585–93
16. Emblem KE, Bjørnerud A, Mouridsen K, et al. **T(1)- and T(2)(*)-dominant extravasation correction in DSC-MRI: part II—predicting patient outcome after a single dose of cediranib in recurrent glioblastoma patients.** *J Cereb Blood Flow Metab* 2011;31:2054–64
17. Zinn PO, Mahajan B, Sathyan P, et al. **Radiogenomic mapping of edema/cellular invasion MRI-phenotypes in glioblastoma multiforme.** *PLoS One* 2011;6:e25451
18. Rubin Grandis J, Melhem MF, Gooding WE, et al. **Levels of TGF- α and EGFR protein in head and neck squamous cell carcinoma and patient survival.** *J Natl Cancer Inst* 1998;90:824–32
19. Pectasides E, Rampias T, Kountourakis P, et al. **Comparative prognostic value of epidermal growth factor quantitative protein expression compared with FISH for head and neck squamous cell carcinoma.** *Clin Cancer Res* 2011;17:2947–54
20. Bauman JE, Michel LS, Chung CH. **New promising molecular targets in head and neck squamous cell carcinoma.** *Curr Opin Oncol* 2012;24:235–42
21. Choi BB, Kim SH, Kang BJ, et al. **Diffusion-weighted imaging and FDG PET/CT: predicting the prognoses with apparent diffusion coefficient values and maximum standardized uptake values in patients with invasive ductal carcinoma.** *World J Surg Oncol* 2012;10:126
22. Mahdey HM, Ramanathan A, Ismail SM, et al. **Cyclin D1 amplification in tongue and cheek squamous cell carcinoma.** *Asian Pac J Cancer Prev* 2011;12:2199–204
23. Feng Z, Guo W, Zhang C, et al. **CCND1 as a predictive biomarker of neoadjuvant chemotherapy in patients with locally advanced head and neck squamous cell carcinoma.** *PLoS One* 2011;6:e26399
24. van Diest PJ, Michalides RJ, Jannink L, et al. **Cyclin D1 expression in invasive breast cancer. Correlations and prognostic value.** *Am J Pathol* 1997;150:705–11
25. Stransky N, Egloff AM, Tward AD, et al. **The mutational landscape of head and neck squamous cell carcinoma.** *Science* 2011;333:1157–60
26. Chung CH, Zhang Q, Hammond EM, et al. **Integrating epidermal growth factor receptor assay with clinical parameters improves risk classification for relapse and survival in head-and-neck squamous cell carcinoma.** *Int J Radiat Oncol Biol Phys* 2011;81:331–38
27. Smith BD, Smith GL, Carter D, et al. **Prognostic significance of vascular endothelial growth factor protein levels in oral and oropharyngeal squamous cell carcinoma.** *J Clin Oncol* 2000;18:2046–52

Reduced Cerebral Arterial Spin-Labeled Perfusion in Children with Neurofibromatosis Type 1

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ABSTRACT

BACKGROUND AND PURPOSE: Neurofibromatosis type 1 is associated with increased risk for stroke, cerebral vasculopathy, and neurocognitive deficits, but underlying hemodynamic changes in asymptomatic children remain poorly understood. We hypothesized that children with neurofibromatosis type 1 have decreased cerebral blood flow.

MATERIALS AND METHODS: Arterial spin-labeled CBF was measured in 14 children with neurofibromatosis type 1 (median age, 9.7 years; mean, 10.2 years; range, 22 months to 18 years) and compared with age-matched control subjects on 3T MR imaging. Three-dimensional pseudocontinuous spin-echo arterial spin-labeled technique was used. Measurements were obtained at cortical gray matter of bilateral cerebral hemispheres and centrum semiovale by use of the ROI method. Comparison by Mann-Whitney test was used, with Bonferroni-adjusted P values $\leq .004$ judged as significant.

RESULTS: We identified 7 of 12 areas with significantly diminished arterial spin-labeled CBF in patients with neurofibromatosis type 1 compared with control subjects. These areas included the anterior cingulate gyrus ($P = .001$), medial frontal cortex ($P = .004$), centrum semiovale ($P = .004$), temporo-occipital cortex ($P = .002$), thalamus ($P = .001$), posterior cingulate gyrus ($P = .002$), and occipital cortex ($P = .001$). Among patients with neurofibromatosis type 1, there were no significant differences in these regions on the basis of the presence of neurofibromatosis type 1 spots or neurocognitive deficits.

CONCLUSIONS: Reduced cerebral perfusion was seen in children with neurofibromatosis type 1, particularly in the posterior circulation and the vascular borderzones of the middle and posterior cerebral arteries.

ABBREVIATIONS: ASL = arterial spin-labeled; NF-1 = neurofibromatosis type 1; UBO = unidentified bright object

Neurofibromatosis type 1 (NF-1) is a common autosomal dominant genetic disorder affecting 1 in 3500 live births¹ and frequently associated with café au lait spots, freckling, neurofibromas, optic pathway gliomas, Lisch nodules, and skeletal abnormalities.² Other significant complications include strokes and neurocognitive dysfunction.

Risk for stroke in NF-1 has been attributed to cerebral vasculopathy, including Moyamoya syndrome.^{3,4} Typical vessels af-

fected are, in order of occurrence, the renal, aortic, mesenteric, and cerebral arteries.⁵⁻⁷ There are few cerebrovascular data on the pediatric NF-1 population, but the largest series of 8 children reported vascular ectasia, stenosis, aneurysms, and Moyamoya changes on the basis of cerebral MR angiogram findings.³

Cognitive complications are relatively common in NF-1, ranging from 30–65%, and include developmental delay, learning disabilities, attention deficit disorder, and headaches.⁸⁻¹¹ Some authors have postulated that impaired cognition may arise from unidentified bright objects (UBOs),¹²⁻¹⁴ though no reliable link exists between the number of UBOs and cognitive performance.¹⁵⁻¹⁷ Others have suggested abnormal cortical connectivity^{9,10} and underlying cerebral dysgenesis¹⁸ as sources of poor cognitive performance, whereas the relationship between NF-1 arteriopathy and cognitive impairment remains unknown.

Given the lack of cerebral hemodynamic data in the setting of risks for cerebral vasculopathy and neurocognitive complications, we sought to understand cerebral perfusion patterns in children with NF-1. Because abnormal perfusion is expected in

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patients with strokes or Moyamoya syndrome, we specifically targeted patients with NF-1 without these features. Although various MR perfusion techniques exist, we applied arterial spin-labeled (ASL) perfusion, given the unique advantages of this technique in children, including labeling efficiency, high signal-to-noise ratio, lack of contrast requirement, and its ability to directly quantify CBF.^{19,20} We hypothesized that children with NF-1 have decreased CBF as compared with normal control subjects.

MATERIALS AND METHODS

Subjects

All patients presenting with history of NF-1 at our children's hospital between April 2010 and April 2012 were retrospectively reviewed after approval was given by the institutional review board (IRB protocol 4223; No. 4947). The study cohort was identified on the basis of the following inclusion criteria: the patient obtained ASL perfusion at 3T as part of routine surveillance MR imaging for NF-1. Patients presenting with acute neurologic symptoms, known underlying vasculopathy (aneurysms, arteriovenous malformations, fistulas, or steno-occlusive disease, including Moyamoya changes), prior strokes or stroke-like symptoms, radiation, or chemotherapy were excluded from the study. Patients with a history of seizures, hydrocephalus or shunt placement, underlying cardiac diseases, or abnormal blood pressures, including hypertension from underlying NF-1-related renal artery stenosis, were also excluded, given their potential effects on CBF. Chart review of these patients was also performed to document the presence of neurocognitive deficits. Patients were considered to have neurocognitive deficits if chart review indicated developmental delay, learning disability, or attention deficit disorder or if they required special education, for example, an individualized education plan on the basis of clinical history and academic performance. Documentation was considered complete if the chart review specifically mentioned that no such deficits were present.

Control Subjects

Age-matched control subjects who had obtained ASL perfusion at 3T as part of routine brain MR imaging were recruited from our data base. The control group consisted of patients with no underlying neurologic disease and normal brain MR imaging. Examples of clinical reasons for imaging in the control group included isolated headaches, dizziness, family history of aneurysms, cholesteatoma of the middle ear, isolated facial lesions (eg, hemangioma), or ophthalmologic work-up (strabismus) without correlative orbital/brain pathology or neurologic symptoms. Children with other neurocutaneous syndromes, psychiatric diseases, migraines, and any chronic diseases, including seizures, cancer, as well as previously treated neurologic diseases, and prior or ongoing medical therapy were excluded from the control group.

Imaging Methods

All patients were examined with brain MR imaging at 3T (Discovery 750; GE Healthcare, Milwaukee, Wisconsin), by use of an 8-channel head coil. The technique used to perform perfusion ASL MR imaging has been described in detail elsewhere.²¹ Briefly, our vendor-supplied ASL was performed by use of a pseudocontinuous labeling period of 1500 ms, followed by a 1500-ms post-label delay. Whole-brain images were acquired with a 3D back-

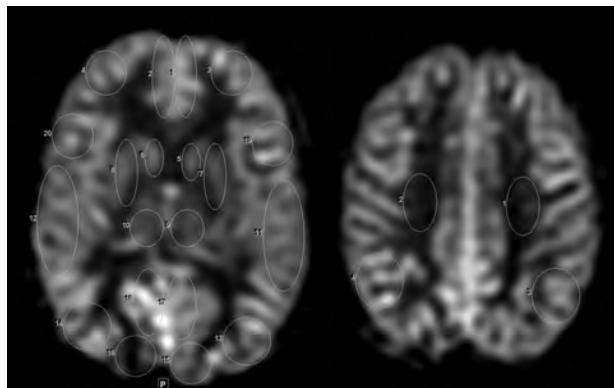


FIG 1. Brain ROI placement. ROI placement is shown in the cortical regions of the bilateral cerebral hemispheres, the deep gray nuclei, and in the centrum semiovale at 2 axial levels: at the level of the thalamus and centrum semiovale.

ground-suppressed FSE stack-of-spirals method, with a TR of approximately 5 seconds. Multi-arm spiral imaging was used, with 8 arms and 512 points acquired on each arm (bandwidth, 62.5 kHz), yielding in-plane and through-plane spatial resolution of 3 and 4 mm, respectively. A high level of background suppression was achieved by the use of 4 separate inversion pulses spaced around the pseudocontinuous labeling pulse. The sequence required 5 minutes to acquire, which included proton attenuation images required for CBF quantification. For graphic prescription of the ASL, the sagittal image following the 3-plane localizer was used for alignment. Postprocessing was performed by use of an automated reconstruction script that returned CBF images directly to the scanner console within 1 minute, by use of the microsphere methodology described by Buxton et al.²² Other ASL MR imaging parameters were TR/TE, 4632/10.5; FOV, 24 × 24 cm; matrix, 512 × 8; and NEX of 3. Conventional MR imaging was also performed, including T1 FLAIR, T2 FSE, FLAIR, T1 spoiled gradient-recalled, DWI/DTI, gradient-recalled, and 3-plane T1 spoiled gradient-recalled and T1 spin-echo gadolinium-enhanced sequences.

Imaging Analysis

Quantitative cerebral cortical CBF was measured at 2 axial sections at the level of the thalamus and the centrum semiovale. Fourteen cortical ROIs and 4 ROIs of the deep gray nuclei were obtained at the level of the thalamus; an additional 4 ROIs were obtained at the level of the centrum semiovale, as shown in Fig 1. These regions included anterior and posterior cingulate gyri, medial frontal lobe, frontal operculum, anterior caudate nucleus, globus pallidus, thalamus, superomedial temporal cortex, temporo-occipital cortex, occipital cortex, centrum semiovale, and parietal cortex. The ROI sizes ranged from 100–800 mm², depending on the size of the structure interrogated. A board-certified neuroradiologist (K.W.Y.) with added Certificate of Added Qualification (7 years of experience) selected ROIs, blinded to clinical information and at the same anatomic levels in all patients. A second blinded board-certified neuroradiologist (P.D.B.) with a Certificate of Added Qualification (>30 years of experience) independently confirmed appropriate anatomic placement of the ROI. To test for significant differences in CBF

Table 1: Patient characteristics and clinical data (n = 14)

Age of diagnosis, y	
Median	9.7
Range	1.8–18
Sex	
Male	7 (50%)
Female	7 (50%)
MRI findings	
NF-1 spots	14 (100%)
Optic nerve/chiasm thickening	7 (50%)
Plexiform neurofibroma	6 (43%)
Clinical findings	
Headaches	6 (43%)
Cognitive or speech delay	5 (36%)
ADHD	2 (14%)

Note:—ADHD indicates attention deficit/hyperactivity disorder.

between the patients and control subjects, comparison by Mann-Whitney test was used, with Bonferroni-adjusted P value $\leq .004$ judged as significant. To test for difference in cerebral perfusion in the brain regions between the sedated and nonsedated groups, as well as between boys and girls, independent samples of the Mann-Whitney test were used, with Bonferroni-corrected $\alpha = 0.004$ (for 12 comparisons).

RESULTS

Clinical Findings

Fourteen children met clinical criteria for NF-1 (median age, 9.7 years; mean, 10.2 years; range, 22 months to 18 years) and were included in the study. There were 7 boys and 7 girls. Patient demographics and clinical data are shown in Table 1.

Four patients were completely asymptomatic except for cutaneous manifestations of NF-1 (eg, café au lait spots, axillary freckling, Lisch nodules, and plexiform neurofibromata) without gross neurocognitive, neuro-ophthalmologic, or behavioral disorders.

Six patients reported chronic or occasional headaches. Five children had cognitive, speech, or intellectual difficulties requiring special education or various forms of neurocognitive therapy. Two children had attention deficit disorder and difficulty focusing at school but were not receiving medical therapy at the time of the study.

Six patients had optic nerve or chiasm thickening (4 showed no enhancement; 2 showed mild enhancement) that was conservatively managed at the time of the study. In 1 patient, T2-high-intensity abnormality was present in left optic tract and portion of the optic radiation without associated abnormal enhancement or signal extending into the posterior regions of the optic radiation or the occipital lobe. Of the 6 patients with thickening or enhancement of the optic apparatus, 4 had no visual acuity or field deficits, 2 required corrective lenses for decreased visual acuity (20/30 and 20/20; 20/400 and 20/30), and 1 patient (22 months old) demonstrated gross asymmetry in visual acuity (by assessing the child's reaction to covering one of the eyes) but without a field cut. All 6 patients with optic nerve or chiasm thickening were deemed stable by ophthalmologic examination and required no therapy at the time of this study.

All patients demonstrated multiple NF-1 spots on their surveillance T2-weighted MR imaging scans predominantly in the basal ganglia, thalami, brain stem, and cerebellum. In the 4 older children (ages 13–18 years), these NF-1 spots were relatively faint in appearance. Except for characteristic NF-1 spots and optic

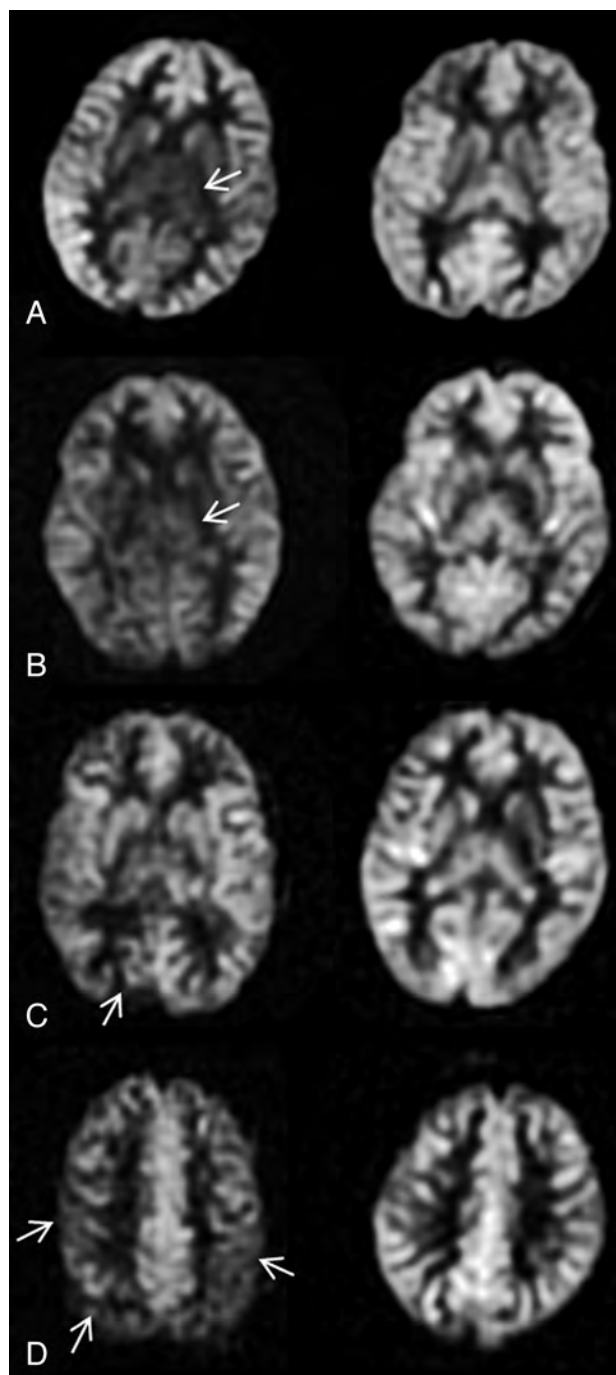


FIG 2. Various patterns of reduced cerebral perfusion in patients with NF-1 are shown compared with age-matched control subjects. Note marked hypoperfusion of bilateral thalami (arrows) in a 7-year-old girl (A) and a 13-year-old boy (B) with NF-1 in the setting of global and patchy hypoperfusion. More focal reduced perfusion is seen in the right occipital cortex (arrow) superimposed on heterogeneous hypoperfusion in a 10-year-old boy with NF-1 (C). More superiorly, there are additional patchy areas of hypoperfusion in this child (D) with asymmetric low ASL signal in bilateral frontoparietal regions (arrows).

nerve/chiasm thickening, no other abnormality, including mass, abnormal brain enhancement, or dysgenesis/dysplasia, was present on conventional MR imaging.

Cerebral Blood Flow

Reduced CBF was seen in children with NF-1 compared with control subjects (Fig 2). The most significant difference in perfu-

Table 2: Comparison of CBF in patients with NF-1 and control subjects by anatomic location and vascular territories

Structure	Control CBF, mL/100 mg per minute (n = 14)	NF-1 CBF, mL/100 mg per minute (n = 14)	Mann-Whitney P Value
ACA territory			
Anterior cingulate gyrus	71 ± 7	61 ± 8	^a .001
Medial frontal cortex	65 ± 7	56 ± 9	^a .004
Anterior caudate nucleus	57 ± 9	51 ± 4	.013
ACA-MCA borderzone			
Centrum semiovale	28 ± 5	22 ± 4	^a .004
MCA territory			
Frontal operculum	68 ± 8	60 ± 8	.013
Globus pallidus	50 ± 6	44 ± 6	.012
MCA-PCA borderzone			
Parietal cortex	65 ± 9	55 ± 9	.008
Superomedial temporal cortex	67 ± 9	60 ± 8	.012
Temporo-occipital cortex	64 ± 10	51 ± 8	^a .002
Anterior choroidal-PcomA-PCA			
Thalamus	55 ± 10	44 ± 8	^a .001
PCA territory			
Posterior cingulate gyrus	70 ± 13	57 ± 8	^a .002
Occipital cortex	61 ± 13	45 ± 10	^a .001

Note:—ACA indicates anterior cerebral artery; PCA, posterior cerebral artery; PcomA, posterior communicating artery.

^a Significant at $\leq .004$.

sion was seen in the anterior cingulate gyrus ($P = .001$), medial frontal lobe ($P = .004$), centrum semiovale ($P = .004$), temporo-occipital lobe ($P = .002$), thalamus ($P = .001$), posterior cingulate gyrus ($P = .002$), and the occipital lobe ($P = .001$). The quantitative results of the CBF values by specific brain regions and vascular territories are summarized in Table 2.

No NF-1 spots were present within the ROIs of the cortical regions and the centrum semiovale; varying degrees of NF-1 spots were present within the ROIs of the deep gray nuclei. There were no significant differences in these regions on the basis of the presence or number of NF-1 spots, optic pathway glioma, or neurocognitive deficits (On-line Table).

Of 28 children (14 NF-1 and 14 control subjects), 12 received sedation and 16 did not require sedation. The mean ages of those patients were 7.1 ± 3.0 years and 13.4 ± 4.4 years, respectively (independent samples Mann-Whitney U test $P < .001$). There was no difference in cerebral perfusion at any location between these groups (independent-samples Mann-Whitney U test; Bonferroni-corrected $\alpha = 0.004$ for 12 comparisons). There were 17 boys and 11 girls in our cohort; no difference in cerebral perfusion at any location between these 2 groups was seen (independent-samples Mann-Whitney U test; Bonferroni-corrected $\alpha = 0.004$ for 12 comparisons).

DISCUSSION

These results demonstrate significantly lower CBF in patients with NF-1 compared with control subjects, occurring most prominently in the posterior circulation and the borderzones of the middle and posterior cerebral arteries. To our knowledge, this is the first study to report perfusion abnormalities in children with NF-1 in the absence of prior strokes or underlying Moyamoya syndrome. There are 2 potential mechanisms to account for this: 1) vasculopathy and associated steno-occlusive changes in the cerebral microvasculature and 2) alteration in cerebral metabolic demand.

Children with NF-1 are known to harbor cerebral vasculopathy.³ Vascular proliferative and dysplastic changes such as con-

centric intimal thickening, spindle cell proliferation, and disruption of the internal elastic have also been observed in brain specimens of patients with NF-1.²³ Reduced expression of neurofibromin, the NF-1 gene product important for maintenance of the endothelial layer, may disrupt vascular wall integrity⁷ and result in intimal thickening and arterial stenosis through the Ras signaling system and smooth muscle proliferation.²⁴

The reasons for more dominant perfusion deficits in the posterior and border zones remain unclear. Vasoconstriction or hypoperfusion superimposed on vaso-autoregulatory dysfunction at these sites²⁵⁻²⁷ may contribute to this pattern, similar to posterior reversible encephalopathy syndrome.²⁸ It is also possible that there are variations of neurofibromin expression within the different regions of the cerebral vasculature,

though this remains unknown.

Alternatively, decreased CBF could reflect underlying reduced cerebral metabolic requirement in children with NF-1. A potential biomarker of regional brain function, CBF is tightly coupled to brain metabolism^{29,30} and may thereby provide information similar to FDG-PET, which is sensitive in detecting disease-related functional changes.³¹ Similar results derived from FDG-PET metabolism, ¹⁵O-PET perfusion, and ASL perfusion in healthy adults and those with neurodegenerative conditions³²⁻³⁴ suggest that neuronal glucose metabolism could be inferred from CBF techniques.

Prior FDG-PET studies in NF-1³⁵⁻³⁷ have shown abnormal cerebral metabolism similar in distribution to the perfusion pattern noted in this study, for example, global hypometabolism with a more marked hypometabolism in the posterior brain regions. For example, in 4 adolescents with NF-1 (9–20 years of age), global hypometabolism with a more marked reduction of FDG activity in the thalamus and the occipital lobes was noted with intact metabolism in the striatum.³⁵ Another study of 10 children with NF-1 (4–15 years of age) observed heterogeneously decreased cortical FDG uptake. Although regional cerebral metabolic differences were not quantitatively analyzed in that study, profound hypometabolism in the thalamus was observed.³⁶ A study of 20 adults with NF-1 also showed reduced FDG-PET metabolism in the thalamus, and to a lesser degree, in the cerebellum. In these studies, the extent of abnormal cerebral metabolism did not correlate with the presence or number of UBOs,^{35,37} degree of cognitive impairment,³⁵ or differences in age or sex,³⁷ similar to the present study.

Although a primary defect of the thalamus or cerebral cortex has not been defined, investigators have postulated that dysfunction in the cortical-thalamic relationship is a potential source of neurocognitive complications in NF-1.^{17,36,37} Marked reduction in CBF in the thalamus and variable alterations in cortical perfusion in our study also implicate these brain regions, potentially

reflecting underlying dysgenesis or a dysfunction in their relationship, or underlying arteriopathy as a source of cognitive deficits, not unlike the adult model for vascular dementia.³⁸

In the present study, we used ASL perfusion to measure CBF because it directly quantifies CBF by use of in-flowing arterial protons as an endogenous tracer^{39,40} and has additional advantages in children because of the high labeling efficiency and signal-to-noise ratio.¹⁹ Direct comparisons of ASL with ¹⁵O-PET have also shown that MR imaging and PET methods for measuring CBF are highly comparable⁴¹ and reproducible across variable time intervals,^{42,43} and therefore ASL is a reliable perfusion method that could also be clinically implemented by use of standard MR imaging equipment and without the need for ionizing radiation or contrast.

Limitations of this study included small sample size and a tertiary care center referral pattern that may attract a more severely affected NF-1 population. Therefore, our results may overestimate cerebral perfusion differences in typical patients with NF-1. Although we did not observe worse perfusion in those reported to have cognitive dysfunction, our analysis was based on the need for special education or cognitive therapy and lacked standardized psychiatric tests. As such, subtle deficits could have been overlooked, and, in the very young, cognitive changes may be difficult to identify or have yet to emerge. Of note, none of our patients underwent cervical or intracranial MRA/CTA because they were not suspected of strokes or vascular anomalies, and it is possible that occult cervical vascular anomalies could have affected cerebral perfusion. Given other causes for cerebral perfusion abnormality, such as seizures, migraines, medications, and changes in cardiac output and blood pressure status, we excluded patients with any acute symptoms at the time of imaging or chronic conditions that might alter cerebral perfusion, and therefore these factors probably did not affect the study.

CONCLUSIONS

Reduced cerebral perfusion was seen in children with NF-1, most significantly in the posterior circulation and borderzones of the middle and posterior cerebral arteries. Future studies may demonstrate an important role for ASL perfusion in the presymptomatic diagnosis of NF-1-related cerebral vasculopathy and the definition of NF-1-related vasculopathy patterns and in providing a link between cerebral perfusion and cognitive performance in NF-1.

REFERENCES

- Friedman JM. **Epidemiology of neurofibromatosis type 1.** *Am J Med Genet* 1999;89:1–6
- Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference.** *Arch Neurol* 1998;45:575–78
- Rosser TL, Vezina G, Packer RJ. **Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1.** *Neurology* 2005;64:553–55
- Sobata E, Ohkuma H, Suzuki S. **Cerebrovascular disorders associated with von Recklinghausen's neurofibromatosis: a case report.** *Neurosurgery* 1998;22:544–49
- Hamilton SJ, Friedman JM. **Insights into the pathogenesis of neurofibromatosis 1 vasculopathy.** *Clin Genet* 2000;58:341–44
- Friedman JM, Arbiser J, Epstein JA, et al. **Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force.** *Genet Med* 2002;4:105–11
- Norton KK, Xu J, Gutmann DH. **Expression of the neurofibromatosis 1 gene product, neurofibromin, in blood vessel endothelial cells and smooth muscle.** *Neurobiol Dis* 1995;2:13–21
- North K, Hyman S, Barton B. **Cognitive deficits in neurofibromatosis 1.** *J Child Neurol* 2002;17:650–12
- North KN, Riccardi V, SamangoSprouse C, et al. **Cognitive function and academic performance in neurofibromatosis 1: consensus statement from the NF1 Cognitive Disorder Task Force.** *Neurology* 1997;48:1121–27
- North K. **Neurofibromatosis type 1.** *Am J Med Genet* 2000;97:119–27
- Hyman SL, Shores A, North KN. **The nature and frequency of cognitive deficits in children with neurofibromatosis type 1.** *Neurology* 2005;65:1037–44
- North K, Joy P, Yuille D, et al. **Specific learning disability in children with neurofibromatosis type 1: significance of MRI abnormalities.** *Neurology* 1994;44:878–83
- Mott SH, Skyrja PA, Baumgardner TL, et al. **Neurofibromatosis type 1: association between volumes of T2-weighted signals on MRI in young children with neurofibromatosis type 1 correlating with cognitive scores, abstract.** *Pediatr Neurol* 1994;11:88
- Feldmann R, Schuierer G, Wessel A, et al. **Development of MRI T2 hyperintensities and cognitive functioning in patients with neurofibromatosis type 1.** *Acta Paediatr* 2010;99:1657–60
- Duffner PK, Cohen ME, Seidel FG, et al. **The significance of MRI abnormalities in children with neurofibromatosis.** *Neurology* 1989;39:373–78
- Ferner RE, Chaudhuri R, Bingham J, et al. **MRI in neurofibromatosis 1: the nature and evolution of increased intensity T2 weighted lesions and their relationship to intellectual impairment.** *J Neurol Neurosurg Psychiatry* 1993;56:492–95
- Moore BD, Slopis JM, Schomer D, et al. **Neuropsychological significance of areas of high signal intensity on brain magnetic resonance imaging scans of children with neurofibromatosis.** *Neurology* 1996;46:1660–68
- Rosman NP, Pearce J. **The brain in multiple neurofibromatosis (von Recklinghausen disease): a suggested neuropathological basis for the associated mental defect.** *Brain* 1967;90:829–38
- Wang J, Licht DJ, Jahng GH, et al. **Pediatric perfusion imaging using pulsed arterial spin labeling.** *J Magn Reson Imaging* 2003;18:404–13
- Pollock JM, Tan H, Kraft RA, et al. **Arterial spin-labeled MR perfusion imaging: clinical applications.** *Magn Reson Imaging Clin North Am* 2009;17:315–38
- Dai W, Garcia D, Bazelaire C, et al. **Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields.** *Magn Reson Med* 2008;60:1488–97
- Buxton RB, Frank LR, Wong EC, et al. **A general kinetic model for quantitative perfusion imaging with arterial spin labeling.** *Magn Reson Med* 1998;40:383–96
- Kwong KL, Wong YC. **Moyamoya disease in a child with neurofibromatosis type-1.** *J Paediatr Child Health* 1999;35:108–09
- Tan RM, Chang SM, Seow WT, et al. **'Moya' than meets the eye: neurofibromatosis type 1 associated with Moyamoya syndrome.** *Singapore Med J* 2008;49:107–09
- Beausang-Linder M, Bill A. **Cerebral circulation in acute arterial hypertension-protective effects of sympathetic nervous activity.** *Acta Physiol Scand* 1981;111:193–99
- Zwienenberg-Lee M, Muizelaar JP. **Clinical pathophysiology of traumatic brain injury.** In: Winn HR, ed. *Youman's Neurological Surgery*. 5th ed. Philadelphia: Saunders; 2004:5039–64
- Langfitt TW, Obrist WD. **Occlusive cerebrovascular disease.** In: Wilkins RH, Rengachary SS, ed. *Neurosurgery*. New York: McGraw-Hill; 1985:1167–73
- Bartynski WS. **Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema.** *AJNR Am J Neuroradiol* 2009;29:1043–49
- Raichle ME. **Behind the scenes of functional brain imaging: a his-**

- torical and physiological perspective.** *Proc Natl Acad Sci U S A* 1998;95:765–72
30. Juepnert M, Wieller C. **Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI.** *Neuroimage* 1995;2:148–56
 31. Landau SM, Harvey D, Madison CM, et al. **Comparing predictors of conversion and decline in mild cognitive impairment.** *Neurology* 2010;75:230–38
 32. Baron JC, Lebrun-Grandie P, Collard P, et al. **Noninvasive measurement of blood flow, oxygen consumption, and glucose utilization in the same brain regions in man by positron emission tomography.** *J Nucl Med* 1982;23:391–99
 33. Chen Y, Wolk DA, Reddin JS, et al. **Voxel-level comparison of arterial spin-labeled perfusion MRI and FDG-PET in Alzheimer disease.** *Neurology* 2011;77:1977–85
 34. Hu WT, Wang Z, Lee VM, et al. **Distinct cerebral perfusion patterns in FTLN and AD.** *Neurology* 2010;75:881–88
 35. Balestri P, Lucignani G, Fois A, et al. **Cerebral glucose metabolism in neurofibromatosis 1 assessed with F-2-fluororo-2-deoxy-D-glucose and PET.** *J Neurol Neurosurg Psychiatry* 1994;57:1479–83
 36. Kaplan AM, Chen K, Lawson MA, et al. **Positron emission tomography in children with neurofibromatosis 1.** *J Child Neurol* 1997;12:499–506
 37. Buchert R, von Borczyskowski D, Wilke F, et al. **Reduced thalamic 18-fluorodeoxyglucose retention in adults with neurofibromatosis type 1.** *Nucl Med Commun* 2008;29:17–26
 38. Baker JG, Williams AJ, Ionita CC, et al. **Cerebral small vessel disease: cognition, mood, daily functioning, and imaging findings from a small pilot sample.** *Dement Geriatr Cogn Dis Extra* 2012;2:169–79
 39. Alsop DC, Detre JA. **Multisection cerebral blood flow MR imaging with continuous arterial spin labeling.** *Radiology* 1998;208:410–16
 40. Yang Y, Frank JA, Hou L, et al. **Multislice imaging of quantitative cerebral perfusion with pulsed arterial spin labeling.** *Magn Reson Med* 1998;39:825–32
 41. Xu G, Rowley HA, Wu G, et al. **Reliability and precision of pseudo-continuous arterial spin labeling perfusion MRI on 3T and comparison with 15O-water PET in elderly subjects at risk for Alzheimer's disease.** *NMR Biomed* 2010;23:286–93
 42. Floyd TF, Ratcliffe SJ, Wang J, et al. **Precision of the CASL-perfusion MRI technique: global and regional cerebral blood flow within vascular territories at one hour and one week.** *J Magn Reson Imaging* 2003;18:649–55
 43. Chen Y, Wang DJ, Detre JA. **Test-retest reliability of arterial spin labeling with common labeling strategies.** *J Magn Reson Imaging* 2011;33:940–49

Cerebral Diffusion Tensor MR Tractography in Tuberous Sclerosis Complex: Correlation with Neurologic Severity and Tract-Based Spatial Statistical Analysis

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ABSTRACT

BACKGROUND AND PURPOSE: The neurologic significance of residual cerebral white matter tracts, identified on diffusion tensor tractography, has not been well studied in tuberous sclerosis complex. We aimed to correlate the quantity of reconstructed white matter tracts with the degree of neurologic impairment of subjects with the use of DTI and determined differences in white matter integrity between patients with tuberous sclerosis complex and controls with the use of voxelwise analysis.

MATERIALS AND METHODS: In this case-control study, 16 patients with tuberous sclerosis complex and 12 control subjects underwent DTI. Major white matter tracts, comprising bilateral PF and CF, were reconstructed and assessed for quantity, represented by NOP and NOF. A neurologic severity score, based on the presence of developmental disability, seizure, autism, and other neuropsychiatric disorders, was calculated for each subject. We then correlated this score with white matter quantity. Voxelwise tract-based spatial statistics was used to determine differences in FA, axial, and radial diffusivity values between the tuberous sclerosis complex group and the control subjects.

RESULTS: NOP and NOF of CF, bilateral PF, and MWT in the tuberous sclerosis complex group were all significantly lower than those in the control subjects ($P < .05$). The neurologic severity score was moderately negatively correlated with NOF and NOP regarding CF ($r = -.70$; $r = -.75$), bilateral PF ($r = -.66$; $r = -.68$), and MWT ($r = -.71$; $r = -.74$). Tract-based spatial statistics revealed that patients with tuberous sclerosis complex showed a widespread reduction ($P < .05$) in FA and axial diffusivity in most cerebral white matter regions.

CONCLUSIONS: Patients with tuberous sclerosis complex with reduced residual white matter were neurologically more severely affected. Tract-based spatial statistics revealed decreased FA and axial diffusivity of the cerebral white matter in the tuberous sclerosis complex group, suggesting reduced axonal integrity.

ABBREVIATIONS: CF = commissural fibers; MWT = major white matter tracts; NOF = number of fibers; NOP = number of tract points; PF = projection fibers

Tuberous sclerosis complex is one of the most commonly identified neurocutaneous disorders and is estimated to affect 1 in 6000 to 10,000 births.¹ Patients with tuberous sclerosis complex typically have seizures, developmental disability, autism, and

other neuropsychiatric signs.² On neuroradiologic examination, tuberous sclerosis complex shows cortical tubers, transmantle white matter lesions, subependymal nodules, and/or tumors.³ Many researchers have studied the relationship between brain MR features and seizures, developmental disability, or autism in patients with tuberous sclerosis complex.⁴⁻⁷ A recent study correlated neurologic outcome with cortical tuber burden and transmantle white matter lesions, resulting in a proposed composite clinical scoring system assessing major neurologic features of tuberous sclerosis complex.⁵

DTI has been used to quantify the 3D distribution of water diffusion in tissue^{8,9} and evaluate the microstructural change of the brain white matter. Diffusion tensor tractography, based on tract orientation information obtained from DTI, is a non-invasive method by which we can create a 3D representation of the white matter tracts^{10,11} to qualitatively and quantitatively assess the tracts.

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In tuberous sclerosis complex, several DTI studies have described decreased FA and increased mean diffusivity in white matter lesions^{12,13} and normal-appearing white matter.¹⁴ Investigators have also studied the relationship between the diffusion characteristics of the white matter and the neurologic severity of patients with tuberous sclerosis complex but found no significant association.¹⁵

Previous quantitative DWI and DTI studies of tuberous sclerosis complex largely involved manually counting and measuring individual brain lesions including cortical tubers, transmantle white matter lesions, and subependymal nodules.^{12,13,16} Because larger tuber volume was correlated with more severe DTI change of white matter tracts,¹⁶ studying the white matter therefore may be a reasonable way to assess the load of brain abnormality in tuberous sclerosis complex. However, in many studies measuring diffusion or DTI parameters of specific regions or white matter tracts, technical errors may arise when drawing ROIs to determine the boundaries of specific structures or white matter tracts. Also, in studies that use ROIs, generally only lesions visible on conventional MR imaging are assessed. Furthermore, the neurologic significance of specific white matter tracts in patients with tuberous sclerosis complex is unknown. Assessing whole-brain white matter by means of voxelwise analysis and correlating the quantity of residual major white matter tracts with neurologic severity of patients may be more clinically feasible and relevant approaches in evaluating patients with tuberous sclerosis complex.

Tract-based spatial statistics, a recently developed voxelwise statistical analytical method for DTI data, is an automatic and operator-independent method with a specific registration algorithm.¹⁷ It needs no data smoothing, which minimizes misregistration. Tract-based spatial statistics has been used to identify microstructural white matter abnormalities in many diseases.^{18–21} Because of its ability to analyze the whole brain, tract-based spatial statistics may be valuable for assessing diseases with diffuse brain lesions, such as tuberous sclerosis complex.

With the use of diffusion tensor tractography to reconstruct brain white matter tracts, we aimed to correlate the quantity of reconstructed white matter tracts with the degree of neurologic impairment of subjects. We also aimed to determine any differences in white matter integrity between patients with tuberous sclerosis complex and control subjects by means of voxelwise analysis. We hypothesized that children with tuberous sclerosis complex have fewer reconstructed major white matter tracts than do control subjects and that this would negatively correlate with neurologic severity. Second, we hypothesized that there is a difference in DTI metrics between the 2 groups.

MATERIALS AND METHODS

Subjects

During a 2-year-period, we prospectively recruited 32 subjects for DTI and diffusion tensor tractography, including 20 consecutive subjects with a clinical diagnosis of tuberous sclerosis complex. The study groups, after the exclusion of 4 patients (ages 0–3 years), consisted of 16 patients (7 male and 9 female; ages 5–29 years; mean $\pm$ SD age, 13 ± 6.48 years) and 12 control subjects (7 male and 5 female; ages 4–34 years; mean $\pm$ SD age, 15.33 ± 8.26 years) with a normal conventional MR imaging. Patients did not

differ from control subjects on age distribution (t test, $P > .4$). Our institutional review board approved the study, and informed consent was obtained from the subjects. Diagnosis of tuberous sclerosis complex was made by an experienced pediatric neurologist (H.-S.W.), and all patients met established revised diagnostic criteria for tuberous sclerosis complex.²² Subjects were excluded if they were <4 years of age or had <2 years of follow-up history and incomplete clinical information. Individuals eligible for selection as control subjects were prospectively recruited during the reading sessions of a particular neuroradiologist (A.M.W.). All control subjects had unremarkable conventional MR imaging findings and no developmental abnormality, neuropsychiatric disorders, or motor deficits. The indications for clinical MR imaging of the control subjects included headaches, vertigo, suspected sellar mass, suspected intracranial vascular lesions, or suspected arachnoid cyst.

Neurologic Severity Assessment

A pediatric neurologist (H.-S.W.), a clinical professor with 30 years of experience in pediatric neurology, who was blinded to MR findings, assessed the neurologic severity of the patients at the time of diffusion tensor tractography by clinical examination and reviewing medical records, if necessary. A severity score was devised to quantify the severity of each subject.^{5,23} According to criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*, the components of neurologic severity assessed included: developmental disability, seizures (controlled or intractable), autism, and other neuropsychiatric disorders (including self-injury, violent behavior, learning disorder, language difficulties, and anger outbursts). Developmental disability was assigned 3 points. Intractable seizure and autism were assigned 2 points each. The “other neuropsychiatric disorders” component, regardless of how many disorders a patient had, and controlled seizure, were assigned 1 point each. Intractable seizure was defined as failure of seizure control after using ≥ 2 first-line antiepileptic medications, 1 seizure per month for 18 months, or freedom from seizures for fewer than 3 consecutive months. The neurologic severity score of each subject was calculated by totaling the points of the components.

MR Imaging

MR imaging was performed with a 1.5T unit (Intera; Philips Medical Systems, Best, The Netherlands) with a slew rate of 150 T/m/s. Conventional MR imaging included coronal T2-weighted FSE and FLAIR sequences, axial T1-weighted spin-echo and FLAIR sequences, and a sagittal T2-weighted FSE sequence. DTI was performed with a 6-channel sensitivity encoding head coil operating in the receive mode by use of a single-shot EPI sequence, with TR = 5188 ms, TE = 78 ms, b-values = 0, 1000 seconds/mm², acquisition matrix = 128×128 , number of sections = 55, section thickness = 3 mm, and number of gradient directions = 16. The gradient strength was 19.5 mT/m for b = 1000 seconds/mm² with diffusion times Δ of 43.8 ms and δ of 26 ms. The DTI sequence was repeated 4 times with 1 signal acquired and with a total image acquisition time of 7 minutes.

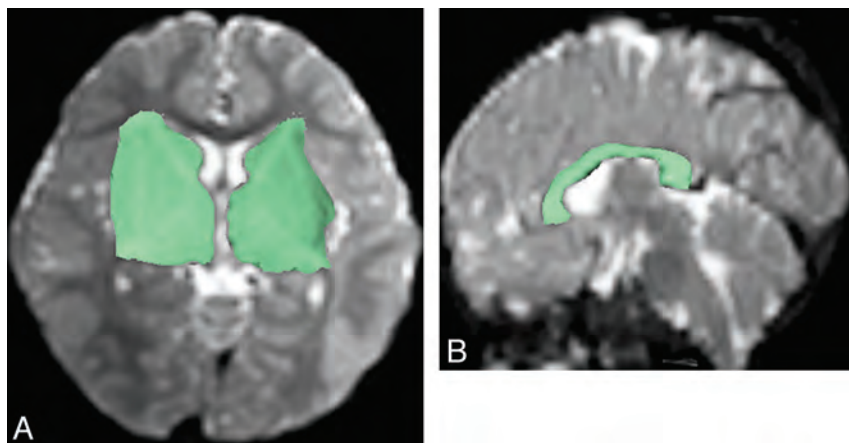


FIG 1. Regions of interest (green shaded areas) were manually drawn on axial B0 image (A) to include the ipsilateral caudate head, internal capsule, lentiform nucleus, external capsule, and thalamus for reconstructing the PF on one side, and on sagittal B0 image (B) to include the corpus callosum for reconstructing the CF.

ROI Tractography Analysis

DTI data were transferred to an off-line computer equipped with an automated image registration software (Diffusion Registration Tool, release 0.4; Phillips Medical Systems, and IDL; ITT, Boulder, Colorado) to correct for eddy current and motion-related misalignment. Diffusion-weighted images, ADC, and FA maps were generated by use of Philips Research Imaging Development Environment software provided by the manufacturer. FA was calculated from the eigenvalues that were obtained by diagonalizing diffusion tensors at each voxel.^{8,24} Fiber tracking was performed with the use of the software, which used a line propagation technique with the assumption of the principal eigenvector indicating the orientation of axons in each voxel. Tracking was started from a seed ROI from which a line was propagated in both forward and backward directions from voxel to voxel, according to the principal eigenvector at each voxel.¹⁰ Tracking was terminated when it reached a pixel with low fractional anisotropy ($FA < 0.25$) and/or a predetermined trajectory curvature between 2 consecutive vectors (turning angle $> 30^\circ$). A lower turning angle was used in tracking termination to decrease false-positive fiber tracts and computational load.²⁵ To reconstruct PF on 1 side, 1 investigator (A.M.W.), who is a neuroradiologist having 1 year of fellowship training in pediatric neuroradiology, 9 years of experience in practicing pediatric neuroradiology, and 5 years of experience in DTI, manually drew an ROI on an axial $b = 0$ section to include the ipsilateral head of the caudate nucleus, internal capsule, lentiform nucleus, external capsule, and thalamus (Fig 1A) and another ROI over the brain stem. CF within the corpus callosum were generated by placing a 2D ROI to include the corpus callosum, which was identified on the sagittal section nearest to the midline (Fig 1B). As a result, the major white matter tracts of each subject were reconstructed in 3 sessions: 2 yielding the PF and 1 yielding the CF. Quantitative results of the generated fibers, including the right and left PF, CF, and the summation of these tracts (MWT), were automatically obtained by the software,²⁶ initiated by right-clicking with the mouse on the fibers. The results include the FA, NOP, and

NOF. NOP was an arbitrary unit proportional to the volume of the generated tracts in a single reconstruction, and NOF was the number of tracts generated in that reconstruction.

Tract-Based Spatial Statistics Analysis

Voxelwise statistical analysis of the DTI data was performed by using tract-based spatial statistics¹⁷ implemented in the Functional MR Imaging of the Brain Software Library toolbox (Version 4.1.6, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation>).²⁷ The raw DTI data were corrected for motion and eddy current effects. FA images were then created by fitting a tensor model to the data by using the Diffusion Toolbox, and automatic brain extraction was performed by using the

Brain Extraction Tool.²⁸ For spatial normalization, all subjects' FA data were then aligned into a common space by using the Nonlinear Registration Tool. Among the 3 options for nonlinear registration (by use of predefined target image, automatically chosen target, and most representative target), we chose the "most representative" option for the registration such that every FA image was aligned to every other one to identify the most representative image as the target image.¹⁷ This option was recommended for generating a study-specific target, particularly in a study containing mostly children. The target image was then affine-aligned into Montreal Neurological Institute 152 space, and every image was transformed into $1 \times 1 \times 1$ mm Montreal Neurological Institute 152 space by combining the nonlinear transform to the target FA image with the affine transform from the target native space to Montreal Neurological Institute 152 space. The mean FA image of all subjects was created and thinned to create the mean FA skeleton, which represented the centers of all tracts common to all subjects. This skeleton was thresholded at $FA > 0.2$. The aligned FA data of each subject were then projected onto this skeleton for voxelwise cross-subject statistics. Tract-based spatial statistics analysis was also applied to maps of axial diffusivity and radial diffusivity.

Statistical Analysis

Independent t tests were used to compare each of the results of fiber tracking (FA, NOP, and NOF) of the PF (left PF, right PF, bilateral PF) and CF between the patient group and the control group. Results of the MWT, calculated by summation of results of the bilateral PF and CF regarding NOP and NOF, and by weighted averaging of results of these tracts regarding FA, were also compared between the patient group and the control group. Pearson correlation tests were used to calculate the strength of association between the neurologic severity score and the results of fiber tracking in all subjects. Voxelwise comparisons of FA, axial diffusivity, and radial diffusivity between groups were performed with the recommended Randomize Tool in the Functional MR Imaging of the Brain Software Library toolbox by use of nonparametric t tests. The data were analyzed by use of permutation-based infer-

Table 1: Composition of neurologic severity score of patients with TSC

Patient No.	Developmental		Neuropsychiatric		Neurologic Severity Score
	Seizure	Disability	Autism	Disorders	
1	1	3	0	1	5
2	0	0	0	0	0
3	1	3	2	0	6
4	2	3	2	1	8
5	1	3	0	1	5
6	1	3	0	1	5
7	1	0	0	0	1
8	1	0	0	1	2
9	1	3	2	1	7
10	1	0	0	0	1
11	1	0	0	1	2
12	2	3	0	1	6
13	1	0	0	0	1
14	1	3	2	1	7
15	1	3	0	0	4
16	1	0	0	1	2

Note:—TSC indicates tuberous sclerosis complex.

ence (5000 permutations) and threshold-free cluster enhancement. The results were corrected for multiple comparisons by controlling the family-wise error rate. A result with $P < .05$ was considered statistically significant.

RESULTS

Of the 16 subjects, 13 had controlled seizures, 2 had intractable seizures, 9 had developmental disability, and 4 had autism (Table 1). Ten subjects had neuropsychiatric disorders including self-injury, violent behavior, learning disorder, language difficulties, or anger outbursts.

ROI Tractography

NOP and NOF of CF, left PF, right PF, bilateral PF, and MWT in the tuberous sclerosis complex group were all significantly smaller than those in the control group ($P < .05$) (Table 2). No significant difference in FA between the tuberous sclerosis complex group and the control group was found in CF, left PF, right PF, bilateral PF, and MWT ($P > .05$). The neurologic severity score was moderately negatively correlated with NOF and NOP regarding CF, left PF, right PF, bilateral PF, and MWT (Fig 2) (Table 3).

Tract-Based Spatial Statistics Analysis

Axial diffusivity of the tuberous sclerosis complex group was lower than that of the control group in all cerebral white matter regions including the corpus callosum, the internal capsules, the external capsules, bilateral frontal, parietal, temporal, and occipital white matter regions ($P < .05$). FA was lower in the tuberous sclerosis complex group in all cerebral white matter regions ($P < .05$) except the bilateral occipital regions, right temporal and parietal regions, and the corpus callosum (Fig 3). We did not

find areas in which FA was lower in the control group. No statistically significant difference in radial diffusivity between the tuberous sclerosis complex and the control groups was found.

DISCUSSION

Our results showed that the NOP and NOF of MWT in the tuberous sclerosis complex group were significantly smaller than those of the control subjects. NOP was proportional to the volume of the generated tracts; NOF was concerned with the number but not the length of the tracts. The lack of statistical difference of FA of MWT between the tuberous sclerosis complex group (95% CI, 0.463–0.478) and the control sub-

jects (95% CI, 0.463–0.483) suggested that the reconstructed white matter tracts in the tuberous sclerosis complex subjects were predominantly normal white matter tracts. Our results therefore implied that patients with tuberous sclerosis complex, when compared with control subjects, had a reduced quantity of residual normal white matter tracts and a widespread decrease in cerebral white matter integrity. Pathologically, atypical cells including balloon cells, giant neurons, and areas of hypomyelination are present in the white matter of patients with tuberous sclerosis complex.²⁹ The presence of these abnormal cells within the WM region, probably a result of faulty neuronal migration and differentiation, may be associated with decreased WM integrity. Decreased FA and increased diffusivity have been reported in both white matter lesions^{12,13} and normal-appearing white matter¹⁴ in patients with tuberous sclerosis complex. Our results also showed a moderate negative correlation between the neurologic severity score and both NOP and NOF in the CF and PF, suggesting that patients with decreased quantity of residual white matter tracts in these regions were neurologically more severely affected. Through the use of diffusion tensor tractography, several studies have revealed reduction of white matter tracts in developmental delay³⁰ and autism³¹ as well as decreased FA in specific white matter networks in temporal lobe epilepsy³²; these neurologic features were major components of the neurologic severity score in our study. We therefore demonstrated a possibility of correlating the neurologic status of patients with tuberous sclerosis complex with the quantity of residual major white matter tracts (CF and bilateral PF) by use of a relatively time-saving region of an interest-based tractography method, instead of assessing individual tuberous sclerosis complex lesions.

Table 2: Mean ($\pm$ SD) NOF, NOP, and FA of the commissural fiber, projection fibers, and major white matter tracts of patients with TSC and control subjects

	NOF			NOP			FA		
	TSC	Control	P	TSC	Control	P	TSC	Control	P
CF	77.1 $\pm$ 27.4	100 $\pm$ 13.7	.01	2440 $\pm$ 1190	3280 $\pm$ 494	.02	.504 $\pm$.026	.522 $\pm$.016	.05
Left PF	169 $\pm$ 32.2	247 $\pm$ 61.3	.01	4200 $\pm$ 1270	6360 $\pm$ 1430	.01	.458 $\pm$.011	.460 $\pm$.022	.05
Right PF	146 $\pm$ 25.7	198 $\pm$ 32.7	.01	3290 $\pm$ 976	4510 $\pm$ 961	.01	.458 $\pm$.016	.453 $\pm$.019	.05
Bilateral PF	315 $\pm$ 53.3	445 $\pm$ 73.0	.01	7490 $\pm$ 2130	10870 $\pm$ 1870	.01	.459 $\pm$.012	.458 $\pm$.020	.05
MWT	391 $\pm$ 76.7	545 $\pm$.770	.01	9900 $\pm$ 3110	14150 $\pm$ 2210	.01	.470 $\pm$.014	.473 $\pm$.017	.05

Note:—TSC indicates tuberous sclerosis complex.

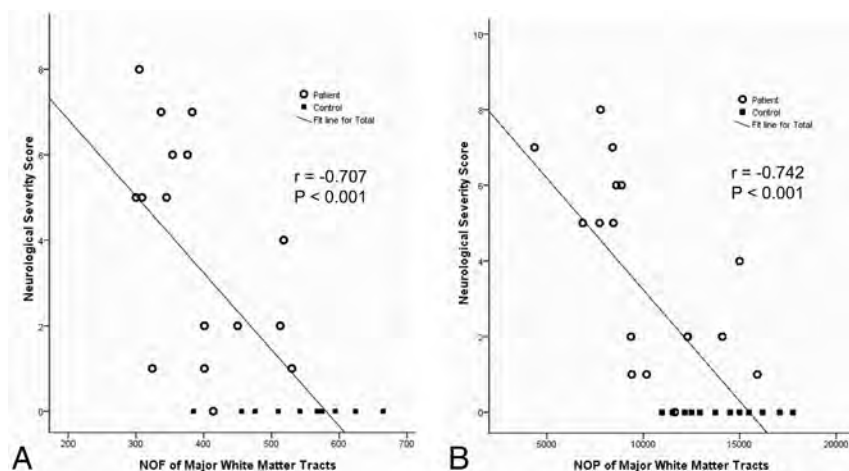


FIG 2. Scatterplots show moderate negative correlation between the neurologic severity score and NOF (A) and NOP (B) in the patients with tuberous sclerosis complex and control subjects.

Similar results of reduction of NOF and NOP were obtained in patients with tuberous sclerosis complex. If the patients and the control subjects had a similar number of fibers but the patients had shorter fibers, the patients would have NOF similar to that in the control subjects but smaller NOP. Furthermore, if the patients had fewer but longer fibers, they would have a lower NOF but probably an NOP similar to that in control subjects. Therefore, the decrease in both NOF and NOP in the tuberous sclerosis complex group suggested that the patients might have fewer fibers with shorter or similar length.

Voxelwise tract-based spatial statistics analysis revealed decreased FA and decreased axial diffusivity in the tuberous sclerosis complex group. A decrease in FA may be attributed to disorganized axons and hypomyelination.^{33,34} Previous DTI studies of tuberous sclerosis complex also revealed a reduction of FA in the white matter lesions^{12,13} and normal-appearing white matter.¹⁴ The lower axial diffusivity in the tuberous sclerosis complex group suggested poor integrity of axons.^{35,36} Moreover, because FA is known to positively correlate with axial diffusivity,³⁷ our result of a decrease in both FA and axial diffusivity was reasonable. We did not find a statistical difference of radial diffusivity between the tuberous sclerosis complex group and the control subjects. Although increased radial diffusivity was reported in a recent tractography study,³⁵ this finding was only found in the callosal splenium but not in most of the white matter regions in that study. Considering the findings reported by Krishnan et al³⁵ and our findings, change in radial diffusivity may not be a predominant

feature of the measured DTI metrics or the change was too small to cause a statistically significant difference.

We did not specifically reconstruct the association fibers because a portion of the association fibers was reconstructed in each of the trackings of the PF and the CF. Thus, the volume of the remaining association fibers was relatively insignificant when compared with the white matter of the entire brain. Moreover, multiple ROIs would have been used to select the diffusely distributed association fibers, and this probably would result in technical errors that would reduce the accuracy and reproducibility of the study. Like other studies of diffusion tensor tractography, our study used a method to reconstruct fibers

dependent on directional consistency computation, which has been a limitation common to current fiber-tracking methods.³⁸ However, we chose to study the CF and the PF that were less likely to have highly curved turns susceptible to this computation limitation. The range of age of our patients was wide (4–30 years). Myelination is active in early childhood and may affect the quantity of generated tracts computed by diffusion tensor tractography. However, in our study, subjects younger than 4 years of age, in whom myelination would be still active, were excluded. Moreover, we recruited control subjects who did not significantly differ from the patients with tuberous sclerosis complex on age distribution. Because the relative significance of each feature was unknown, it would have been ideal to correlate the DTI and tractography results with individual neurologic features rather than by use of a composite score; however, this would lead to fewer samples in each group with a single feature.

Early behavioral intervention may be beneficial to children with tuberous sclerosis complex,³⁹ particularly during the period of brain plasticity. Newer therapeutic agents, such as rapamycin, have been reported to prevent epilepsy and to reverse mental retardation and learning problems in mouse models of tuberous sclerosis complex.^{40,41} Subgroup analysis of a recent phase I/II trial of everolimus, a mammalian target of rapamycin inhibitor, demonstrated increased FA and decreased radial diffusivity in the normal-appearing white matter of the treated subjects.⁴² Objectively assessing the cerebral white matter quantity and comparing diffusion tensor metrics between patient groups, diffusion tensor tractography may be a clinically practical neuroimaging technique to evaluate treatment efficacy.

Table 3: Pearson correlation coefficients between the neurologic severity score versus NOF and NOP in the commissural fiber, projection fibers, and major white matter tracts

	NOF	NOP
CF	$r = -.70; P < .001$	$r = -.75; P < .001$
Left PF	$r = -.55; P < .001$	$r = -.60; P < .001$
Right PF	$r = -.66; P < .001$	$r = -.67; P < .001$
Bilateral PF	$r = -.66; P < .001$	$r = -.68; P < .001$
MWT	$r = -.71; P < .001$	$r = -.74; P < .001$

CONCLUSIONS

Patients with tuberous sclerosis complex with reduced residual cerebral white matter were neurologically more severely affected. Voxelwise tract-based spatial statistics analysis revealed decreased FA and decreased axial diffusivity of the cerebral white matter in the tuberous sclerosis complex group, suggesting reduced axonal integrity. Diffusion tensor tractography may be a clinically appli-

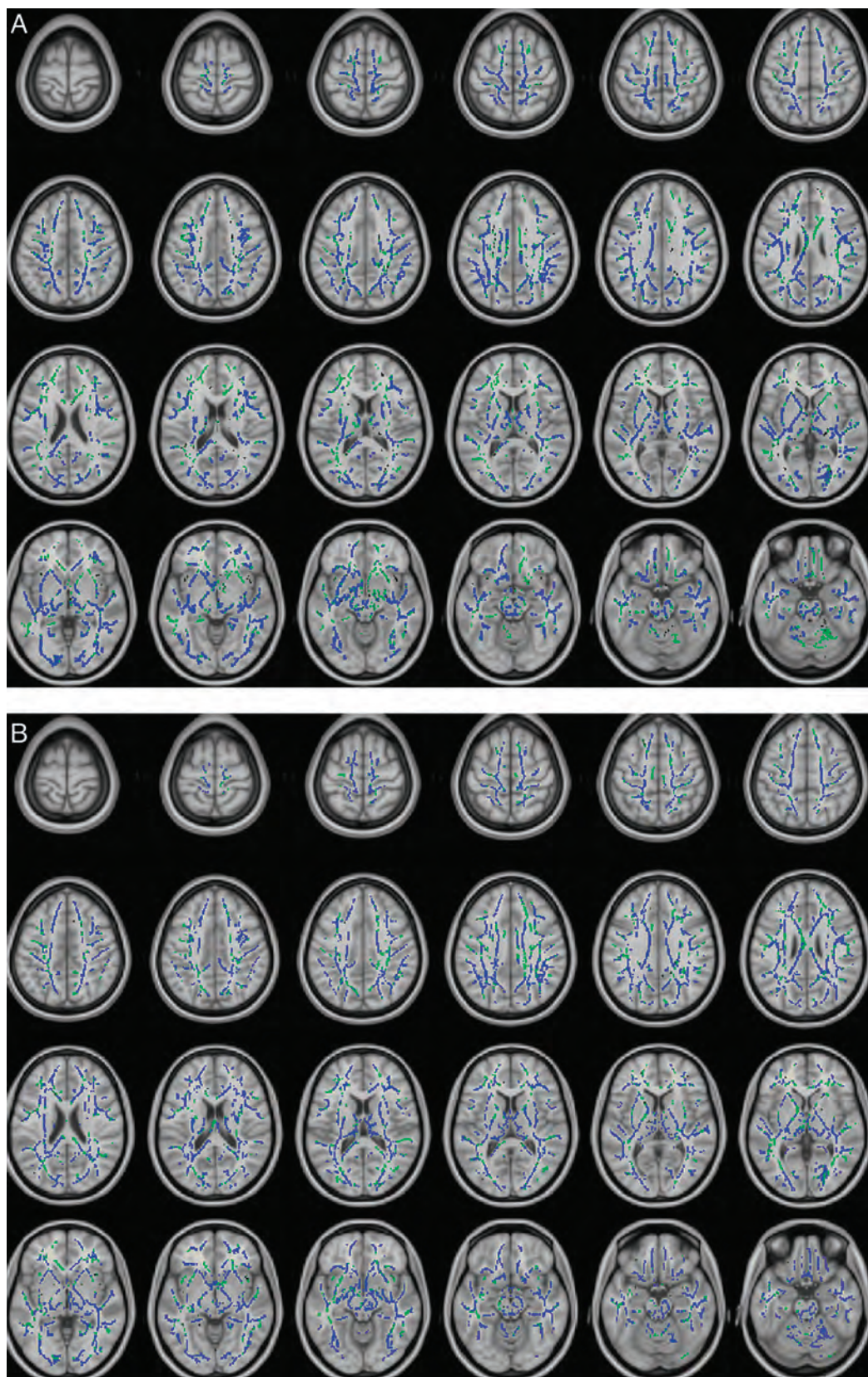


FIG 3. Results of tract-based spatial statistics analysis revealed significant differences between the tuberous sclerosis complex and control groups in FA (A) and axial diffusivity (B) maps, with overlaid mean value skeleton. Regions of the skeleton in *green* represent areas of no significant differences in values between the tuberous sclerosis complex group and the control subjects. Regions in *blue* are areas in which the value was significantly lower in the tuberous sclerosis complex group.

cable neuroimaging approach to assess the tuberous sclerosis complex brain abnormalities in a global way.

Disclosures: Alex Wong—RELATED: Grant: National Science Council (Taiwan).

REFERENCES

- Webb DW, Osborne JP. Tuberous sclerosis. *Arch Dis Child* 1995;72:471–74
- Curatolo P, Verdecchia M, Bombardieri R. Tuberous sclerosis complex: a review of neurological aspects. *Eur J Paediatr Neurol* 2002;6:15–23
- Braffman BH, Bilaniuk LT, Naidich TP, et al. MR imaging of tuberous sclerosis: pathogenesis of this phakomatosis, use of gadopentetate dimeglumine, and literature review. *Radiology* 1992;183:227–38
- Bolton PF, Griffiths PD. Association of tuberous sclerosis of temporal lobes with autism and atypical autism. *Lancet* 1997;349:392–95
- Chou IJ, Lin KL, Wong AM, et al. Neuroimaging correlation with neurological severity in tuberous sclerosis complex. *Eur J Paediatr Neurol* 2008;12:108–12
- Shepherd CW, Houser OW, Gomez MR. MR findings in tuberous sclerosis complex and correlation with seizure development and mental impairment. *AJNR Am J Neuroradiol* 1995;16:149–55
- Takanashi J, Sugita K, Fujii K, et al. MR evaluation of tuberous sclerosis: increased sensitivity with fluid-attenuated inversion recovery and relation to severity of seizures and mental retardation. *AJNR Am J Neuroradiol* 1995;16:1923–28
- Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B* 1996;111:209–19
- Basser PJ, Pierpaoli C. A simplified method to measure the diffusion tensor from seven MR images. *Magn Reson Med* 1998;39:928–34
- Mori S, Crain BJ, Chacko VP, et al. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol* 1999;45:265–69
- Mori S, van Zijl PC. Fiber tracking: principles and strategies: a technical review. *NMR Biomed* 2002;15:468–80
- Karadag D, Mentzel HJ, Gullmar D, et al. Diffusion tensor imaging in children and adolescents with tuberous sclerosis. *Pediatr Radiol* 2005;35:980–83
- Piao C, Yu A, Li K, et al. Cerebral diffusion tensor imaging in tuberous sclerosis. *Eur J Radiol* 2009;71:249–52
- Makki MI, Chugani DC, Janisse J, et al. Characteristics of abnormal diffusivity in normal-appearing white matter investigated with diffusion tensor MR imaging in tuberous sclerosis complex. *AJNR Am J Neuroradiol* 2007;28:1662–67
- Arulrajah S, Ertan G, Jordan L, et al. Magnetic resonance imaging and diffusion-weighted imaging of normal-appearing white matter in children and young adults with tuberous sclerosis complex. *Neuroradiology* 2009;51:781–86
- Simao G, Raybaud C, Chuang S, et al. Diffusion tensor imaging of commissural and projection white matter in tuberous sclerosis complex and correlation with tuber load. *AJNR Am J Neuroradiol* 2010;31:1273–77
- Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 2006;31:1487–505
- Anjari M, Srinivasan L, Allsop JM, et al. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. *Neuroimage* 2007;35:1021–27
- Hattori T, Ito K, Aoki S, et al. White matter alteration in idiopathic normal pressure hydrocephalus: tract-based spatial statistics study. *AJNR Am J Neuroradiol* 2012;33:97–103
- Lee H, Cohen OS, Rosenmann H, et al. Cerebral white matter disruption in Creutzfeldt-Jakob disease. *AJNR Am J Neuroradiol* 2012;33:1945–50
- Sun B, Brown RC, Hayes L, et al. White matter damage in asymptomatic patients with sickle cell anemia: screening with diffusion tensor imaging. *AJNR Am J Neuroradiol* 2012;33:2043–49
- Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol* 1998;13:624–28
- Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med* 2006;355:1345–56
- Jellison BJ, Field AS, Medow J, et al. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. *AJNR Am J Neuroradiol* 2004;25:356–69
- Mukherjee P, Chung SW, Berman JL, et al. Diffusion tensor MR imaging and fiber tractography: technical considerations. *AJNR Am J Neuroradiol* 2008;29:843–52
- Khalil C, Hancart C, Le Thuc V, et al. Diffusion tensor imaging and tractography of the median nerve in carpal tunnel syndrome: preliminary results. *Eur Radiol* 2008;18:2283–91
- Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004;23(Suppl 1):S208–19
- Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002;17:143–55
- DeRecondo J, Hagenau M. Neuropathologic survey of the phakomatoses and allied disorders. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology: The Phakomatoses*. Amsterdam: North Holland; 1972:19–71
- Sundaram SK, Sivaswamy L, Makki MI, et al. Absence of arcuate fasciculus in children with global developmental delay of unknown etiology: a diffusion tensor imaging study. *J Pediatr* 2008;152:250–55
- Pardini M, Garaci FG, Bonzano L, et al. White matter reduced streamline coherence in young men with autism and mental retardation. *Eur J Neurol* 2009;16:1185–90
- Ahmadi ME, Hagler DJ Jr, McDonald CR, et al. Side matters: diffusion tensor imaging tractography in left and right temporal lobe epilepsy. *AJNR Am J Neuroradiol* 2009;30:1740–47
- Beaulieu C, Allen PS. Water diffusion in the giant axon of the squid: implications for diffusion-weighted MRI of the nervous system. *Magn Reson Med* 1994;32:579–83
- Gulani V, Webb AG, Duncan ID, et al. Apparent diffusion tensor measurements in myelin-deficient rat spinal cords. *Magn Reson Med* 2001;45:191–95
- Krishnan ML, Commowick O, Jeste SS, et al. Diffusion features of white matter in tuberous sclerosis with tractography. *Pediatr Neurol* 2010;42:101–06
- Simao GN, Zarei Mahmoodabadi S, Snead OC, et al. Abnormal axial diffusivity in the deep gray nuclei and dorsal brain stem in infantile spasm treated with vigabatrin. *AJNR Am J Neuroradiol* 2011;32:199–203
- Le Bihan D, Mangin JF, Poupon C, et al. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging* 2001;13:534–46
- Chung HW, Chou MC, Chen CY. Principles and limitations of computational algorithms in clinical diffusion tensor MR tractography. *AJNR Am J Neuroradiol* 2011;32:3–13
- Dawson G, Rogers S, Munson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics* 2010;125:e17–23
- Ehninger D, Han S, Shilyansky C, et al. Reversal of learning deficits in a Tsc2+/- mouse model of tuberous sclerosis. *Nat Med* 2008;14:843–48
- Zeng LH, Xu L, Gutmann DH, et al. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. *Ann Neurol* 2008;63:444–53
- Tillema JM, Leach JL, Krueger DA, et al. Everolimus alters white matter diffusion in tuberous sclerosis complex. *Neurology* 2012;78:526–31

Retrospective Review of Rapid Pediatric Brain MR Imaging at an Academic Institution Including Practice Trends and Factors Affecting Scan Times

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ABSTRACT

BACKGROUND AND PURPOSE: In an effort to reduce radiation exposure in children requiring regular follow up for shunted hydrocephalus, our institution implemented a rapid brain MR imaging protocol. The purpose of this study was to review an academic practice experience with pediatric rapid brain MR imaging without patient sedation in the evaluation of hydrocephalus and a limited group of other conditions.

MATERIALS AND METHODS: We retrospectively analyzed limited-sequence, rapid brain MR imaging scans performed in nonsedated patients younger than 14 years between April 2009 and December 2011. So-called failed examinations were determined by consensus of 2 authors as insufficiently diagnostic for evaluation of ventricular size. CT and MR imaging quarterly volumes for hydrocephalus-related indications were determined from 2005–2012. Multivariable logistic regression analysis was performed to elucidate factors potentially affecting scan durations including examination indication and patient age, sex, inpatient status, and clinical conditions.

RESULTS: A total of 398 examinations were performed on 168 patients (103 boys, 65 girls; median age, 13 months). None were deemed to be failed examinations. Median scan duration was 4.43 minutes (interquartile range, 4.42 minutes–5.88 minutes; SD, 2.42 minutes). Examination indication of altered mental status was the only factor associated with increased scan duration (+1.77 minutes; $P = .0021$). Hydrocephalus-related imaging volumes approximately doubled in the 7 years reviewed, but rapid MR imaging introduced in 2009 is quickly replacing CT scanning for these indications, accounting for nearly 7 of every 8 examinations at the end of the study period.

CONCLUSIONS: In every case of initial work-up and follow-up, rapid brain MR imaging effectively evaluated ventricular size and/or intracranial fluid and represents a viable alternative to CT scanning, irrespective of a child's age or clinical condition. For this indication and patient group, MR imaging is now the predominant imaging method in our practice.

ABBREVIATIONS: EMR = electronic medical record; HASTE = half-Fourier acquisition single-shot turbo spin-echo; true FISP = true fast imaging with steady-state precession

CT scanning has historically been the preferred imaging technique for the initial evaluation and follow-up of hydrocephalus and intracranial cysts within the pediatric population at many institutions. Compared with traditional MR imaging methods, pediatric head CT imaging offers much faster acquisition times, comparable anatomic resolution, and lower patient cost.

Furthermore, the prolonged scan time of traditional MR imaging methods often demands use of general anesthesia in pediatric patients because of poor compliance and image motion artifacts. Such measures significantly increase cost and result in risk from anesthetic administration^{1–3} and result in substantial delays within the imaging suite. However, ongoing parental and physician concern for the potential long-term effects of ionizing radiation,^{4–6} particularly to young patients who require subsequent imaging studies, have resulted in increased interest in alternatives to CT scanning. The Alliance for Radiation Safety in Pediatric Imaging, a collaboration of 13 leading medical societies, has led the way in promoting appropriate low-dose and limited use of radiation in pediatric imaging through its Image Gently campaign,⁷ with an emphasis of the Society for Pediatric Radiology As Low as Reasonably Achievable (ALARA) principles.⁸

Recent developments in MR pulse sequences now allow for rapid evaluation of ventricular size in the pediatric population

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without the need for sedation.⁹⁻¹⁴ Although various techniques have been used, heavily T2-weighted single-shot fast spin-echo and gradient recalled-echo imaging are the 2 most common pulse sequence methods used to interrogate ventricular size and shunt catheter tip location, respectively.¹⁵ Starting in April 2009, our institution introduced a similar T2-weighted HASTE rapid-sequence MR imaging protocol.

A significant factor affecting resolution of anatomic detail in MR imaging is patient motion, which is directly related to the time required to complete each sequence. Thus, shorter sequences are desirable and beneficial. Heavily T2-weighted sequences, which typically require less than 30 seconds of imaging for each anatomic plane, provide excellent imaging with high intrinsic contrast between intracranial fluid and brain tissue and maintain short scan durations for the nonsedated child. Standard spin-echo sequences can require up to several minutes to complete, which is an unacceptably long time for a nonsedated and potentially uncooperative infant or child. Our institution, along with most radiology practices, is continually striving to minimize scan durations, not only for the purpose of patient comfort but also for efficient patient throughput. Understanding patient factors that increase scan durations could potentially guide informed consent discussions before examinations, as well as triage potential so-called failed examinations that may require sedation or general anesthesia for diagnostic MR imaging. The purpose of this study was to review an academic practice experience with pediatric rapid brain MR imaging without the need for patient sedation in the evaluation of hydrocephalus and a limited group of other conditions.

MATERIALS AND METHODS

Study Design and Data Extraction

Design and implementation of this single-center retrospective study met institutional review board and Health Insurance Portability and Accountability Act guidelines. Informed consent was waived. All data for this study were extracted from the institutional EMR. Selected imaging and clinical notes within the EMR were searched to identify clinical indications and comorbidities pertinent to this study. Scanner time and total imaging time were extracted from the proprietary institutional radiology image-viewing platform. The total number of pediatric imaging examinations, sorted by month, was extracted from the radiology information management system.

For each patient record identified, the following data were extracted from the EMR: date of scan, scan type and duration, magnet strength of the scanner, primary diagnoses, imaging indications, whether a ventricular shunt was in place, patient location (inpatient, outpatient, or emergency department), and demographic data including date of birth and sex. The number and type of each scan sequence, including repeated scans and plane of imaging, were also recorded. Total scan duration was determined from differences in image time stamps between the first scout image and the last sequences obtained.

Departmental imaging volumes for hydrocephalus, including the number of rapid MR imaging and pediatric head CT scans performed per month, were collected. The number of noncontrast CT examinations during the 3-year period leading up to the

introduction of the rapid MR imaging protocol was determined by searching the radiology data base for all pediatric head CT examinations with indications of “hydrocephalus,” “shunt,” “cyst,” “macrocephaly,” “ventricles,” “ventricular,” “aqueductal stenosis,” and “vp” and was compared with rapid MR imaging examinations performed for the same indications.

Imaging Protocol

Our rapid MR imaging technique used for evaluation of ventricular size in pediatric patients was HASTE, a T2-weighted MR imaging technique (matrix size, 256 × 179; field of view, 22 cm; TR, 2000 ms; TE, 105 ms; section thickness, 4 mm; imaging time to cover the entire brain, approximately 30 seconds per plane, typically in both axial and coronal planes). This technique was implemented at our institution beginning in April 2009. Additional imaging sequences were added ad hoc as appropriate per the interpreting radiologist’s discretion to avoid repeated or return examinations. In this patient population, additional sequences most commonly consisted of sagittal views or multiplanar T2 balanced gradient true FISP sequences (matrix size, 256 × 192; field of view, 29 cm; TR, 3.3 ms; TE, 1.3 ms; flip angle, 70 degrees; section thickness, 4 mm).

Patient Population

Inclusion criteria were patients younger than 14 years with suspected or confirmed hydrocephalus or intracranial cysts who underwent a rapid MR imaging scan between April 1, 2009, and December 31, 2011. Patients were excluded if the limited MR imaging study was not performed according to defined rapid-sequence protocol parameters. In addition, imaging studies that included 3 or more pulse-sequence types or administration of intravenous contrast were excluded because they did not meet the strict definitions of a rapid MR imaging protocol.

Definition of Failure

Rapid MR imaging failure was defined as an examination unable to answer the clinical question (most commonly, ventricular size assessment) because of inadequate resolution or enough patient motion artifacts requiring further imaging with same-day or next-day subsequent rapid MR imaging, CT imaging, or MR imaging with the patient under sedation. To determine whether a scan was considered a failure, we searched radiology reports for key words or phrases such as *inadequate* and *nondiagnostic* or whether recommendation was made to pursue additional imaging with CT scanning, repeated MR imaging, or MR imaging with the patient under sedation. In addition, we reviewed radiology reports for all head CT and MR imaging examinations performed within 2 weeks subsequent to the identified rapid MR imaging examination, along with the accompanying clinical notes to further gain an understanding of whether multiple examinations in a short period were the result of rapid MR imaging failure. Cases of potential failure were analyzed by a consensus of 2 radiologists (B.D.N. and L.J.E.) after full clinical and radiologic record review. Cases requiring additional imaging to further evaluate findings other than the ventricle size or shunt position on the limited MR imaging, such as mass, encephalocele, etc, were not considered failures of rapid MR imaging.

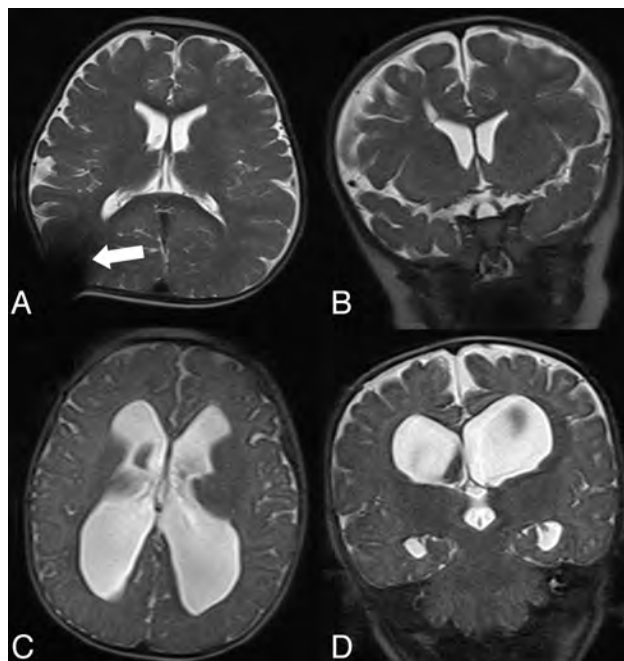


FIG 1. Axial (A) and coronal (B) HASTE sequence MR imaging of the brain in a 4-year-old child with shunted hydrocephalus demonstrating excellent delineation of the ventricles and mild shunt reservoir artifacts (white arrow) with few motion artifacts despite lack of sedation. Similar axial (C) and coronal (D) HASTE MR imaging of the brain in a 6-month-old child performed for follow-up of known hydrocephalus demonstrating adequate ventricular delineation despite significant patient motion.

Statistical Methods

We performed all statistical analyses by using JMP version 9 (SAS Institute, Cary, North Carolina). Categorical data were displayed as relative frequencies (percentages) and were compared by use of χ^2 tests. Continuous data were presented as median scores with interquartile ranges because of non-normal data distributions, and were compared by use of the Wilcoxon signed-rank test of significance. Linear regression models were generated to determine the effect of imaging indication, demographic variables (age, sex), and comorbidities on total scan and examination room times. We estimated trends in imaging volumes with time by using regression analysis.

RESULTS

Demographic and Clinical Characteristics

A total of 404 rapid MR imaging examinations were performed in 168 patients during the designated time. Six examinations were excluded for ad hoc addition of at least 3 MR imaging sequences, for a total study sample of 398 rapid MR imaging examinations. Examinations were performed on various MR imaging scanners, including 1.5 and 3T; however, 341 (86%) of 398 examinations were completed on a Magnetom Espree 1.5T MR imaging scanner with a 70-cm bore (Siemens, Erlangen, Germany). The demographic characteristics of the study population are shown in On-line Table 1. All examinations consisted of HASTE images in the axial plane, and nearly all (> 99% [397/398]) examinations included additional coronal plane acquisitions (Fig 1). A total of 265 (67%) of 398 examinations were performed on patients in the outpatient setting, 93 (23%) on inpatients, and 40 (10%) on patients in the emergency department. Of these 398

examinations, 248 (62%) were performed on patients with ventricular shunts in place.

Study Indications

The breakdown of indications and clinical situations for all rapid MR imaging examinations is shown in On-line Table 1. Evaluation of ventricular size was the most common reason for ordering rapid MR imaging in this population, accounting for 318 (79.9%) of 398 imaging indications. Less common requests included follow-up of known intracranial blood or fluid (9.0% [36/398]), unspecified macrocephaly (3.0% [12/398]), and evaluation of intracranial cyst (2.3% [9/398]). A total of 23 (5.8%) of 398 requests were performed for other reasons, including evaluation of known encephalocele, infarction, or intracranial mass. Of the 327 examinations performed specifically to evaluate ventricular size or intracranial cyst, 162 (49.5%) were performed as routine clinical follow-up in asymptomatic patients; 38 (11.6%) for headache; 37 (11.3%) for postoperative evaluation; 35 (10.7%) for vomiting; 23 (7.0%) for “shunt malfunction”; 19 (5.8%) for altered mental status; 12 (3.7%) for macrocephaly; 6 (1.8%) for “fussy”; 5 (1.5%) for seizure; and 15 (4.6%) for other clinical symptoms such as localized pain, history of intracranial hemorrhage, or cranial dysmorphism. Some patients (21/327, 6.4%) had multiple symptoms such as headache plus vomiting.

Rapid MR Imaging Study Quality and Failure

No examination failures were identified. That is, all (398/398) rapid MR imaging examinations in this study provided the diagnostic information necessary to answer the clinical question posed. This included 9 (2.3%) of 398 rapid MR imaging reports that described image degradation by motion artifacts. A total of 6 (1.5%) same-day or next-day examinations were performed with either MR imaging with the patient under sedation ($n=2$) or with CT imaging ($n=4$). However, none of these were determined to have been the result of inadequate rapid MR imaging, and each was performed to obtain additional data not available on rapid MR imaging. These cases included: 1) a patient who had a seizure in the MR imaging suite after images were obtained and was then transferred to CT for an emergent scan; 2) a patient who presented to the emergency department with symptoms of obstructive hydrocephalus on 2 consecutive weeks and had negative results on rapid MR images, but then was referred within 48 hours for CT scan on the next similar presentation, which was also negative for hydrocephalus; 3) a patient who was evaluated from the emergency department with MR imaging for symptoms of obstructive hydrocephalus who received a CT for evaluation of possible craniosynostosis the following day; 4) a patient who had a report of a mass on an outside CT scan and received a rapid MR imaging for confirmation and an operative planning CT scan the following day; 5) a patient in whom an unusual intracranial mass abutting the inner table of the skull was identified by rapid MR imaging and a same-day CT scan was obtained to evaluate further for bony erosion; and 6) a patient with craniosynostosis, ventriculoperitoneal shunt, and an encephalocele being evaluated for shunt malfunction who received a next-day CT scan because the radiology report stated that the encephalocele was not well seen.

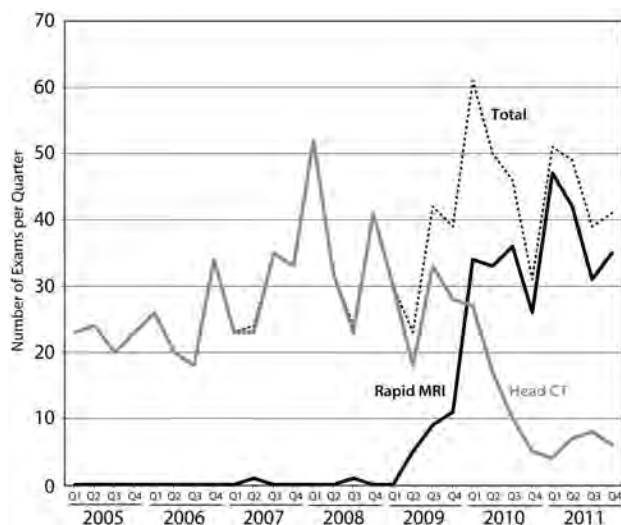


FIG 2. Trends in CT and rapid MR imaging use for hydrocephalus-related conditions, 2005–2011. Note that although overall imaging volumes for these indications have increased, rapid MR imaging is rapidly replacing CT imaging.

None of these 6 cases overlapped with those 9 in which reports mentioned significant motion.

Rapid MR Imaging Performance

The average scan duration was 4.43 minutes (SD, 2.42 minutes). Linear regression analysis (On-line Table 2) revealed that altered mental status, as an indication for imaging, was the only variable significantly associated with longer scan duration, resulting in increased average scan duration of 6.20 minutes compared with 4.43 minutes (On-line Table 2). No other indication, comorbidity, or demographic variable was significantly associated with scan duration. There were 40 (10.1%) of 398 examinations that had additional sequences added on ad hoc by the interpreting radiologist, most commonly axial gradient-echo true FISP sequences.

Trends in Rapid MR Imaging Use

During the 6-year period of this study, 643 unenhanced CT scans were performed in pediatric patients younger than 14 years for indications relating to intracranial cyst or ventricular size. From the beginning of 2005 to the end of 2011, the average number of monthly imaging studies used to diagnose ventricular pathologic conditions has increased from an average of 22.5 to 45 (Fig 2). Before mid-2009, this upward trend was entirely attributable to greater use of pediatric CT scanning. However, beginning in the second quarter of 2009, rapid MR imaging has steadily replaced CT scanning as the primary technique used for evaluation of ventricular pathologic conditions in the pediatric population. In the last quarter of 2011, rapid MR imaging accounted for 85.4% (35/41) of all cross-sectional brain imaging performed on children with suspected or known ventricular abnormalities, not including transcranial sonography.

DISCUSSION

The results from our retrospective study indicate that, across a wide age range, rapid-scan pediatric brain MR imaging with the patient nonsedated allows fast and successful assessment of ven-

tricular size without the need for repeated examination because of motion artifacts or poor study quality. Referral patterns within our institution suggest that providers are increasingly favoring rapid MR imaging vs CT scanning for pediatric ventricular evaluation. In addition, our study demonstrates that no particular patient demographic or clinical presentation precludes attempting rapid MR imaging in evaluation of ventricular size or intracranial cyst, because all patients completed an examination without the need for additional imaging to answer the clinical question. Only those with an indication of altered mental status required nominally increased scan durations, which is likely clinically and economically inconsequential.

These results are clinically relevant because the rapid MR imaging technique represents a reasonable means to evaluate hydrocephalus within the pediatric population and can be performed quickly, with nearly the same speed as conventional head CT scanning. It avoids the time and risk associated with conventional pediatric MR imaging scans of the head with the patient under sedation, as well as the ionizing radiation from CT scanning.

Several previous studies relating to pediatric rapid MR imaging have either focused on techniques to optimize shunt catheter tip localization, to describe its various uses, or to estimate potential benefits of radiation dose reduction.^{9,11–15} A recent study demonstrated value in an 8-second gradient-echo technique for determining ventricular size; however, this technique was performed in cases of failed examinations and provides scarce anatomic detail and, subsequently, minimal additional diagnostic information aside from ventricular size.¹⁶ Despite substantial motion artifacts in some cases, meaningful diagnostic value can be inferred from our results because no cases required conversion to a CT scan or to sedated, standard MR imaging.

We believe that proper selection of appropriate patients for rapid MR imaging examinations can reduce or eliminate the number of CT or sedated MR imaging examinations performed for a number of indications, as long as the referring clinician has a good understanding of its limitations and value. For example, this rapid MR imaging protocol would not be appropriate in pediatric trauma cases or in cases needed to evaluate tumors or infection, given the low sensitivity of rapid MR imaging in the detection of fractures and small amounts of subarachnoid hemorrhage and presumed low specificity in the evaluation of masses and extra-axial fluid collections. As such, these results show how standard CT imaging for indications of hydrocephalus or intracranial cyst has been considerably reduced but remains an essential part of our emergency medicine and oncologic practices. In our institution, these studies are now routinely performed when outpatient, nonemergent imaging of these pediatric patients is needed.

Our study had several limitations, including its retrospective nature. Identifying the causes of imaging failure via subjective chart review can lead to erroneous conclusions regarding the clinical reasoning that brought about a repeated examination. In addition, given the overlap between indications for use of MR imaging and CT scan in the pediatric population, we limited our comparisons to a limited set of hydrocephalus-related indications. Lastly, we did not have long-term follow-up on these patients, and further analysis is needed to determine how rapid MR imaging affects clinical decision-making and outcomes.

Rapid MR imaging examinations being obtained for indications other than hydrocephalus represent an area of potential mismatch between the expectations of the ordering clinicians and the realistic capabilities of this technique. Despite some strengths, rapid MR imaging has a potential limitation in patients with programmable shunts because repeated exposure to magnetic fields may require shunt reprogramming. At our institution, these patients are usually monitored with pre- and post-MR imaging skull radiographs, and as such, the patient's examination risk and exposure to radiation are not zero. In addition, costs to both the patient and the institution should also be factored into decisions to perform rapid MR imaging. We do not recommend eliminating CT scanning in the practice of imaging hydrocephalus, as evening and nighttime MR imaging coverage is not readily available in many centers and timely off-hours imaging is therefore not feasible. In addition, MR imaging carries with it additional safety issues such as projectile injury, which could potentially carry a greater health risk than the dose of radiation from CT, particularly as new low-dose CT techniques are developed.

CONCLUSIONS

Pediatric rapid brain MR imaging without the need for sedation is an effective and efficient alternative to standard CT imaging for assessment of ventricular size and/or intracranial fluid spaces, irrespective of a child's age or clinical condition. Only patients with altered mental status required nominally increased scan duration, but the time difference was minimal and was without substantial clinical implication. Our practice trends confirm that rapid MR imaging has nearly completely replaced routine, nonemergent CT scanning for these indications.

Disclosures: David Kallmes—UNRELATED: Consultancy: ev3,* Medtronic,* Codman,* Comments: Planning and implementation of clinical trials and core laboratory duties; Grants/Grants Pending: ev3,* Sequent Medical,* Cordis,* Codman,* MicroVention,* Royalties: UVA Patent Foundation, Comments: Spine fusion license; Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: MicroVention.*

REFERENCES

- Coté CJ. Strategies for preventing sedation accidents. *Pediatr Ann* 2005;34:625–33
- Coté GA, Hovis RM, Ansstas MA, et al. Incidence of sedation-related complications with propofol use during advanced endoscopic procedures. *Clin Gastroenterol Hepatol* 2010;8:137–42
- Cravero JP, Beach ML, Blike GT, et al. The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. *Anesth Analg* 2009;108:795–804
- Brenner D, Elliston C, Hall E, et al. Estimated risks of radiation-induced fatal cancer from pediatric CT. *AJR Am J Roentgenol* 2001;176:289–96
- Brenner DJ, Sachs RK. Estimating radiation-induced cancer risks at very low doses: rationale for using a linear no-threshold approach. *Radiat Environ Biophys* 2006;44:253–56
- Brenner DJ. Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. *Pediatr Radiol* 2002;32:228–23; discussion 242–44
- Goske MJ, Applegate KE, Boylan J, et al. The Image Gently campaign: working together to change practice. *AJR Am J Roentgenol* 2008;190:273–74
- The ALARA (as low as reasonably achievable) concept in pediatric CT intelligent dose reduction. Multidisciplinary conference organized by the Society of Pediatric Radiology. August 18–19, 2001. *Pediatr Radiol* 2002;32:217–313
- Koral K, Blackburn T, Bailey AA, et al. Strengthening the argument for rapid brain MR imaging: estimation of reduction in lifetime attributable risk of developing fatal cancer in children with shunted hydrocephalus by instituting a rapid brain MR imaging protocol in lieu of head CT. *AJNR Am J Neuroradiol* 2012;33:1851–54
- Forbes KP, Pipe JG, Karis JP, et al. Brain imaging in the unsedated pediatric patient: comparison of periodically rotated overlapping parallel lines with enhanced reconstruction and single-shot fast spin-echo sequences. *AJNR Am J Neuroradiol* 2003;24:794–98
- Iskandar BJ, Sansone JM, Medow J, et al. The use of quick-brain magnetic resonance imaging in the evaluation of shunt-treated hydrocephalus. *J Neurosurg* 2004;101(2 Suppl):147–51
- Missios S, Quebada PB, Forero JA, et al. Quick-brain magnetic resonance imaging for nonhydrocephalus indications. *J Neurosurg Pediatr* 2008;2:438–44
- Penzkofer AK, Pfluger T, Pochmann Y, et al. MR imaging of the brain in pediatric patients: diagnostic value of HASTE sequences. *AJR Am J Roentgenol* 2002;179:509–14
- Ashley WW Jr, McKinstry RC, Leonard JR, et al. Use of rapid-sequence magnetic resonance imaging for evaluation of hydrocephalus in children. *J Neurosurg* 2005;103(2 Suppl):124–30
- Miller JH, Walkiewicz T, Towbin RB, et al. Improved delineation of ventricular shunt catheters using fast steady-state gradient recalled-echo sequences in a rapid brain MR imaging protocol in nonsedated pediatric patients. *AJNR Am J Neuroradiol* 2010;31:430–35
- Wait SD, Lingo R, Boop FA, et al. Eight-second MRI scan for evaluation of shunted hydrocephalus. *Childs Nerv Syst* 2012;28:1237–41

Bilateral Cavitations of Ganglionic Eminence: A Fetal MR Imaging Sign of Halted Brain Development

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ABSTRACT

SUMMARY: Ganglionic eminence is the main transitory proliferative structure of the ventral telencephalon in human fetal brain and it contributes for at least 35% to the population of cortical interneurons; however data on the human GE anomalies are scarce. We report 5 fetal MR imaging observations with bilateral symmetric cavitations in their GE regions resembling an inverted open C shape and separating the GE itself from the deeper parenchyma. Imaging, neuropathology, and follow-up features suggested a malformative origin. All cases had in common characteristics of lissencephaly with agenesis or severe hypoplasia of corpus callosum of probable different genetic basis. From our preliminary observation, it seems that GE cavitations are part of conditions which are also accompanied by severe cerebral structure derangement.

ABBREVIATIONS: CC = corpus callosum; GA = gestational age; GE = ganglionic eminence

The ganglionic eminence is a transitory proliferative structure of the ventral telencephalon localized in human fetal brain along the lateral walls of the frontal (and to a less extent the temporal) horns of the lateral ventricles. During development, the GE persists longer than other proliferative areas and only by term has nearly disappeared. The GE contains precursor neurons of the basal ganglia and amygdala; it also contributes at least 35% to the population of interneurons that tangentially migrate toward to the cerebral cortex^{1,2} and to a population of the thalamic neurons. In rodents, the medial GE represents the major source of the cortical interneurons; the caudal GE is an additional source of tangentially migrating interneurons to the cortex and hippocampus and the lateral GE is the major source of striatal gamma-aminobutyric acid projection neurons. Although data in humans are scant, the partition of GE has been recently proposed.^{3,4} The GE also represents an intermediate target for corticofugal and thalamocortical axons.⁵

Despite the pivotal importance of the GE in human brain de-

velopment, data on GE anomalies are scarce, for example, the recent report on hemorrhage occurring in this region in premature babies.⁶

Recently in our institution, in a clinical fetal MR imaging observation, we found bilateral symmetric cavitations in the GE region. To better understand the significance of this unusual finding, we then set out to analyze similar cases possibly present in our prenatal MR imaging data base. We found 4 additional fetal cases, all of which also had bilateral symmetric cavitations in the GE regions (probably of malformative origin). All 5 cases also had in common characteristic features of lissencephaly with agenesis or severe hypoplasia of the corpus callosum of probable different genetic basis.

The main purpose of this report is to present the imaging and, when available, pathology data of this rare finding.

MATERIALS AND METHODS

From our 10-year prenatal MR imaging data base (containing approximately 2200 cases), we collected 5 fetal cases (22, 29, 23, 22, and 25 weeks of gestational age, respectively; 4 female and 1 male) with reported “cavitations or cysts in the GE-basal ganglia region.” Two of these cases had familial recurrence (cases 2 and 3 in On-line Table 1).

All 5 MR imaging studies had been performed for clinical purposes, after expert sonography study. All mothers had signed the specific consent form for fetal MR imaging in use at our institution, and the study complied with the internal guidelines for clinical retrospective studies used at our institution.

Follow-up data analysis was based on the following methods (On-line Table 1): 2 cases (case 1 and 4) after pregnancy termina-

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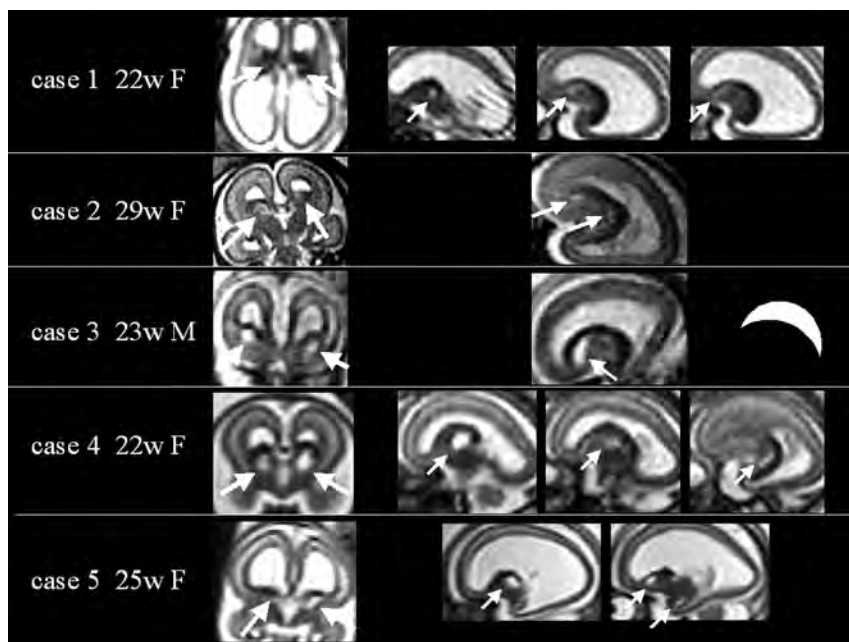


FIG 1. Prenatal single-shot FSE T2-weighted MR images of the 5 reported cases, each case displayed horizontally in a row. Case number, GA, and sex are reported. *White arrows* indicate GE region cavitations. In the case 3 row, an inverted open C shape is drawn, showing how cavitation appears on sagittal sections. The corpus callosum is agenetic or severely hypoplastic in all cases. Frontal opercula are shallow and dysmorphic.

tion underwent pathology examination, 1 case (case 3) after pregnancy termination was studied solely by MR-autopsy, 1 case (case 2) underwent neonatal MR imaging, and 1 pregnancy (case 5) was terminated outside of our institution without available autopsy or MR autopsy data.

MR Imaging Methods

A 1.5T scanner was used for fetal MR imaging, with a phased-array abdominal or cardiac coil. All the selected 5 cases had been investigated through T2-weighted single-shot fast spin-echo multiplanar sections: 3–4-mm section thickness, TR/TE 3000/180 ms, 1.1 mm² in-plane resolution; in some cases BALANCE 2–3-mm thick sections were also acquired (Philips Medical Systems, Eindhoven, the Netherlands). In the 2 most recent cases (cases 1 and 4), T1-weighted FSE 5.5-mm-thick sections (TR/TE = 300/14 ms, turbo factor = 3, 1.4 mm² in-plane resolution) and diffusion-weighted imaging 5.5-mm-thick sections (TR/TE = 1000/90 ms, *b* factor = 0–600 seconds/mm², FOV = 320 × 320 mm, matrix = 128 × 128) were also available.

Two senior pediatric neuroradiologists (A.R., C.P.), with 12 years of experience in fetal MR imaging, evaluated the images in consensus.

MR-autopsy and neonatal MR imaging studies were performed with the use of a neonatal dedicated head coil and 1.5T scanner; 2–3-mm-thick T2-weighted FSE sequences (TR/TE 6000/200 ms), with 0.3 mm² in-plane resolution, were acquired.

Pathology Methods

The autopsy brains from cases 1 and 4 (On-line Table 1) were fixed in 10% formalin, subsequently embedded in paraffin,

and cut in 10-μm-thick coronal sections. Sampled sections of the anterior part of the brain, at the level of the GE, were stained with thionin (0.1% in distilled water) and hematoxylin and eosin and examined with the use of an Aperio Image Scope (Nikon, Tokyo, Japan). Additional series of sections were cut and processed for immunolocalization of the neuronal calcium-binding proteins calbindin and calretinin, of the intermediate filament protein vimentin, which is early-expressed in the radial glia. After incubation in 10% (volume-volume percent) normal serum to mask nonspecific adsorption sites, sections were processed with the use of the following primary antibodies: polyclonal anti-Calbindin (1:600; Swant, Bellinzona, Switzerland), polyclonal anti-Calretinin (1:300; Swant), and monoclonal anti-Vimentin (1:200, DAKO, Glostrup, Denmark). Unfortunately, the scanty preservation of tissue caused by the autolytic processes hampered a reliable result of immunohistochemistry. Thus, only routine histologic staining was reliably used for neuropathologic examination.

Genetic Analysis

DNA was extracted from formalin-fixed, paraffin-embedded tissue sections from cases 1 and 4 by use of the QIAamp DNA FFPE Tissue Kit (QIAGEN, Hilden, Germany). Mutation analysis of the *LIS1* (genebank accession: NM_000430.3) and *TUBA1A* (genebank accession: NM_006009.2) genes, known to be involved in lissencephalies, was performed by direct sequencing. No mutations were identified. Unfortunately, genomic rearrangements involving the *LIS1* gene could not be excluded by multiplex ligation-dependent probe amplification analysis because of poor DNA quality. Sequence analysis of the *ARX* gene could not be performed either, because of the poor quality of DNA and the high guanine-cytosine content of this gene.

RESULTS

The findings reported in expert sonography examinations (On-line Table 1) were CC agenesis in all 5 cases, as well reduced cranial and cerebellar biometry, mild-moderate ventriculomegaly in 3 cases, and reduced whole-body biometry in 2 cases. None of the sonography reports mentioned basal ganglia region cavitations.

At prenatal MR imaging, all 5 cases displayed bilateral symmetric cavitations in the GE region, separating the GE itself from the deeper parenchyma and resembling an inverted open C shape (Fig 1). In 2 cases (cases 2 and 4), GE appeared to be clearly larger than in healthy controls at the same GA (On-line Fig 1). In T1-weighted and diffusion-weighted imaging (available exclusively in cases 1 and 4), the GE showed a hyperintensity comparable to that of the periventricular-germinal matrix area and slightly higher than that of the cortical plate

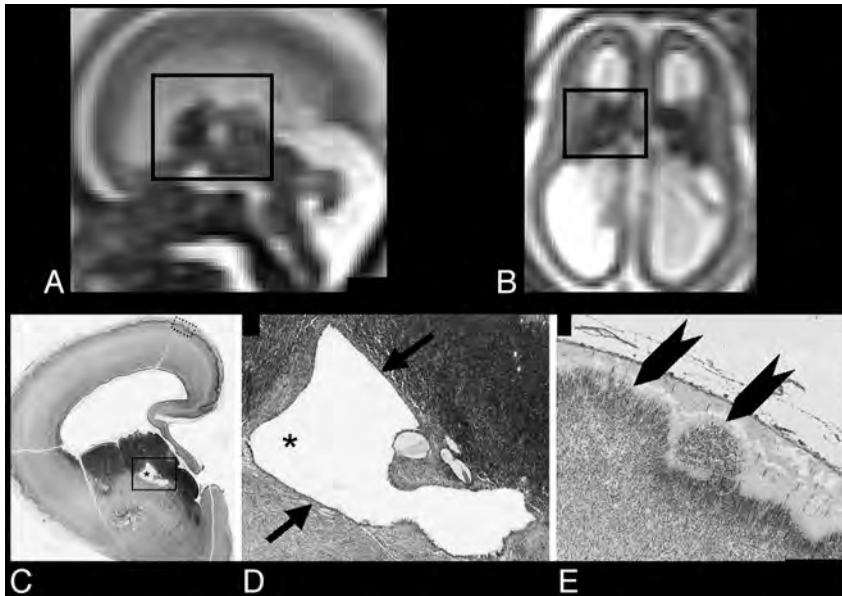


FIG 2. A and B, Sagittal and axial single-shot FSE T2-weighted sections of case 1 (22-week GA), respectively; *black rectangle* encompasses GE and relative cavitation. C, Thionin-stained paraffin coronal section shows a hemisphere at the level of GE cavitation (*asterisk*). D, Higher magnification of the *black rectangle* area in C, illustrating the regular border (epithelium-like structure) of cavitation (*arrows*). E, Higher magnification of the cortex (*dotted rectangle* in C); heterotopic cortical plate neurons extending in the marginal zone (*arrowheads*). Scale bar = 300 μm .

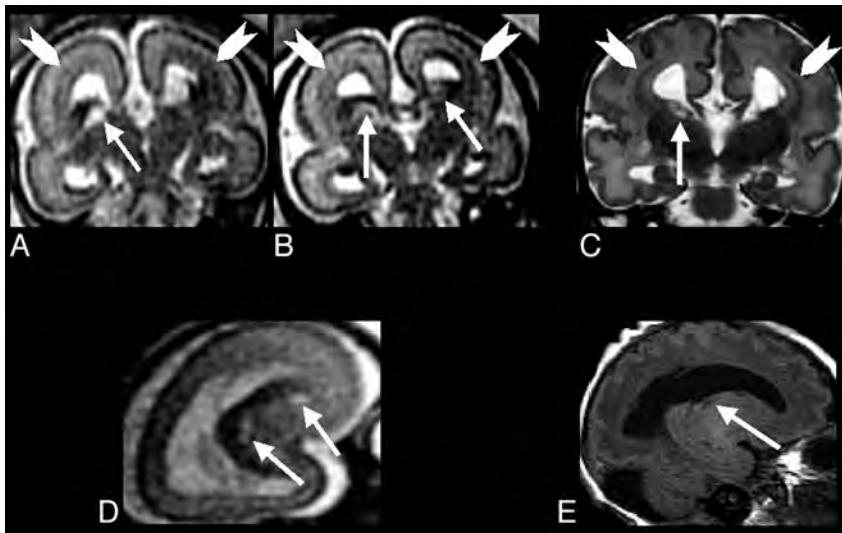


FIG 3. A–C, Single-shot FSE T2-weighted sections from case 2 (29-week GA) prenatal study shows GE region cavitations (*arrows*), which tend to be relatively smaller with respect to the brain size in this older fetus. *Arrowheads* indicate bilateral bands of heterotopias. Gyration appears to be poor. D, Coronal FSE T2-weighted and sagittal (E) spin-echo T1-weighted sections show cavitations now relatively smaller and confirming band heterotopias (*arrowheads*).

(On-line Fig 2); however, the associated apparent diffusion coefficient tended to be slightly lower (0.85 SD, $0.09 \mu\text{m}^2/\text{s}$) than in GE of healthy controls (0.95 SD, $0.13 \mu\text{m}^2/\text{s}$, unpublished data).

All 5 cases demonstrated reduction of biometric brain parameters (below the 10th percentile with respect to normal data of reference⁷) (On-line Table 1), agenesis or severe hypoplasia of the CC, and defective gyration such as shallow opercula and absent/reduced parieto-occipital sulcus (normally visible before

the 23 weeks of GA). One case (case 2) had bilateral frontal band heterotopias (Fig 3), confirmed by neonatal MR imaging. No case showed a disproportionate reduction of the pontine bulging.

MR autopsy (case 3, Fig 4), pathology (cases 1 and 4, Figs 2 and 5), and neonatal MR imaging (case 2, Fig 3) confirmed the presence of lissencephaly. Furthermore, in all cases, lesions were symmetric; they appeared to be lined by an epithelium-like structure at pathologic examination (cases 1 and 4), and cavitation margins were regular, without apparent signs of previous or ongoing hemorrhage.

In addition, both cases, in which histology was available (cases 1 and 4) demonstrated a disorganization of the developing cortex. In particular, the cortical plate surface appeared to be irregular, with heterotopic cellular extension into the marginal zone (Figs 2 and 5). None of the cases presented at autopsy (cases 1, 3, and 4) or at clinical examination after birth (case 2) had ambiguous genitalia, which could be related to some type of lissencephaly such as the one X-linked ARX gene.

DISCUSSION

From our preliminary observation, it appears that GE cavitations are an aspect of more complex conditions associated with severe cerebral structural derangement. The awareness of this rare developmental abnormality involving the GE region may have implications in better understanding of the complex malformations caused by defective cellular proliferation and migration, such as lissencephalies. The fact that the lesions were bilateral and symmetric with an inverted “regular” open C shape, an epithelium-like lining, regular margins, and no apparent signs of hemorrhage (including the 2 cases with T1-weighted images) suggests a malformative rather than necrotic-clastic origin. Familial recurrence in 2 cases and the presence of

frontal band heterotopias in 1 case further support such a hypothesis. Although the data are not extensive enough to conclude a statistical significance, the available ADC values (cases 1 and 4), albeit showing a slight trend toward mild reduction (0.85 SD, $0.09 \text{ m}^2/\text{s}$), remained higher than ADC values reported in fetal brain acute ischemia cases (ie, $0.4 \text{ m}^2/\text{s}$ in Righini et al⁸). Moreover, in the case illustrated in On-line Fig 2, GE histology showed a higher cell body/interstitial space ratio (a possible sign of structural developmental anomaly) but

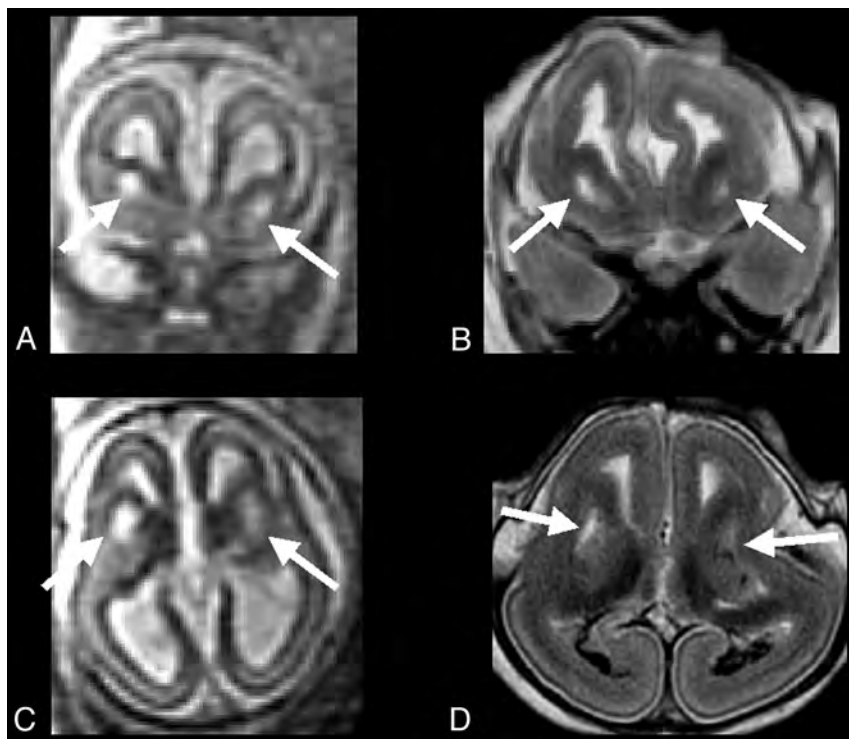


FIG 4. A and C, Single-shot FSE T2-weighted sections from case 3 (23-week GA) prenatal study, show large symmetric GE region cavitations (*arrows*). B and D, FSE T2-weighted corresponding MR autopsy sections, which confirm the prenatal findings (*arrows*): cavitations appear to have regular smooth margin, albeit brain was compressed and deformed during delivery.

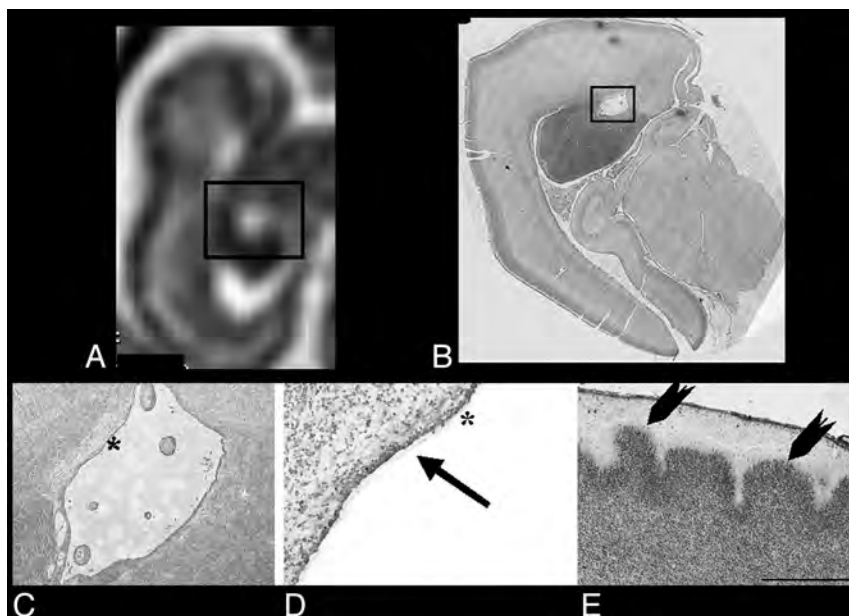


FIG 5. A, Coronal single-shot FSE T2-weighted section from case 4 (22-week GA); brain is shown upside-down to better match the corresponding coronal oblique histologic section in B, Thionin-stained paraffin section with *black rectangle* encompassing part of GE and related cavitation; C, higher magnification of the *black rectangle* in B; D, inside part of the cavitation (*asterisks* in C and D) lined by epithelium-like structure (*arrow*); E, detail of the developing cortex shows heterotopic cortical plate neurons extending in the marginal zone (*arrowheads*). Scale bar = 410 μ m.

not signs of acute cytotoxic edema (such as neuropil swelling). Nevertheless, because we do not have detailed histologic data for all of our cases, we cannot completely rule out the necrotic

nature of the observed GE region cavitations. Moreover, the existence of a recent report,⁹ which showed basal ganglia vasculopathy in a lissencephaly case, further warns of the possibility that ischemia may play a role in cavitation onset.

According to Barkovich et al,¹⁰ lissencephalies are primarily caused by abnormal neuronal migration. In such conditions, abnormal development of the GE, together with deficiency of other fetal transient structures such as the germinal matrix, may play a key role. We may speculate that cavitations associated with GE might derive from abnormal proliferation of neural precursors in the region and subsequently affect migration of inhibitory interneurons from GE toward their final cortical destination. However, detailed cytologic-immunohistochemical assessment could not be performed in our cases because of faulty tissue preservation. However, the cystic anomaly of the GE region might contribute to causing lissencephaly even by simply physically affecting cell migration, even in the absence of proliferation defect, because, in at least 2 of our cases, GE was larger than in healthy controls of the same GA.

The presence in our 5 cases of opercularization defects, agenesis-severe hypoplasia of CC, abnormal cortical plate findings at histology, and heterotopic bands, further supports the hypothesis that GE cavitation anomalies are part of complex malformations, which involve cell migration and possibly a cell differentiation phase.

To the best of our knowledge, GE cavitations have not been described in animal models of lissencephaly; neither have they been reported in the existing extensive postnatal neuroimaging literature regarding human lissencephalies. This could be explained by their size decrease as the whole brain progressively grows. In postnatal MR studies, cavitation remnants might have been occasionally interpreted in the past just as enhanced perivascular spaces in the basal ganglia region; cavitations may relatively decrease in size with respect to the progressive growth of the whole brain.

A major limitation of our report is the lack of substantial molecular genetics characterization of our cases. Banded karyotyping, which turned out to be normal, was available in 3 cases (On-line Table 1); however, karyotyping is usually of limited

diagnostic power in lissencephaly. Molecular study of the X-linked gene *ARX*, which was not possible, might have been indicated in cases 2 and 3, although the severe phenotype observed in the sister and parental consanguinity makes it unlikely to be an X-linked inheritance. Converging experimental, neuropathologic, and imaging evidence suggests that mutations in this gene cause an abnormal developmental process primarily affecting GE development. Impaired proliferation of neuronal elements in the GE and subsequent abnormal proliferation of GABAergic interneurons has been demonstrated in the *ARX* knock out model.¹¹ Microcystic changes in the basal ganglia are observed in the brains of children with X-linked lissencephaly with abnormal genitalia, both at neuropathology¹² and by use of MR imaging scan.¹³ Multiple small areas of abnormal signal intensity, possibly representing microcystic changes, are observed in the basal ganglia of boys with *ARX* mutations and profound cognitive impairment but no lissencephaly.¹⁴

Albeit limited by the rarity of these findings and by the difficulty of histology studies on fetal human brain before the third trimester of GA, additional cases investigated by cytologic labeling of GE-originating neuroblasts and cortical interneurons are needed to further elucidate the meaning of the anomaly we have reported and to definitively rule out the possibility of a lesional etiology.

REFERENCES

1. Letinic K, Zoncu R, Rakic P. **Origin of GABAergic neurons in the human neocortex.** *Nature* 2002;417:645–49
2. Zecevic N, Hu F, Jakovcevski I. **Interneurons in the developing human neocortex.** *Dev Neurobiol* 2011;71:18–33
3. Corbin JG, Gaiano N, Juliano SL, et al. **Regulation of neuronal progenitor cell development in the nervous system.** *J Neurochem* 2008;106:2272–87
4. Métin C, Baudoin JO, Rakic S, et al. **Cell and molecular mechanisms involved in the migration of cortical interneurons.** *Eur J Neurosci* 2006;23:894–900
5. Ulfing N. **Ganglionic eminence of the human fetal brain: new vistas.** *Anat Rec* 2002;267:191–95
6. Del Bigio MR. **Cell proliferation in human ganglionic eminence and suppression after prematurity-associated haemorrhage.** *Brain* 2011;134:1344–61
7. Parazzini C, Righini A, Rustico M, et al. **Prenatal magnetic resonance imaging: brain normal linear biometric values below 24 gestational weeks.** *Neuroradiology* 2008;50:877–83
8. Righini A, Kustermann A, Parazzini C, et al. **Diffusion-weighted magnetic resonance imaging of acute hypoxic-ischemic cerebral lesions in the survivor of a monochorionic twin pregnancy: case report.** *Ultrasound Obstet Gynecol* 2007;29:453–56
9. Jagla M, Kruczek P, Kwinta P. **Association between X-linked lissencephaly with ambiguous genitalia syndrome and lenticulostriate vasculopathy in neonate.** *J Clin Ultrasound* 2008;36:387–90
10. Barkovich AJ, Guerrini R, Kuzniecky RI, et al. **A developmental and genetic classification for malformations of cortical development: update 2012.** *Brain* 2012;135:1348–69
11. Kitamura K, Yanazawa M, Sugiyama N, et al. **Mutation of *ARX* causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans.** *Nat Genet* 2002;32:359–69
12. Bonneau D, Toutain A, Laquerrière A, et al. **X-linked lissencephaly with absent corpus callosum and ambiguous genitalia (XLAG): clinical, magnetic resonance imaging, and neuropathological findings.** *Ann Neurol* 2002;51:340–49
13. Kato M, Das S, Petras K, et al. **Mutations of *ARX* are associated with striking pleiotropy and consistent genotype-phenotype correlation.** *Hum Mutat* 2004;23:147–59
14. Guerrini R, Moro F, Kato M, et al. **Expansion of the first PolyA tract of *ARX* causes infantile spasms and status dystonicus.** *Neurology* 2007;69:427–33

A Better Characterization of Spinal Cord Damage in Multiple Sclerosis: A Diffusional Kurtosis Imaging Study

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ABSTRACT

BACKGROUND AND PURPOSE: The spinal cord is a site of predilection for MS lesions. While diffusion tensor imaging is useful for the study of anisotropic systems such as WM tracts, it is of more limited utility in tissues with more isotropic microstructures (on the length scales studied with diffusion MR imaging) such as gray matter. In contrast, diffusional kurtosis imaging, which measures both Gaussian and non-Gaussian properties of water diffusion, provides more biomarkers of both anisotropic and isotropic structural changes. The aim of this study was to investigate the cervical spinal cord of patients with MS and to characterize lesional and normal-appearing gray matter and WM damage by using diffusional kurtosis imaging.

MATERIALS AND METHODS: Nineteen patients (13 women, mean age = 41.1 ± 10.7 years) and 16 controls (7 women, mean age = 35.6 ± 11.2 -years) underwent MR imaging of the cervical spinal cord on a 3T scanner (T2 TSE, T1 magnetization-prepared rapid acquisition of gradient echo, diffusional kurtosis imaging, T2 fast low-angle shot). Fractional anisotropy, mean diffusivity, and mean kurtosis were measured on the whole cord and in normal-appearing gray matter and WM.

RESULTS: Spinal cord T2-hyperintense lesions were identified in 18 patients. Whole spinal cord fractional anisotropy and mean kurtosis ($P = .0009$, $P = .003$), WM fractional anisotropy ($P = .01$), and gray matter mean kurtosis ($P = .006$) were significantly decreased, and whole spinal cord mean diffusivity ($P = .009$) was increased in patients compared with controls. Mean spinal cord area was significantly lower in patients ($P = .04$).

CONCLUSIONS: Diffusional kurtosis imaging of the spinal cord can provide a more comprehensive characterization of lesions and normal-appearing WM and gray matter damage in patients with MS. Diffusional kurtosis imaging can provide additional and complementary information to DTI on spinal cord pathology.

ABBREVIATIONS: DKI = diffusional kurtosis imaging; EDSS = Expanded Disability Status Scale; GM = gray matter; MK = mean kurtosis; SC = spinal cord

Multiple sclerosis is a chronic inflammatory/demyelinating and neurodegenerative disease of the central nervous system and the most common cause of nontraumatic disability in

young adults.¹ The spinal cord is a site of predilection for MS lesions,² and SC damage contributes to the onset of neurologic deficits and the development of clinical disability.³ At postmortem examination, 86% of patients with MS have spinal cord lesions,² and MR imaging cord abnormalities are detected in up to 89% of patients with established disease.⁴ However, previous MR imaging studies of patients with MS found a poor correlation between the number and volume of T2-hyperintense SC lesions and disability,⁵ very likely due to the presence of additional microscopic abnormalities in the so-called normal-appearing white matter, not detectable by conventional MR imaging techniques.^{6,7}

Several pathologic studies of MS spinal cord samples have shown that not only SC WM but also GM is affected by demyelination and neuronal loss.⁸⁻¹¹ Despite these reports and unlike findings reported in the brain, only a few in vivo MR imaging studies to date have investigated the presence and extent of spinal cord GM damage in patients with MS.¹²⁻¹⁴

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DTI is a clinically important MR imaging method used to measure the micron scale displacement of water molecules in the brain and can provide information about tissue structural integrity at a microscopic level.¹⁵ Recent DTI studies of the spinal cord in patients with MS indeed showed a significant decrease in fractional anisotropy, a measure of WM fiber integrity and directionality, compared with healthy controls in both lesions and normal-appearing tissue.¹⁶⁻²⁴ The DTI model, however, is based on the assumption that the displacement probability function of diffusing water molecules follows a Gaussian distribution, which is only the first approximation to the true behavior in complex tissue. Therefore, while the anisotropic sensitivity of DTI is useful for the study of highly organized systems such as WM tracts, it provides fewer useful biomarkers in tissues such as GM. This is because for the length scales studied with diffusion MR imaging (ie, a few microns), the microstructure of GM is characterized as isotropic. Conversely, non-Gaussian diffusion may be more sensitive to subtle pathologic changes in GM because diffusional non-Gaussianity is a direct consequence of diffusion barriers and compartments, regardless of the presence of microstructural anisotropy.²⁵

Among the MR imaging techniques that have been developed to assess non-Gaussian diffusion in spinal cord tissue,^{13,15} diffusional kurtosis imaging²⁵ represents the minimal extension of DTI that, in acquisition times compatible with clinical application, enables the quantification of non-Gaussian diffusion through the estimation of the diffusional kurtosis. A DKI-derived metric, the mean kurtosis, provides a measure of the deviation of the diffusion probability distribution from a Gaussian form.^{25,26} MK has been shown to be sensitive to structural changes in both anisotropic tissue, such as WM, and isotropic tissue such as GM and therefore may provide information on tissue microarchitecture complementary to that given by fractional anisotropy and mean diffusivity.²⁵ Using a moderately expanded diffusion-sampling scheme, MK can be obtained simultaneously with conventional DTI,^{27,28} and it has already been used to study the brain in normal aging,²⁷ Alzheimer disease,²⁹ traumatic brain injury,³⁰ brain tumors,³¹ stroke,³² and the spinal cord in patients with cervical myelopathy.³³

The aims of our study were the following: 1) to investigate global and regional (WM and GM) microstructural abnormalities in the cervical spinal cord of patients with MS compared with healthy controls by using MK, mean diffusivity, and fractional anisotropy; 2) to determine whether cervical cord MK provides additional information about the underlying structural abnormalities compared with mean diffusivity and fractional anisotropy; 3) to assess the relationship between cervical spinal cord DKI-derived parameters and measures of cord area and volume; and 4) to determine the clinical impact of global and regional cervical spinal cord DKI-derived metrics.

MATERIALS AND METHODS

Patients

The study was approved by the institutional review board of New York University and complies with the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants. For this prospective study, we recruited 21 consecutive patients with clinically definite MS³⁴ who were referred from the New York University MS Center to our



FIG 1. Sagittal T2 image from a healthy control demonstrating the coverage of the axial diffusion kurtosis sequence, centered on the C2–3 intervertebral space.

department for cervical spinal cord MR imaging between August 2009 and March 2010 and who met the following inclusion criteria: 1) had a diagnosis of relapsing-remitting MS, 2) were between 18 and 60 years of age, and 3) had an absence of clinical relapse and/or steroid treatment in the 3 months before MR imaging. The exclusion criteria were the presence of other relevant diseases and contraindications to performing MR imaging. Two patients were excluded because of claustrophobia.

All subjects underwent a neurologic evaluation. The following demographic and clinical variables were collected for each patient: age, disease duration from diagnosis, disease duration from symptom onset, and level of disability assessed by the EDSS. The 19 patients had a mean age of 41.1 ± 10.7 years. There were 13 women (mean age = 40.1 ± 10.7 years) and 6 men (mean age = 43.1 ± 11.5 years).

Sixteen healthy controls (mean age = 35.6 ± 11.2 years, 9 men and 7 women) with no known brain abnormalities and no neurologic symptoms were recruited as controls and given the same MR imaging examination as described above.

MR Imaging Acquisition

MR imaging was performed by using a 3T scanner (Tim Trio; Siemens, Erlangen, Germany) with a 4-channel neck phased array coil, and the following imaging protocol was used in all subjects during a single MR imaging session:

1) A sagittal T2-weighted TSE sequence with 15 contiguous sections (TR = 3500 ms, TE = 113 ms, FOV = 240 mm, matrix = 512×512 , section thickness = 3 mm, in-plane resolution = 0.46×0.46 mm²).

2) Sagittal T1-weighted 3D MPRAGE on 24 contiguous sections (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FOV = 240 mm, matrix = 230×256 , isotropic voxel size = $1 \times 1 \times 1$ mm³).

3) An axial DKI sequence, centered on the spinal intervertebral disk between C2 and C3 (a slab position is visible in Fig 1), by using a twice-refocused spin-echo diffusion sequence with an echo-planar imaging readout³⁵ with 30 different diffusion-encoding directions by using an optimized sampling strategy^{36,37} and 20 contiguous axial sections. For each direction, 6 b-values (0, 500, 1000, 1500, 2000, 2500 s/mm²) were used (TR = 3100 ms,

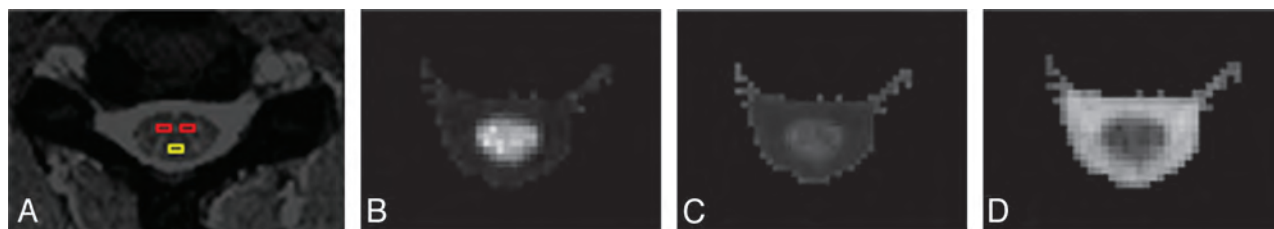


FIG 2. Axial T2 image (A) of the cervical spinal cord at C2 shows the location of ROIs placed in the gray matter of the ventral horns (red) and white matter of the dorsal column (yellow). Corresponding fractional anisotropy (B), mean kurtosis (C), and mean diffusivity (D) maps. The size of the region of interest is 2 voxels (3.1 mm²). Diffusion and kurtosis tensors were calculated by using in-house software to generate maps of the derived parameters, fractional anisotropy, mean diffusivity, and MK.

TE = 110 ms, FOV = 160 mm, matrix = 128 × 128, section thickness = 3 mm, number of averages = 2, in-plane resolution = 1.25 × 1.25 mm², acquisition time = 15 minutes 7 seconds).

4) An axial T2-weighted fast low-angle shot MR imaging sequence, centered on the spinal intervertebral disk between C2 and C3, with 24 contiguous sections (TR = 500 ms, TE = 7.38 ms, FOV = 176 mm, matrix = 192 × 320, section thickness = 3 mm, in-plane resolution = 0.68 × 0.68 mm²).

5) Only in the 19 patients, an additional sagittal T2 STIR sequence with 13 contiguous sections was acquired (TR = 4500 ms, TE = 53 ms, TI = 200 ms, FOV = 240 mm, matrix = 480 × 480, section thickness = 3 mm, in-plane resolution = 0.37 × 0.37 mm²).

Postprocessing

Image data processing and evaluation were performed by an MR imaging expert and a neuroradiologist. T2-weighted and STIR images were used to identify and count the lesions in the spinal cord.

DKI/DTI Analysis

Diffusion and kurtosis tensors were calculated by using in-house software (Diffusion and Kurtosis Estimator) in Matlab, Version 7.0 (MathWorks, Natick, Massachusetts); maps of derived parameters, fractional anisotropy, mean diffusivity, and MK, were generated after first coregistering all diffusion-weighted images with a 2D rigid-body algorithm.³⁸ After we derived apparent diffusion and kurtosis along each applied gradient direction via a quadratic fit to the logarithm of the signal intensity, the analysis algorithm, described in detail in Tabesh et al,³⁸ used a linearly constrained linear least-squares formulation to solve for both the diffusion and kurtosis tensors at each voxel. Using region-of-interest analysis, we measured mean fractional anisotropy, mean diffusivity, and MK values of the entire cross-sectional cord area between C1 and C4 (5 contiguous sections for each level), generating 20 values for each of the DTI metrics in each subject (altogether 380 SC sections for 19 patients). Of 380 sections, 165 included T2 visible lesions, whereas the remaining 215 were classified as normal-appearing spine tissue.

The lesions were outlined on the T2-weighted images by using Medical Image Processing, Analysis, and Visualization (<http://mipav.cit.nih.gov>). Then, the outlined regions of interest were automatically transferred onto the corresponding DKI/DTI maps, and the mean lesional fractional anisotropy, mean diffusivity, and MK values were measured. In addition, mean fractional anisotropy, mean diffusivity, and MK values of normal-appearing

GM and WM were measured by using rectangular ROIs (size: 2 voxels, 3.1 mm²) placed on the T2 images in the left and right ventral horns and in the dorsal columns over 2 contiguous sections at the C2 level, as described in Freund et al (Fig 2).³⁹ The regions of interest were then opened on the registered DKI/DTI maps, and the mean values for GM/WM were calculated by averaging the results obtained in all ROIs (4 ROIs for GM, 2 ROIs for WM). This regional analysis was performed on patients (14 of 19) who did not show any lesions at the C2 level.

Cervical Spinal Cord Area and Volume Measurement

Cervical cord area and volume were measured on T1 MPRAGE images. For each subject, five 3-mm-thick axial sections perpendicular to the spinal cord were reconstructed, centering on the C2–3 intervertebral disk, and an established semiautomated technique was used to measure the cross-sectional cord area.⁴⁰ The volume of the cervical cord section between C2 and C4 was evaluated by using BrainMask software (<http://www.nitrc.org/projects/brainmask>)⁴¹ by using 3D edge-detection algorithms, allowing volume selection with 3 simultaneous reference planes. Because the software is suboptimal for the evaluation of a curved object, the volume between C2 and C4 was selected as representative of the entire cervical cord volume.

Statistical Analysis

Statistical analysis was performed by using SAS (SAS Institute, Cary, North Carolina). The DKI/DTI values were represented for each subject as an average over the values recorded for each spine location. As a result, each subject contributed 1 value of each of MK, mean diffusivity, and fractional anisotropy for the total SC (including lesions) and over the normal-appearing SC. Additionally, in patients with MS without visible lesions at the C2 level and in healthy controls, fractional anisotropy, mean diffusivity, and MK were measured in normal-appearing spinal cord tissue (GM and WM). Analysis of covariance was used to compare patients and controls in terms of the total and regional values of MK, mean diffusivity, and fractional anisotropy, adjusting for age, sex, and disease duration, and to compare the 2 groups of patients stratified according to the EDSS score (group 1: EDSS score ≤ 2.5, female/male ratio = 9:2, mean age = 39.0 ± 8.9 years, mean disease duration = 8.5 ± 6.0 years; group 2: EDSS score ≥ 3.0, female/male ratio = 4:4, mean age = 44.0 ± 12.0 years, mean disease duration = 5.7 ± 3.0 years) adjusting for age, sex, disease duration, number of lesions, and cord area.

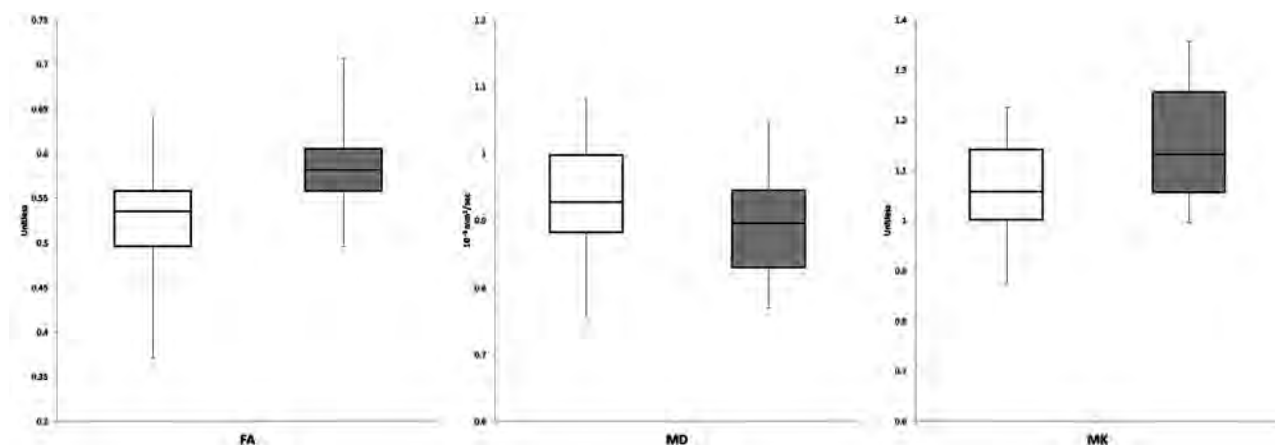


FIG 3. Box-and-whisker plots show the distribution of fractional anisotropy, mean diffusivity, and MK values in patients (white boxes) and in healthy controls (gray boxes). ANCOVA comparing patients with controls and adjusted for age, sex, and disease duration gave the following *P* values: fractional anisotropy, *P* = .0009; mean diffusivity, *P* = .009; MK, *P* = .003.

Table 1: The mean of DKI/DTI measures of the whole spinal cord over sections with lesions (*n* = 145) and over sections of normal-appearing spine tissue (*n* = 215) in patients with MS^a

Measure ^c	Lesions	NAST	<i>P</i> Value ^b
FA	0.42 ± 0.02	0.52 ± 0.04	<.0001
MD	1.17 ± 0.08	0.92 ± 0.05	<.0001
MK	0.91 ± 0.03	1.08 ± 0.08	<.0001

Note:—NAST indicates normal-appearing spine tissue; FA, fractional anisotropy; MD, mean diffusivity.

^a Only data from subjects with lesions (*n* = 18) were included in the computations.

^b *P* values are from ANCOVA, comparing lesions to normal-appearing spine tissue in terms of the indicated DKI measure adjusted for age, sex, and disease duration.

^c FA and MK are unitless. MD is measured in $\times 10^{-3}$ mm²/s.

Table 2: The mean of DKI measures at the C2–3 level in patients with MS and controls

Measure	Location	Controls	Patients with MS	<i>P</i> Value ^a
FA	GM	0.81 ± 0.11	0.70 ± 0.19	.4
	WM	0.63 ± 0.07	0.52 ± 0.07	.01
MD	GM	0.56 ± 0.08	0.72 ± 0.21	.1
	WM	0.86 ± 0.14	0.99 ± 0.13	.06
MK	GM	1.16 ± 0.13	1.11 ± 0.09	.006
	WM	1.15 ± 0.17	1.08 ± 0.12	.08

Note:—FA indicates fractional anisotropy; MD, mean diffusivity.

^a *P* values are from ANCOVA, comparing patients with normal-appearing spine tissue at the C2–3 level (*n* = 14) with controls in terms of WM and GM DKI measures adjusted for age, sex, and disease duration.

The error variance was allowed to differ across subject groups to remove the unnecessary assumption-of-variance homogeneity. A paired-sample *t* test was used to compare WM and GM at the lesion level with corresponding normal-appearing tissue in terms of each DKI measure.

Pearson correlations were used to characterize the association of the DKI measures from the whole cervical spine and from the GM and WM, separately, with spinal cord volume and area and EDSS. All *P* values are reported as 2-sided significance levels without adjustment for multiple comparisons and were considered statistically significant when *P* < .05.

RESULTS

Nineteen patients had a median EDSS score of 2.5 (range = 1–6.5). Mean disease duration from the diagnosis was 7.3 ± 5.2 years, while mean disease duration from symptom onset was 10.1 ± 7.8 years. Fifty-nine T2 hyperintense lesions were identified in 18 of 19 patients, with a median of 3 lesions per patient (range = 0–8).

Cross-sectional mean MK and fractional anisotropy (both unitless) and mean diffusivity ($\times 10^{-3}$ mm²/s) values in patients and controls for the whole cervical spinal cord examined are reported in Fig 3. Compared with controls, fractional anisotropy and MK were significantly decreased (respectively, *P* = .0009 and *P* = .003) and mean diffusivity was increased (*P* = .009) in patients.

In patients with MS, when mean diffusivity, MK, and fractional anisotropy values of sections with lesions were compared with the values in sections of normal-appearing spine tissue, the 3 parameters differed significantly (Table 1): fractional anisotropy and MK were lower and mean diffusivity was higher in lesions than in normal-appearing spine tissue (all *P* < .0001).

Mean MK, fractional anisotropy, and mean diffusivity values of GM and WM ROIs were compared at the C2–3 level in healthy subjects and patients with MS without visible lesions at that level (*n* = 14); the results are reported in Table 2. In patients, normal-appearing WM fractional anisotropy and normal-appearing GM MK values were significantly decreased compared with those in healthy controls while mean diffusivity, GM fractional anisotropy, and WM MK were not significantly different across the 2 groups of subjects.

MK and mean diffusivity values were significantly inversely correlated to each other in the whole SC, in lesions, and in normal WM (*r* = −0.76, *P* = .0006; *r* = −0.2, *P* = .01; and *r* = −0.69, *P* = .001, respectively) but not in the gray matter (*P* = .9).

The mean cervical cord cross-sectional area measured at C2–3 was 0.93 ± 0.06 cm² in the patient group, significantly lower than that in the control group (0.94 ± 0.08 cm², *P* = .04). Mean C2–4 volume of the cervical spinal cord was 2.70 ± 0.34 cm³ in patients and 2.96 ± 0.36 cm³ in controls (*P* = .7).

Table 3: The mean of DKI measures for the 2 groups, based on the median EDSS score^a

Measure	Location	Group 1 (n = 11)	Group 2 (n = 8)	P Value ^b
FA	WC	0.54 ± 0.04	0.49 ± 0.06	.002
	GM	0.74 ± 0.19	0.65 ± 0.22	.01
	WM	0.53 ± 0.09	0.50 ± 0.09	.1
MD	WC	0.92 ± 0.09	0.95 ± 0.09	.001
	GM	0.70 ± 0.21	0.75 ± 0.23	.001
	WM	0.96 ± 0.15	1.03 ± 0.14	.5
MK	WC	1.07 ± 0.11	1.06 ± 0.10	.01
	GM	1.13 ± 0.13	1.10 ± 0.09	<.0001
	WM	1.09 ± 0.15	1.08 ± 0.14	.3

Note:—FA indicates fractional anisotropy; MD, mean diffusivity; WC, whole cord.

^a Group 1: EDSS score ≤ 2.5; group 2: EDSS score ≥ 3.0.

^b P values are from ANCOVA, comparing groups 1 and 2 in terms of the indicated DKI measure adjusted for age, sex, and disease duration.

Finally, we did not find any significant correlation of SC, MK, fractional anisotropy, and mean diffusivity values with either spine volume or spine area, except for the WM MK and cervical spine volume ($r = 0.58$ and $P = .0089$).

Likewise, no significant correlations were found among any MK, fractional anisotropy, and mean diffusivity values and EDSS. However, when the patients were stratified into 2 groups on the basis of the median EDSS score, more disabled patients (group 2) showed significantly lower fractional anisotropy and MK and higher mean diffusivity of the total cervical SC after correcting for age, sex, disease duration, and number of lesions. Most interesting, the locally sampled GM region showed lower MK and fractional anisotropy and higher mean diffusivity in the more disabled class, while the locally sampled WM did not show significant differences between the EDSS groups. Total and regional SC MK, fractional anisotropy, and mean diffusivity values from the 2 groups of patients are compiled in Table 3.

DISCUSSION

The spinal cord is frequently involved in MS, and it is a clinically eloquent site of damage with a relevant contribution to the accumulation of irreversible physical disability.⁴² There is growing evidence indicating that MS tissue damage in both the brain and SC is not limited to WM but also involves the GM.¹³ Our DKI study in patients with MS showed extensive cervical spinal cord damage and particularly more severely at the lesional level than in normal-appearing tissue. This is in agreement with previous DTI studies that found decreased fractional anisotropy values and increased mean diffusivity values in the cervical SC of patients with MS in comparison with healthy controls.^{16,20} The pathologic substrate underlying the changes in DTI metrics is represented by demyelination and axonal loss occurring in spinal cord T2-visible lesions and in normal-appearing tissue.^{43,44} Both demyelination and axonal loss lead to an increase of the extracellular volume,⁸ which is reflected by reduced fractional anisotropy and increased mean diffusivity. In addition, intracellular abnormalities that determine the formation of new barriers, such as cell debris, inflammatory changes, and gliosis, restrict water isotropically and can cause reductions in fractional anisotropy.⁸

More recently, several pathologic studies^{8-11,45} demonstrated that extensive demyelination and neuronal loss occur in the SC GM. Although neuronal loss appears to be predominantly related to local GM plaques, interneuron atrophy occurs in both myelinated and demyelinated areas.⁴⁶ In line with these findings, our

study showed a significant decrease of MK in the SC normal-appearing GM of patients compared with controls. Although we can only speculate about the pathologic nature of the GM MK change, it is likely to reflect both the presence of GM lesions below the resolution of conventional T2-weighted scans and the degeneration of GM neurons secondary to axonal transactions in the WM. Although we did not find a significant association between SC lesion count and GM MK ($r = 0.3$, $P = .1$),

there was a trend toward a significant positive association between the decrease of WM MK and that of GM MK ($r = 0.44$, $P = .06$), suggesting a possible interplay between injury in WM and GM.

While in WM, fractional anisotropy was sensitive to disease-related tissue damage and there was a trend toward significance for mean diffusivity and MK, in GM, only MK was significantly different between patients and controls, suggesting that it could be a more sensitive metric for evaluating the GM than mean diffusivity and fractional anisotropy. While standard DTI metrics can characterize the diffusion of water molecules in 3D space, they are not able to provide more specific information about its microenvironment. For example, mean diffusivity can indicate that the average water diffusion distance is small, but it cannot differentiate whether the small diffusion distance is due to a more viscous environment or the presence of more barriers, such as cell membranes.²⁵ A decrease in MK more clearly represents a reduction in diffusional heterogeneity; in the case of spinal cord tissue, this is very likely associated with degenerative changes and neuronal shrinkage.^{25,26,29,47} Hence, MK is a more natural indicator of tissue microstructural properties because diffusional non-Gaussianity is a direct consequence of the presence of barriers and compartments.

The lack of correlation between average mean diffusivity and MK in the GM of our patients and the poor correlation between the 2 metrics in lesional SC further supports the notion that MK of the GM can provide information about the underlying tissue microarchitecture that is different and complementary to that obtained with conventional DTI.

We did not find a significant correlation between any of the DKI-derived metrics in the global and regional cervical SC and the EDSS score. This result may be influenced by the small sample size and the narrow range of EDSS scores for most patients. However, when the patients were stratified on the basis of the median EDSS score into 2 groups with high and low disability, more disabled patients showed significant differences in total SC and GM DKI metrics compared with less disabled patients. This finding suggests that the severity of SC GM damage might have a role in the development of irreversible disability and is consistent with the results of previous MR imaging studies of SC GM by using magnetization-transfer imaging.^{12,14}

This study has some limitations. The number of patients enrolled allowed us to investigate the potential of a new MR imaging technique such as DKI, but it is relatively low, and our results will

need to be confirmed in a larger sample including patients with different disease courses.

The small size of the SC and the moderate resolution of DWI sequences make it difficult to avoid partial volume effects especially in relation to GM and WM assessment; however, the group level changes in the DKI metrics are robust and consistent with expectations. We acknowledge that even though patients and controls were not exactly sex-matched, all our statistical analyses were corrected for age and sex, thus limiting the possibility of lack of sex-matching being a confounding factor. In addition, although we found a moderate correlation between WM injury and cord volume as already reported in the literature,⁹ we found no association between any of the GM DKI metrics and cord volume or area, suggesting that the difference between patients and controls is not entirely attributable to partial volume effects. Furthermore, because the spatial resolution of our DKI images did not allow a more detailed identification of the ventral and lateral white matter columns, we limited our laminar assessment to the dorsal columns and the central GM region. Finally, a better interpretation of MK changes in the GM of the MS spinal cord will be available when the pathologic substrates are identified by post-mortem high-resolution MR imaging and/or quantitative histopathologic studies.

CONCLUSIONS

DKI of the cervical spinal cord in patients with MS can be useful for a better characterization of lesions and normal-appearing white and gray matter damage, with acquisition times compatible with clinical applications. With DKI, MK can be obtained simultaneously with conventional DTI-derived parameters; because its structural sensitivity is not limited to spatially oriented tissue structures, it can provide additional information complementary to that provided by DTI. Although our SC DKI findings are preliminary, our study supports the results of previous studies on DTI of the SC and suggests that gray matter damage may play a key role in accrual of disability in MS.

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REFERENCES

- Noseworthy JH, Lucchinetti CF, Rodriguez M, et al. Multiple sclerosis. *N Engl J Med* 2000;343:938–52
- Ikuta F, Zimmerman HM. Distribution of plaques in seventy autopsy cases of multiple sclerosis in the United States. *Neurology* 1976;26:26–28
- Bjartmar C, Wujek JR, Trapp BD. Axonal loss in the pathology of MS: consequences for understanding the progressive phase of the disease. *J Neurol Sci* 2003;206:165–71
- Rocca MA, Mastrorlando G, Horsfield MA, et al. Comparison of three MR sequences for the detection of cervical cord lesions in patients with multiple sclerosis. *AJNR Am J Neuroradiol* 1999;20:1710–16
- Kidd D, Thorpe JW, Thompson AJ, et al. Spinal cord MRI using multi-array coils and fast spin echo. II. Findings in multiple sclerosis. *Neurology* 1993;43:2632–37
- Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited. *Curr Opin Neurol* 2002;15:239–45
- Filippi M, Campi A, Colombo B, et al. A spinal cord MRI study of benign and secondary progressive multiple sclerosis. *J Neurol* 1996;243:502–05
- Nijeholt GJ, Bergers E, Kamphorst W, et al. Post-mortem high-resolution MRI of the spinal cord in multiple sclerosis: a correlative study with conventional MRI, histopathology and clinical phenotype. *Brain* 2001;124:154–66
- Gilmore CP, DeLuca GC, Bö L, et al. Spinal cord atrophy in multiple sclerosis caused by white matter volume loss. *Arch Neurol* 2005;62:1859–62
- Gilmore CP, Bö L, Owens T, et al. Spinal cord gray matter demyelination in multiple sclerosis—a novel pattern of residual plaque morphology. *Brain Pathol* 2006;16:202–08
- Gilmore CP, Geurts JJ, Evangelou N, et al. Spinal cord grey matter lesions in multiple sclerosis detected by post-mortem high field MR imaging. *Mult Scler* 2009;15:180–88
- Agosta F, Absinta M, Sormani MP, et al. In vivo assessment of cervical cord damage in MS patients: a longitudinal diffusion tensor MRI study. *Brain* 2007;130:2211–19
- Farrell JA, Smith SA, Gordon-Lipkin EM, et al. High b-value q-space diffusion-weighted MRI of the human cervical spinal cord in vivo: feasibility and application to multiple sclerosis. *Magn Reson Med* 2008;59:1079–89
- Zackowski KM, Smith SA, Reich DS, et al. Sensorimotor dysfunction in multiple sclerosis and column-specific magnetization transfer-imaging abnormalities in the spinal cord. *Brain* 2009;132:1200–09
- Inglese M, Bester M. Diffusion imaging in multiple sclerosis: research and clinical implications. *NMR Biomed* 2010;23:865–72
- Agosta F, Benedetti B, Rocca MA, et al. Quantification of cervical cord pathology in primary progressive MS using diffusion tensor MRI. *Neurology* 2005;64:631–35
- Benedetti B, Valsasina P, Judica E, et al. Grading cervical cord damage in neuromyelitis optica and MS by diffusion tensor MRI. *Neurology* 2006;67:161–63
- Ciccarelli O, Wheeler-Kingshott CA, McLean MA, et al. Spinal cord spectroscopy and diffusion-based tractography to assess acute disability in multiple sclerosis. *Brain* 2007;130:2220–31
- Clark CA, Werring DJ, Miller DH. Diffusion imaging of the spinal cord in vivo: estimation of the principal diffusivities and application to multiple sclerosis. *Magn Reson Med* 2000;43:133–38
- Hesseltine SM, Law M, Babb J, et al. Diffusion tensor imaging in multiple sclerosis: assessment of regional differences in the axial plane within normal-appearing cervical spinal cord. *AJNR Am J Neuroradiol* 2006;27:1189–93
- Ohgiya Y, Oka M, Hiwatashi A, et al. Diffusion tensor MR imaging of the cervical spinal cord in patients with multiple sclerosis. *Eur Radiol* 2007;17:2499–504
- Reich DS, Smith SA, Zackowski KM, et al. Multiparametric magnetic resonance imaging analysis of the corticospinal tract in multiple sclerosis. *Neuroimage* 2007;38:271–79
- Valsasina P, Rocca MA, Agosta F, et al. Mean diffusivity and fractional anisotropy histogram analysis of the cervical cord in MS patients. *Neuroimage* 2005;26:822–28
- van Hecke W, Nagels G, Emonds G, et al. A diffusion tensor imaging group study of the spinal cord in multiple sclerosis patients with and without T2 spinal cord lesions. *J Magn Reson Imaging* 2009;30:25–34
- Jensen JH, Helpern JA. MRI quantification of non-Gaussian water diffusion by kurtosis analysis. *NMR Biomed* 2010;23:698–710
- Wu EX, Cheung MM. MR diffusion kurtosis imaging for neural tissue characterization. *NMR Biomed* 2010;23:836–48

27. Falangola MF, Jensen JH, Babb JS, et al. **Age-related non-Gaussian diffusion patterns in the prefrontal brain.** *J Magn Reson Imaging* 2008;28:1345–50
28. Hui ES, Cheung MM, Qi L, et al. **Towards better MR characterization of neural tissues using directional diffusion kurtosis analysis.** *Neuroimage* 2008;42:122–34
29. Lu H, Jensen JH, Ramani A, et al. **Three-dimensional characterization of non-gaussian water diffusion in humans using diffusion kurtosis imaging.** *NMR Biomed* 2006;19:236–47
30. Grossman EJ, Ge Y, Jensen JH, et al. **Thalamus and cognitive impairment in mild traumatic brain injury: a diffusional kurtosis imaging study.** *J Neurotrauma* 2012;29:2318–27
31. Raab P, Hattingen E, Franz K, et al. **Cerebral gliomas: diffusional kurtosis imaging analysis of microstructural differences.** *Radiology* 2010;254:876–81
32. Jensen JH, Falangola MF, Hu C, et al. **Preliminary observations of increased diffusional kurtosis in human brain following recent cerebral infarction.** *NMR Biomed* 2011;24:452–57
33. Hori M, Fukunaga I, Masutani Y, et al. **New diffusion metrics for spondylotic myelopathy at an early clinical stage.** *Eur Radiol* 2012;22:1797–802
34. Polman CH, Reingold SC, Edan G, et al. **Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria.”** *Ann Neurol* 2005;58:840–46
35. Reese TG, Heid O, Weisskoff RM, et al. **Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo.** *Magn Reson Med* 2003;49:177–82
36. Jones DK, Horsfield MA, Simmons A. **Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging.** *Magn Reson Med* 1999;42:515–25
37. Skare S, Li T, Nordell B, et al. **Noise considerations in the determination of diffusion tensor anisotropy.** *Magn Reson Imaging* 2000;18:659–69
38. Tabesh A, Jensen JH, Ardekani BA, et al. **Estimation of tensors and tensor-derived measures in diffusional kurtosis imaging.** *Magn Reson Med* 2011;65:823–36
39. Freund P, Wheeler-Kingshott C, Jackson J, et al. **Recovery after spinal cord relapse in multiple sclerosis is predicted by radial diffusivity.** *Mult Scler* 2010;16:1193–202
40. Losseff NA, Webb SL, O’Riordan JI, et al. **Spinal cord atrophy and disability in multiple sclerosis: a new reproducible and sensitive MRI method with potential to monitor disease progression.** *Brain* 1996;119(pt 3):701–08
41. Mikheev A, Nevsky G, Govindan S, et al. **Fully automatic segmentation of the brain from T1-weighted MRI using Bridge Burner algorithm.** *J Magn Reson Imaging* 2008;27:1235–41
42. Rashid W, Davies GR, Chard DT, et al. **Increasing cord atrophy in early relapsing-remitting multiple sclerosis: a 3 year study.** *J Neurol Neurosurg Psychiatr* 2006;77:51–55
43. DeLuca GC, Ebers GC, Esiri MM. **Axonal loss in multiple sclerosis: a pathological survey of the corticospinal and sensory tracts.** *Brain* 2004;127:1009–18
44. Mottershead JP, Schmierer K, Clemence M, et al. **High field MRI correlates of myelin content and axonal density in multiple sclerosis: a post-mortem study of the spinal cord.** *J Neurol* 2003;250:1293–301
45. Bot JC, Blezer EL, Kamphorst W, et al. **The spinal cord in multiple sclerosis: relationship of high-spatial-resolution quantitative MR imaging findings to histopathologic results.** *Radiology* 2004;233:531–40
46. Gilmore CP, Donaldson I, Bö L, et al. **Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord.** *J Neurol Neurosurg Psychiatr* 2009;80:182–87
47. Jensen JH, Helpert JA, Ramani A, et al. **Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging.** *Magn Reson Med* 2005;53:1432–40

Is Severe Pain Immediately after Spinal Augmentation a Predictor of Long-Term Outcomes?

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ABSTRACT

BACKGROUND AND PURPOSE: Severe, immediate postprocedural pain and the need for analgesics after vertebroplasty can be a discouraging experience for patients and caregivers. The goal of this study was to investigate whether the presence of severe pain immediately after vertebroplasty predicts short- and long-term pain relief.

MATERIALS AND METHODS: A chart review was performed to categorize patients regarding pain severity and analgesic usage immediately after vertebroplasty (< 4 h). "Severe" pain was defined as at least 8 of 10 with the 10-point VAS. Outcomes were pain severity and pain medication score and usage at 1 month and 1 year after vertebroplasty. Outcomes and clinical characteristics were compared between groups by using the Wilcoxon signed-rank test and the Fisher exact test.

RESULTS: Of the 429 vertebroplasty procedures identified, 69 (16%) were associated with severe pain, and 133 (31%) were associated with analgesic administration immediately after the procedure. The group experiencing severe pain had higher preprocedure median VAS rest pain scores (5 [IQR, 2–7]) and activity pain scores (10 [IQR, 8–10]) compared with patients who did not experience severe pain (3 [IQR, 1–6]; $P = .0208$, and 8 [IQR, 7–10]; $P = .0263$, respectively). At 1 month postprocedure, VAS rest and activity pain scores were similar between the severe pain group and the nonsevere pain group ($P = .16$ and $P = .25$, respectively) and between the group receiving pain medication and the group not receiving pain medication ($P = .25$ and $P = .67$, respectively). This similarity continued for 1 year after the procedure. Analgesic usage was similar among all groups at 1 year postprocedure.

CONCLUSIONS: Patients with severe pain immediately after vertebroplasty have similar long-term outcomes compared with patients without severe pain.

ABBREVIATIONS: IQR = interquartile range; VAS = visual analog scale

Spinal augmentation procedures, including vertebroplasty and kyphoplasty, have been used widely for palliation of pain-related osteoporotic and pathologic compression fractures of the spine. The literature abounds with both prospective and retrospective studies attempting to characterize many different aspects of the spinal augmentation procedures such as procedure efficacy, characteristics of fractures in success of augmentation, sequelae of spinal augmentation procedures, and a variety of other topics.^{1–4} However, there is a paucity of research investigating clinical signs or symptoms directly related to the procedure as predictors of outcome after spinal augmentation.

Severe, immediate postprocedural pain; pain before hospital discharge; and the need for analgesics after vertebroplasty can be a discouraging experience for patients and caregivers. Despite the literature establishing vertebroplasty as a technique for management of painful compression fractures, the short- and long-term outcomes in patients with severe, immediate postprocedural pain, to our knowledge, have not been investigated previously. The goal of our current study is to investigate whether the presence of severe pain immediately after spinal augmentation procedures or the need for immediate postprocedure analgesics predicts short- and long-term pain relief. In addition, our study will attempt to determine whether characteristics of the patient or the procedure can predict which patients will experience severe pain immediately after the procedure.

MATERIALS AND METHODS

Study Population and Data Retrieval

Institutional review board approval was obtained before this retrospective study. A vertebroplasty patient data base maintained at

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Table 1: Vertebroplasty patient and procedure characteristics

	Type of Pain				Pain Medication		
	All	Severe	Nonsevere	P Value	Given	Not Given	P Value
No. patients	429	69	360		133	296	
Patient characteristics							
Age (median, IQR)	75 (65–82)	75 (65–82)	75 (65–83)	.99	75 (65–83)	75 (65–82)	.66
Female (%)	257 (40)	41 (59)	216 (60)	.99	88 (66)	169 (57)	.09
No. with chronic, untreated fractures (%)	142 (33)	27 (39)	115 (32)	.27	59 (44)	83 (28)	.0012
No. with fractures because of malignancy (%)	74 (18)	15 (24)	59 (17)	.21	25 (20)	49 (18)	.49
Median VAS rest pain score (IQR)	4 (1–6)	5 (2–7)	3 (1–6)	.0208	3 (1–6)	4 (1–6)	.54
Median VAS activity pain score (IQR)	9 (7–10)	10 (8–10)	8 (7–10)	.0263	10 (8–10)	9 (7–10)	.0022
Median pain duration (months, IQR)	2 (1–4)	2 (1–3)	2 (1–4)	.76	1 (1–3)	2 (1–4)	.0317
No. receiving pain medication (%)	401 (99)	60 (98)	341 (99)	.56	126 (99)	275 (99)	.99
Median pain medication score (IQR)	3 (3–3)	3 (3–3)	3 (3–3)	.85	3 (3–3)	3 (3–3)	.0058
Vertebroplasty procedure characteristics							
Median cement volume (mL) (IQR)	3.5 (2.0–5.0)	3.5 (2.0–5.0)	3.2 (2.0–4.6)	.88	3.7 (2.0–5.0)	3.0 (2.0–4.5)	.15
Unilateral needle placement (%)	306 (77)	46 (74)	260 (78)	.51	89 (75)	217 (78)	.51
Median no. levels treated (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	.84	1 (1–2)	1 (1–2)	.28
3+ levels treated (%)	48 (11)	11 (16)	37 (10)	.21	22 (17)	26 (9)	.0205
Complications (%)	95 (23)	17 (25)	78 (22)	.75	30 (23)	65 (22)	.99
Cement embolus (%)	19 (4)	4 (6)	15 (4)	.53	7 (5)	12 (4)	.62
Extravertebral leakage (%)	75 (17)	12 (18)	63 (18)	.87	22 (17)	53 (18)	.89

our institution was the source of data for this study. Patients in this data base have previously been included in other published studies that have not specifically examined patients with immediate postprocedure severe pain.^{1,4–14} Patients who underwent a vertebroplasty procedure at our institution from 2005–2011 were included in the study. Patients were excluded if they did not have immediate postprocedure pain data within 3 hours after the vertebroplasty or at either 1 month or 1 year postprocedure.

Retrospective medical chart review was performed to confirm data base records and retrieve additional clinical information. Data recorded included preprocedure descriptors (demographics; pain severity; prescribed analgesics; number, level, and acuity of each fracture; number of chronic fractures that were not treated because they were not amenable to vertebroplasty; and benign or malignant nature of the fracture), procedural descriptors (unilateral vs bilateral transpedicular approach, number of augmentations performed, distribution of cement, and complications), and postprocedural descriptors (pain severity and medications administered within 3 hours after the procedure and at 1-month and 1-year follow-ups). Pain severity was measured at both rest and activity by using the 10-point VAS.¹⁵ Medication scores were recorded as follows: 0 = no medications, 1 = over-the-counter analgesics, 2 = non-narcotic prescription medication as needed, 3 = oral narcotic analgesic as needed, 4 = scheduled oral narcotic or analgesic patches, and 5 = intravenous narcotics.

Patients were categorized by pain and analgesic requirements within 3 hours of vertebroplasty. Patients were divided into 2 groups: those with immediate postprocedure pain scores ≥ 8 (“severe pain group”) and those whose pain scores were < 8 (“non-severe pain group”) in the 3 hours after the vertebroplasty procedure. “Immediate postprocedure pain” was defined as that recorded before discharge from the hospital on the day of the procedure, typically 2–4 hours after vertebroplasty. Patients were also divided into whether they received pain medication in the 3 hours immediately after the procedure.

Statistical Analysis

We performed statistical analyses by using JMP (version 9; SAS Institute, Cary, North Carolina). Continuous variables were presented as median and IQR, and categorical variables were presented as percentages. Preprocedural, procedural, and postprocedural characteristics and outcomes were compared between groups by using the Wilcoxon signed-rank test and the Fisher exact test. Statistical significance was defined as $P < .05$.

RESULTS

All vertebroplasty procedures performed from 2005–2011 by 8 independent operators were identified. Of 877 total procedures performed during this timeframe, 448 (51%) procedures were excluded because they lacked 3-hour postprocedure pain data or lacked either 1-month or 1-year follow-up information on pain and medication, leaving 429 included procedures. Of these 429 procedures, 69 (16%) were associated with severe pain in the 3 hours after the vertebroplasty procedure. A total of 133 (31%) of 429 procedures were associated with administration of some pain medications in the 3 hours after the vertebroplasty procedure.

Overall characteristics were very similar between the severe pain/pain medication groups and their respective control groups (Table 1). The severe pain group had significantly higher preprocedure median VAS rest pain scores (5 [IQR, 2–7]) compared with the nonsevere pain group (3 [IQR, 1–6]) ($P = .0208$). Median VAS activity pain scores were also significantly higher in the severe pain group (10 [IQR, 8–10]) compared with the nonsevere pain group (8 [IQR 7–10]) ($P = .0263$). The patient group that received pain medication immediately after the procedure also had higher median VAS activity pain scores (10 [IQR, 8–10]) compared with the group that did not receive pain medication (9 [IQR, 7–10]) ($P = .0022$). There was a higher percentage of patients in the pain medication group with chronic fractures who were not treated because they were not amenable to vertebroplasty compared with the control group (59 [44%] of 133 vs 83 [28%] of 296; $P = .0013$). Patients in the pain medication group

Table 2: Postvertebroplasty pain and medication usage at 1-month and 1-year follow-ups

	Type of Pain			P Value	Pain Medication		P Value
	All	Severe	Nonsevere		Given	Not Given	
One-month follow-up							
No. patients (% lost to follow-up)	399 (7)	68 (1)	331 (8)		123 (8)	276 (7)	
No. patients with pain scores	369	61	308		113	256	
Median VAS rest pain score (IQR)	0 (0–3)	2 (0–3)	0 (0–3)	.16	0 (0–2)	0 (0–3)	.25
Median VAS activity pain score (IQR)	4 (0–6)	3 (0–5)	4 (0–6)	.25	3 (0–6)	4 (0–6)	.67
No. patients with pain medication scores	383	60	323		119	264	
Median pain medication score (IQR)	3 (0–4)	3 (0–4)	3 (1–4)	.17	3 (1–4)	3 (0–4)	.33
Change in pain medication score from prevertebroplasty							
Unchanged (%)	99 (26)	12 (20)	87 (27)	.34	31 (26)	68 (26)	.99
Improved (%)	167 (43)	21 (35)	146 (45)	.16	52 (43)	115 (44)	.99
Worsened (%)	117 (31)	27 (45)	90 (28)	.0097	36 (31)	81 (31)	.99
One-year follow-up							
No. patients (% lost to follow-up)	307 (28)	46 (33)	261 (28)		100 (25)	207 (30)	
No. patients with pain scores	288	44	244		93	195	
Median VAS rest pain score (IQR)	0 (0–2)	0 (0–3)	0 (0–2)	.0247	0 (0–3)	0 (0–2)	.43
Median VAS activity pain score (IQR)	3 (0–6)	4 (0–6)	3 (0–6)	.17	3 (0–6)	3 (0–6)	.78
No. patients with pain medication scores	176	29	147		59	117	
Median pain medication score (IQR)	3 (1–4)	3 (1–4)	3 (1–4)	.30	3 (1–4)	3 (1–4)	.65
Change in pain medication score from prevertebroplasty							
Unchanged (%)	63 (36)	9 (31)	54 (37)	.67	25 (42)	38 (32)	.24
Improved (%)	63 (36)	9 (31)	54 (37)	.67	23 (39)	40 (34)	.62
Worsened (%)	50 (28)	11 (38)	39 (27)	.26	11 (19)	39 (33)	.0514

also had a shorter median duration of pain before the procedure compared with the control group (1 month [IQR 1–3] vs 2 months [IQR 1–4]; $P = .0378$). There was no difference in the percentage of patients who had 3 or more levels treated between the severe pain group and the nonsevere pain group ($P = .21$). However, there was a higher percentage of these patients in the pain medication group compared with the control group (22 [17%] of 133 vs 26 [9%] of 296; $P = .0205$). All other clinical and procedural characteristics were similar between the severe pain group and the nonsevere pain group and between the pain medication group and the no-pain-medication group.

Rates of loss to follow-up were similar between the severe pain group and the nonsevere pain group and between the pain medication group and the no-pain-medication group at 1 month and 1 year after the procedure (Table 2). At 1 month postprocedure, VAS rest and activity pain scores were similar between the severe pain group and the nonsevere pain group ($P = .16$ and $P = .25$, respectively) and between the pain medication group and the no-pain-medication group ($P = .25$ and $P = .67$, respectively). However, a significantly higher percentage of patients had worsened medication scores (ie, from a score of 1 for over-the-counter narcotics to a score of 3 for prescription narcotics) in the severe pain group at 1 month compared with the nonsevere pain group (27 [45%] of 60 vs 90 [28%] of 323; $P = .0097$). At 1 year postprocedure, VAS rest and activity pain scores were similar between the severe pain group and the nonsevere pain group and between the pain medication group and the no-pain-medication group. Medication scores at 1 year were statistically similar between all groups, though the severe pain group still demonstrated a higher percentage of patients with worsened medication scores compared with the nonsevere pain group (11 [38%] of 29 vs 39 [27%] of 147; $P = .26$).

DISCUSSION

This study demonstrated that severe, postprocedure pain after spine augmentation did not predict greater pain severity at either 1 or 12 months after the procedure compared with patients not experiencing severe, postprocedure pain. This equivalence in pain outcomes was present, though the patients with severe, immediate postprocedure pain presented with greater baseline pain compared with the control group. We did observe that patients with severe pain were more likely to have a worsened medication score, indicating a need for stronger analgesics, at 1 month and 1 year postprocedure compared with patients who did not have severe pain. This finding may explain why patients with severe pain reported similar levels of pain at 1 month and 1 year postprocedure compared with patients without severe pain; however, we could not confirm if or how frequently patients were taking these analgesics. Taken together, these findings are highly relevant to spinal augmentation practitioners, as they can reassure patients that severe, postprocedure pain does not mean that their medium-term and long-term pain outcomes will be suboptimal.

In addition to providing prognostic clarity, our study can also be used to identify which factors, if any, will predict the occurrence of severe, immediate postprocedure pain. The only factor noted to correlate with such pain was the severity of baseline pain, but that parameter alone likely will not provide substantial guidance. Among the numerous factors that logically might predict immediate pain severity—including numbers of treated levels, unipedicular or bipedicular approaches, cement leakage, or chronic fractures that were untreated because they were not amenable to vertebroplasty—none correlated with severe, immediate pain. Patients who had 3 or more levels treated were more likely to receive pain medication immediately after the procedure compared with patients who had fewer levels treated; however, the

incidence of reported severe pain was similar between these 2 groups.

Previous studies have evaluated the predictive value of early pain severity after spine augmentations. In a study of 181 vertebroplasty procedures, Hodler et al¹⁶ described that immediate postprocedural pain relief was the best predictor of midterm outcome of vertebroplasty. Weill et al¹⁷ showed that pain reduction achieved initially remained stable in 73% of their patients after 6 months. Heini et al¹⁸ also found stable results after 1 year. Our current study expands on this prior literature by offering larger patient cohorts and detailed analysis of potential factors that might influence long-term outcomes.

Our study had several limitations. First, a large number of patients were excluded from the study on the basis of incomplete records at 3 hours postprocedure or at 1 month or 1 year postprocedure. It is unclear how this may have affected the findings of the study. Second, although pain is the most common complaint and can be debilitating, the use of the subjective pain scoring (0–10) was likely a suboptimal evaluation tool of the effectiveness of vertebroplasty.^{19–22} In some cases in our study, pain at the puncture site continued for a few days after the procedure; therefore, VAS scores may have improved further if they had been evaluated later.²⁰ Better functional assessment of patient response to vertebroplasty is likely necessary, as subjective assessment of pain scales is subject to substantial interobserver and intraobserver variability. Third, as with most studies on vertebroplasty, there was a potential for bias when patients are evaluated at follow-up. It is possible that the nurse or physician administering the follow-up questions could have influenced the responses of the patients. Furthermore, it is possible that responses to the follow-up questions were occasionally provided by family members or health care providers who interacted with the patients on a daily basis, particularly with cases in which the patient was unable to give responses because of disability or dementia.¹ Fourth, although we could identify new prescriptions for analgesics after the procedure, we could not confirm if and how frequently patients were actually taking this medication. Finally, new fractures during the follow-up interval may have confounded pain outcomes. A number of patients who had immediate postprocedure relief had recurrent pain symptoms at the short- or long-term follow-up secondary to factors such as new metastatic lesions or development of new compression fractures.

CONCLUSIONS

Patients with severe pain after vertebroplasty have similar long-term outcomes and improvements compared with patients with no severe pain. Patient and procedural characteristics did not predispose patients to having immediate severe pain after vertebroplasty.

Disclosures: Jennifer McDonald—UNRELATED: Grants/Grants Pending: GE Healthcare. David Kallmes—UNRELATED: Consultancy: ev3,* Codman,* Medtronic,* Grants/Grants Pending: MicroVention,* Micrus,* ev3,* Benvenue,* Sequent,* Royalties: UVA Patent Foundation; Payment for Development of Educational Presentations: ev3,* CareFusion,* Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: MicroVention.* (*Money paid to institution.)

REFERENCES

1. Layton KF, Thielen KR, Koch CA, et al. **Vertebroplasty, first 1000 levels of a single center: evaluation of the outcomes and complications.** *AJNR Am J Neuroradiol* 2007;28:683–89
2. Masala S, Mastrangeli R, Petrella MC, et al. **Percutaneous vertebroplasty in 1,253 levels: results and long-term effectiveness in a single centre.** *Eur Radiol* 2009;19:165–71
3. McKiernan F, Faciszewski T, Jensen R. **Quality of life following vertebroplasty.** *J Bone Joint Surg Am* 2004;86-A:2600–06
4. Rad AE, Kallmes DF. **Pain relief following vertebroplasty in patients with and without localizing tenderness on palpation.** *AJNR Am J Neuroradiol* 2008;29:1622–26
5. Rad AE, Kallmes DF. **Correlation between preoperative pain duration and percutaneous vertebroplasty outcome.** *AJNR Am J Neuroradiol* 2011;32:1842–45
6. Rad AE, Gray LA, Sinaki M, et al. **Role of physical activity in new onset fractures after percutaneous vertebroplasty.** *Acta Radiol* 2011;52:1020–23
7. Miller FG, Kallmes DF, Buchbinder R. **Vertebroplasty and the placebo response.** *Radiology* 2011;259:621–25
8. McDonald RJ, Gray LA, Cloft HJ, et al. **The effect of operator variability and experience in vertebroplasty outcomes.** *Radiology* 2009;253:478–85
9. McDonald RJ, Achenbach SJ, Atkinson EJ, et al. **Mortality in the vertebroplasty population.** *AJNR Am J Neuroradiol* 2011;32:1818–23
10. Leake CB, Brinjikji W, Cloft HJ, et al. **Trends of inpatient spine augmentation: 2001–08.** *AJNR Am J Neuroradiol* 2011;32:1464–68
11. Knavel EM, Rad AE, Thielen KR, et al. **Clinical outcomes with hemi-vertebral filling during percutaneous vertebroplasty.** *AJNR Am J Neuroradiol* 2009;30:496–99
12. Khosla A, Diehn FE, Rad AE, et al. **Neither subendplate cement deposition nor cement leakage into the disk space during vertebroplasty significantly affects patient outcomes.** *Radiology* 2012;264:180–86
13. Harvey RE, Kallmes DF. **Discharge disposition following vertebroplasty.** *AJNR Am J Neuroradiol* 2011;32:1614–16
14. Ehteshami Rad A, Luetmer MT, Murad MH, et al. **The association between the duration of preoperative pain and pain improvement in vertebral augmentation: a meta-analysis.** *AJNR Am J Neuroradiol* 2012;33:376–81
15. Dworkin RH, Turk DC, Farrar JT, et al. **Core outcome measures for chronic pain clinical trials: IMMPACT recommendations.** *Pain* 2005;113:9–19
16. Hodler J, Peck D, Gilula LA. **Midterm outcome after vertebroplasty: predictive value of technical and patient-related factors.** *Radiology* 2003;227:662–68
17. Weill A, Chiras J, Simon JM, et al. **Spinal metastases: indications for and results of percutaneous injection of acrylic surgical cement.** *Radiology* 1996;199:241–47
18. Heini PF, Walchli B, Berlemann U. **Percutaneous transpedicular vertebroplasty with PMMA: operative technique and early results. A prospective study for the treatment of osteoporotic compression fractures.** *Eur Spine J* 2000;9:445–50
19. McGraw JK, Cardella J, Barr JD, et al. **Society of Interventional Radiology quality improvement guidelines for percutaneous vertebroplasty.** *J Vasc Interv Radiol* 2003;14:S311–15
20. Kobayashi K, Shimoyama K, Nakamura K, et al. **Percutaneous vertebroplasty immediately relieves pain of osteoporotic vertebral compression fractures and prevents prolonged immobilization of patients.** *Eur Radiol* 2005;15:360–67
21. Grados F, Depriester C, Cayrolle G, et al. **Long-term observations of vertebral osteoporotic fractures treated by percutaneous vertebroplasty.** *Rheumatology (Oxford)* 2000;39:1410–14
22. Alvarez L, Perez-Higueras A, Quinones D, et al. **Vertebroplasty in the treatment of vertebral tumors: postprocedural outcome and quality of life.** *Eur Spine J* 2003;12:356–60

Physiology-Based MR Imaging Assessment of CSF Flow at the Foramen Magnum with a Valsalva Maneuver

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ABSTRACT

BACKGROUND AND PURPOSE: MR imaging is currently not used to evaluate CSF flow changes due to short-lasting physiological maneuvers. The purpose of this study was to evaluate the ability of MR imaging to assess the CSF flow response to a Valsalva maneuver in healthy participants.

MATERIALS AND METHODS: A cardiac-gated fast cine-PC sequence with ≤ 15 -second acquisition time was used to assess CSF flow in 8 healthy participants at the foramen magnum at rest, during, and immediately after a controlled Valsalva maneuver. CSF mean displacement volume $\bar{V}_{CSF}$ during the cardiac cycle and CSF flow waveform A_{pp} were determined. A work-in-progress real-time pencil-beam imaging method with temporal resolution ≤ 56 ms was used to scan 2 participants for 90 seconds during resting, Valsalva, and post-Valsalva CSF flow, respiration, and HR were continuously recorded. Results were qualitatively compared with invasive craniospinal differential pressure measurements from the literature.

RESULTS: Both methods showed 1) a decrease from baseline in $\bar{V}_{CSF}$ and A_{pp} during Valsalva and 2) an increase in $\bar{V}_{CSF}$ and A_{pp} immediately after Valsalva compared with values measured both at rest and during Valsalva. Whereas fast cine-PC produced a single CSF flow waveform that is an average over many cardiac cycles, pencil-beam imaging depicted waveforms for each heartbeat and was able to capture many dynamic features of CSF flow, including transients synchronized with the Valsalva maneuver.

CONCLUSIONS: Both fast cine-PC and pencil-beam imaging demonstrated expected changes in CSF flow with Valsalva maneuver in healthy participants. The real-time capability of pencil-beam imaging may be necessary to detect Valsalva-related transient CSF flow obstruction in patients with pathologic conditions such as Chiari I malformation.

ABBREVIATIONS: A_{pp} = CSF flow waveform peak-to-peak amplitude; cine-PC = cine phase-contrast; HR = heart rate; PBI = pencil-beam imaging; $\bar{V}_{CSF}$ = CSF mean displacement volume

Invasive pressure studies have shown that physiologic challenges such as the Valsalva maneuver or coughing produce transient changes in intracranial and intraspinal pressures.¹ Although such transients are rarely of significance in healthy participants, for

patients with foramen magnum obstruction such as Chiari I malformation, these physiologic alterations may be responsible for producing headache and syringomyelia.²⁻⁵ In the past, attempts were made to use CSF pressure measurements with physiologic challenges as a clinical test.^{4,6} However, these methods have not gained widespread acceptance because they are invasive. Although noninvasive assessment of CSF flow pulsations by MR imaging that measure bidirectional CSF flow from pressure changes between the head and spine during a cardiac cycle^{7,8} can be used as a surrogate, all but one of the prior implementations of cine-PC MR imaging for CSF flow assessment required approximately 100 heartbeats, making it too long to use with a transient physiologic challenge. As a result, most cine-PC studies of CSF flow have only been used during quiet breathing, both in healthy participants and in patients with suspected CSF circulation abnormalities.⁷⁻¹⁴ The 1 exception is a 2006 abstract by Wentland et al¹⁵ reporting CSF flow during rest and Valsalva by using an undersampled projection reconstruction method with data acquisi-

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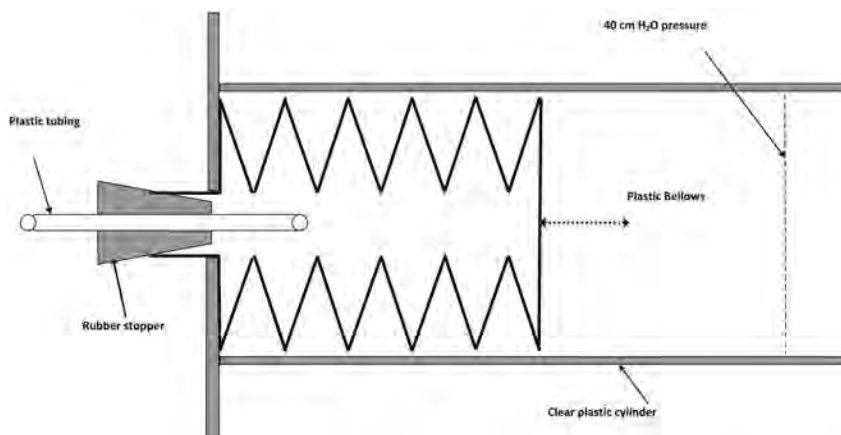


FIG 1. Schematic of Valsalva device used for experiments. Participants were directed to exhale into the plastic tubing with sufficient force to hold the end of the bellows at the 40-cm H₂O mark on the clear plastic cylinder. This provided a consistent and reproducible Valsalva-generated pressure.

tion times of as little as 16 heartbeats. For healthy participants, however, only minimal differences in flow were seen.

Our purpose was to evaluate the ability of MR imaging to assess the CSF flow response to a Valsalva maneuver. To determine this, we studied healthy participants and compared the assessed CSF flow response with that which can be inferred from known invasive craniospinal differential pressure measurements in healthy participants.¹

At first, we used a standard 2D cine-PC method with phase encoding and with a combination of undersampling and acceleration techniques to produce CSF flow images in approximately 15 seconds. We used this fast 2D cine-PC method to measure CSF flow before, during, and after a Valsalva maneuver. Even with these improvements in speed, the resultant images of CSF flow as a function of heart phase are nonetheless weighted averages of the phasic behavior over all of the cardiac cycles during the roughly 15-second data acquisition. Thus, the cine-PC method does not capture heartbeat-to-heartbeat transient behavior during the Valsalva maneuver, as demonstrated in the invasive pressure measurements of Williams.¹ Therefore, we also investigated a second method, that is, a work-in-progress real-time 1D PBI method with a temporal resolution of ≤ 56 ms. Cine-PC has superior spatial resolution compared with PBI but with a trade-off of longer data acquisition time than PBI. Because these 2 methods are quite different, they do not lend themselves to direct comparison. Therefore, we report here on the strengths and weaknesses of each in the evaluation of Valsalva-related changes in CSF flow at the foramen magnum.

MATERIALS AND METHODS

Nine healthy participants (mean age, 34.0 ± 11.1 years; 4 women) underwent MR imaging on a 3T scanner (Achieva; Philips Healthcare, Best, the Netherlands). Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act–compliant prospective study, and each participant signed an informed consent. None of the participants had a history of cardiovascular or neurologic disorders.

CSF Flow-Imaging Sequences

CSF flow pulsations were assessed with 2 different techniques. The first flow-imaging technique was a fast cine-PC sequence that was achieved by use of a combination of parallel imaging (sensitivity encoding factor = 2.1), half Fourier acquisition (half-Fourier factor = 0.6), and multiple-phase encodes per cardiac phase (turbo field-echo factor = 3). Other imaging parameters were TR, 11 ms; TE, 7.3 ms; field of view, 15×15 cm; and voxel size, $1 \times 1 \times 5$ mm. The velocity encoding was performed at 5 cm/s in all participants. This was repeated at 7 cm/s in a single patient because of aliasing. The sequence was retrospectively gated to the heartbeat via electrocardiographic leads.

The second flow-imaging technique was PBI. This pulse sequence excites a narrow cylinder or “pencil” region and has been described in detail previously.^{16,17} Because this sequence is not available for routine clinical use, a research version was used. The sequence consisted of a nominal 20-mm diameter cylindrical excitation by using a 2D spatially localized radio-frequency pulse with 8-turn spiral gradients, followed by a bipolar velocity-encoding gradient and a readout gradient applied along the axis of the cylinder (pencil beam). PBI thus provides spatial resolution only along the axis of the cylinder. The pencil beam was 64 mm in length, with a velocity encoding of 5 cm/s along the superior to inferior direction. Other imaging parameters were TR, 25–28 ms; TE, 3.8 ms; and flip angle, 10° . The bipolar phase-encoding gradient was alternated on sequential TRs, making the effective temporal resolution $2 \times \text{TR}$ (ie, 50–56 ms). No gating was used, but HR (from the electrocardiogram) and respiration (from the respiratory bellows) were continuously monitored by using the scanner’s physiologic recording system.

Confirmation of Bipolar Phase-Encoding Gradient Velocity Encoding

Using a MR imaging compatible flow pump (Compuflow 1000; Shelly Medical Technologies, Ontario, Canada), we performed a phantom study. The pump was programmed to provide waveforms with various shapes, flow rates, and amplitudes (in the physiologic range of CSF flow rates and amplitudes). The MR-measured flow in the phantom experiments was in excellent agreement ($\pm 5\%$) with the actual flow programmed in the pump.

Valsalva Maneuver

A nonmagnetic mechanical bellows device was designed and built to perform a controlled Valsalva maneuver in the MR imaging environment (Fig 1). It consists of flexible plastic bellows tubing closed at 1 end, and with the extension of the closed end calibrated for pressures ranging from 20–40 cm H₂O. To perform a Valsalva maneuver, a participant was asked to blow into the tube until the pressure reached a target pressure, typically 40 cm H₂O, indicated by the bellows extension to a mark on the cylinder. The participant was asked to

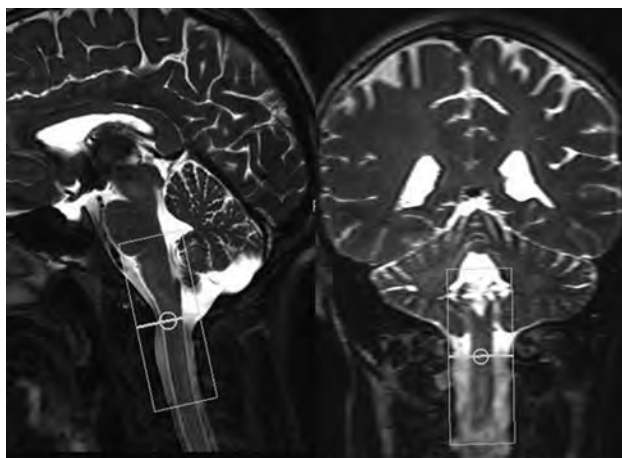


FIG 2. Sagittal and coronal T2-weighted images show PBI excitation cylinder extending from above the level of the foramen magnum to the C2–3 disk level.

continue to hold the bellows extension (and hence the pressure) in the tube for the duration of the Valsalva maneuver, typically 15–20 seconds. The Valsalva device was placed on the patient bed between the participant's legs, allowing the participant (via a mirror) and the operator to observe the airway pressure.

MR Imaging

Sagittal T1- or T2-weighted images were obtained to provide anatomic details. A total of 9 participants underwent scanning, along with use of the Valsalva maneuver. Before the availability of PBI, 7 participants were studied by use of fast cine-PC. The eighth participant underwent scanning with both fast cine-PC and PBI, and the ninth participant underwent scanning with PBI alone.

Fast cine-PC scans were performed in the axial plane at the level of the posterior arch of the first cervical vertebra (to avoid including the vertebral arteries in the imaging plane). Initially, the participant was asked to breathe quietly, and a resting scan was performed. The participant was then asked to blow into the tube and maintain a target pressure. Within a few seconds of the start of the Valsalva maneuver, a second cine-PC scan was obtained. A post-Valsalva cine-PC scan was then obtained approximately 5 seconds after the participant returned to quiet breathing. The resting, Valsalva, and post-Valsalva scans were repeated 3 times. The scans were also repeated if scanning stopped during acquisition because of interruption in gating from sudden and large changes in HR during the Valsalva maneuver. Mean HR during each scan was calculated and saved in the image header.

For PBI, the pencil beam was positioned along the cervical spinal canal extending from just above the level of the foramen magnum to the C2–3 disk level (Fig 2). Serial PBI scans were continuously acquired for approximately 90 seconds in duration. For each set of scans, the participant was asked 1) to breathe quietly for the first 15–20 seconds (by counting from 1–20), 2) to then start blowing into the tube to perform the Valsalva maneuver for a similar duration, and 3) to breathe quietly again after the end of Valsalva. Each set of PBI scans was repeated 3 times.

Image Analysis

QFLOW software (Phillips) was used to analyze the cine-PC data. Analysis of resting, Valsalva, and post-Valsalva images was performed by drawing a region of interest around the thecal sac. Output measures were flow rate (average velocity in the region of interest times its cross-sectional area), mean CSF displacement volume $\bar{V}_{CSF}$ during the cardiac cycle (defined as the average of the absolute values of systolic and diastolic displacement volumes), and oscillatory A_{pp} (sum of the absolute value of the maximal systolic and diastolic flow rates).

PBI data were analyzed by custom software written in Matlab (MathWorks, Natick, Massachusetts). CSF flow waveforms of average velocity (ie, averaged over the cross-section of the pencil beam) at each position along the PBI cylinder were plotted as a function of time, along with synchronously acquired HR and respiration data. To determine $\bar{V}_{CSF}$ from PBI, average velocity was multiplied by the cross-sectional area of the thecal sac, which was determined by using an independent anatomic scan.

Data Analysis

For each participant studied with cine-PC, values of $\bar{V}_{CSF}$, A_{pp} , and HR from 3 experiments were averaged. Using a paired *t* test, all 3 parameters were compared between resting vs Valsalva, Valsalva vs post-Valsalva, and resting vs post-Valsalva periods. All statistical analyses were performed with SPSS software (SPSS, Chicago, Illinois), with *P* < .05 considered significant. Because only 2 participants underwent scanning with PBI, statistical analyses were not performed. For these participants, the measured real-time CSF flow, HR, and respiration for the entire 90-second data acquisition that comprised the 3 periods are reported. To interpret these results, we evaluated them in qualitative comparison with craniospinal differential pressure measurements from the literature.¹

RESULTS

Fast Cine-PC

All participants were able to undergo scanning without difficulty. Measured values of $\bar{V}_{CSF}$, A_{pp} , and HR during the 3 different physiologic states are given in Table 1. CSF flow from 1 participant is shown in Fig 3. A decrease in both CSF flow parameters and an increase in HR were observed during Valsalva compared with the resting values. An increase in both CSF flow parameters and a decrease in HR were seen in post-Valsalva compared with during Valsalva. Finally, when comparing values in the post-Valsalva period with resting conditions, both $\bar{V}_{CSF}$ and A_{pp} were significantly higher, indicating a post-Valsalva rebound effect, but changes in HR were not statistically significant (Table 1).

Pencil-Beam Imaging

The On-line figure shows PBI results in the 2 participants studied. Although PBI can display flow at various positions along the 6.4-cm-long excitation cylinder, we focused on measurements restricted to the level of the C1 vertebra for this preliminary study. Although in both participants, changes in bidirectional CSF flow during the resting, Valsalva, and post-Valsalva periods were similar to those observed with fast cine-PC, simultaneous real-time display of respiration made it straightforward to observe the pre-

Table 1: CSF flow displacement volume per cardiac cycle, peak-to-peak amplitude, and heart rate at rest, during, and post-Valsalva maneuver, from fast cine-PC measurements

	R	VAL	P-VAL	Comparison (P Value)		
				R vs VAL	VAL vs P-VAL	R vs P-VAL
Mean CSF $\bar{V}_{CSF}$ (mL) per cardiac cycle	0.57 ± 0.24	0.37 ± 0.17	0.68 ± 0.19	<.001	<.001	<.05
A_{PP} (mL/s)	4.51 ± 1.61	3.52 ± 1.59	5.28 ± 1.49	<.007	<.001	≤.01
Heart rate (beats/min)	67.1 ± 10.4	78.5 ± 9.9	64.22 ± 6.6	<.002	<.001	NS

NS indicates not significant; P-VAL, post-Valsalva; R, resting; VAL, Valsalva.

Note:—All values are expressed as mean ± SD.

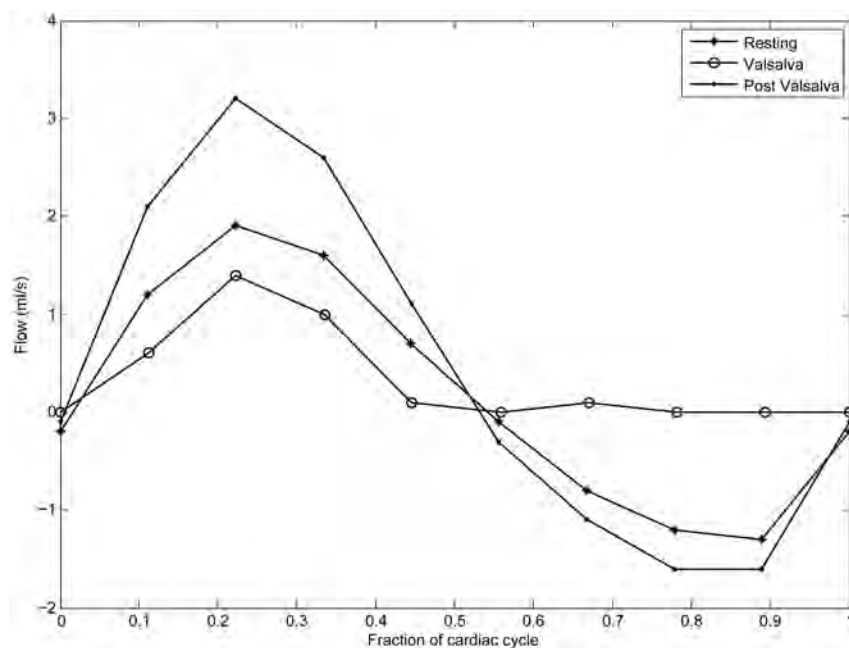


FIG 3. Cardiac cycle–dependent CSF flow before, during, and after a Valsalva maneuver in 1 participant by using fast cine-PC imaging. Flow in milliliters per second is shown as a function of time, normalized to the cardiac cycle. During Valsalva, $\bar{V}_{CSF}$ and A_{PP} decreased compared with resting. After Valsalva, both $\bar{V}_{CSF}$ and A_{PP} increased compared with during the maneuver, rebounding to values larger than resting.

cise timing of the Valsalva as well as the coincident heartbeat-to-heartbeat variations in both $\bar{V}_{CSF}$ and A_{PP} .

Qualitative Comparison with Previous Invasive Pressure Measurements

Both flow-imaging methods showed a CSF flow response to Valsalva consistent with invasive craniospinal differential pressure measurements by Williams,¹ (Fig 4, trace 4). The advantage of measuring CSF flow in real-time with PBI compared with fast cine-PC can be most appreciated by comparing the On-line figure with Fig 4. Here, similarities between transient changes in CSF flow waveforms during the resting, Valsalva, and post-Valsalva periods and the craniospinal differential pressure tracing (trace 4) are most apparent.

DISCUSSION

The results show that both fast cine-PC and PBI can be used to assess changes in CSF flow in response to a physiologic challenge, and lead to objective analysis of differences in response. CSF flow between the head and the spine decreases during Valsalva and increases past the resting flow rate in the post-Valsalva period. These findings are consistent with previous experiments performed by Williams¹ by using simultaneous invasive measure-

ments of CSF pressure in the head and spine. Table 2 shows the expected respiratory and cardiovascular changes as well as expected changes in intracranial and spinal pressure and CSF flow in 4 phases of the Valsalva maneuver.^{1,18} During performance of the Valsalva maneuver (phases I–II), spinal CSF pressure increases because of transmission of high intrathoracic pressure and consequent distension of the epidural veins.¹ The intracranial pressure also increases, but this increase is much less because of the associated decrease in cardiac output and reduced systolic arterial inflow to the head.^{1,18} The higher spinal pressure relative to intracranial pressure reduces CSF flow across the foramen magnum. Immediately after normal breathing resumes (phases III–IV), spinal pressure decreases because of reduction in intrathoracic pressure and collapse of the epidural veins. However, increased cardiac output and cranial arterial inflow momentarily increase intracranial pressure above resting value, resulting in the post-Valsalva rebound.¹ The

higher intracranial pressure relative to spinal pressure increases CSF flow across the foramen magnum.

Although fast cine-PC was able to show changes in CSF flow averaged during its 15-second acquisition time, PBI captured many dynamic features of CSF flow, including transients synchronized with the beginning and end of the Valsalva. In addition, our PBI results show that it is possible to noninvasively demonstrate heartbeat-to-heartbeat changes in CSF flow induced by differences in craniospinal pressure during Valsalva.¹ This finding is evident by comparing CSF flow changes seen in the On-line Figure to invasive pressure measurements of Williams¹ shown in Fig 4 (trace 4). Specifically, the gradual decrease in pressure during the Valsalva followed by the sharp rebound in pressure fluctuation amplitude on its termination is mirrored in the flow behavior revealed by the PBI approach. This is consistent with flow, especially in its transient behavior, being driven by corresponding fluctuations in pressure in the spinal column coincident with the heartbeat. It is important to note that these transient flow changes associated with the onset and termination of the Valsalva maneuver are seen with PBI and not with cine-PC. Finally, unlike fast cine-PC, PBI can simultaneously assess changes both above and below the level

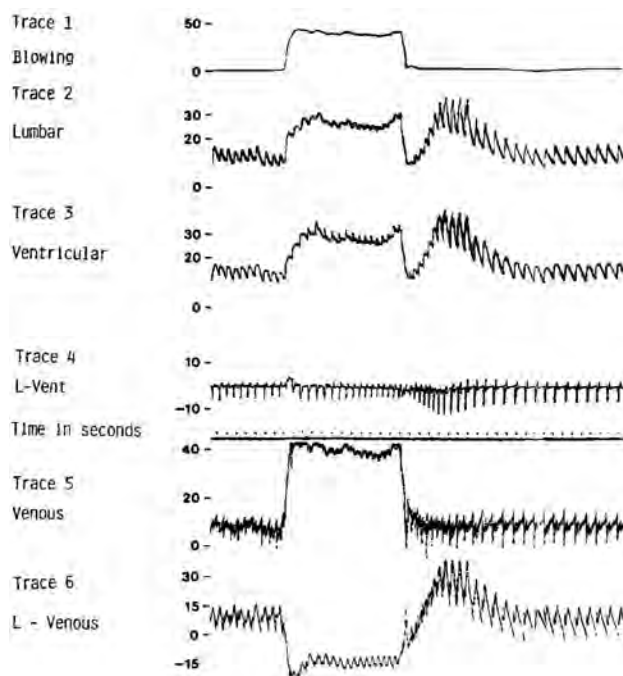


FIG 4. Figure shows invasive pressure measurements vs time. Trace 4 shows heartbeat-by-heartbeat changes in lumbar minus ventricular pressure (craniospinal pressure differential) with Valsalva. Note the similarities between trace 4 and CSF flow waveforms (panel 2) in the On-line figure. Note further that PBI captured many dynamic CSF flow features including transients precisely synchronized with timing of Valsalva similar to that seen here. Reproduced from Williams B. **Simultaneous cerebral and spinal fluid pressure recordings. I. Technique, physiology, and normal results.** *Acta Neurochir (Wein)* 1981; 58:167–85 with kind permission from Springer Science and Business Media.

of the foramen magnum, along the length of the excitation cylinder, and it does not require cardiac gating. This eliminates the possibility of gating interruption because of sudden changes in HR during the Valsalva maneuver (as described in the Results section). We believe that the real-time capability of PBI may be necessary to detect pathologically altered Valsalva-induced transient CSF flow changes in patients with pathologic conditions such as Chiari I malformation. PBI may also prove useful in evaluating a differential CSF flow response between pathology and health for other physiologic challenges such as cough, the Mueller maneuver, or neck flexion. Also, future work can include a Fourier analysis of the CSF flow waveform to determine changes synchronous with respiration during free breathing.

Although the physiology-based challenge approach we describe here to study alterations in CSF flow by MR imaging is not

a novel idea,^{15,17,19,20} its potential has not been fully explored. The justification for this approach comes from numerous previous experimental studies on CSF pressure in humans that used a physiologic challenge to assess the CSF pressure dynamics.^{1,2,4,6,21} Because CSF flow estimation by MR imaging is currently done in resting conditions, limited clinical usefulness has been found for quantitative CSF flow imaging in patient populations.^{12,22} This is likely because of a high variability in CSF flow pulsation amplitudes among patients because of differences in cerebral arterial and venous flow amplitudes, intracranial compliance, and the anatomy of CSF pathways.^{7,23,24} The major benefit of our approach is that by comparing cardiac cycle-related CSF flow for a participant at rest with that during and after a Valsalva maneuver, compensatory CSF flow changes can be assessed on an individualized basis, eliminating the need to compare CSF flow across participants.

Although physiology-based assessment of CSF flow may have a variety of clinical applications, we believe that the most immediate and obvious application is in the assessment of CSF flow in patients with Chiari I malformation. It is generally agreed that many of the symptoms and signs associated with Chiari I malformation are attributed to abnormal CSF circulation between the head and the spine secondary to obstruction of the foramen magnum.^{3,6,9–11,13,25,26} Williams and others^{1,4–6} have previously demonstrated this in patients with Chiari I malformation. On the basis of these results, we hypothesize that in patients with Chiari I malformation with a significant foramen magnum obstruction, the immediate post-Valsalva rebound in CSF flow shown here will be either absent or significantly reduced. We further expect that PBI will be able to observe this altered CSF flow transient and be of diagnostic value. We plan to address this hypothesis in future work.

Although we believe that PBI is superior to fast cine-PC in studying transient alterations in CSF flow in response to a physiologic challenge, it is still an emerging technology for quantitative estimation of CSF flow. As such, there are several limitations. First, the MR phase signal is not completely determined by flow within the spinal cord, as the nominal boundaries of the pencil beam may extend outside of the cord, allowing contributions from other flow sources such as the epidural veins. The shape and size of the pencil beam need to be selected so that non-CSF flow is minimally included in the PBI cross-section. Second, quantitative estimates of volume displacement similar to that obtained with cine-PC require determination of the size of the CSF pathway being assessed, which may also change during the Valsalva maneuver. This will also be the subject of future work. Finally, PBI at present is available only as a research sequence that limits its wide-

Table 2: Effects of Valsalva maneuver on intrathoracic pressure, cardiovascular system, intracranial and spinal pressures, and CSF flow

Mechanical Effect	Phase I	Phase II	Phase III	Phase IV
Intrathoracic pressure	↑	↑↑	↓	↓↓
Venous return	↓	↓↓	↑↑	↑↑
Left ventricular stroke volume	↑	↓↓	↓	↑↑
Blood pressure	↑	↓↓	↓	↑↑
Pulse rate		↑↑		↓↓
Intracranial pressure		↑		↑↑
Intraspinal pressure		↑↑		↓↓
CSF flow across foramen magnum		↓↓		↑↑

spread use. However, we believe that research may stimulate MR imaging vendors to make this sequence more readily available for routine clinical use.

CONCLUSIONS

Both fast cine-PC and PBI demonstrate a CSF flow response to Valsalva, consistent with previous invasive pressure measurements. Because cine-PC is a 2D technique, one can determine the CSF cross-sectional area allowing computation of absolute CSF flow. PBI must rely on a separate anatomic scan to translate measured average velocity over the pencil beam cross-section to flow. On the contrary, PBI captures transient changes in flow that cine-PC cannot. We believe that the real-time capability of PBI may be necessary to detect transient CSF flow changes in a pathologically altered Valsalva response in a patient population.

Disclosures: Rafeeqe Bhadelia—**RELATED:** Grant: Conquer Chiari Foundation,* Comments: money to pay for MR imaging scans, equipment, and volunteers. Neel Madan—**RELATED:** Grant: Conquer Chiari Foundation,* Comments: The institution received money for the research MR imaging scans. No money otherwise to me or my institution; **UNRELATED:** Consultancy: Near Infrared Imaging, Comments: Company developing a medical imaging device using photoacoustic tomography. There is no relevance to this study, other than it is in the broad category of medical imaging. Received stocks/options; **Expert Testimony:** expert testimony on imaging, although no cases relevant to this study. Yansong Zhao—**UNRELATED:** Employment: I am an employee of Philips Healthcare, Cleveland, Ohio. Mark Wagshul—**UNRELATED:** Payment for Lectures (including service on speaker bureaus): DoD,* NIH,* James Butler—**RELATED:** Consulting Fee or Honorarium: Beth Israel Deaconess Hospital. Samuel Patz—**RELATED:** Consulting Fee or Honorarium: Beth Israel Deaconess Hospital, Comments: I was paid as a Consultant Investigator for assistance with the research reported in the submitted manuscript. This also covered my assistance with data analysis and preparation of this manuscript. The Consultant fee was budgeted in a grant to Dr. Bhadelia (first author) and awarded to Beth Israel Deaconess Hospital from the Conquer Chiari Foundation. (*Money paid to institution.)

REFERENCES

- Williams B. Simultaneous cerebral and spinal fluid pressure recordings. I. Technique, physiology, and normal results. *Acta Neurochir (Wien)* 1981;58:167–85
- Heiss JD, Patronas N, DeVroom HL, et al. Elucidating the pathophysiology of syringomyelia. *J Neurosurg* 1999;91:553–62
- Sansur CA, Heiss JD, DeVroom HL, et al. Pathophysiology of headache associated with cough in patients with Chiari I malformation. *J Neurosurg* 2003;98:453–58
- Tachibana S, Iida H, Yada K. Significance of positive Queckenstedt test in patients with syringomyelia associated with Arnold-Chiari malformations. *J Neurosurg* 1992;76:67–71
- Williams B. On the pathogenesis of syringomyelia: a review. *J R Soc Med* 1980;73:798–806
- Williams B. Cough headache due to craniospinal pressure dissociation. *Arch Neurol* 1980;37:226–30
- Bhadelia RA, Bogdan AR, Wolpert SM. Analysis of cerebrospinal fluid flow waveforms with gated phase-contrast MR velocity measurements. *AJNR Am J Neuroradiol* 1995;16:389–400
- Enzmann DR, Pelc NJ. Normal flow patterns of intracranial and spinal cerebrospinal fluid defined with phase-contrast cine MR imaging. *Radiology* 1991;178:467–74
- Alperin N, Kulkarni K, Loth F, et al. Analysis of magnetic resonance imaging-based blood and cerebrospinal fluid flow measurements in patients with Chiari I malformation: a system approach. *Neurosurg Focus* 2001;11:E6
- Bhadelia RA, Bogdan AR, Wolpert SM, et al. Cerebrospinal fluid flow waveforms: analysis in patients with Chiari I malformation by means of gated phase-contrast MR imaging velocity measurements. *Radiology* 1995;196:195–202
- Hofkes SK, Iskandar BJ, Turski PA, et al. Differentiation between symptomatic Chiari I malformation and asymptomatic tonsillar ectopia by using cerebrospinal fluid flow imaging: initial estimate of imaging accuracy. *Radiology* 2007;245:532–40
- Krueger KD, Houghton VM, Hetzel S. Peak CSF velocities in patients with symptomatic and asymptomatic Chiari I malformation. *AJNR Am J Neuroradiol* 2010;31:1837–41
- McGirt MJ, Nimjee SM, Floyd J, et al. Correlation of cerebrospinal fluid flow dynamics and headache in Chiari I malformation. *Neurosurgery* 2005;56:716–21; discussion 716–21
- Bhadelia RA, Frederick E, Patz S, et al. Cough-associated headache in patients with Chiari I malformation: CSF flow analysis by means of cine phase-contrast MR imaging. *AJNR Am J Neuroradiol* 2011;32:739–42
- Wentland AL, Wieben O, Mistretta CA, et al. Technique for acquiring MR images of CSF flow during a Valsalva maneuver. *Proc Intl Soc Mag Reson Med*; 2006:1525
- Hardy CJ, Pearlman JD, Moore JR, et al. Rapid NMR cardiography with a half-echo M-mode method. *J Comput Assist Tomogr* 1991;15:868–74
- Maier SE, Hardy CJ, Jolesz FA. Brain and cerebrospinal fluid motion: real-time quantification with M-mode MR imaging. *Radiology* 1994;193:477–83
- Looga R. The Valsalva manoeuvre—cardiovascular effects and performance technique: a critical review. *Respir Physiol Neurobiol* 2005;147:39–49
- Bhadelia RA, Bogdan AR, Wolpert SM. Cerebrospinal fluid flow waveforms: effect of altered cranial venous outflow. A phase-contrast MR flow imaging study. *Neuroradiology* 1998;40:283–92
- Schroth G, Klose U. Cerebrospinal fluid flow. II. Physiology of respiration-related pulsations. *Neuroradiology* 1992;35:10–15
- Williams B. Simultaneous cerebral and spinal fluid pressure recordings. 2. Cerebrospinal dissociation with lesions at the foramen magnum. *Acta Neurochir (Wien)* 1981;59:123–42
- Tubbs RS, Beckman J, Naftel RP, et al. Institutional experience with 500 cases of surgically treated pediatric Chiari malformation type I. *J Neurosurg Pediatr* 2011;7:248–56
- Alperin N, Sivaramakrishnan A, Lichter T. Magnetic resonance imaging-based measurements of cerebrospinal fluid and blood flow as indicators of intracranial compliance in patients with Chiari malformation. *J Neurosurg* 2005;103:46–52
- Bhadelia RA, Bogdan AR, Kaplan RF, et al. Cerebrospinal fluid pulsation amplitude and its quantitative relationship to cerebral blood flow pulsations: a phase-contrast MR flow imaging study. *Neuroradiology* 1997;39:258–64
- Armonda RA, Citrin CM, Foley KT, et al. Quantitative cine-mode magnetic resonance imaging of Chiari I malformations: an analysis of cerebrospinal fluid dynamics. *Neurosurgery* 1994;35:214–23; discussion 223–24
- Houghton VM, Korosec FR, Medow JE, et al. Peak systolic and diastolic CSF velocity in the foramen magnum in adult patients with Chiari I malformations and in normal control participants. *AJNR Am J Neuroradiol* 2003;24:169–76

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