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ORIGINAL RESEARCH

Short- and Long-Term Hemodynamic and Clinical Effects of Carotid Artery Stenting

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BACKGROUND AND PURPOSE: Stenosis of the carotid artery may cause reduced hemodynamic and neural function that may be ameliorated with CAS. The goal of this study was to evaluate short- and long-term hemodynamic and clinical effects after CAS.

MATERIALS AND METHODS: Hemodynamic parameters were acquired by PCT within 1 week before CAS and at 1 week and 1 year (10–13 months) after CAS. In ACA territory, MCA territory, PCA territory, basal ganglia, anterior and posterior CWS and IWS, the rCBF, rCBV, and rMTT were determined in 20 patients with unilateral carotid artery stenosis who underwent CAS. MR and noncontrast CT were performed within 1 week before CAS. Noncontrast CT and carotid arteriography were performed immediately after CAS. Carotid arteriography was performed 1 year after CAS. MRS was performed in 3 measurements. The variance analysis was performed to determine whether there were significant differences among the 3 measurements.

RESULTS: No significant differences were found among rCBV in any territory ($P > .05$). In the non-PCA territories, rMTT decreased and rCBF increased at 1 week after CAS ($P < .01$), but there was no significant difference between 1-week and 1-year effects ($P > .05$). For MR spectroscopy, no significant differences were found between 1 week after CAS and pretreatment ($P > .05$); the 1-year scores improved significantly ($P < .01$).

CONCLUSIONS: The long-term hemodynamic and clinical results after treatment validated that CAS is a durable procedure. The 1-week hemodynamic effects can predict long-term effects.

ABBREVIATIONS: ACA = anterior cerebral artery; CAS = carotid artery stenting; CEA = carotid endarterectomy; CWS = cortical watershed; ISR = in-stent restenosis; IWS = internal watershed; PCA = posterior cerebral artery; PCT = perfusion CT; rCBF = relative cerebral blood flow; rCBV = relative cerebral blood volume; rMTT = relative mean transit time

Extracranial internal carotid artery stenosis accounts for 15%–20% of ischemic strokes, moreover, 14% and 23% of the patients with a TIA or stroke attributable to a high-grade intracranial stenosis had a further ipsilateral ischemic stroke over the next year, despite medical therapy.[1-3] CEA, as the treatment cornerstone, is of some benefit for patients with 50%–69% symptomatic stenosis and highly beneficial for those with 70% symptomatic stenosis or greater.[4] CEA, although effective, does have limitations, such as the strict indications and contraindications. Thanks to the development of safe and effective protection systems that have helped reduce the periprocedural neurologic complications in recent years, CAS is increasingly used as an alternative method to CEA for treatment of ICA stenosis.[5-7] Moreover, among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing CAS and the group undergoing CEA.[8]

Before or after CAS, PET, SPECT, PCT, and MR imaging have all been applied in the study of brain hemodynamics.[9] However, the scarce availability in most radiology departments is considered as a large obstacle in the choice of PET and SPECT. In addition, difficulty in obtaining a quantitative measurement by MR imaging has drawn attention for many years. PCT, applied more and more widely, can be easily performed and has further simplified the approach to brain perfusion evaluation.[10] Furthermore, PCT can be used to quantitatively estimate cerebral perfusion changes, such as an asymmetry in the hemisphere corresponding to the affected ICA, in patients with unilateral severe ICA stenosis.[11]

Some studies have investigated short-term hemodynamic effects after CAS by hemodynamic parameter measurement in the hemisphere on the side of the carotid stenosis,[9,12] but few studies have been designed to evaluate short- and long-term hemodynamic effects after CAS in the territories of main cerebral arteries, and few studies have evaluated not only hemodynamic but also clinical effects after CAS. The aim of our study was to evaluate short- and long-term hemodynamic and clinical changes after CAS, and to analyze the relevance between the 2 changes.

Materials and Methods

We included 20 patients (17 men, 3 women; mean age 64 ± 8 years; range 46–75 years) in this study between April 2006 and March 2009. Inclusion criteria were as follows: 1) patients with unilateral ICA stenosis (≥60%) and without contralateral ICA steno-occlusive disease

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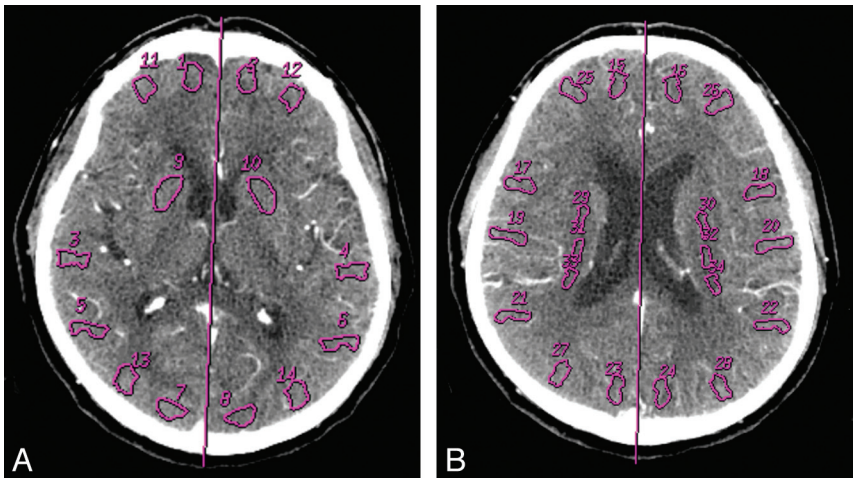

Fig 1. The ROIs of the 2 slabs in bilateral hemispheres. ROI maps show the level of the basal ganglia (*A*), including ACA territory (1–2), MCA territory (3–6), PCA territory (7–8), basal ganglia (9–10), anterior CWS (11–12), and posterior CWS (13–14); and also show the level of the body lateral cerebral ventricle (*B*), including ACA territory (15–16), MCA territory (17–22), PCA territory (23–24), anterior CWS (25–26), posterior CWS (27–28), and IWS (29–34).

who met criteria for CAS and who were treated with CAS; 2) carotid DSA performed within 1 week before CAS to investigate the stenosis vessel and degree; cerebral PCT performed within 1 week before CAS to evaluate hemodynamic changes attributable to a high-grade carotid stenosis; cerebral MR imaging and noncontrast CT performed within 1 week before CAS to define the intracranial diseases, such as cerebral infarction or any other diseases affecting cerebral perfusion; 3) cerebral noncontrast CT performed immediately after CAS to define intracranial complications, such as intracranial hemorrhage; PCT performed at 1 week and at 1 year (10–13 months) after CAS; carotid arteriography performed immediately after CAS to define the residual stenosis and at 1 year (10–13 months) after treatment to define ISR if present; 4) neural function testing performed with MR spectroscopy in the 3 measurements; and 5) possible complications of CAS and the adverse effects of radiographic examinations were fully explained to every patient, and all patients in this study signed informed consent for research.

Exclusion criteria were as follows: 1) in addition to ICA, any other intracranial artery steno-occlusive diseases, such as contralateral ICA; 2) except cerebral infarction, any other diseases affecting cerebral perfusion, such as brain tumor; 3) cerebral MR imaging, noncontrast CT, or cerebral PCT not performed in 1 week before CAS; and 4) patients who were lost to follow-up at 1 week or 1 year after treatment.

MR imaging examination was performed on a Signa Excite 1.5 MR scanner (GE Healthcare; Milwaukee, Wisconsin) with the following scanning sequences: 1) (FLAIR) T1WI: TR 2100 ms, TE 27 ms, TI 750 ms, FOV 24 cm × 24 cm; 2) T2WI: TR 4400 ms, TE 102 ms, FOV 24 cm × 18 cm, matrix 256 × 192; and 3) DWI: TR 5000 ms, TE 100 ms, b-value of 1000 seconds/mm^2.

DSA examination was performed with the Allura Xper FD 20 angiographic unit (Philips Medical Systems, Best, the Netherlands). On the angiograms of each patient (contrast medium 10 mL, bolus 3.5 ~ 4.0 mL/s, pressure 150 ~ 200 psi, 80 kVp, 20 mAs), the principal neuroradiologist measured the degree of carotid stenosis by percent diameter ratios.[13-16]

All CT scans were performed on a 16-section multidetector CT scanner (Light Speed 16; GE Healthcare). Noncontrast CT scans of the whole brain in an orientation parallel to the orbito-meatal line were obtained (5-mm section thickness, 5-mm section interval, 80 kVp, 120 mAs). From these images, 4 target sections for PCT examination were selected, which were judged from the level of the basal ganglia to the level of the upper portion of the lateral ventricles. Once the target cross-sections were selected, a bolus of 50 mL nonionic iodinated contrast agent was injected into the antecubital vein at an injection rate of 4.0 mL/s. Dynamic CT scans were then initiated 7 seconds after the start of injection with the following acquisition parameters: 80 kVp, 200 mAs, 50-second scanning time, and 50 images per section.

Postprocessing was performed by 1 neuroradiologist (with 6 years' experience in generating and interpreting PCT) from our institution, and he had no other involvement in the study. The image data were transferred to a dedicated workstation (Advantage Window 4.2; GE Healthcare) for postprocessing. In each patient, for the manual method, an arterial input ROI was placed in the ACA contralateral to the stenosis, and the venous input ROI was placed in the superior sagittal sinus.[17] By calculation of the software, he got the maps that could show the absolute parameter values: CBF (expressed in mL per 100 g brain per minute), CBV (expressed in mL per 100 g brain), and MTT (expressed in seconds).

To quantify changes in perfusion parameters in all the territories, the rater chose ROIs on the 2 slabs, the level of the basal ganglia, and the level of the body lateral cerebral ventricle. In consideration of perfusion differences between gray matter and white matter, the rater chose ROIs including only gray matter, except IWS ROIs, and ensured the exclusion of bone tissue, CSF, large vessels, and cerebral infarction from the ROIs. Because long-term variability increased with the use of a small ROI, though improved with the averaging of more pixel values,[17] the rater obtained some small ROIs in the same territory for the average parameter values. On the level of the basal ganglia (Fig 1*A*), the rater defined 5 ROIs in unilateral cerebral hemisphere as ACA territory, PCA territory, basal ganglia, anterior CWS, and posterior CWS, and, in view of many vessels in MCA territory, defined 2 ROIs as MCA territory. On the level of the body lateral cerebral ventricle (Fig 1*B*), the rater defined 4 ROIs in unilateral cerebral hemisphere corresponding to ACA territory, PCA territory, and anterior and posterior CWS, and, respectively, chose 3 ROIs as IWS and MCA territory. To the greatest extent possible, the rater kept the ROI size of every patient consistent in the same territory (basal ganglia ROI approximately 120 mm^2 in size, IWS ROI approximately 40 mm^2, any other ROI approximately 70 mm^2). Through this

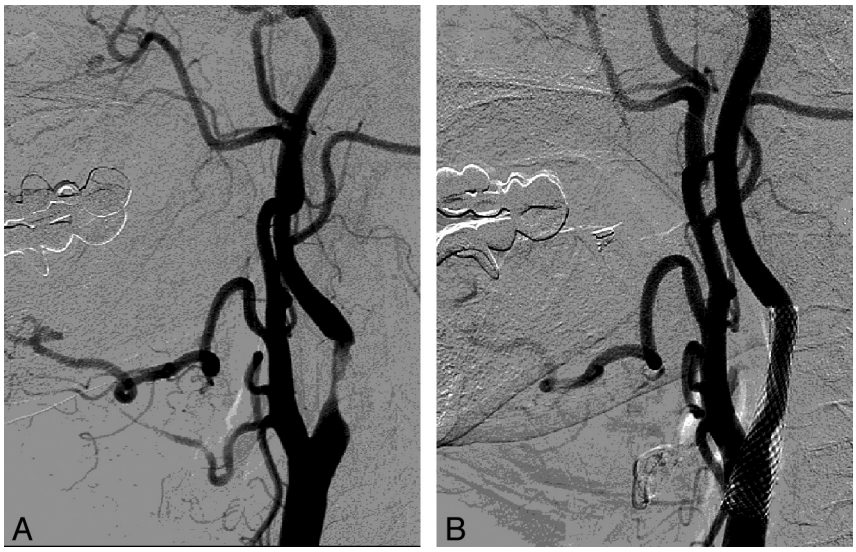

Fig 2. 95% stenosis (*A*) of right carotid artery in a patient aged 71 years and basically normal (*B*) after CAS.

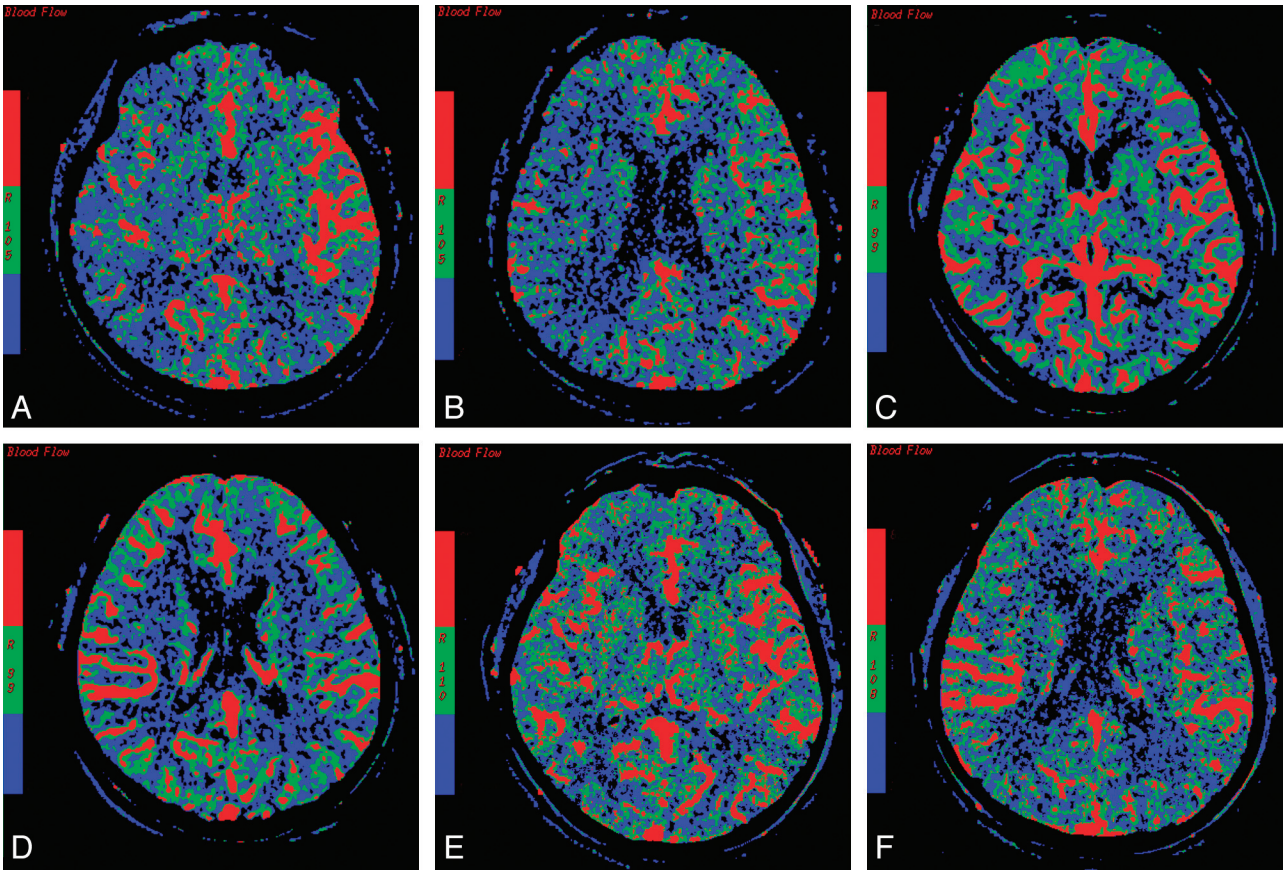

Fig 3. On the level of the basal ganglia (left) and the body lateral cerebral ventricle (right), CBF is decreased before CAS in the right hemisphere (*A, B*); CBF in the affected hemisphere is improved significantly at 1 week after CAS (*C, D*); at 1 year after CAS, CBF is similar to that shown at 1 week after CAS (*E, F*).

method, the rater obtained 7 territories and 17 ROIs in the unilateral cerebral hemisphere, and, except in the basal ganglia, calculated the average absolute values of CBF, CBV, and MTT in any other territory. In the analysis, to avoid the impact of intersubject variation, the rater chose relative perfusion values (the symptomatic hemisphere to asymptomatic hemisphere ratios), and then, respectively, obtained rCBF, rCBV, and rMTT. The rater assessed the imaging independently, blinded to clinical information.

Within 1 week before CAS, and at 1 week and 1 year after CAS, MR spectroscopy was performed by 1 neurologist (with 6 years' clinical experience) who had no other involvement in the study.

All of the statistical analyses were performed by SPSS statistical software (Version 17.0, SPSS, Chicago, Illinois). A P value $< .05$ was considered to indicate statistical significance. The variance analysis was performed to determine whether there were significant differences among 3 PCT parameters in all territories and among MR spec-

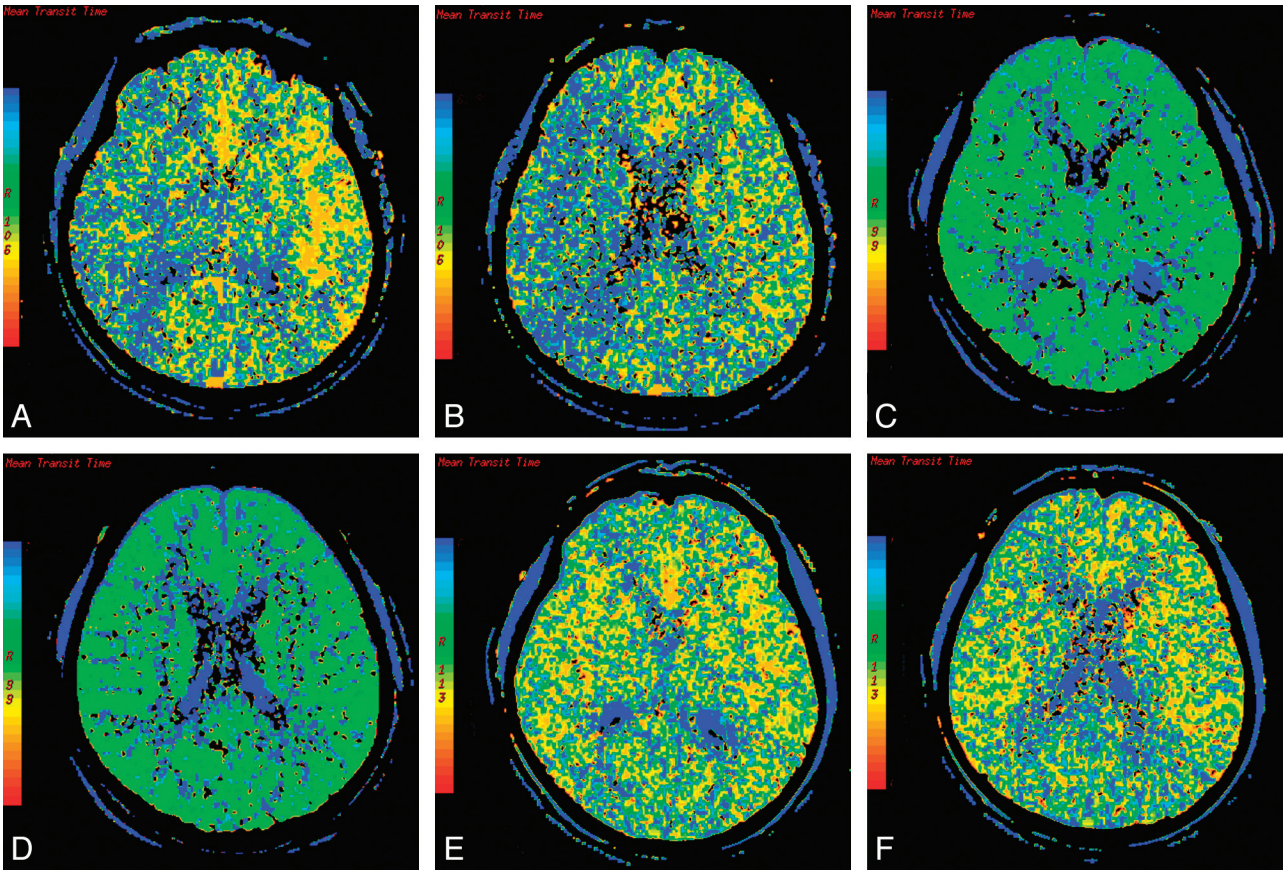

Fig 4. On the level of the basal ganglia (left) and the body lateral cerebral ventricle (right), MTT is increased before CAS in the right hemisphere compared with the left hemisphere (*A, B*). This hemispheric difference disappeared at 1 week after CAS (*C, D*); compared with 1 week after CAS, no hemodynamic changes were found at 1 year after CAS (*E, F*).

troscopy in the 3 measurements, and the least significant difference *t* test was used between any 2 measurements.

Results

The main MR imaging findings of 14 patients were multiple lacunar infarcts; 6 patients were observed with infarcts in the territory of stenosis of the ICA (the frontal lobe, 312 mm^2; the parietal lobe, 338 mm^2; the temporal lobe, 432 mm^2, 552 mm^2; and the basal ganglia, 112 mm^2, 120 mm^2). All 20 patients enrolled in this study did not present with any other diseases.

The mean stenosis degree of the ICAs in the 20 patients was 87% (range: 80 ~ 95%) before CAS (Fig 2*A*). In 17 patients, ICAs immediately restored to normal, according to arteriography after CAS (Fig 2*B*), and the residual stenosis range of 3 patients was 10 ~ 20%. The mean ICA stenosis degree of the 20 patients decreased to 2.5% (range: 0 ~ 20%). At 1 year after CAS, the carotid arteriography indicated that none of the 20 patients underwent significant ISR.

Hyperperfusion is classically defined as >100% increase in CBF compared with preoperative values,[18] so none was observed with hyperperfusion after CAS (Fig 3). The results showed the comparison of cerebral hemodynamics (Figs 3–5) and the comparison of relative perfusion parameters among the 3 measurements (Table 1). In the 3 measurements, no significant differences were found among rCBVs in any territory ($P > .05$). In the non-PCA territories, rMTT decreased and rCBF increased at 1 week after CAS ($P < .01$), but there was no significant difference between 1-week and 1-year effects after CAS ($P > .05$).

The results showed the comparison of MR spectroscopy among the 3 measurements (Table 2). No significant differences were found between 1 week after CAS and pretreatment ($P > .05$); at 1 year after CAS, the scores improved significantly ($P < .01$).

Discussion

In the presence of ICA stenosis, protective collateral circulation could rapidly open to maintain normal CBF.[19] In cases of severe ICA stenosis and deficient collateral circulation, hemispheric perfusion pressure is severely reduced, thus leading to maximal dilation of resistance vessels and chronic cerebral hypoperfusion,[20] which may cause cerebral autoregulation dysfunction.[21] Cerebral autoregulation protects the brain against changes in systemic blood pressure.[21] The normal autoregulator response following a change in systemic blood pressure is rapid, and is initiated and completed within 15–30 seconds.[22] After restoration of normal perfusion pressure after CAS, impaired autoregulatory mechanisms may adjust to the new steady state.[20] However, in the absence of cerebral autoregulation due to critical hypoperfusion, CBF is directly dependent on the systemic blood pressure, so correction of critical stenosis causes rapid and large changes in CBF leading to hyperperfusion and intracranial hemorrhage.[21]

Ogasawara et al[23] found that the onset of hyperperfusion

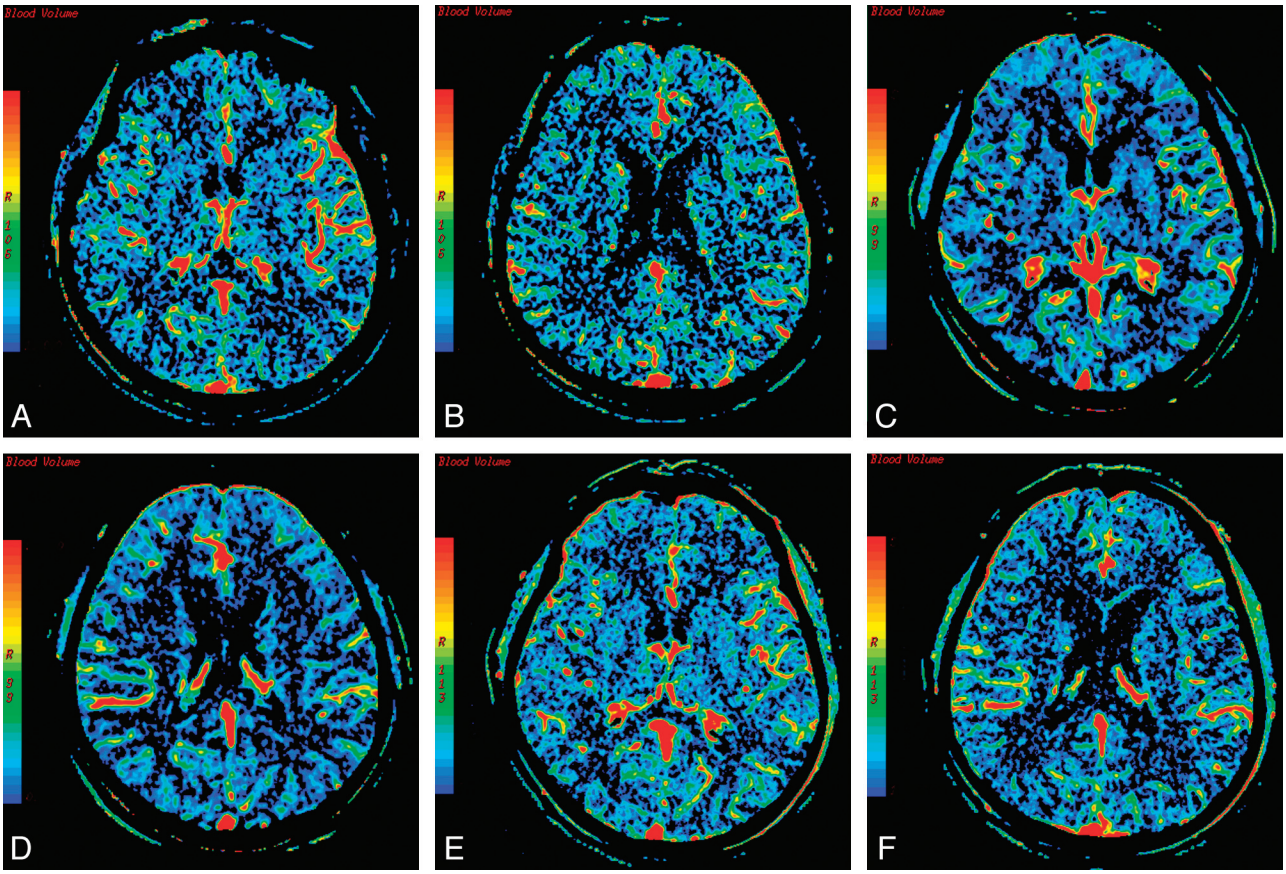

Fig 5. On the level of the basal ganglia (left) and the body lateral cerebral ventricle (right), CBV is decreased before CAS in the right hemisphere (*A, B*); this hemispheric difference has not disappeared at 1 week after CAS (*C, D*) or at 1 year after CAS (*E, F*).

Table 1: Comparison of relative perfusion parameters among pretreatment, 1 week, and 1 year groups

	rCBF				rCBV				rMTT			
	Pre	1 week	1 year	*P*	Pre	1 week	1 year	*P*	Pre	1 week	1 year	*P*
ACA territory	0.86 ± 0.06	0.95 ± 0.04	0.97 ± 0.07	0.00	1.02 ± 0.03	1.00 ± 0.01	0.99 ± 0.04	0.12	1.17 ± 0.05	1.03 ± 0.04	1.01 ± 0.06	0.00
MCA territory	0.81 ± 0.04	1.06 ± 0.05	1.03 ± 0.07	0.00	1.13 ± 0.09	1.12 ± 0.07	1.07 ± 0.08	0.06	1.41 ± 0.06	1.08 ± 0.04	1.07 ± 0.04	0.00
PCA territory	0.96 ± 0.06	1.00 ± 0.04	0.99 ± 0.02	0.08	1.02 ± 0.06	1.02 ± 0.04	1.03 ± 0.05	0.57	1.07 ± 0.05	1.05 ± 0.05	1.03 ± 0.06	0.06
Basal ganglia	0.85 ± 0.06	0.97 ± 0.04	0.96 ± 0.04	0.00	1.02 ± 0.07	0.98 ± 0.02	1.01 ± 0.05	0.16	1.20 ± 0.06	1.06 ± 0.04	1.05 ± 0.04	0.00
Anterior CWS	0.78 ± 0.03	0.97 ± 0.03	0.96 ± 0.02	0.00	1.08 ± 0.05	1.06 ± 0.06	1.05 ± 0.07	0.24	1.41 ± 0.05	1.10 ± 0.05	1.09 ± 0.04	0.00
Posterior CWS	0.77 ± 0.03	1.00 ± 0.02	0.98 ± 0.03	0.00	1.10 ± 0.07	1.09 ± 0.09	1.04 ± 0.06	0.11	1.43 ± 0.10	1.07 ± 0.06	1.08 ± 0.06	0.00
IWS	0.80 ± 0.04	0.94 ± 0.03	0.93 ± 0.04	0.00	1.05 ± 0.06	1.02 ± 0.05	1.04 ± 0.05	0.19	1.29 ± 0.10	1.09 ± 0.05	1.11 ± 0.07	0.00

Note:—For rCBF and rMTT, except in PCA territory, pretreatment vs 1 week or 1 year after CAS, $P < 0.01$; 1 week vs 1 year, $P > 0.05$.

Table 2: Comparison of MRS among pretreatment, 1 week, 1 year groups

	Pre	1 week	1 year	*P*
MRS Score	2.10 ± 0.64	2.05 ± 0.61	0.91 ± 0.30	0.00

Note:—For MRS, 1 week after CAS vs pretreatment, $P > 0.05$; 1 year after CAS vs pretreatment or 1 week after CAS, $P < 0.01$.

peaked within a period of 12 hours postoperation in those who had undergone CAS. According to Abou-Chebl et al,[24] hyperperfusion symptoms developed between 6 hours and 4 days postoperatively. Several authors have demonstrated, after surgery, maximal blood flow may occur in 3–4 days and fall to a steady state by day 7.[25,26] According to these conclusions, we analyzed that blood flow could achieve steady state by 1 week after CAS. In addition, long-term results in a large cohort of patients validated that the ISR rate was acceptable and the need for reintervention was low, unrelated to the characteristics of the device.[8] Progression of ISR after 6–12 months is uncommon over a 2- to 3-year period.[27] In view of long-term clinical outcomes, we evaluated 1-year (10–13 months) hemodynamic and clinical changes after CAS to predict long-term effects and analyzed the relevance between 1-week and 1-year changes.

In our study, except in PCA territory, rCBF increased significantly in other territories at 1 week after CAS ($P < .01$). Our data indicated that CBF improved significantly after amelioration of ICA stenosis, and the conclusion of Markus and Cullinane[28] was similar: there was no significant difference between rCBF measured at 1 week after CAS and that mea-

sured at 1 year after CAS ($P > .05$). The possible reason was that CBF could achieve a steady state at 1 week and 1 year after CAS.

Our results demonstrated that, in the 3 measurements, no significant differences were found between rCBV in all territories ($P > .05$). Similarly, Soinne et al[29] quantitatively evaluated hemodynamic changes before surgery and 3 and 100 days afterward, and then showed, for CBV values, that there were no significant interhemispheric differences at any stage. However, Waaijer et al[12] reported that rCBV was increased after treatment. We suggest this may be because, first, our ROIs were different from Waaijer et al's,[12] who chose ROIS only in MCA territory. Second, CBV, as a complex physiologic parameter,[30] depends on arterial, capillary, and venous compartments as well as parenchymal and pial components.

Except in PCA territory, rMTT decreased significantly in other territories at 1 week after CAS ($P < .01$). The results indicate that cerebral perfusion obviously improved after CAS. There was no significant difference between rMTT in any territory measured at 1 week after CAS and that measured at 1 year after CAS ($P > .05$). The conclusion shows the coherence of results between 1 week and 1 year, and, consequently, validated CAS as a durable procedure for amelioration of ICA stenosis. Our conclusion agrees with the study published by Soinne et al,[29] where, partly, they concluded rMTT decreased significantly in 3 and 100 days after surgery. However, Kluytmans et al[31] demonstrated that no significant alterations in MTT were observed in the hemisphere ipsilateral to the stenosed ICA 2–6 months after treatment. One reason might be that the variability of relative MTT was significantly lower than absolute MTT.[32]

In ACA territory, rCBF increased and rMTT decreased after CAS ($P < .01$). The absence or hypoplasia of the proximal ACA in 10% of subjects may allow similar perfusion parameters in both ACA distributions, even in tandem with a unilateral ICA stenosis. But in addition to the arterial segments of the circle of Willis, the ophthalmic artery, leptomeningeal vessels, and anastomoses between distal segments of the major cerebral arteries constitute secondary collaterals, and the number and size of these anastomotic vessels are greatest between the anterior and middle cerebral arteries.[33] Secondary collateral pathways are presumed to be recruited once primary collaterals at the circle of Willis have failed, and increasing severity of carotid stenosis has been correlated with a greater extent of collateralization,[33] so anastomoses between anterior and middle cerebral arteries may lead to differences between both ACA distributions in conjunction with unilateral ICA stenosis. In addition, absence of the anterior communicating artery could cause significant differences between both ACA distributions. However, rCBF and MTT changed nonsignificantly in PCA territory in the 3 measurements ($P > .05$). The results indicated that the influence of ICA stenosis in the territory is extremely small. The possible reasons for this are as follows: first, the number and size of these anastomotic vessels are smaller and fewer between the middle and posterior cerebral arteries, with even fewer between the posterior and anterior cerebral arteries;[33] second, the absence or hypoplasia of either posterior communicating artery in 30% may allow similar perfusion parameters in both PCA distributions.

For MR spectroscopy, no significant differences were found between 1 week after CAS and pretreatment ($P > .05$)—a possible reason for this is the short recovery time. However, at 1 year after CAS, the scores improved significantly ($P < .01$). The 1-year results showed long-term improvements in neural function in patients treated with CAS, and the results were similar in Turk et al,[34] who analyzed 3-month follow-up scores.

Our study analyzed hemodynamic and clinical effects before and after CAS, and evaluated the coherence of hemodynamic effects between 1 week and 1 year after CAS, emphasizing that 1-week hemodynamic follow-up has great value for predicting long-term effects and can help to avoid additional radioactive examinations. Moreover, we were able to evaluate cerebral hemodynamic changes after CAS in different cerebral artery territories. We chose ROIs in ACA territory, MCA territory, PCA territory, basal ganglia, and anterior and posterior CWS and IWS in bilateral hemispheres. Especially with IWS, we emphasized its improvement in hemodynamics after CAS, because Momjian-Mayor and Baron[35] demonstrated that severe hemodynamic compromise might underlie IWS infarction, and artery-to-artery embolism might play an important role in isolated CWS infarcts. Taking into consideration the influences of physiologic variations, individual differences, and postprocessing steps,[36] we specifically chose relative perfusion parameters in our study.

A limitation of the technique used in this study is that the 16-section multidetector CT scan was performed on just 4 levels, including the 4 levels of the basal ganglia and the body of the lateral cerebral ventricle, so it was short of total brain parameters, especially the posterior circulation parameters. Furthermore, with only 20 patients in our study, there were not enough cases to reflect the parameter variation trends, and, for this reason, more patients should be enrolled to acquire more authoritative data. Otherwise, taking drugs might influence the measurement results to a certain extent. Also, we only analyzed patients with unilateral ICA stenosis rather than bilateral ICA steno-occlusive disease.

Conclusions

The long-term hemodynamic and clinical results after treatment validated CAS as a durable procedure for amelioration of unilateral ICA stenosis. In addition, the coherence of hemodynamic results between 1 week and 1 year indicated that the 1-week hemodynamic effects after CAS could predict long-term effects.

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