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ORIGINAL RESEARCH

Analysis of the Influence of 4D MR Angiography Temporal Resolution on Time-to-Peak Estimation Error for Different Cerebral Vessel Structures

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BACKGROUND AND PURPOSE: Time-resolved MRA imaging is a promising technique for blood flow evaluation in case of cerebrovascular malformations. Unfortunately, 4D MRA imaging is a trade-off between spatial and temporal resolution. The aim of this study was to investigate the influence of temporal resolution on the error associated with TTP estimation from indicator dilution curves derived from different vascular structures.

MATERIALS AND METHODS: Monte Carlo simulation was performed to compute indicator dilution curves with known criterion standard TTP at temporal resolutions between 0.1 and 5 seconds. TTPs were estimated directly and by using 4 hemodynamic models for each curve and were compared with criterion standard TTP. Furthermore, clinical evaluation was performed by using 226 indicator dilution curves from different vessel structures obtained from clinical datasets. The temporal resolution was artificially decreased, and TTPs were estimated and compared with those obtained at the original temporal resolutions. The results of the clinical evaluations were further stratified for different vessel structures.

RESULTS: The results of both evaluations show that the TTP estimation error increases exponentially when one lowers the temporal resolution. TTP estimation by using hemodynamic model curves leads to lower estimation errors compared with direct estimation. A temporal resolution of 1.5 seconds for arteries and 2.5 seconds for venous and arteriovenous malformation vessel structures appears to be reasonable to achieve TTP estimations adequate for clinical application.

CONCLUSIONS: Different vessel structures require different temporal resolutions to enable comparable TTP estimation errors, which should be considered for achieving a case-optimal temporal and spatial resolution.

ABBREVIATIONS: CFM = curve fit model; GVM = gamma variate model; IDC = indicator dilution curve; LDRWM = local density random walk model; LNM = log-normal model; MI = model independent; mLNM = modified log-normal model; sGVM = simplified gamma variate model; TREAT = time-resolved echo-shared angiographic technique

Indicator and tracer dilution techniques are important diagnostic tools in today's clinical routine to obtain knowledge about macrovascular blood flow,[1] microvascular tissue perfusion,[2] or tracer kinetics between plasma and extravascular extracellular compartments.[3] All indicator dilution techniques have in common that a contrast agent is injected into a blood vessel upstream. As the contrast agent bolus travels through the vascular system, it is influenced by dispersion effects, which lead to a spreading of the bolus. The dispersed IDCs[4] of the contrast agent can then be measured downstream by using a variety of techniques.

Classic methods for acquisition of IDCs comprise the catheter-based acquisition of dye and thermodilution curves.[5,6] The spatial resolution of these techniques is very limited; this limitation has motivated the development of improved time-resolved imaging techniques, such as DSA[7] and 4D MRA.[8] The main benefits of DSA are the high spatial and temporal resolutions (<0.2 seconds). However, DSA image sequences provide only 2D projections. Therefore, multiple injections and image acquisitions are necessary to obtain a detailed overview of the 3D positions and courses of different vessels.

In contrast to DSA, time-resolved (4D) MRA allows monitoring of the whole cerebrovascular system at once, while no ionizing radiation is required. Furthermore, 4D MRA is less invasive, leading to a reduction of complication risks. The acquisition of 4D MRA image sequences has several benefits compared with DSA, but it is usually a trade-off between spatial and temporal resolutions. High spatial resolution is desired for improved differentiation of vascular structures and reduction of partial volume effects. Likewise, a high temporal resolution, in terms of more acquired images within a given time interval, is desired for proper blood flow reconstruction. So far, how the temporal resolution influences the precision of blood flow analysis and which temporal resolution is clinically required for a reasonable hemodynamic analysis, so that a case-optimal spatial resolution can be chosen for image acquisition, have not been evaluated in depth, to our knowledge.

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To date, only 2 studies have been performed to investigate the impact of the temporal resolution on the precision of parametric model fitting to IDCs. Benner et al[9] used computer simulations to measure the accuracy of gamma variate fits,[10] with respect to the time resolution and maximal signal drop. Lu and Monhan[11] investigated the error propagation of gamma variate fits, comparing different fitting algorithms. Both studies concluded that a temporal resolution of 2.6 seconds is necessary to yield good results by using the gamma variate model. However, both studies focused only on the gamma variate function and used only signal curves derived from MR perfusion-weighted imaging datasets. Therefore, a direct transfer of these findings to IDCs obtained from macrovascular blood flow may not be appropriate.

The aim of this study was to investigate the relation between 4D MRA temporal resolution and the precision of hemodynamic analysis in terms of time-to-peak estimation error. Therefore, Monte Carlo simulations and IDCs from clinical 4D MRA datasets were used for evaluation. It was hypothesized that higher temporal resolution does not lead to significant gains for hemodynamic analyses below a certain threshold. With this information, the minimal required number of frames per second can be estimated, allowing a case-specific optimization of the spatial resolution for MRA examinations.

Materials and Methods

4D MRA Image Acquisition

TREAT MRA[8] datasets were used in this study as the basis for Monte Carlo simulations and for evaluating the impact of the temporal resolution on TTP estimation errors by using real indicator dilution curves.

Overall, 20 TREAT MRA datasets of patients with AVMs were available for this evaluation. These datasets were acquired with a temporal resolution of 0.5 second on a 3T Trio scanner (Siemens, Erlangen, Germany) by using an 8-channel phased array head coil after application of contrast agent (approximately 20 mL of gadobenate dimeglumine, MultiHance; Bracco Altana Pharma, Konstanz, Germany) by using view sharing with $n = 3$ regions, TR = 2.54 ms, TE = 0.69 ms, flip angle = 20°, bandwidth = 810 Hz/Px, 6/8 partial Fourier in all 3 dimensions, an in-plane image resolution of 1.875 mm^2, 16 sections with 5-mm section thickness, and an FOV of 150×200 mm^2. Parallel imaging with a generalized autocalibrating partially parallel acquisition factor of 2 with 24 reference *k*-space lines for calibration was applied for acquisition speedup. The contrast agent was injected at a constant rate of 4 mL/s, leading to a total injection time of 5 seconds. The contrast agent injection was followed by a 20-mL isotonic saline flush.

Informed consent was obtained from all patients. The study was approved by the local ethics committee (No. 2706/2005).

Time-to-Peak Criterion and Parametric Models

Depending on the type of 4D MR image, several parameters of interest can be extracted from an IDC $s(t)$, which describes the concentration of the applied contrast agent at a time point t. Among others, these parameters comprise the regional blood flow and volume, mean transit time, and microvascular permeability. One parameter of general interest, which can be extracted from nearly any IDC, is the TTP. This parameter is defined as the time when the IDC achieves its maximum.

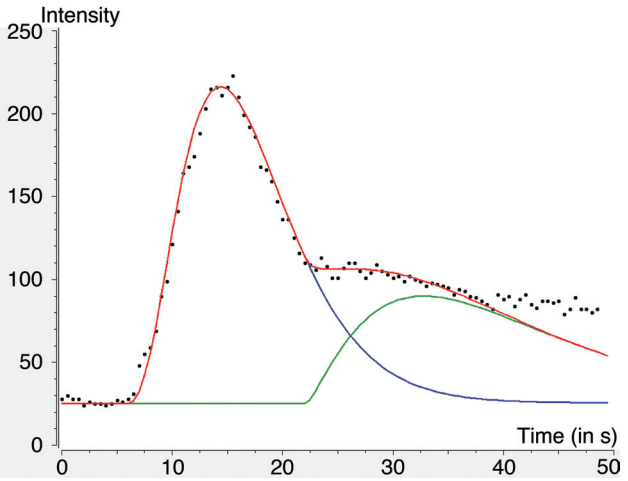

Fig 1. Discrete indicator dilution curve (*black dotted*) and fitted combination of 2 gamma variate functions (red) modeling the first (blue) and second bolus passages (green).

This criterion has been used in most previous indicator dilution studies. It has been shown that this parameter leads to better results[12] compared with other criteria, such as the time-to-maximum-slope parameter. An overview of typically used alternative bolus arrival time criteria is, for example, given by Shpilfoygel et al.[13]

The TTP parameter is especially important for 4D MRA imaging techniques because it reflects the temporal distribution of the contrast agent and can, therefore, be used as an indirect estimate of the blood flow velocity. Due to the discrete IDC representation, recirculation effects, and noise artifacts, which affect the shape of the curves, the direct estimation of the TTP parameter is often imprecise. Several parametric models have been proposed in the past to overcome these problems. Here, the main idea is to fit a model curve to the discrete IDC and estimate the TTP on the basis of the fitted model curve.

Apart from the MI TTP estimation based on the raw curves, 4 parametric models were evaluated in this work. These models comprise the sGVM, the LDRWM, the mLNM, and the reference-based linear CFM. The formulations and an outline of these models are given in the On-line Appendix.

Monte Carlo Evaluation

The Monte Carlo simulations were performed to investigate the influence of the temporal resolution on the TTP estimation error with known ground truth. The simulation setup used for this is similar to that described in a previous study.[12] Briefly, this setup consists of 7 parameter sets, which were extracted from different arterial and venous IDCs. These parameter sets were generated by manually fitting 2 gamma variate functions to the IDC extracted from a selected 4D TREAT dataset (Fig 1). The 2 gamma variate functions were used to model the first and second contrast agent bolus passage, respectively. The main benefit of this simulation setup is that the TTPs can be defined unambiguously on the basis of the parameters of the manual fit and can be used for criterion standard comparison. To enable a realistic simulation setup, the simulated curves can be shifted in the time dimension, random Gaussian noise can be added, and the temporal resolutions can be varied via discretization.

Using this setup, we performed Monte Carlo simulations by using 50 different temporal resolutions (0.1, 0.2,…, 5 seconds) and an SNR of 60, which is comparable with the clinically acquired 4D MRA datasets used in this study. In this manner, 2^12 = 4096 discrete IDCs were generated in each simulation run and used for TTP estimation

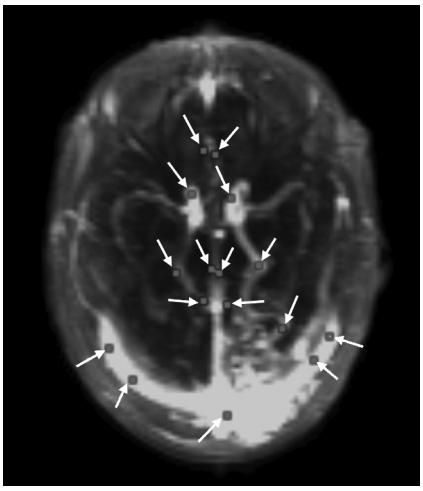

Fig 2. Locations of vessel structures used for clinical evaluation displayed in a maximum intensity projection of a selected 4D TREAT dataset.

with the described parametric models (sGVM, LDRWM, mLNM, and CFM) or MI direct estimation. After TTP estimation, the calculated values were compared voxel-by-voxel with the corresponding criterion standard TTP values for calculation of a mean absolute temporal error for each TTP estimation technique and temporal resolution.

Clinical Dataset Evaluation

For comparison and validation of the results from the Monte Carlo simulation, real unprocessed IDCs from 20 TREAT datasets were used in the second clinical evaluation. For this test, vessel voxels of diagnostic interest were manually selected in each dataset by a neuroradiologist (T.I.) with several years of specific experience in this area. If covered by the 4D MRA dataset and clearly identifiable, the following vessel structures were defined in each dataset: the proximal anterior cerebral artery, middle cerebral artery, posterior cerebral artery, a vein of the superficial venous system (transverse sinus or a cortical vein), and the deep venous system (basal vein of Rosenthal or the internal cerebral vein). Furthermore, the AVM feeders and draining veins were defined in each dataset (Fig 2). Overall, 226 vessel structures were manually defined in the available datasets (64 arteries, 122 veins, and 40 AVM feeding arteries and draining veins).

The general procedure for this evaluation is illustrated in Fig 3. In a first step, the IDCs for every selected vessel structure are extracted and the TTPs are estimated by using the 5 TTP estimation techniques. These determined TTPs are then used as ground truth for the calculation of the TTP estimation error in the following iterations. Therefore, the temporal resolution is artificially varied in terms of keeping every nth image while leaving out all others. More precisely, $n = 1, \ldots, 10$ was used in this evaluation, which is equal to an investigated temporal resolution between 1 and 5 seconds. For every timestep, the TTPs are estimated again in consideration of the possible time shifts. In doing so, the mean absolute temporal differences to the ground truth TTPs were calculated for each artificially reduced temporal resolution. This analysis was performed for all selected vessel structures in total as well as stratified for the arterial, venous, and arteriovenous malformation vessel structures.

Results

The results of the Monte Carlo and clinical dataset evaluations are illustrated in Fig 4. In general, these results show that the TTP estimation by using parametric models leads to reduced temporal errors compared with the MI direct TTP estimation. The average MI TTP estimation error is approximately 3 times higher than the model-based TTP estimation errors.

The reference-based linear CFM leads to the lowest TTP estimation errors for temporal resolution, between 0.1 and 4 seconds, while the LDRWM leads to slightly lower TTP estimation errors for temporal resolutions between 4 and 5 seconds.

The sGVM, which has been used most often in previous studies, leads to the highest TTP estimation errors among model-based approaches for temporal resolutions, between 2.5 and 5 seconds, while the mLNM leads to the highest TTP estimation errors for temporal resolutions between 0.1 and 2.5 seconds. Overall, the LDRWM yields comparable stable TTP estimation errors for all temporal resolutions analyzed.

In general, the TTP estimation error is increased exponentially with lower temporal resolutions. In the case of the CFM, the mean temporal error t_{err} of TTP estimation for a given temporal resolution t_{res} can be approximated with $t_{err} = 0.2e^{0.25t_{res}}$ ($R^2 = 0.977$). The fact that the mean temporal errors of the different TTP estimation techniques do not diminish as the temporal resolution approaches zero can be ascribed to the noise that has been added to the curves during Monte Carlo simulation.

In general, the results of the clinical dataset evaluation show the same tendencies as the Monte Carlo simulation results. A temporal resolution of 0.5 second per image was used for ground truth estimation. For this reason, the error associated with the ground truth TTP estimation at this temporal resolution is not included in this evaluation, which leads to lower TTP estimation errors compared with the results of the Monte Carlo simulation.

Figure 5 illustrates the results of the clinical evaluation stratified for the different vessel structures analyzed solely for the CFM. Here, it can be seen that IDCs obtained from arterial vessel structures should be sampled at higher temporal resolutions to obtain TTP estimation errors comparable with those obtained from indicator dilution curves from venous structures. Practically, if blood flow within arterial structures is the main interest, the temporal resolution should be chosen approximately twice as high compared with when the blood flow only within venous structures is of interest. It may be concluded from these stratified results that a temporal resolution of 1.5 seconds per image appears reasonable to evaluate arterial blood flow, while a temporal resolution of 2.5 seconds per image appears reasonable to evaluate blood flow within venous as well as in arteriovenous malformation structures. If arterial and venous vessel structures are of interest, the temporal resolution should be set to 1.5 seconds per image, which corresponds to that in the arterial structures. These suggested thresholds allow an average TTP estimation error, which is only roughly 0.1 second higher than the error at a temporal resolution of 0.5 second per image. This appears to be a reasonable trade-off compared with the possible gains in spatial resolution.

Furthermore, the results of the clinical dataset evaluation stratified by different vessel structures show that feeding arteries and draining veins of AVMs require a temporal resolution comparable with that of venous structures. Because AVMs may alter the blood flow within the whole affected hemi-

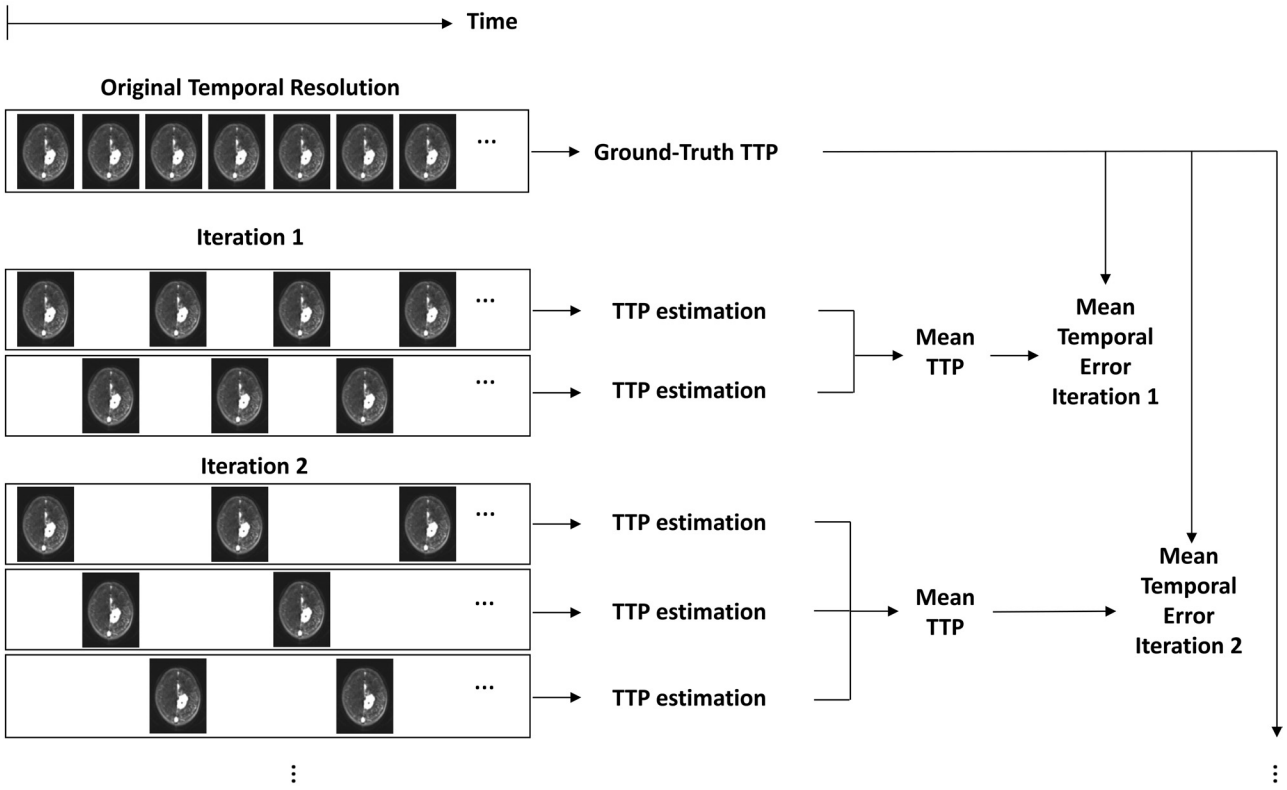

Fig 3. Illustration of the clinical evaluation.

sphere, possible differences between the affected versus the nonaffected side regarding the requirement of different temporal resolutions were also investigated. However, no considerably different TTP estimation errors were found.

Discussion

The central finding of this study was that the temporal resolution required for a satisfactory and adequate curve fitting was as low as 1.5 seconds for the clinical routine if using model-based CFM TTP estimation. We believe that this finding is generalizable and will apply broadly to other 4D MRA imaging techniques from other manufacturers.

Our results suggest that the Monte Carlo simulation represents a realistic setup for validation of hemodynamic models because strong correlations were found between the simulation and clinical results. Furthermore, it may be concluded from the results that the use of parametric models offers significantly lower TTP estimation errors compared with model-independent direct TTP estimation. Regardless of the TTP estimation technique used, the results of the evaluation illustrate that the TTP estimation error increases exponentially when one lowers the temporal resolution. In general, the lowest TTP estimation errors can be obtained by using the reference-based linear CFM, which is in agreement with earlier findings.[12] Finally, the presented evaluation showed that it may be beneficial to adjust the temporal resolution to the vessel structures of interest to achieve a case-specific optimal spatial resolution. For example, if venous structures are the main clinical interest, lower temporal resolution can be chosen, leading to the possibility of acquiring the 4D MRA image sequence at a higher spatial resolution.

The results of this study have shown that IDCs from arterial vessel structures should be sampled at a higher temporal resolution compared with those from venous vessel structures. This finding may be ascribed to different flow properties in arterial and venous vessel structures because arterial blood flow usually exhibits higher flow velocities. A second explanation for this finding may be that dispersion effects have a stronger influence on the contrast agent bolus in venous structures, leading to a spreading of the bolus. On the basis of these 2 possible explanations, one might expect that the temporal resolution of AVM feeding arteries and draining veins should be chosen with parameters comparable with those for arterial structures. However, the temporal resolution requirements of AVM structures appear rather similar to those for venous structures. One explanation for this might be that AVMs usually lead to a dilation of the connected vessel structures so that partial volume effects have less impact on the corresponding indicator dilution curves. This explanation would further confirm that high spatial resolutions are most important for the screening of cerebral blood flow.

It has been shown that 4D MRA datasets analyzed in terms of TTP estimation provide several benefits for rating of different diseases. Zou et al[14] investigated the benefit of time-resolved MRA compared with standard 3D contrast-enhanced MRA imaging for 126 patients with diseases such as aneurysms, ICA stenosis, and gliomas. Overall, additional important findings were made in 48% of all patients by using 4D MRA imaging. Furthermore, Zou et al found that the TTP parameter correlates with the glioma grade and can be used to discriminate epithelial from nonepithelial meningiomas. Moreover, it has been shown that this parameter enables the

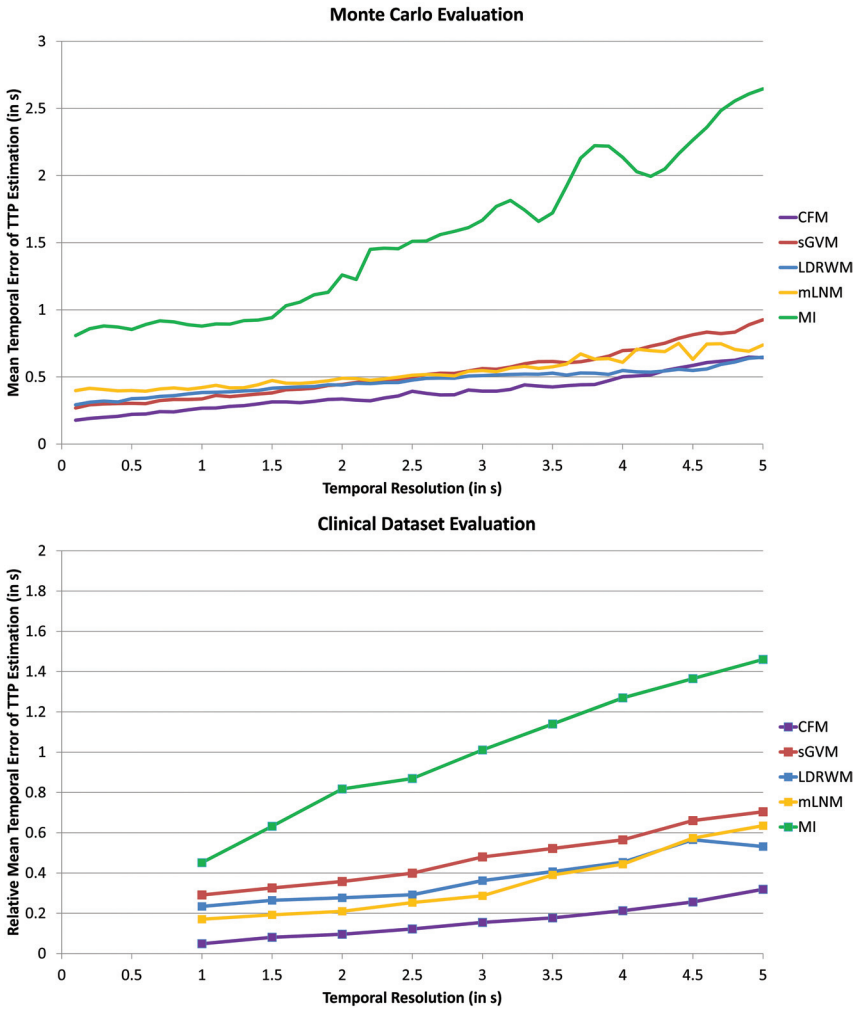

Fig 4. Results of the Monte Carlo and clinical evaluations.

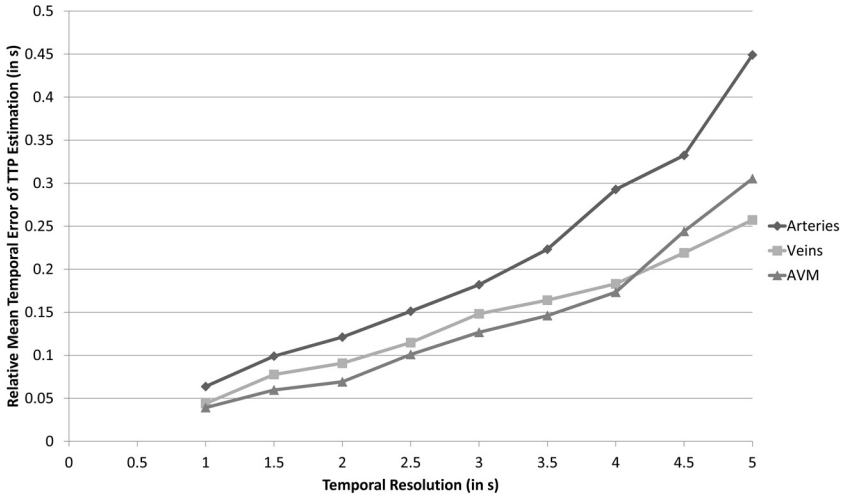

Fig 5. Results of the clinical evaluation by using the reference-based linear curve fit approach stratified by different vessel structures.

discrimination of feeding arteries and draining veins of an AVM.[15] Fiehler et al[16] found that the degree of the AVM perfusion steal effect is negatively correlated with the affected/nonaffected TTP ratio. This ratio was used in this work as an indirect measure of blood flow velocity. Barfett et al[17] demonstrated that the TTP estimation allows a precise determination of the blood flow velocity, which may be of interest for several cerebrovascular diseases. Although Barfett et al used 4D CTA for TTP estimation, the findings of this study should be transferable to 4D MRA imaging techniques. Finally, Taschner et

al[18] successfully applied time-resolved MRA datasets in dosimetry planning for gamma knife surgery of brain arteriovenous malformations.

It can be concluded from these previous studies that 4D MRA imaging is a valuable technique in the clinical routine for the evaluation of several cerebral diseases. The evaluation of these datasets by estimating the TTP parameter provides additional benefits for quantitative analysis and computer-aided diagnosis. The TTP of a given IDC is a valuable and yet simple parameter to estimate.

The calculation of the TTP of 1 given IDC can be performed in real-time on a standard computer with each of the 5 tested TTP estimation techniques. However, considerable computation time differences arise when calculating a TTP map for a whole dataset. Specifically, the required calculation times for a typical 4D MRA dataset with a temporal resolution of 0.5 second differ between 30 seconds (MI) and 83 minutes (LDRWM),[12] whereas the calculation time is linearly dependent on the number of sample points of an IDC. A considerable speedup may be achieved by graphics processing unit–based calculations, leading to a realistic use in a clinical setting.

The Monte Carlo and the clinical dataset evaluations have some drawbacks. First, gamma variate functions were used for constructing the parameter sets for the Monte Carlo evaluation, which may result in biased results for the GVM and CFM approaches. The second drawback is that only the temporal resolution was varied for the clinical dataset evaluation, while the spatial resolution was kept constant. However, lower temporal resolutions allow an acquisition of 4D MRA image sequences with higher spatial resolution in a real clinical setup. Consequently, the higher spatial resolution would result in decreased partial volume effects, which lead to an improved display of blood flow within smaller vessels and subsequent lower TTP estimation errors.

The current study is based on a retrospective analysis of 4D MRA image sequences that were acquired during clinical routine. The main objective of the acquisition was to ensure full brain coverage between the middle cerebral artery and superior sagittal sinus so that each AVM and all feeding arteries and draining veins were included completely and with certainty in the image sequences. To meet this criterion, we acquired the image sequences by using a section thickness of 5 mm. Although this section thickness seems rather coarse and might lead to increasing partial volume effects, first experiments by using the software phantom described by Säring et al[19] suggest that the in-plane spatial resolution is more important than the section thickness for a sufficient display of cerebral vessels. Still, more detailed evaluations need to be conducted by using physical or software blood flow phantoms[19] to ensure this finding and investigate the importance of partial volume effects to TTP estimation errors. Because phantom evaluations do not allow differentiating between arterial and venous structures, animal models might also be of high interest for more sophisticated evaluations of temporal resolution requirements of different vessel structures.

Indicator dilution curves derived from 4D MRA imaging are known to depend on the injection scheme (contrast dose and injection rate) as well as on the cardiac output and pharmacokinetics,[20] whereas only the injection scheme can be varied without any major problems for image acquisition. The injection rate is known to contribute mainly to the width of the first bolus passage[21] and is consequently responsible for the maximal signal drop after the peak of the first bolus passage. In general, faster injection rates lead to higher maximal signal drops, which allow improved fitting results of parametric models.[9] On the other hand, higher contrast doses are known to improve the peak signal-to-noise ratio.[22]

Although it may be assumed that a higher contrast agent dose and faster injection should enable the best hemodynamic analysis, Kopka et al[23] reported that flow rates higher than 4 mL/s may lead to reduced image contrast due to problems with typically applied *k*-space sampling techniques during image acquisition. The main idea of the *k*-space sampling technique is to sample the center of the *k*-space, which mainly contributes to the image contrast, more often than the peripheral segments. Therefore, the *k*-space sampling technique should have no major effect on the indicator dilution curves if the injection rate is not too high. As a consequence of this, the dose volume is also limited to prevent a total fusion of the first and second bolus passages. The influence of the contrast dose and injection rate on the TTP estimation error was not investigated in this study because these 2 parameters were kept constant for all image acquisitions. Hence, the results of this study may only be applicable if using a similar injection protocol.

Strictly speaking, the results of this study apply only to adult patients with AVMs without severe cardiac output impairment. However, Deegan et al[24] did not find a considerable correlation between the cerebral blood flow and cardiac output. On the basis of previous findings that cerebral hemodynamics are related to the blood flow velocities in the middle cerebral arteries,[25] it might be expected that the impact of cardiac output on the TTP estimation is of minor importance in adults. This generalization does not necessarily apply to a pediatric population in which significant variations in cerebral perfusion have been found between 6 months and 8 years of age.[26] Therefore, the validity of the findings of our study for pediatric patients needs to be investigated further.

Conclusions

The results of the Monte Carlo as well as the clinical dataset evaluations showed that TTP estimation error depends on the temporal resolution of the indicator dilution curves. Lowering the temporal resolution leads to exponentially higher TTP estimation errors. However, a temporal resolution of 1.5 seconds for arteries and 2.5 seconds for venous and AVM vessel structures appears reasonable for achieving TTP estimations adequate for clinical applications if using model-based TTP estimation techniques.

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