Chapter 6: Evaluation of signal formation in local arterial input function measurements of dynamic susceptibility contrast MRI

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ABSTRACT

Correct arterial input function (AIF) measurements in dynamic susceptibility contrast-MRI are crucial for quantification of the hemodynamic parameters. Often a single global AIF is selected near a large brain-feeding artery. Alternatively, local AIF measurements aim for voxel-specific AIFs from smaller arteries. Because local AIFs are measured higher in the arterial-tree, it is assumed that these will reflect the true input of the microvasculature much better. However, do the measured local AIFs reflect the true concentration-time curves (CTC) of small arteries? To answer this question, a 3D numerical model that simulated partial-volume effects (PVEs) in local AIF measurements was created and the simulated local AIFs were compared to the ground truth. In addition, in vivo data were used to evaluate local AIF candidates selected using two angiograms. The findings are two-fold. First, the simulations show that PVEs in the local AIF measurements lead to broader CTCs than the ground truth AIF due to extravascular susceptibility effects and the contrast agent passing through surrounding microvasculature. Second, the in vivo data showed that the shape-characteristics of local AIFs are similar to the shape-characteristics of gray matter CTCs. These findings suggest that local AIF measurements do not reflect the true CTC in small arteries.

Under revision
INTRODUCTION

Dynamic susceptibility contrast (DSC-) MRI measures brain-perfusion by monitoring the passage of a bolus of contrast agent through the brain-vasculature. Voxel-based measurements of the bolus passage in tissue give information about local cerebral blood flow (CBF), cerebral blood volume (CBV) and subsequently the mean transit time (MTT) (1, 2). These local perfusion estimates are useful, for example, for staging tumors and assessing the tissue at risk of permanent damage after a stroke (3, 4). However, the tissue response needs to be calibrated via deconvolution with an arterial input function (AIF) i.e., the passage of contrast agent through a brain-feeding artery. Most DSC-MRI studies use a single (often manually selected) global AIF for all voxels.

Alternatively, it has been suggested that local or regional AIF measurements can improve determination of the perfusion parameters (5-7). These local AIFs are measured closer to the capillaries of the brain tissue compared to global AIF measurements. Deconvolution with a local AIF produces residue functions that are less affected by delay and dispersion effects due to the transport of the contrast agent from the location of the AIF determination to the beginning of the capillary bed (8). The former can be corrected for by using delay-insensitive deconvolution techniques, but dispersion corrupts the perfusion estimates (2, 9, 10). In addition, local AIF measurements are flow territory specific, which can be especially beneficial when there is a stenosed or occluded large artery, since such large vessel pathologies lead to additional delay and dispersion in the corresponding flow territory (11). The use of a global AIF measured contralaterally from the stenosis or occlusion would create perfusion estimates for the flow territory of the stenosed artery that include the dispersive properties of the stenosis, leading to underestimation of CBF (12).

However, such local AIF measurements are performed with voxels larger than the small brain-feeding arteries from which the AIF is obtained. The MR-signal from such a voxel will be influenced by the contrast agent within the artery, the magnetic field changes outside the artery induced by the intravascular contrast agent and by the contrast agent passing through the microvasculature of the tissue surrounding the artery (tissue response). The combination of the relaxation effects and local field changes can lead to shape changes in the AIF due to differences in phase evolution of the different compartments. For larger arteries, such non-linear partial-volume effects (PVEs) have been shown to lead to erroneous perfusion estimates (13-15).

Validation of local AIF measurements is ideally performed by comparing the measured local AIF with the true concentration-time curve (CTC) within the small brain-feeding artery. However, blood sampling cannot be performed at that point in the brain-vasculature. Therefore, previous validations of local AIF measurements have been performed by comparing the perfusion maps (and sometimes the CTCs) from local AIF measurements to those obtained from manually selected global AIF measurements (5-7, 16, 17). A single report showed additional
comparison to PET perfusion maps (16). When validating local AIF methods one should keep in mind that all methods to automatically select (local) AIFs are based on features of a “proper” AIF, such as small width, early time-of-arrival (TA), high peak-height, etc, and the selected curves will therefore always exhibit exactly these properties (6, 7, 18-21). The important question in validation is: do the curves of the local AIF measurements really reflect the true CTC of small arteries? A previous simulation study by Kjølby and coworkers reported that the contribution of the tissue response to an AIF measured in or near a large artery can lead to broadening of the measured bolus passage inside the artery, although the simulations only modeled two orientations (parallel and perpendicular to the main magnetic field) and in vivo verification was absent (14).

In this study, the properties of the bolus passage curves in voxels located on top of small arteries are compared to curves obtained in the gray matter. The properties of these two collections of voxels should differ, with a much higher percentage of AIF-like curves in the first group required to justify a local AIF approach. In addition to the in vivo study, numerical simulations of partial-volume effects in local AIF measurement were used to investigate the influence of the tissue passage and extravascular magnetic field changes on the shape of local AIFs.

**METHODS**

**Simulations**

A small brain-feeding artery was modeled as a cylinder at different orientations to the main magnetic field and different locations within the voxel. Intra- and extravascular MR-signal was modeled using Maxwell equations and normal gradient echo signal formation formulas, including relaxation changes and dephasing due to the local field changes. Local AIF measurements were modeled for single shot EPI and PRESTO (an ultra fast $T_2^*$-weighted 3D acquisition with echo shifting (22)) sequences. Single shot EPI with voxels of 2x2x6 mm$^3$ was simulated on a high-resolution 3D grid, with 250 μm interspacing, spanning 12x12 mm$^2$ by 24 mm. The imaging settings, $t_E/tr$ 25/1500 msec and $FA=75^\circ$, were set to resemble typical in vivo settings. The PRESTO simulations consisted of voxels of 2.5x2.5x3.5 mm$^3$ on a high-resolution 3D grid, with 250 μm interspacing, spanning 15x15 mm$^2$ by 14 mm. The imaging settings, $t_E/tr$ 30/20 msec and $FA=8^\circ$, were set the same as the in vivo settings employed in this study. Distortions due to the long echo train were ignored in the simulations due to computational limitations (13, 23). In order to generate a larger range of partial-volume effects in the simulations all voxels were shifted over the 3D grid in steps of 250 μm in all three directions. The numerical model was implemented in MATLAB (R2007b, Natick, MA, USA).

The orientation of the cylinder with spherical angles $\theta$ (angle between the vessel axis and the direction of the main magnetic field) and $\varphi$ varied for $\theta$ from 0$^\circ$ to 90$^\circ$ in steps of 15$^\circ$, and
for \( \varphi \) from 0\(^\circ\) to 45\(^\circ\) in steps of 15\(^\circ\). The vessel size was set to have a radius of 0.5 mm, 1.0 mm and 1.5 mm.

Inside the cylinder the arterial CTC is simulated with a modeled AIF (24), outside the cylinder the tissue response is simulated by the same modeled AIF but convolved with an exponential residue function (CBF = 60 ml/100 g/min, MTT = 4 sec, CBV = 4 ml/100 g).

The relaxation times were set to resemble blood and tissue at 3 Tesla (\( T_1 \) blood 1.7 sec (25), \( T_2 \) blood 70 msec, \( T_1 \) tissue 1.1 sec (26), \( T_2 \) tissue 70 msec). A quadratic relation taken from 1.5 Tesla experiments and rescaled to 3 Tesla was used for the relation between the intravascular \( \Delta R_2^* \) and the concentration of gadolinium (linear term 15.24 l/mmol/sec, quadratic term 2.28 l\(^2\)/mmol\(^2\)/sec (27)). The relaxivity in tissue was set to 87 l/mmol/sec (28), longitudinal relaxivity was ignored. The local field changes, resulting from the susceptibility difference (molar susceptibility of the contrast agent \( \chi_m = 0.3209 \times 10^{-3} \) l/mol (27)), were calculated using the Maxwell equations corrected for the sphere of Lorentz.

To study the effect of the tissue response inside the voxel on local AIF measurements, simulations were performed with and without the tissue response in the surroundings of the small artery. In addition, the effect of crushing the intravascular signal in PRESTO due to the large gradients employed for echo shifting was investigated by setting the intravascular signal to zero.

**Simulation post processing**

The simulated signals were transformed to \( \Delta R_2^* \). Profiles were excluded from further analysis when a reference point on top of the axis of the simulated artery was not located within the simulated voxel, because otherwise the signal changes induced by the arterial passage are too minimal. The middle of the volume was chosen as the abovementioned reference point. The different orientations, radii and shifts for PVEs, all experienced some degree of partial-volume effects, and were treated as one group. Profiles with severe partial-volume shape errors were excluded using the steady state to the area-under-the-curve (AUC) of the first passage ratio (SS:AUC\(^{1st}\) criterion (29). This SS:AUC\(^{1st}\) criterion used the modeled tissue response as a reference and a gamma variate fit was used to determine the AUC of the first passage. Additional exclusion of profiles was based on the time-to-peak (exclusion of too high TTPs, defined as ground truth AIF TTP value +2\(^\times\)standard deviation (SD) over all TTPs of the simulated profiles). The profiles were compared to the ground truth using the Pearson correlation coefficient.

For evaluation of the shape-characteristics of the simulated local AIFs three metrics were used. Two metrics (TA and relative TTP (rTTP=TTP-TA)) were determined using the gamma variate fit and one metric (full-width-at-half-maximum (FWHM)) was determined using the \( \Delta R_2^* \) profile. The histograms were evaluated and the mean values of the metrics were compared to the metrics of the ground truth.
In vivo experiments

In vivo DSC-MRI exams (five in total) of three patients suffering from arteriovenous malformation were employed in this study. One patient was scanned three times; the other two were scanned a single time. In vivo experiments were performed at 3 Tesla (Achieva, Philips, Best, The Netherlands) using an 8-channel receive array head coil, 0.1 mmol/kg-bodyweight Gd-DTPA was injected at 5 ml/sec followed by a saline chaser of 25 ml injected at the same speed. The imaging sequences had the following settings: PRESTO, data matrix 96x87, zero-filled to 128x101, 30 slices 3.5 mm thick with no interslice gap, FOV 240x190 mm$^2$, 75 dynamic scans, scan duration 120 sec, TE/TR 30/20 msec, FA 8º, EPI factor 15, SENSE factor 2.2, phase encoding was set from right to left; time-of-flight (TOF), data matrix 512x325, zero-filled to 512x488, 220 slices 0.6 mm thick, FOV 180x172 mm$^2$, TE/TR 3.5/23 msec, FA 15º; T1FE, data matrix 192x192, zero-filled to 256x256, 130 slices 1.2 mm thick, FOV 220x175 mm$^2$, TE/TR 4.6/10 msec, FA 8º. The study was approved by the local ethics committee.

In vivo post processing

In vivo data were all post processed using SPM5 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London UK – http://www.fil.ion.ucl.ac.uk/spm) and MATLAB. The entire hemisphere affected by the AVM was excluded. Local AIF candidates were determined using two different angiograms: one based on the TOF angiogram and another based on the pre- and post-contrast T$_1$-weighted images. A small artery TOF mask was created by thresholding the TOF to such a level that the cortex and skull were excluded. In addition, a separate large artery TOF mask was created using an empirical threshold approximately twice the threshold for the small artery mask. Both small artery mask and large artery mask were coregistered to the first T$_2$*-weighted DSC-MR image and the large arteries were subsequently removed from the small artery mask.

The small artery T$_1$-based mask was constructed by subtracting the pre-contrast T$_1$-weighted image from the coregistered post-contrast T$_1$-weighted image. The T$_1$-based mask was coregistered to the first T$_2$*-weighted DSC-MRI image using the T$_1$ pre-contrast image.

In addition, a gray matter mask was created as a reference dataset to compare the CTCs of the small artery masks to. This gray matter mask was created using empirically thresholded rCBV values that were formed using the area under the Δr$_2$* profile. Skull stripping was performed on both small artery masks and the gray matter mask based on an image of the maximum difference of the contrast agent passage that was smoothed and subsequently eroded.

From all Δr$_2$* profiles selected by the small artery masks and the gray matter mask severe partial-volume shape errors were excluded using the SS:AUC$^{1st}$ ratio criterion (29). Additional exclusions of profiles were based on the TTP (larger than the mean value +2*SD), TA (larger than the mean value +2*SD) and relative (r)CBV (smaller than lower-threshold of the gray matter mask). To evaluate the shape-characteristics of the local AIF candidates and the gray matter profiles the same three metrics (TA, rTTP, FWHM) as used in the evaluation of the simulation
data were calculated. First, the metric-histograms of the small arteries masks and gray matter mask were compared. In addition, the average for each metric was computed. The metrics of the local AIF candidates were compared to the metrics of the gray matter profiles and to each other using a paired t-test over the five DSC-MRI scans using \( \alpha = 0.05 \) corrected for multiple comparison using Bonferroni correction (3 variables) leading to \( p_{\text{bonf}} < 0.0167 \) (one-sided) and \( p_{\text{bonf}} < 0.0083 \) (two-sided).

**RESULTS**

The results of the shape-characteristics of the local AIFs in the numerical simulations are presented in Table 1 and Figures 1-4. Figure 1 shows the histograms of the different metrics for the simulated PRESTO data with tissue passage and crushing. The three metrics have approximately a Gaussian distribution. Figure 2 shows the mean value and SD of the three timing metrics TA, rTTP, FWHM for the ground truth AIF, the simulated tissue passage, and the different simulations of EPI and PRESTO. As shown in Table 1 and Figure 2, the TA of all simulations are closer to the TA of the ground truth AIF than the TA of the ground truth tissue response. Furthermore, including the tissue response (wT) in the simulations did not significantly delay TA for the two investigated sequences. The addition of the tissue response in the local AIF voxel does, however, increase the rTTP for both sequences. Whereas, the rTTP of the simulations without the tissue response in the surrounding are similar to the rTTP of the ground truth AIF, the rTTP of the simulations with tissue response is delayed and even close to the rTTP of the ground truth of the tissue response. The FWHM of the simulations is larger than the FWHM of the ground truth AIF and close to the FWHM of the ground truth of the tissue response, except for PRESTO without the tissue response (wOT). The addition of the tissue response has a small effect on the FWHM for single shot EPI and a relatively large effect for PRESTO. In PRESTO without the tissue response, the intravascular signal is crushed and therefore only the susceptibility effects in the tissue response.

| Table 1: Shape-characteristic metrics used for evaluating the simulations of single shot EPI and PRESTO. Simulations were performed with the tissue response (wT) and without the tissue response (wOT). In addition, the PRESTO simulations were performed with crushing (wOT, wT) and without crushing of the intravascular signal due to the large gradients employed for echo shifting (wT wO). The ground truths (GT) of the AIF and the tissue response are presented as well. The timing metrics are in seconds and SD is the standard deviation over the group of local AIFs. |
|---------------------------------|------------|------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| GT AIF tissue                  | EPI wOT wT | PRESTO wOT wT wO | GT AIF tissue | EPI wOT wT | PRESTO wOT wT wO |
|--------------------------------|------------|-------------------|----------------|------------|-------------------|----------------|-----------------|----------------|
| TA (mean SD)                   | 9.5 (11.1) | 9.8 (0.2)         | 9.9 (0.2)      | 9.9 (0.3)  | 9.9 (0.3)         | 9.9 (0.3)      | 8.7 (0.6)       | 8.7 (0.6)       |
| rTTP (mean SD)                 | 8.1 (9.7)  | 7.6 (0.3)         | 8.9 (0.5)      | 7.5 (0.4)  | 8.5 (0.6)         | 8.7 (0.6)      | 12.8 (1.8)      | 12.8 (1.8)      |
| FWHM (mean SD)                 | 9.8 (12.5) | 12.7 (1.8)        | 13.3 (1.6)     | 11.2 (1.8) | 12.5 (1.7)        | 12.8 (1.8)     | 12.8 (1.8)      | 12.8 (1.8)      |
surrounding of the small artery can explain the increase in FWHM. The effect of crushing the intravascular signal in PRESTO on the TA and rTTTP compared to PRESTO without crushing (wT woC) is minimal.

Subdividing the group of local AIF profiles (of PRESTO (wT)) by artery size shows that smaller arteries have a larger rTTTP compared to the rTTTP of the larger arteries, although the effect is small (see Figure 3). Note that the ground truth AIF of these simulations were the same for small and large arteries, that is the diameter of the simulated arteries was the only difference. The small arteries also have a broader profile compared to the larger arteries (see Figure 3). Figure 4 shows the histograms of the correlation of the $\Delta R_2^*$ profiles with the ground truth for the different simulations. This figure shows that the distribution of the correlation with the ground truth is shifted to higher correlation values for the simulations without the tissue passage. The correlation of the ground truth tissue response with the ground truth AIF is 0.81.

Figure 1: The histograms of the time-of-arrival (TA), relative time-to-peak (rTTTP) and full-width-at-half-maximum (FWHM) of the simulated local AIFs. All distributions are close to Gaussian distributions.

Figure 2: Three timing characteristics (time-of-arrival (TA), relative time-to-peak (rTTTP) and full-width-at-half-maximum (FWHM)) in seconds to compare the simulated local arterial input functions (AIFs) (of single shot EPI and PRESTO) with the ground truth AIF (white bar) and ground truth tissue response (black bar). Without tissue response (woT), with tissue response (wT) and without crushing (woC).
Table 2 and Figure 5 show the in vivo metrics of gray matter (GM) and the local AIF candidates based on the two angiograms. GM has the latest TA but the value is very close to the TA of the $T_1$-based local AIF candidates. The TA of the TOF-based local AIF candidates are significantly lower than GM and significantly lower than the $T_1$-based local AIF candidates. The average rTTP of the TOF-based local AIF candidates is larger than the rTTP of gray matter although not
Table 2: Shape-characteristic metrics used for evaluating the in vivo local AIF candidates based on two angiograms (TOF and $T_1$). The metric values are compared to gray matter (GM), since the ground truth is unknown.

<table>
<thead>
<tr>
<th>Metric</th>
<th>GM mean</th>
<th>SD</th>
<th>TOF mean</th>
<th>SD</th>
<th>T1 mean</th>
<th>SD</th>
<th>GM vs TOF diff</th>
<th>p-value</th>
<th>GM vs T1 diff</th>
<th>p-value</th>
<th>T1 vs TOF diff</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA</td>
<td>25.4</td>
<td>1.0</td>
<td>24.8</td>
<td>1.0</td>
<td>25.3</td>
<td>1.0</td>
<td>-0.6</td>
<td>0.0075</td>
<td>-0.1</td>
<td>0.5529</td>
<td>-0.5</td>
<td>0.0008</td>
</tr>
<tr>
<td>rTTP</td>
<td>4.9</td>
<td>0.2</td>
<td>5.2</td>
<td>0.4</td>
<td>5.4</td>
<td>0.4</td>
<td>0.3</td>
<td>0.0343</td>
<td>0.5</td>
<td>0.0050</td>
<td>-0.2</td>
<td>0.0028</td>
</tr>
<tr>
<td>FWHM</td>
<td>6.3</td>
<td>0.6</td>
<td>6.8</td>
<td>0.7</td>
<td>6.8</td>
<td>0.7</td>
<td>0.0</td>
<td>0.8605</td>
<td>0.5</td>
<td>0.0039</td>
<td>-0.5</td>
<td>0.0109</td>
</tr>
</tbody>
</table>

significantly, whereas the average rTTP of the $T_1$-based local AIF candidates is significantly larger than the average rTTP of gray matter. The TOF-based local AIF candidates have $\Delta R_2^*$ profiles as broad as GM, as measured with the average FWHM. The $T_1$-based local AIF candidates have a significantly larger FWHM than the average FWHM of GM. The distributions of the in vivo metrics are shown in Figure 6; all show a distribution close to a Gaussian distribution. Furthermore, there is much overlap between the distributions of the shape-characteristics of GM and the local AIF candidates. Moreover, the distribution in the lower tails for the three timing metrics differ little in absolute numbers between GM and the local AIF candidates.

**DISCUSSION AND CONCLUSIONS**

The aim of this study was to investigate whether automatic local AIF measurements would reflect the true concentration-time curve of small brain-feeding arteries, since partial-volume effects in the local AIF measurement can lead to broadening of the measured $\Delta R_2^*$ profile (14). For this purpose, a 3D numerical model was created that simulates local AIF measurements with single shot EPI and PRESTO acquisition at different orientations and with different artery sizes. In addition, in vivo data were used to identify true local AIF candidates using two different
angiograms and the shape-characteristics from these candidates were compared to gray matter CTC shape-characteristics. The findings of this study are two-fold. First, the simulations show that partial-volume effects in local AIF measurements lead to erroneously broader measured AIFs. The broadening is both caused by the tissue response and the extravascular local field changes. Second, in vivo data shows (based on shape-characteristics of the measured ΔR₂ * profiles) that local AIF selection do not have a higher number of AIF-like profiles than GM profiles. Therefore, local AIF measurements using shape-criteria cannot reliably measure the CTC in small arteries, since the overlap in the distributions of GM and local AIF candidates is too high.

The simulations show that partial-volume effects lead to broader local AIF profiles. For single shot EPI the FWHM was even larger than the FWHM of the ground truth of the tissue response. For single shot EPI, the broadening is caused by extravascular susceptibility effects and intravascular relaxation changes, because the simulations with and without tissue response show little difference in FWHM. For PRESTO, separation between extravascular susceptibility effects and intravascular relaxation changes was made by simulating the sequence with and

Figure 6: Histograms of the shape-characteristic metrics for gray matter (a) for T₁-based local arterial input function (AIF) candidates (b) and TOF-based local AIF candidates (c). The distributions are close to Gaussian distributions and the lower tail of the timing metrics shows a large degree of overlap. Note that the number of voxels in the gray matter (GM) mask is much larger than the two small artery masks.
without crushing of the intravascular signal. These simulations showed that the influence of the intravascular signal on the broadening of the simulated local AIF is small. The simulations of PRESTO (with crushing) with and without tissue response show that the tissue response causes, on average, broadening of the simulated local AIFs as do the extravascular susceptibility effects. The fraction between the effect of tissue response and extravascular susceptibility effects on the broadening is likely to change for different orientations, but on average, both effects lead to comparable broadening. The TA of the simulated local AIFs are close to the TA of the ground truth AIF. The rTTP is sensitive to the tissue response and for the simulation without the tissue response, the rTTP is close to the rTTP of the ground truth AIF. For the simulations with the tissue response, the rTTP is close to the rTTP of the ground truth of the tissue response. Subdividing the simulated local AIF profiles by vessel radius showed that smaller arteries result in more erroneous broadening of the local AIF measurement compared to the larger arteries. The smallest studied arteries with a radius of 1.5 mm, however, result in local AIF measurements still broader than the ground truth AIF. The simulations show that these smaller arteries show later TA (note that the ground truth AIF is the same) and longer FWHM.

The in vivo data were used to investigate local AIF candidates based on angiogram information and, because the ground truth is unknown, the shape-characteristics of the local AIF candidates are compared to gray matter CTs. For this purpose, two different angiograms were used (TOF angiogram and T1 pre- and post-contrast angiogram). The properties of angiogram-based local AIF candidates should differ from the properties of the GM profiles, with a much higher number of AIF-like curves in the first group to justify a local AIF approach. The results show that the TA is significantly lower for the TOF-based local AIFs compared to GM and compared to T1-based local AIFs (one sided t-test was used since larger TA were not expected). This suggests that the TOF-based local AIF candidates are likely to be more upstream than the local AIF candidates determined with the T1 pre- and post-contrast images. The local AIF candidates of the TOF angiogram have an average FWHM equal to the FWHM value of GM. The T1-based local AIF candidates have a significantly larger FWHM than the FWHM of GM. Note that these findings confirm the observation of the simulations where FWHM were observed equal or larger than the ground truth of the tissue response FWHM value. The distributions of the shape metrics angiogram local AIF candidates and GM overlap. One should take in account that the number of voxels in the GM mask is much larger than the small artery masks. Therefore, the absolute number of voxels in the lower tail of the shape-characteristics plays a role in determining whether the chance of selecting a local AIF candidate is higher for the angiogram-based local AIFs compared to GM profiles. Since there is a large overlap, differentiation between GM profiles and local AIF candidates will be difficult. This is supported by the simulations that show that the rTTP and FWHM of the simulated local AIF (with tissue response) are close to the rTTP and FWHM of the ground truth of the tissue response.

In the TOF-based artery mask large arteries were removed and small arteries selected. The pre- and post-contrast agent T1-based angiogram reveals predominantly small arteries (since
the large arteries are subtracted due to fresh inflow) and possibly small veins. Therefore, it is possible that the $T_1$-based small arteries mask is contaminated with small veins and this would result in longer $TA$, $rTTP$ and FWHM. However, the distribution of the $T_1$-based small artery mask is approximately Gaussian and does not show two peaks. In summary, the TOF-based small artery mask reflects more the arterial side of the vasculature, but does not show the smallest vessels, whereas the $T_1$-based angiogram selects smaller vessels but at risk of including veins.

The current study simulated PVEs in local AIF measurements for a large range of orientations and for different vessel radii. A previous simulation study reported that the broadening of the measured AIF profile in local AIF measurements is caused by the tissue response (14). This study shows that the broadening is not only caused by the tissue response in the surrounding but also by extravascular susceptibility effects and to a smaller extent by intravascular relaxation changes.

A broader AIF than the true AIF corrupts the perfusion estimates, and is likely to result in an overestimation of CBF. When comparing the CTCs of global AIFs to local AIFs, local AIFs are more delayed and more dispersed. The observed broadening is, however, much larger than one would expect based on the dispersion resulting from the transport properties of the vascular network.

The numerical model used in this study models the small brain-feeding artery as an infinite straight cylinder. The infinite cylinder is valid for a straight section at least four times the diameter of the vessel (30). Small arteries, however, often curve and can have branches. The orientation of the cylinder affects the extravascular susceptibility effects the most. Because the orientation is often unknown a full range of orientations were simulated and subsequently analyzed as a single group. Because the cylinder was simulated at different orientations, only the central voxels (that encompassed the middle of the vessel axis) of the volume were selected for local AIF measurements. This implies that voxels completely outside the small brain-feeding artery were not selected, because $\Delta R_2^*$ changes are too small in such voxels, since the extravascular effect drops off with distance.

In conclusion, partial-volume effects in local AIF measurements lead to broader $\Delta R_2^*$-curves. These broader local AIFs will lead to errors in the perfusion estimates. Furthermore, automatic local AIF selections will not be able to select local AIF candidates without including gray matter profiles.
REFERENCES


