A new criterion to aid manual and automatic selection of the arterial input function in dynamic susceptibility contrast MRI

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ABSTRACT

Dynamic susceptibility contrast MRI requires an arterial input function (AIF) to obtain cerebral blood flow, cerebral blood volume (CBV) and mean transit time. The current AIF selection criteria discriminate venous, capillary and arterial profiles based on shape- and timing-characteristics of the first passage. Unfortunately, partial volume effects (PVEs) can lead to shape errors in the bolus passage, including a narrower and higher peak, which might be selected as a “correct” AIF. In this study, a new criterion is proposed that detects shape errors based on tracer kinetic principles for computing CBV. This criterion employs the ratio of the steady-state value to the area-under-the-curve of the first passage, which should result in an equal value for tissue and arterial responses. By employing a reference value from tissue, PVEs-induced shape errors of the AIF measurement can be detected. Different factors affecting the ratio were investigated using simulations. These showed that the new criterion should only be used in studies with $T_1$-insensitive acquisition. In vivo data were used to evaluate the proposed approach. The data showed that the new criterion enables detection of shape errors, although false positives do occur, which could be easily avoided when combined with current AIF selection criteria.

Published in Magnetic Resonance in Medicine (2011) Feb; 65(2):448-456
INTRODUCTION

Dynamic susceptibility contrast (DSC)-MRI is a valuable clinical tool to aid in the diagnosis and staging of many brain diseases (1). DSC-MRI provides a set of hemodynamic parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) (2, 3). These three parameters can be obtained after deconvolution of the tissue response (the passage of contrast agent through the capillaries in tissue) with the arterial input function (AIF, the passage of contrast agent through a brain-feeding artery).

The AIF is often selected manually by a trained expert, but a number of automatic AIF selection procedures have been proposed (4-9). The major advantages of automatic selection are operator independence and speeding up of the analysis resulting in fast, standardized and reproducible results. Fast analysis is especially important for clinical decision-making in acute stroke as evidenced by the frequently used slogan “time is brain” (10). Automatic selection is often performed using criteria such as early time-to-peak, steep rise, low first moment, high peak-height and small full-width-half-maximum (FWHM) (4-7, 9) or a metric using a set of these criteria combined with a gamma-variate fit through the first passage (8). With these criteria, venous, capillary and arterial profiles can be discriminated.

Unfortunately, AIF measurements are susceptible to partial volume effects (PVEs) due to the relatively low spatial resolution of the acquisitions, and these PVEs alter the shape of the AIF measurement (11-13). Ideally, automatic procedures would only select AIF profiles unaffected by PVEs. However, some specific shape errors, such as a narrower peak with a higher peak-height than the true shape (13), fulfill the currently used AIF selection criteria and could therefore easily be selected as a “correct” AIF measurement. Therefore, we propose an additional criterion for automatic AIF selection, which could also be useful for guiding manual AIF selection. This criterion relies on the fact that, theoretically, perfusion parameters cannot only be measured from the first passage but also from the second passage. This would however, require that the signal-versus-concentration relation is linear and this condition fails for AIFs that exhibit shape changes due to PVEs (12, 13). Shape errors could therefore be detected by comparing perfusion parameters obtained from the first and second passage. The second passage is, however, difficult to determine due to the overlap with the first and subsequent passage. The theory, described in this manuscript, shows that the first passage in combination with the steady-state (or post-bolus equilibrium) can be used in a similar manner to detect shape errors in the AIF. Therefore, we propose to use the ratio of the mean steady-state value to the area-under-the-curve (AUC) of the first passage of contrast agent as a metric to detect PVEs in AIF measurements. This metric is compared to a reference value obtained from tissue in the same DSC-MRI data, since linearity of the signal versus concentration contrast agent has been proven for brain tissue (14).

The purpose of this study is to describe a new AIF selection criterion based on tracer kinetic theory that can detect AIF measurements corrupted by PVEs. AIF selection guided by the new
A new criterion to aid selection of the AIF in DSC-MRI

proposed criterion was studied by means of numerical simulations and evaluated using six in vivo exams. Both the reference ratio value of tissue and the ratio value of AIF measurements (with and without PVEs) were investigated.

METHODS

Partial volume effects
The presence of contrast agent in an artery will lead, except for arteries at the magic angle (54.7°) or parallel to the main magnetic field $B_0$, to a homogenous magnetic field change inside the artery and a lobular shaped pattern of magnetic field changes outside the artery (15). For a partial volume voxel, this implies that the total complex MRI signal from that voxel is made up of several components that show different phase changes for a particular contrast agent concentration. The amplitude of the total signal will therefore depend on how much the different components are in-phase or out-of-phase. For different concentrations of contrast agent, the same voxel may show different gradations of in- or out-of-phase contributions, thereby leading to non-linear shape changes of the estimated contrast concentration profile. Different manifestations of PVEs were simulated using the Maxwell equations corrected for the sphere of Lorenz by shifting of a voxel partly encompassing a cylinder oriented perpendicular to the main magnetic field (described in more detail in the Methods section Simulations). Subsequently,

Figure 1: Different manifestations of partial volume effects manually grouped into three groups. A group with narrower and higher peaks in the first passage than the true shape (a), a group with two peaks in the first passage in close succession (b) and a third group with almost no first passage peak (c). The black line is the ground truth and all profiles are rescaled to have equal area-under-the-curve. The corresponding complex trajectory of the $\Delta R_2^*$ profiles in (a, b and c) are respectively (d, e and f).
the curves were manually grouped according to common shape features as presented in figure 1. Figure 1a, 1b and 1c show the \(\Delta R_2^*\) profiles together with the ground truth, these profiles were scaled according to their area-under-the-curve. Figure 1d, 1e and 1f show the corresponding complex trajectories of the \(\Delta R_2^*\) profiles in 1a, 1b and 1c respectively. The first group (Figure 1a), consists of curves showing a narrower and higher peak than the true shape. The high and narrow peak in \(\Delta R_2^*\) is formed when, at the maximum concentration, all components add destructively (see Figure 1d). This leads to an underestimation of the amplitude of the MR signal, resulting in a severe overestimation of \(\Delta R_2^*\) (12, 13). The second group of curves (Figure 1b) show, instead of a single peak in the first passage, two peaks in close succession. This occurs when the complex signal passes close to the zero for a concentration lower than the maximum concentration (see Figure 1e). The third group (Figure 1c) shows curves with almost no peak in the first passage and a high post-bolus equilibrium. Automatic AIF selection criteria are likely to exclude AIF measurements suffering from partial volume errors of the second and third group, but AIF measurements with PVEs such as those in the first group are not excluded, because these curves have a small width, early time-to-peak and high peak-height.

**The proposed criterion**

The aim of the proposed criterion is to identifying voxels with minimal shape distortions due to PVEs. The proposed metric is the ratio of the mean steady-state value to the area-under-the-curve (AUC) of the first passage of contrast agent, further referred to as “SS:AUC\(^{1st}\) ratio”. This metric follows from tracer kinetic principles to calculate CBV. The CBV can be calculated, using the area-under-the-curve of the different passages or the steady-state concentration (16), by taking the ratio of the tissue response to the AIF:

\[
CBV = \frac{\int_{1st\ passage} C(t)dt}{\int_{1st\ passage} C_{AIF}(t)dt} = \frac{\int_{2nd\ passage} C(t)dt}{\int_{2nd\ passage} C_{AIF}(t)dt} = \frac{\int_{1st\ passage} C_{AIF}(t)dt}{\int_{1st\ passage} C(t)dt} = \frac{C(t_{ss})}{C_{AIF}(t_{ss})}
\]

where \(C(t)\) is the concentration contrast agent in tissue, \(C_{AIF}(t)\) is the concentration contrast agent in the brain-feeding artery, \(t_{ss}\) is the time at which the concentration of contrast agent is in steady-state (17, 18). Rewriting equation 1 results in three ratios that are constant for arterial and tissue concentration-versus-time profiles of a single experiment:

\[
\frac{\int_{2nd\ passage} C(t)dt}{\int_{1st\ passage} C(t)dt} = \frac{\int_{2nd\ passage} C_{AIF}(t)dt}{\int_{1st\ passage} C_{AIF}(t)dt} = constant
\]
These relations are only valid when \( C(t) \) reflects the true concentration-time curve, although a general scaling factor would not affect the validity of these relations. In DSC-MRI the MR-signal changes are converted to \( \Delta R_2^* \). The \( \Delta R_2^* \) profiles of the AIF measurements in or close to a brain-feeding artery are often hampered by PVEs. These PVEs lead to scaling errors and more importantly to shape errors with respect to the true concentration-versus-time profile. When such shape errors are present the SS:AUC\(^{1st}\) ratio of the AIF measurement deviates from the ground truth SS:AUC\(^{1st}\) ratio. The reference value reflecting the ground truth SS:AUC\(^{1st}\) ratio can be determined in tissue, because the \( \Delta R_2^* \) profile in tissue is linear with respect to the concentration of contrast agent under the assumption that the arterioles and capillaries are randomly oriented (14).

Two of the three metrics were not investigated because of practical considerations: (i) the second passage has lower signal-to-noise than the first passage (where SNR is defined as the signal difference between pre-bolus and peak concentration over the noise at baseline), and (ii) the gamma-variate fit through the second passage is more difficult to determine than the steady-state due to its overlap with the first and subsequent bolus passages (see Figure 2).

![Figure 2: The gamma-variate estimation of the first (a) and second passage (b) and the steady-state estimation (c). The gamma-variate fit through the first passage is feasible but the gamma-variate fit through the second passage only contains a few data points due to the overlap with the first and subsequent tissue passage. Two of these three measurements can be used to determine the ratio, which assesses the shape error in the AIF due to PVEs.](image-url)
the gamma-variate fitting values through the simulated tissue curve (to reflect closer the in vivo situation, see below); the tissue curve was calculated from the first passage of the ground truth AIF convolved with an exponential residue function.

Simulations
All simulations were implemented in MATLAB (R2007b, Natick, MA, USA). In the simulations, a modeled AIF (19) and a modeled tissue response were used. The tissue contrast agent concentration was created after convolving the modeled AIF with an exponential residue function (CBF = 60 ml/100g/min, MTT = 4 sec, CBV = 4 ml/100g).

Partial volume effects simulations
The numerical model to study partial volume shape errors in the AIF measurements included local magnetic field changes and relaxation rate changes due to the passing contrast agent. For these simulations, only the contrast agent passage within the artery is modeled. The artery is assumed to be a cylinder (diameter = 4 mm) oriented perpendicular to B₀ and the artery is surrounded by tissue. The longitudinal, transverse relaxation times and the relaxivity values were set to in vivo values at 1.5 T (which are used for all other simulations): T₁ is 0.95 sec and 1.4 sec for tissue and blood respectively (20), T₂* is 0.1 sec for tissue and blood (20), transverse relaxivity of the contrast agent in arterial blood with a linear term 7.62 l/mmol/sec and a quadratic term 0.57 l²/mmol²/sec (21). The local field changes, resulting from the susceptibility difference (molar susceptibility χₘ = 0.3209·10⁻³ l/mol (21)), were calculated using the Maxwell equations corrected for the sphere of Lorenz on a spatial grid of 250 μm. The double-dose experiment at 1.5 T is also representative for a single-dose experiment at 3 T (11). A rectangle voxel with a size of 1x3 times the radius of the cylinder was used (due to symmetry in the direction of the vessel, only two dimensions need to be included). This voxel was shifted over the local field map and the gradient-echo signal was calculated taking into account the relaxivity effects of the contrast agent within the artery. The shifting generates a large range of PVEs that can occur when there is a linear phase effect inside the artery and a blooming effect outside the artery. The simulated AIF profiles were studied and three groups were manually selected (see Figure 1).

Factors affecting the SS:AUC₁ˢᵗ ratio
The effects of T₁ relaxation changes on SS:AUC₁ˢᵗ ratio of the tissue response for a gradient-echo MR-signal were studied using the modeled tissue response. The effect of T₁ relaxation changes on the arterial response is expected to be minimal due to fresh inflow of spins and were not further studied. The flip angle and repetition time were varied in the simulations, since these two parameters influence the T₁-effect in tissue the most (22). Gradient echo signals with TE/TR 31/1500 msec and TE/TR 31/600 msec were simulated and the flip angle was varied from 5° to 90° in steps of 5° using a longitudinal relaxivity (r₁) of 4.3 l/mmol/sec (23).
The second factor that can affect the SS:AUC_{1st} ratio is the SNR, since the ratio measured in the AIF and the reference ratio obtained from the tissue response are subject to noise. The effect of noise on the SS:AUC_{1st} ratio was studied using the modeled tissue response. Four different SNR levels were simulated (20:1, 30:1, 40:1 and 50:1) with 10000 random noise repeats. From these simulations the mean value and the standard deviation of the SS:AUC_{1st} ratio were calculated.

It has been shown that AIF measurements are best selected in locations where PVEs do not corrupt the measurements (11, 12). These locations are, for example, in homogenous tissue close to but completely outside the middle cerebral artery (MCA) (11). Unfortunately, AIF measurements performed in tissue are hampered by the tissue response. Therefore, the third factor studied is the contamination of the AIF measurement by the tissue response. The influence of the tissue response on the extravascular susceptibility induced contrast was studied using a previously published numerical model (11). This model, which was validated using phantom experiments, simulates AIF measurements in and near a cylinder that is oriented perpendicular to B_0 (a model for arteries such as the MCA). The model is based on the numerical model used to study PVEs (see above), but is extended and includes also imaging effects such as the phase-shifts and distortions from the EPI readout train as well as a tissue passage of the contrast agent in the surrounding. The imaging settings for the simulations were the following: segmented EPI, matrix size 96x96, TE/TR 31/600 msec, flip angle (FA) 40º, field of view (FOV) 220x220 mm², 10 slices of 6.2 mm thickness with 1 mm gap, number of echoes per echo-train 21. The SS:AUC_{1st} ratios of the simulated AIF measurements were calculated, the difference with the ground truth in percent was determined and the AUC of the first passage was used as a measure for SNR.

**In vivo**

In vivo DSC-MRI exams of six patients (1 man, 5 women; mean age 36, range 16-46) suffering from Systemic Lupus Erythematosus were used for evaluation of both the reference SS:AUC_{1st} ratio obtained from the tissue response and measured AIF SS:AUC_{1st} ratio in and around the MCA. In vivo experiments were performed at 3 T (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 sequence had the following settings: dual-echo segmented EPI: data matrix 96x96, T_E1/T_E2/TE/11/31/600 msec, FA 40º, FOV 220x220 mm², SENSE factor of 2.2, 10 slices of 6.2 mm thickness with 1 mm interslice gap with one additional slice through the carotid artery just above the bifurcation, number of echoes per echo-train 21. The study was approved by the local ethics committee.

**In vivo post processing**

The in vivo DSC-MRI exams were acquired with two echo times. By using a dual-echo sequence, correction for T_1-relaxation effects (caused by the passage of contrast agent) is possible (24, 25):
\[
\Delta R_2^*(t) = \frac{1}{T E_2 - T E_1} \left( \ln \left( \frac{S_{T E_1}(t)}{S_{T E_2}(t)} \right) - \ln \left( \frac{S_{T E_1}(0)}{S_{T E_2}(0)} \right) \right)
\]

where TE is the echo time and \( S(t) \) is the magnitude of the MR-signal.

To segment gray matter, white matter and vessels, a relative CBV was calculated using the AUC of the \( \Delta R_2^* \)-curves. The CBV value intervals for the segmentation were empirically determined and the resulting gray and white matter segmentation was compared to the pre-bolus \( T_2^* \) image. Furthermore, a lobular mask was used to segment the tissue in the following lobes and areas: the frontal, parietal, occipital and temporal lobe, the cerebellum, the insula and a combined area of thalamus, caudate nucleus and putamen (26). Before segmentation, the dataset was normalized using an EPI template in SPM 5 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London UK – http://www.filion.ucl.ac.uk/spm). The average tissue response was determined for the gray matter and white matter part of the different lobe-areas. The SS:AUC\(^{1st} \) ratio was determined and a two-sided paired t-test was used to compare the SS:AUC\(^{1st} \) ratio obtained from gray matter and white matter. The mean value and the standard deviation of the SS:AUC\(^{1st} \) ratios for the different gray matter and white matter areas of the lobular mask were calculated. The acceptance range for the SS:AUC\(^{1st} \) ratio was defined as the mean value plus or minus two times the standard deviation (referred to as “range of acceptance”). The in vivo DSC-MRI exams were also used to evaluate AIF measurements near the MCA, and to illustrate whether PVEs can be detected in vivo.

**RESULTS**

**Simulations: The influence of \( T_1 \)-effects, noise and the tissue passage curve on the proposed criterion**

Figure 3 shows the influence of \( T_1 \)-effects on the SS:AUC\(^{1st} \) ratio of the tissue response. The \( T_1 \)-effects for relatively short repetition times (as used in segmented EPI) are large for normal flip angles. Flip angles close to the Ernst angle result in a post-bolus equilibrium around zero and therefore the SS:AUC\(^{1st} \) ratio is close to zero. For flip angles around 5° the \( T_1 \)-effect is reduced and the SS:AUC\(^{1st} \) ratio is close to the ground truth, but with such small flip angles the SNR of the acquisition is reduced. Single shot EPI with its longer repetition time is less sensitive to \( T_1 \)-effects, as shown in figure 3c and d. Nevertheless, flip angles around the Ernst angle reduce the SS:AUC\(^{1st} \) to around 50% of the ground truth. These results show that the error in the SS:AUC\(^{1st} \) ratio due to \( T_1 \)-effects is large for techniques that are \( T_1 \)-sensitive. The dual-echo approach can make the acquisition \( T_1 \)-insensitive and for this reason, \( T_1 \)-effects were ignored in further simulations.
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The influence of noise on determining the SS:AUC\textsuperscript{1st} ratio was studied using repeated simulations with random noise. The SNR was varied from 20:1 to 50:1 in steps of 10:1, and the results are presented in table 1 (the ground truth of the SS:AUC\textsuperscript{1st} ratio for this simulated case was 0.0176). The standard deviation of the SS:AUC\textsuperscript{1st} estimation reduces with increasing SNR. However, a single voxel AIF measurement with a typical SNR of 50:1 still has a 95% confidence interval of the mean value ± 7.6%.

The third factor influencing the SS:AUC\textsuperscript{1st} ratio is the contamination of the AIF with the tissue response. Figure 4a shows the SS:AUC\textsuperscript{1st} ratio for the simulated AIF measurements in and around the MCA (presented as a sagittal section); the ground truth is 0.0176. The % deviation from the ground truth better shows the accuracy of the SS:AUC\textsuperscript{1st} ratio (see Figure 4b). Figure 4b shows that the SS:AUC\textsuperscript{1st} ratio is higher than the ground truth in voxels encompassing the MCA. Furthermore, it can be seen that the tissue remote from the vessel in the superior-inferior

Table 1: The mean SS:AUC\textsuperscript{1st} ratio, the standard deviation (SD) and the standard deviation as percent of the mean value for the modeled AIF with different SNR levels and 10000 random noise repeats. Ground truth for this case: 0.0176

<table>
<thead>
<tr>
<th>SNR</th>
<th>Mean</th>
<th>SD</th>
<th>SD [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>20:1</td>
<td>0.0175</td>
<td>0.0015</td>
<td>8.8</td>
</tr>
<tr>
<td>30:1</td>
<td>0.0176</td>
<td>0.0011</td>
<td>6.1</td>
</tr>
<tr>
<td>40:1</td>
<td>0.0176</td>
<td>0.0008</td>
<td>4.7</td>
</tr>
<tr>
<td>50:1</td>
<td>0.0176</td>
<td>0.0007</td>
<td>3.8</td>
</tr>
</tbody>
</table>
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direction has a SS:AUC\textsuperscript{1st} ratio close to the ground truth. However, in this region, the AUC of the first passage is low (see figure 4c). More importantly, Figure 4b shows that AIF measurements in the vicinity of the MCA also have a correct SS:AUC\textsuperscript{1st} ratio, but only in a narrow rim because further anterior and posterior the SS:AUC\textsuperscript{1st} ratio reduces to a value lower than the ground truth. The AUC of the first passage indicates regions with high SNR and low SNR; high SNR is found in voxels encompassing the MCA and low SNR is found in tissue.

**In vivo: Evaluation of the proposed criterion**

The reference SS:AUC\textsuperscript{1st} ratio was determined for different lobes and areas in the segmented gray and white matter, since averaging over a large number of voxel increases the SNR substantially and hence improves the accuracy. Unfortunately, for small regions (such as the insula) averaging over a number of voxels did not provide particularly high SNR, SNR values were as low as 26:1 for gray matter and 16:1 for white matter. However, the average SNR over all regions and patients is high with an average SNR value of 169:1 for gray matter and 126:1 for white matter. The average SS:AUC\textsuperscript{1st} ratio and the standard deviation over the different lobes and areas are presented in table 2.

**Table 2:** The mean SS:AUC\textsuperscript{1st} ratio for gray matter (GM) and white matter (WM), the standard deviation (SD) and the standard deviation in percent of the mean value for 6 patients based on the gray matter and white matter segmentation and averaged over the different brain lobes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean GM</th>
<th>SD</th>
<th>SD [%]</th>
<th>Mean WM</th>
<th>SD</th>
<th>SD [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.0236</td>
<td>0.0022</td>
<td>9.3%</td>
<td>0.0211</td>
<td>0.0038</td>
<td>17.8%</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.0208</td>
<td>0.0014</td>
<td>7.0%</td>
<td>0.0194</td>
<td>0.0019</td>
<td>9.8%</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0.0262</td>
<td>0.0025</td>
<td>9.6%</td>
<td>0.0234</td>
<td>0.0016</td>
<td>7.0%</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.0363</td>
<td>0.0036</td>
<td>10.0%</td>
<td>0.0319</td>
<td>0.0018</td>
<td>5.5%</td>
</tr>
<tr>
<td>Patient 5</td>
<td>0.0261</td>
<td>0.0023</td>
<td>8.9%</td>
<td>0.0240</td>
<td>0.0018</td>
<td>7.6%</td>
</tr>
<tr>
<td>Patient 6</td>
<td>0.0349</td>
<td>0.0034</td>
<td>9.7%</td>
<td>0.0317</td>
<td>0.0023</td>
<td>7.4%</td>
</tr>
</tbody>
</table>
Figure 5: AIF measurements in and around the MCA of an in vivo example (patient 1). The profiles within the MCA, as well as the profile touching the artery, show partial volume effects. The profile anterior to the MCA shows a high and narrow peak resulting in a low SS:AUC\textsuperscript{1st} ratio. The metric can also provide AIF measurements with minimal PVEs, these are located outside the MCA which is in agreement with the simulations.
The mean SS:AUC\textsuperscript{1st} ratio of the tissue response varies over subjects; the SS:AUC\textsuperscript{1st} ratio for patients 4 and 6, for example, are much higher for both gray matter and white matter than the other patients. This could be due to a different fraction of blood flowing to the brain vasculature. The mean SS:AUC\textsuperscript{1st} ratio of the gray matter is significantly higher than the white matter SS:AUC\textsuperscript{1st} ratio (p<0.005) for each patient. The standard deviation (in percent of the mean value) for gray matter as calculated from different lobes is not larger than 10%; using this value the range of acceptance is formed with an interval of the mean value ± 20%. This range of acceptance was used to evaluate the SS:AUC\textsuperscript{1st} ratio of AIF measurements in and around the MCA. The profiles of one patient are presented in figure 5; the range of acceptance for this patient (patient 1) is [0.019 0.028]. The individual profiles of the AIF measurements partly encompassing the MCA have SS:AUC\textsuperscript{1st} ratios that fall outside the range of acceptance (see red dots in Figure 5) except for one profile. That profile has a first passage that is distorted and the gamma-variate model is not the right model to fit this first passage. The first passage of the second plot on the bottom row in figure 5 also has a different shape than the gamma-variate function, but here the result is that the SS:AUC\textsuperscript{1st} ratio falls outside the range of acceptance. It is therefore important to test whether the gamma-variate fit is the right model to fit the first passage. A profile with a very high peak and a small width is observed in the bottom row first plot; it should be noted that the sharp peak of this profile is similar to the first group of the simulated PVEs. Therefore, this profile may not necessarily be recognized as distorted by previously proposed automatic AIF selection algorithms; however, the SS:AUC\textsuperscript{1st} ratio falls outside the range of acceptance since the mean steady-state value is close to zero and the AUC of the first passage is high. A number of voxels with SS:AUC\textsuperscript{1st} ratios that fall inside the range of acceptance (see green dots in Figure 5) are superior to the vessel and posterior to the vessel, which is in agreement with predictions from a previous study (11).

**DISCUSSION AND CONCLUSIONS**

The most important findings of this study are four-fold. First, a new criterion based on tracer kinetic theory can detect non-linear shape errors due to PVEs in the estimated evolution of the AIF (measured using the ΔR\textsubscript{2}\textsuperscript{+}) using a reference value obtained from tissue. Second, for correct use of the ratio approach, T\textsubscript{1}-insensitive techniques should be employed for the DSC-MRI acquisition, because T\textsubscript{1}-effects predominantly affect the steady-state of the tissue response, leading to different SS:AUC\textsuperscript{1st} ratios for AIF versus tissue. Third, we suggest that the best reference SS:AUC\textsuperscript{1st} ratio is obtained from the gray matter tissue. Finally, the proposed criterion should be used as an additional criterion in automatic AIF selection procedures and not as a stand-alone criterion.

In this study, a new criterion is proposed to aid in the AIF selection to exclude shape errors arising from PVEs. The criterion uses a metric that is based on tracer kinetic principles. The
A new criterion to aid selection of the AIF in DSC-MRI

A metric is the ratio of the mean steady-state (determined using a number of time-points of the post-bolus equilibrium) to the AUC of the first passage (determined using a gamma-variate fit through the time-points of the first passage). The SS:AUC\textsuperscript{1st} ratio for the AIF measurement is guided by the reference SS:AUC\textsuperscript{1st} ratio obtained from tissue. The gray matter voxels, which are used for the reference SS:AUC\textsuperscript{1st} ratio, can for example be selected by a simple gray matter segmentation based on the relative CBV determined using the AUC of the tissue response. We determined a range of acceptance for the SS:AUC\textsuperscript{1st} ratio based on in vivo data. The in vivo example in figure 5 confirms that AIF measurements with severe PVEs fall outside the range of acceptance (the mean value ± 20\%). In particular, it was found that PVEs voxels with high and narrow peaks do occur in vivo (see figure 5, bottom row left; compare figure 1(a)); such peaks would be selected as good examples of AIF voxels using most automated approaches, but they can be identified and excluded using the proposed additional criterion.

There are, however, a number of factors that influence the SS:AUC\textsuperscript{1st} ratio either of the AIF, the tissue reference value or both. \textit{T}_1 relaxation effects affect the shape of the tissue response and, especially, the steady-state signal, which in turn affect the SS:AUC\textsuperscript{1st} ratio. In general, \textit{T}_1-effects lead to an underestimation of the reference SS:AUC\textsuperscript{1st} ratio. The simulations showed that for segmented EPI, with its relatively short repetition time, the \textit{T}_1-related error in SS:AUC\textsuperscript{1st} ratio is large. Using a very small flip angle can reduce \textit{T}_1-effects (22), but this also reduces the baseline SNR. Acquiring segmented EPI with two echo times makes correction for \textit{T}_1-effects possible, and is therefore advantageous over normal segmented EPI acquisition. Single shot EPI does also suffer from \textit{T}_1-effects although in a lesser extent. When there is fresh inflow of spins, such as in arteries, these \textit{T}_1-effects can be ignored. Finally, it could be studied whether the influence of \textit{T}_1-effects on the SS:AUC\textsuperscript{1st} ratio of tissue could be corrected for e.g. by assuming a certain average steady-state concentration.

We suggest that the reference SS:AUC\textsuperscript{1st} ratio is best obtained from gray matter in areas distant from arteries and veins. In vivo, differences in reference SS:AUC\textsuperscript{1st} ratio were observed between the gray and white matter, which is not in line with the findings of Kjølby et al. (14), who predicted, based on simulations and analytical models, a linear relation between Δ\textit{R}_2* and concentration of contrast agent for both white and gray matter. Although the reason is not fully understood, this difference could be because the area of dephased signal from a particular vessel touches the dephasing area of other vessels for the higher concentrations of contrast agent in gray matter. The overlapping dephasing areas would induce a leveling off of the Δ\textit{R}_2* versus gadolinium concentration curve, thereby indeed leading to a higher SS:AUC\textsuperscript{1st} ratio for gray matter than white matter as was observed. The theoretical model of Kjølby et al. assumes that each vessel can be treated as a separate object, not influencing or influenced by other vessels and this leveling-off effect is therefore not included. An alternative reason could be that the static dephasing regime is not valid for low concentrations that occur in the steady-state of white matter (27, 28), or the fact that the mesoscopic structure of the gray matter is different from that of the white matter, or the fact that diffusion is more anisotropic in white matter (29).
Contamination of white matter voxels in the gray matter average would lower the reference ratio value. This effect is however expected to be small due to the small difference between the white and gray matter values.

Since the SS:AUC\textsuperscript{1st} is determined over a region of interest with many voxels, the SNR is increased compared to a single voxel. However, the SNR for a small ROIs (e.g. the insula) in the lobular mask had low SNR values resulting in reduced accuracy of that specific SS:AUC\textsuperscript{1st} ratio. The simulations show that for these low SNR values (approximately 20:1) the 95% confidence interval is the true value ± 18%. However, the average SNR over all ROIs and all patients is high for gray and white matter. In addition, the frontal and temporal areas show for all patients a higher SS:AUC\textsuperscript{1st} ratio than the occipital and parietal areas (data not shown). These regional differences together with the inaccuracy due to low SNR of a few regions lead to the approximately 10% standard deviation in the ratio estimation of gray matter. It can be expected that averaging the total gray matter would further reduce this source of error.

The new proposed selection criterion is not designed as a stand-alone criterion, but as an additional selection criterion for automatic AIF selection or for guiding manual AIF selection. Errors can occur when the gamma-variate fit no longer describes the first passage accurately. Estimation of the SS:AUC\textsuperscript{1st} ratios for the AIF measurement shows false positives for some partial volume errors. However, these false positives could be easily avoided by including boundary constraints on the gamma-variate fit through the first passage, or by using an additional standard criterion, such as a small FWHM. Alternatively, more specialized methods for first passage extraction can also be used to improve the ratio estimation (27, 30, 31).

Errors in the SS:AUC\textsuperscript{1st} ratio can also occur when there are motion artifacts. In the post-bolus equilibrium, motion artifacts can lead to a sudden increase, sudden decrease or sharp transient peaks (data not shown). When incorporating the proposed criterion in an automatic AIF selection program, these motion artifacts should be detected. In addition, the post-bolus equilibrium should have a sufficient number of time-points, therefore the acquisition of the DSC-MRI exam should be long enough to properly characterize the tail of the bolus passage. Moreover, since the SS:AUC\textsuperscript{1st} ratio is highly dependent on the AUC\textsuperscript{1st} passage, having proper starting values for the gamma-variate fit is of high importance. We used as starting values for the simulation the fitting values of the fit through the ground truth, and as starting values for the in vivo ratio estimates the fitting values of the whole brain average, which is primarily weighted to the tissue response. Both approaches led to appropriate fitting of the first passage.

Since the new criterion aims at detecting PVEs, AIF measurements that are only hampered by noise will not be excluded. Noise originating from physiological pulsations or instrumental noise can alter the AIF profile to produce a wider peak and a smaller peak-height. Including these AIF measurements is crucial for unbiased averaging. Less stringent criteria concerning the first passage can aid in unbiased averaging of several “correct” AIF measurements.

Although the simulations are only performed for an artery perpendicular to B\textsubscript{0}, the generic pattern of a linear phase effect inside and a blooming phase effect outside the artery is typical
for all angles except arteries at the magic angle or parallel to $B_0$. The shifting of the voxel in steps smaller than the voxel size generated a large range of PVEs. We expect that the shape errors encountered in the simulations are representative for shape errors of arteries with other orientations.

In conclusion, we propose a metric that can aid in either manual or automatic AIF selection. The metric checks whether the AIF is corrupted by PVEs. Having an AIF that is not corrupted by PVEs greatly improves the quantification of the hemodynamic parameters. Since the proposed approach is a post-processing method, the ratio can also be used retrospectively in previously acquired data with sufficient sampling of the post-bolus equilibrium.
REFERENCES


