Correcting Partial Volume Artifacts of the Arterial Input Function in Quantitative Cerebral Perfusion MRI

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To quantify cerebral perfusion with dynamic susceptibility contrast MRI (DSC-MRI), one needs to measure the arterial input function (AIF). Conventionally, one derives the contrast concentration from the DSC sequence by monitoring changes in either the amplitude or the phase signal on the assumption that the signal arises completely from blood. In practice, partial volume artifacts are inevitable because a compromise has to be reached between the temporal and spatial resolution of the DSC acquisition. As the concentration of the contrast agent increases, the vector of the complex blood signal follows a spiral-like trajectory. In the case of a partial-volume voxel, the spiral is located around the static contribution of the surrounding tissue. If the static contribution of the background tissue is disregarded, estimations of the contrast concentration will be incorrect. By optimizing the correspondence between phase information and amplitude information one can estimate the origin of the spiral, and thereafter correct for partial volume artifacts. This correction is shown to be accurate at low spatial resolutions for phantom data and to improve the AIF determination in a clinical example. Magn Reson Med 45:477–485, 2001. © 2001 Wiley-Liss, Inc.

Key words: partial volume artifacts; arterial input function; dynamic susceptibility contrast MRI (DSC-MRI); cerebral perfusion; contrast agents

Quantitative measurements of cerebral perfusion are of great clinical interest and are particularly useful for monitoring patients with ischemia, chronic vascular disease, or degenerative disorders (1–3). The most mature method for cerebral perfusion MRI, namely dynamic susceptibility contrast MRI (DSC-MRI), involves monitoring the first passage of contrast material through the brain tissue. To quantify these measurements one needs to determine the arterial input function (AIF), defined as the concentration of contrast agent in blood entering the brain as a function of time (4,5). However, measurements of the AIF are error prone and therefore one of the major sources of inaccuracy (6).

Cerebral perfusion studies are generally performed with the contrast agent gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA), which exhibits $T_1$, $T_2$, and $T_2^*$ effects (7). Although all these effects can be exploited for perfusion imaging, we will focus on the $T_2^*$ effects. By using $T_2^*$-weighted imaging one can quantify the AIF, whereas a $T_1$-weighted method produces only the shape of the input function (8,9). For the AIF measurement an image-slice has to be positioned through a large brain-feeding artery, e.g., the internal carotid artery. The TE of this slice must be short in view of the high concentration of contrast material (4,10).

The conversion of MR signal to concentration of contrast agent can be based on two different physical processes. The first and most common method uses the decrease in the transverse relaxation time of blood, which is caused by the increase in local field inhomogeneities (4). The second method exploits the phase shift of the blood signal, which is caused by the increased plasma susceptibility that stems from the presence of contrast material (11). Both processes are based on the assumption that the MR signal inside the selected voxels arises exclusively from blood. Unfortunately, tissue surrounding the vessel lumen also contributes to the MR signal because the spatial resolution is limited by the need for a high sampling rate of the AIF.

The purpose of this work is to minimize partial volume artifacts that distort the arterial input function, and thus improve the accuracy of cerebral perfusion imaging. To this end, we will first investigate the theoretical influence of the partial volume effect and show that it leads to substantial errors in the determination of contrast concentration. This influence will be examined in an artery model in which the surroundings make a controlled contribution to the MR signal. On the basis of the theory, a correction method will be proposed which analyzes the evolution of the complex signal over time and combines the information of the amplitude and phase signals. The partial volume effect and the correction method are further investigated by analyzing at different spatial resolutions the MR signal during the passage of contrast agent through a tubular phantom, which will demonstrate the accuracy and robustness of our correction method even at low resolutions. Finally, we illustrate the clinical applicability of the method by determining the AIF in a patient study.

THEORY

Signal Formation During the Passage of a Bolus of Contrast Agent

We modeled the MR signal during the passage of contrast agent by assuming the vessel to be an infinite cylinder, oriented parallel to the main magnetic field with the imaging slice orthogonal to the cylinder. The spatial distribution of the contrast agent is assumed to be homogeneous over the artery and constant during the acquisition of each dynamic image. Finally, the blood velocity is assumed to be high enough to guarantee total refreshment of spins...
during one TR, which prevents contrast concentration dependent T₁-weighting.

First we describe the signal formation of a voxel consisting of pure blood. The amplitude of the MR signal will decrease exponentially with increasing concentration of contrast agent because of the increase in local field inhomogeneities (7,12,13). Additionally, the magnetic field inside the vessel will change in response to the higher susceptibility of the contrast agent, leading to a phase shift of the blood signal (11):

\[
S_{\text{blood}}([Gd]) \propto \rho_{\text{blood}} \cdot \sin \alpha \cdot e^{-TE/T_{2,\text{blood}}([Gd])} \cdot \rho_{\text{Gd}}([Gd])
\]  

\[
\frac{1}{T_{2,\text{blood}}([Gd])} = \frac{1}{T_{2,blood}^0} + r_s^\text{blood} \cdot [Gd]
\]  

\[
\theta([Gd]) = \theta(0) + \frac{1}{3} \cdot \omega_0 \cdot \chi_m \cdot TE \cdot [Gd]
\]  

with \( S \) the complex MR signal, \( [Gd] \) the concentration of Gd-DTPA, \( \rho_{\text{blood}} \) the proton density of blood, \( \alpha \) the flip angle, TE the echo time, \( T_{2,blood}([Gd]) \) the transverse relaxation time of blood as a function of the concentration of Gd-DTPA, \( \theta([Gd]) \) the phase of the MR signal as a function of the concentration of Gd-DTPA, \( r_s^\text{blood} \) the transverse relaxation rate of gadolinium, \( \omega_0 \) the resonance frequency, and \( \chi_m \) the molar susceptibility.

With increasing Gd-DTPA concentration, the complex MR signal follows a spiral-shaped trajectory around the origin of the complex plane (see Fig. 1a). This means that during the upslope of the passage of a bolus the complex signal propagates inwards along the spiral and unwinds along the same spiral when the contrast concentration decreases to the equilibrium concentration.

The conventionally used parameters \( \Delta R_s^2 = \Delta(1/T_s^2) \) and \( \Delta \theta \) are defined as:

\[
\Delta R_s^2([Gd]) = \Delta \left[ \frac{1}{T_{2,\text{blood}}([Gd])} \right] = \frac{1}{TE} \ln \left[ \frac{|S(0)|}{|S([Gd])|} \right]
\]  

\[
\Delta \theta = \text{arg}(S([Gd])) - \text{arg}(S(0)).
\]

Substituting Eqs. [1]–[3] into Eqs. [4] and [5] shows the assumed linear dependence of both parameters on the Gd-DTPA concentration for a blood-only voxel:

\[
\Delta R_s^2_{\text{blood}} = r_s^\text{blood} \cdot [Gd]
\]

\[
\Delta \theta_{\text{blood}} = \frac{1}{3} \cdot \omega_0 \cdot \chi_m \cdot TE \cdot [Gd].
\]

A partial volume voxel is sensitive not only to blood, but also to the surrounding tissue (see Fig. 2). The signal of such a voxel is described by the vectorial sum of the blood signal and the tissue signal (14):

\[
S_{\text{voxel}}([Gd]) = f_{\text{blood}} S_{\text{blood}}([Gd]) + f_{\text{tissue}} S_{\text{tissue}}
\]

where \( f_{\text{blood}} \) and \( f_{\text{tissue}} \) are the volume fractions of blood and tissue, respectively. The tissue signal can be calculated from the equilibrium magnetization parallel to \( B_0 \) (15,16) and is independent of the contrast concentration within the vessel, because of the parallel orientation.
where $M_z$ is the equilibrated transverse magnetization for a partial-volume voxel as a function of the Gd-DTPA $D_u$ signal can therefore be estimated by iteratively maximizing (Fig. 1b). If rounding the vessel causes the origin of the spiral to shift gradient echo sequence. This contribution of tissue surrounded the complex MR signal and the parameters monitored the static contribution from the surrounding tissue. Equations [1]–[3] imply that the origin of the spiral represents the static contribution from the surrounding tissue. The proposed correction method is based on a search for this static contribution, and thus for the origin of the spiral. Subtraction of the static signal from the total signal will develop with respect to the Gd-DTPA concentration (Fig. 1c and d). This can result in errors exceeding the 100% in the measured gadolinium concentration (Fig. 1c).

Correction for Partial Volume Effects

In the previous section it was shown that the complex signal of the input function follows a spiral-like trajectory. Equations [1]–[3] imply that the origin of the spiral represents the static contribution from the surrounding tissue. The proposed correction method is based on a search for this static contribution, and thus for the origin of the spiral. Subtraction of the static signal from the total signal of a voxel leaves the contribution of blood, which makes it possible to calculate correctly the concentration of contrast agent through Eqs. [4] and [5] and this shift is ignored, oscillating behavior will develop with respect to the Gd-DTPA concentration (Fig. 1c and d). This can result in errors exceeding the 100% in the measured gadolinium concentration (Fig. 1c).

**METHODS**

All experiments were performed on a Gyroscan ACS-NT (Philips Medical Systems, Best, The Netherlands) 1.5 T whole body scanner equipped with high gradient hardware (Powertrak 6000).

**Phantom Experiments**

**Partial Volume Effect in a Static Situation**

To validate the model of partial volume artifacts, we monitored the complex MR signal and the parameters $\Delta R_z^2$ and $\Delta \theta$ for a partial-volume voxel as a function of the Gd-DTPA concentration. By measuring in a static situation, we ensured that there was no influence of flow or fast acquisition techniques. A drawback of measuring in a static situation is that the assumption of total refreshment of spins is not met. As a result, there is some $T_1$-influence, which causes deviations from linear behavior in the case of low-contrast concentrations.

A tube (6.4 mm diameter, 0.4 mm thickness; DSG Schrumpfschlauch GmbH, Meckenheim) was oriented parallel to the main magnetic field in a box filled with an aequous solution (19.2 mg/l MnCl$_2 \cdot 4$H$_2$O) of manganese-chloride. The tube was connected to a pump and reservoir so that the contrast concentration inside the tube could be increased without changing its position inside the magnet (total volume of aqueous solution in tube and reservoir = 0.500 l). During the measurements the flow inside the tube was stopped. We achieved a controlled contribution from the surroundings by imaging with a parallel slice through the tube-axis. We varied the slice thickness (4, 6, 8, and 10 mm) to obtain different degrees of partial volume. Manganese-chloride-spiked tap water (19.2 mg/l MnCl$_2 \cdot 4$H$_2$O) was used to mimic blood inside the tube. The concentration of Gd-DTPA (Magnevist, Schering, Germany) in this solution was increased in steps of 2 mM. Ten points located on the axis of the tube were averaged and used for statistical analysis.

The acquisition parameters of the dual-echo gradient-echo sequence were: $T_E = 9$ msec, $T_E_2 = 16$ msec, TR = 185 msec, field of view (FOV) = $125 \times 125$ mm$^2$, matrix = $256 \times 256$, 1 readout per RF pulse, number of averages = 4, and flip angle = $10^\circ$. A quadrature knee coil (diameter = 18 cm) was used as receiver.

**Dynamic Monitoring of the Passage of a Bolus**

To quantify the influence of the partial volume effect on the input function, we studied the passage of contrast agent at different in-plane resolutions. We verified the accuracy of the proposed correction method by comparing the corrected and uncorrected low-resolution data with the data at the highest resolution. After acquiring the passage of contrast agent at a high resolution, we generated lower resolutions by artificially broadening the point-spread function (PSF) by zeroing lines in $k$-space (in both the phase-encoding and readout directions, starting at the edges of $k$-space). True voxel-width (in contrast to the reconstructed voxel-width, which is kept constant) is defined as the distance from the maximum of the resulting point spread function to the first zero-crossing, which yields:

$$
\text{True voxel – width} = \frac{[\text{Total number of } k - \text{ lines}]}{[\text{Total number of } k - \text{ lines}] - [\text{number of zeroed } k - \text{ lines}]} \cdot [\text{Original voxel – width}].
$$

This method is preferred to actual imaging at different resolutions, because the shape and the timing of the underlying bolus and the position of the tube with respect to the reconstruction grid remain identical.
The passage of the bolus was monitored at a high temporal resolution (0.4 sec) and a spatial resolution of 1.95 × 1.95 × 10 mm³ (FOV = 47 × 125 mm²; matrix = 24 × 64, interpolated in k-space to 64 × 64). The aqueous solution was circulated at a steady flow of approximately 7 ml/sec. The injection protocol of the bolus was: injection of 5 ml of Magnevist at 0.3 ml/sec by a power injector (Medrad, Pittsburgh, PA). The layout of the experiment was almost identical to the previous experiment, but the image plane was oriented perpendicular to the tube. In front of the imaged tube a dispersive network was mounted to create a bolus shape more typical of the clinical situation. Scan parameters were also identical, except for the number of readouts per RF pulse, which were set to 3, and the number of averages, which were set to 1 to increase the temporal resolution.

At the original spatial resolution the voxel located closest to the center of the tube was selected. It is assumed that this voxel is not distorted by partial volume effects. The uncorrected ΔR₂* and Δθ curves at this resolution were used as gold standards for evaluating uncorrected and corrected curves at lower resolutions. The similarity to the gold standard was tested both with regard to the shape by means of the correlation coefficient, and with regard to the amplitude by means of the linear regression coefficient.

In Vivo Measurements

The AIF was measured in patients admitted to the hospital with a suspected neuroma acousticus. Informed consent was obtained prior to the investigation. The study was approved by the ethical committee of our hospital. The AIF was measured in an extra slice positioned through the image plane parallel to the one used as gold standards for evaluating uncorrected and corrected curves at lower resolutions. The similarity to the gold standard was tested both with regard to the shape by means of the correlation coefficient, and with regard to the amplitude by means of the linear regression coefficient.

Correction Method

As explained in the Theory section, correction boils down to the estimation and subsequent subtraction of the static tissue signal. The estimation is based on the voxel-wise optimization of the resemblance between the ΔR₂* and Δθ curves as a function of the subtracted complex signal. As a measure of resemblance, we have chosen the cross-correlation (19), which is independent of the mean of the two parameters, and is defined by:

$$ r = \frac{\sum_i (\Delta R_2^*(t_i) - \text{mean}(\Delta R_2^*)) \cdot (\theta(t_i) - \text{mean}(\theta))}{\sqrt{\sum_i (\Delta R_2^*(t_i) - \text{mean}(\Delta R_2^*))^2 \cdot \sum_i (\theta(t_i) - \text{mean}(\theta))^2}} $$

where the summations run over all sample points during the passage of the contrast agent.

The optimization was implemented with a downhill simplex method (20), with the real and imaginary part of the static signal as the parameters to be optimized, and the reciprocal of the cross-correlation as error measure (only positive values are used). The average complex signal during the peak of the bolus passage (typically 5–10 time points are averaged) was used as initialization. After each iteration the ΔR₂* and Δθ curves were calculated for the new estimate of the static signal, and the correlation was calculated by means of Eq. [11]. If no further significant increase in the correlation could be observed, the optimization was terminated, resulting in the corrected ΔR₂* and Δθ curves.

Unwrapping Phase Curves

Throughout the experiments described in this article, we unwrapped the phase signal by keeping the phase-difference between two consecutive time points between −π and +π by successive addition or subtraction of 2π.

RESULTS

Phantom Experiments

Partial Volume Effect in a Static Situation

Figure 3 demonstrates that the ΔR₂* and Δθ curves calculated from the total signal of a partial volume voxel show nonlinear, nonmonotonic behavior as a function of the Gd-DTPA concentration (see Fig. 3a and b). This behavior occurs because the origin of the spiral trajectory has shifted in the complex plane due to the signal from surrounding material (see Fig. 3c and d). We unraveled the underlying linear relationship of Δθ and ΔR₂* with respect to the gadolinium concentration by automatically estimating the static signal of the surrounding fluid, and by subtracting this from the total signal (see the arrow in Fig. 3f and the corrected curves in Fig. 3c and d). T₁-enhancement can be observed both in the original ΔR₂* curves and in the corrected curves (see Fig. 3a and c) in the form of a negative lobe at low concentrations. In principle, it is possible to prevent this T₁ influence by using the data of the second TE, although in our measurements the signal-to-noise ratio (SNR) of the second echo series was too low in the case of concentrations larger than 10 mM.

Applying regression analysis to the corrected ΔR₂* and Δθ curves yields a value of 6.2 ± 0.1 sec⁻¹mM⁻¹ for the relaxation rate, and a value of (3.30 ± 0.03) · 10⁻⁴ M⁻¹ for the molar susceptibility when averages are taken over all curves and only concentrations of gadolinium higher than 5 mM are used to minimize T₁ influences. These contrast properties are close to values reported in the literature and specifications supplied by the manufacturer, which are reproduced in the caption of Fig. 1.

Dynamic Monitoring of the Passage of a Bolus

Figure 4 shows the influence of the voxel-width on the AIF. The shape of the AIF is evaluated relative to the high-resolution gold standard by cross-correlation; the amplitude of the curve is evaluated by linear regression. For a quantitatively correct representation of the input function, both descriptors should be 1. Even at true voxel-
FIG. 3. Contrast signal curves measured in a tubular phantom for different degrees of contribution from the surroundings for a TE of 9 msec. Curves are averaged over 10 voxels on the axis of the tube. 

- **a, b:** $D\Delta R^*_2$ and $\Delta \theta$ curves for varying slice thickness.
- **c, d:** Same curves after correction with the proposed method.
- **e, f:** Complex data with increasing contrast concentration along the spiral for slice thickness of 4 mm (e) and 10 mm (f); arrow indicates the fitted estimate of the static signal, error bars indicate the standard deviation over the 10 voxels. The fitted estimate of static signal for a slice thickness of 4 mm was too small to indicate with an arrow on this scale.
widths three times larger than the tube diameter, the AIF is recovered correctly after application of the proposed correction method. In Fig. 5 the uncorrected and corrected AIFs are shown for three illustrative true voxel-widths. At the original resolution, the corrected and uncorrected curves overlap, implying that the selected voxel was indeed unaffected by partial volume effects. Note also that the origin of the spiral is located in the third quadrant of the complex plane in the middle column and moves to the first quadrant at lower resolutions (third column). The inversion of the static signal is caused by the increasing contribution of the positive central lobe of the PSF. In the case of higher resolutions, the negative side lobes of the PSF predominate.

Theoretically, the upslope and downslope of the bolus passage should lie on the same spiral. It can be seen in Fig. 5 that the trajectories do not overlap completely; we refer to the Discussion section for possible causes of these minor deviations.

In Vivo Measurements

Figure 6 shows three different voxels located in the carotid arteries of the same patient. The top row represents the \( \Delta R_2^* \) curves that illustrate various influences of the partial volume effect on the uncorrected curves. From left to right, the voxels illustrate high peaks near the maximum concentration, an underestimation, and an overestimation of the curve. Also, the \( \Delta \theta \)-curves clearly differ from the corrected curves. In the bottom row the evolutions of the complex signal are shown together with the estimate of the tissue signal. From these graphs it can be observed that SNRs are lower for voxels that contain less blood (e.g., middle vs. left column).

DISCUSSION

In this work we have described partial volume artifacts that affect measurements of the arterial input function as part of a quantitative cerebral perfusion protocol. This partial volume effect gives rise to nonlinear, nonmonotonic relationships of \( \Delta R_2^* \) and \( \Delta \theta \) with respect to the gadolinium concentration. These artifacts can be circumvented by the estimation and subsequent subtraction of the background signal.

The proposed correction method optimizes the correspondence between concentration determination based on amplitude and phase changes, and allows us to estimate the contribution made by the surroundings. This correction made it possible to correctly measure the passage of contrast agent through an artery model, even after the resolution was decreased to voxel-widths three times larger than the tube diameter (Figs. 4 and 5). The correction method was also successfully applied to patient data, which illustrates its applicability to clinical practice (Fig. 6).

This method for correcting partial volume artifacts could be considered to be less valuable if in the majority of perfusion examinations one could identify at least one voxel containing only blood. By calculating the effective broadening of the point-spread function for a typical acquisition protocol and an average size internal carotid artery, it can be shown that the chance of such a voxel occurring is very small (see Appendix). This implies that the occurrence of partial volume errors in clinical practice can and should be expected.

The correction method requires accurate sampling of the spiral-like trajectory. This implies that the dynamic scan time should be short enough to yield enough sample
points during the passage of the bolus. A dynamic resolution of approximately 1 sec, which is often considered to be necessary for accurate quantification, yields approximately 15 points on the spiral, which seems to be adequate. The choice of the TE is also important. Too short a TE would allow only a small part of the spiral to be sampled, but too long a TE would give rise to signal-to-noise problems. We established clinically that a first TE of 8–12 msec is ideal for a double-dose injection.

Although the partial volume effect has been identified previously as a possible source of error, the influence of its effect has been grossly underestimated in the literature. Rempp et al. (4) have, for example, proposed rules to eliminate partial volume voxels on the basis of amplitude information only. They selected voxels that had a small width of the concentration-time curve, which appeared early and had a peak concentration higher than 75% of the highest peak concentration of all voxels. This method would, for example, result in the selection of the voxel depicted on the right side of Fig. 6 as a good estimate of the input function. Evaluation of the complex data of this voxel makes it clear that the high maximum in the $\Delta R_2^*$-curve is caused by a global shift of the spiral’s origin to the first quadrant. Because the selection rules of Rempp et al. (4) are based on the maximum peak concentration, this voxel would give rise to an overall overestimation of the input function, which in turn would lead to an underestimation of the cerebral blood flow and volume. This voxel demonstrates that it is essentially impossible to judge whether a voxel is unaffected by partial volume errors simply by observing the $\Delta R_2^*$ or $\Delta \phi$ curve.

In clinical examinations, some of the assumptions of our model will not hold. A change in the concentration of contrast material during one dynamic scan will, for example, lead to an averaging of the complex blood signal. This involves averaging over vectors with different angles, lead-
ing to dephasing and an underestimation of the mean amplitude; averaging will have only a minor effect on the \( \Delta \theta \) curves. An inhomogeneous distribution of contrast agent in the direction of the vessel-axis will affect the induced magnetic field inside the vessel. The fact that this distribution and the temporal averaging differ for the steep upslope and gradual downslope of the AIF could explain the small differences in spiral trajectories during the passage of the bolus (see, e.g., the bottom row of Fig. 5 or Fig. 6).

When a vessel is not oriented parallel to the main magnetic field, the contrast material will also induce changes in the magnetic field outside the vessel (21). We incorporated this effect in our model, but we did not find any significant changes for small deviations from parallel orientation. For larger deviations (above 15°), correction is no longer feasible because both the blood vector and the background vector rotate. During the planning of the image slice for the AIF measurement, the orientation needs to be watched carefully.

The correction method is based on the assumption of a linear relationship between contrast concentration and the \( \Delta R^*_2 \) and \( \Delta \theta \) curves. It has been suggested in the literature that this linear relationship does not hold for whole blood (15,22). We found indications to support these findings in our study of the complex signal of patient data. This effect could easily be integrated into our correction method, although the exact underlying relationships have still to be established.

In summary, it can be concluded that quantitative arterial input function measurements become feasible only if the complete complex data are used.
To obtain insight into the occurrence of blood-only voxels in a quantitative perfusion study, we calculate numerically the PSF for a simple 2D artery model (23). This model consists of a circle with a radius of one voxel-width. This size is based on the average diameter of the internal carotid artery, namely 4 mm (24), and a typical in-plane resolution of $2 \times 2$ mm$^2$. The intensity is set to 1 inside this circle and 0 outside. Continuous Fourier transformation of the analytical model results in the infinitely large $k$-space, representing the perfect acquisition. Because the model is defined in voxel dimensions, the acquired frequencies for an MR acquisition are bordered by $+\pi$ and $-\pi$. The inverse transformation of the bordered $k$-space results in the sensitivity of the voxel to the interior of a vessel, relative to the sensitivity of a blood-only voxel, which is normalized to 1. Furthermore, it can be shown that the relative sensitivity of a voxel to the background is equal to 1 minus its sensitivity to the inside of the circle. A relative sensitivity to the lumen of the vessel larger than 1 implies an inversion of the direction of the complex background signal, caused by the negative side-lobes of the PSF. The surroundings will always contribute to the signal of the voxel except when the relative sensitivity is 1.

Figure 7 shows for every position of the center of a voxel the relative sensitivity to the inside of the vessel-model. The small ring of values close to 1 justifies the statement that the chance of the existence of at least one blood-only voxel per examination is negligibly small.

REFERENCES