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Accurate, Localized Quantification of White Matter Perfusion With Single-Voxel ASL

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Quantification of perfusion in white matter is still difficult due to its low level, causing an often insufficiently low signal-to-noise ratio, and its long and inhomogeneous transit delays. Here, a technique is presented that accurately measures white matter perfusion by combining a spectroscopic single-voxel localization technique (point-resolved spectroscopy) with a pulsed arterial spin labeling encoding scheme (flow-sensitive alternating inversion recovery) to specifically address the properties of white matter. The transit delay was measured by shifting the position of a slice-selective saturation pulse between inversion and acquisition. Perfusion measurements resulted in values of 15.6 ± 3.2 mL/100 g/min in the left and 15.2 ± 4.8 mL/100 g/min in the right hemispheric white matter and 83.2 ± 15.2 mL/100 g/min in cortical gray matter. Taking dispersion of the transit times into account does not cause a significant change in the measured values. Magn Reson Med 64:1109–1113, 2010. © 2010 Wiley-Liss, Inc.

Key words: perfusion; arterial spin labeling; white matter; cerebral blood flow; single-voxel localization

Arterial spin labeling (1) is increasingly used for measuring perfusion in the brain and other organs by using the blood water as endogenous tracer. In contrast to other techniques, this method allows obtaining quantitative values noninvasively and repeatedly, with a high temporal and spatial resolution.

While arterial spin labeling is applied with great success to measure cerebral blood flow in gray matter both at rest (2) and during stimulation-induced brain activity (3), measuring the perfusion in white matter still remains a challenge. A recent paper (4) has examined the difficulties involved in white matter perfusion measurements, the major problem being the intrinsically low perfusion in white matter, which limits the signal-to-noise ratio (SNR) to a level that is often insufficient for reliable quantification. A frequently used method to maximize SNR is adding the signals from all white matter voxels, thereby not only losing the spatial information but also introducing partial-volume effects that gravely affect the quantification. Because of the large difference in perfusion between white and gray matter, even small contributions from gray matter signal strongly distort the result. Recently, a technique to correct for these effects has been published (5). However, adding voxel signals is an inefficient way to increase the signal strength because SNR only grows with the square root of the number of voxels.

Another major problem when trying to measure the perfusion in white matter is the long and inhomogeneous transit delay that, on the one hand, generates the need for long postlabeling delays, which further affect SNR due to longitudinal relaxation, and on the other hand complicates the quantification, which requires knowledge of the transit delay.

In spite of these difficulties, the possibility of quantifying white matter perfusion with the use of state-of-the-art techniques in parts of the brain has recently been shown (6).

Here, we present a technique that enables the quantification of white matter perfusion with high accuracy and retains a certain degree of localization by combining a spectroscopic single-voxel technique with an arterial spin labeling perfusion preparation. This method is designed to specifically address the properties of white matter perfusion. A similar sequence has been used for quantifying the perfusion in rat brain (7), as well as in skeletal muscle of rats (8) and humans (9) at rest, which suffers from low perfusion values as well.

This technique allows the use of relatively large voxel sizes without partial-volume effects, thereby maximizing SNR, by applying highly selective localization pulses and outer volume suppression procedures well known in spectroscopy. In addition, transit delay duration is reduced by minimizing the distance between tag and imaging positions.

Thus, by restricting the examined volume to one voxel only, it is possible to obtain the necessary SNR for accurate quantification of white matter perfusion, which may be used to examine localized white matter pathologies or to detect stimulation-induced perfusion changes.

MATERIALS AND METHODS

The Sequence

The applied sequence (Fig. 1) combines a point-resolved spectroscopy (PRESS) (10) single-voxel localization with a flow-sensitive alternating inversion recovery (FAIR) (11) perfusion-encoding module. The latter technique uses the signal difference between an image that was acquired after a global inversion pulse and one after a local inversion only. By applying a highly selective adiabatic inversion pulse, it is possible to move the edges of the inversion slice very close to the voxel of interest, thus minimizing the transit delay.

To avoid contamination from gray matter signal due to imperfect localization pulses, six 5-cm slices around the

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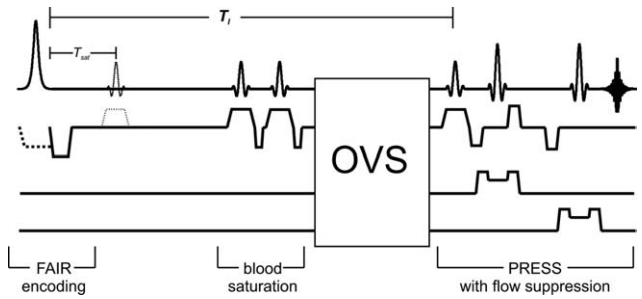

FIG. 1. The FAIRPRESS pulse sequence. The outer volume suppression module consists of six saturation slices around the selected voxel. The two additional saturation pulses suppress blood signal flowing in from 10-cm slices distal and proximal to the voxel. The additional pulse and gradient (thin dotted lines) are only added for the transit time estimation.

selected voxel are saturated immediately before the PRESS module for outer volume suppression. Signal of blood flowing through the voxels in larger vessels is reduced by three pairs of gradients in all three dimensions. For additional suppression of vascular signal, two 10-cm slices are saturated proximal and distal to the voxel, 60 and 50 msec before the start of the PRESS module in both tag and control scan, respectively. Saturating the blood in the vessels before it even reaches the voxel further reduces the influence of vascular blood on the signal.

Control scans with global inversion and tag scans are acquired in turn. In the first scan, the inversion pulse is omitted to obtain the completely relaxed magnetization M_0, which is required for quantification. All scans are stored separately; averaging is performed during reconstruction.

Volunteer Measurements

All experiments were performed on a Siemens Magnetom Trio (Siemens Medical Solutions, Erlangen, Germany) scanner with a magnetic field strength of 3 T, using a 12-channel birdcage coil for reception. A total of 21 volunteers with ages between 22 and 35 years were examined with permission of the review board of the University of Tübingen.

For quantification of the white matter perfusion, a $15 \times 15 \times 5$ mm^3 voxel was positioned in the left hemispheric centrum semiovale of 14 volunteers at positions carefully selected to avoid gray matter contributions. The inversion time was 1200 msec, the echo time was 36 msec, and the repetition time was 2300 msec. The flow suppression gradients had a duration of 4 msec, with a gradient strength of 20 mT/m. The thickness of the inversion slice was 10 mm, resulting in a 2.5 mm distance from the edge of the inversion slice to the voxel. A total of 130 tag/control pairs were acquired within almost 10 min. For two subjects, the number of averages was reduced to 98, and for one subject to 66, with otherwise equal parameters.

To get an estimation for the signal variation inherent to the measurement, the same experiment was repeated immediately afterward in the same voxel in four volunteers.

In seven volunteers, the perfusion in a corresponding voxel in the right hemisphere was measured, using the same technique and parameters. In four subjects, gray matter perfusion was measured in a voxel located in the cingulate gyrus. Because of the finer structure of gray matter, the voxel size was reduced to $5 \times 5 \times 5$ mm^3; all other parameters were kept constant. In one subject, the perfusion in a voxel positioned in the ventricle was recorded, again using the same parameters.

To estimate the mean transit delay, knowledge of which is necessary for quantification, an additional slice-selective pulse was inserted between inversion and acquisition (Fig. 1) to saturate a slice coinciding with the acquired voxel (four subjects). The time between inversion and saturation, T_{Sat}, was varied in nine steps between 100 and 900 msec; for each, 82 repetitions were acquired for averaging.

The T_1 of white matter and the inversion efficiency α of the inversion pulse were measured with the same sequence in the same voxels, using a series of around nine T_{I} values and a long repetition time of 10 sec, and with the inversion slice gradient turned off. Data from 19 voxels in 10 subjects (10 left hemisphere, nine right hemisphere) were acquired. Similarly, T_1 in gray matter was measured in four subjects, as well as in the ventricle of one volunteer.

Postprocessing

All postprocessing was performed on the raw data, using home-written routines in Matlab (The MathWorks Inc., Natick, MA). For all measurements, the single Free Induction Decays (FIDs) from the individual coil channels of each scan were filtered with an exponential causing a line broadening of 10 Hz for noise reduction and better integration, 4-fold zero-filled, Fourier-transformed, and combined by taking the root of the sum of squares. The central 100 points of the water line of the resulting spectrum were used for analysis.

The equation

$$\Delta M(t) = \frac{f}{\lambda} \cdot \frac{e^{-t/T_{1t}}}{1/T_a} \cdot M_0 \cdot 2\alpha \cdot \left(e^{t/T_a} - e^{\Delta t/T_a}\right) \qquad [1]$$

was used to obtain quantitative values for the perfusion f (12). Here, λ is the blood/tissue partition coefficient of water, which is assumed to be 0.98 mL/g in gray matter and 0.82 mL/g in white matter (13). T_a is defined as $1/T_a = 1/T_{1t} - 1/T_{1b}$, where T_{1b} is the T_1 of water in blood and T_{1t} is the apparent T_1 in tissue.

The inversion efficiency α describes the effect of the inversion pulse, ranging from zero for no inversion to 1 for perfect inversion. ΔM is the magnetization difference between tag and control scan, and Δt is the transit delay, the time needed in the tag scan for the uninverted blood to reach the voxel.

To obtain both α and T_{1t} for white and gray matter and the ventricles, the data were fitted to the equation

$$M(T_I) = M_0 \cdot \left(1 - 2\alpha e^{-T_I/T_{1t}}\right). \qquad [2]$$

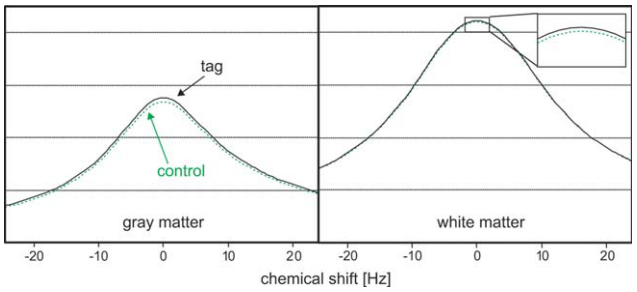

FIG. 2. Spectra of tag and control (dotted) scans from gray (left) and white matter voxel. Only the central part of the water line, which is used for quantification, is shown. The difference between tag and control scans is considerably weaker for white than for gray matter. Shown are magnitude spectra after zero-filling, line broadening, and averaging. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

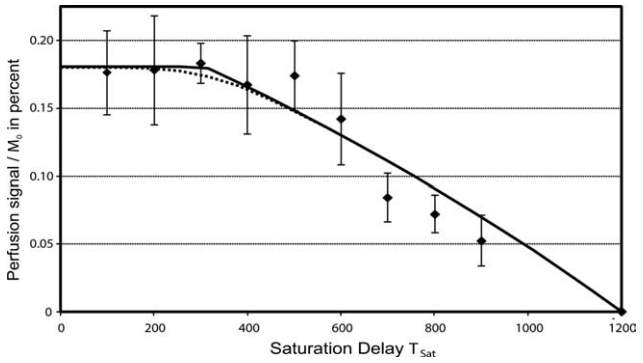

FIG. 3. Measured perfusion signal for increasing values of the delay between inversion and a slice-selective saturation pulse (mean of four subjects with standard deviations) and the fitted signal course, assuming a constant (continuous line) and a dispersed (broken line) transit delay.

The T_1 of arterial blood was assumed to be equal to that of gray matter.

For the estimation of the mean transit delay, it is assumed that the additional saturation pulse has no effect as long as T_{sat} is smaller than Δt, while for longer T_{sat}, the Δt in Eq. 1 is replaced by T_{sat} (14). Thus, the signal course for varying T_{sat} is fitted to Eq. 1, using the nonlinear least squares fitting routine from the Matlab curve-fitting toolbox.

For the determination of ΔM in the perfusion experiments, the two first scan/control pairs were discarded. The integrals over the water line of all tag scans were added, those of the control scans subtracted, and the results scaled by the number of averages. M_0 was taken from the first scan of each series, which was acquired without the preceding inversion pulse. Equation 1 was then used to obtain the quantitative perfusion values.

Because of the large voxel size, blood may travel over a large number of different pathways, introducing a dispersion of the transit delays. To assess the influence of this effect on the perfusion quantification, an alternative reconstruction was performed, assuming a gaussian dispersion with a standard deviation of 100 msec, based on the approach by Hrabe and Lewis (15). In this model, the flow builds up over 400 msec (from 5 to 95% of the flow profile) around the mean transit time. The bolus duration was assumed to be infinite because its end is determined only by the sensitivity profile of the body coil used for inversion.

RESULTS

Figure 2 shows spectra from control and tag scan in gray and white matter. Only the central region of the water line, which is also used for further analysis, is shown. The much lower perfusion in white matter manifests itself in the small difference between tag and control scan.

The measurements of the T_1 in white matter and the inversion efficiency yielded values of $T_{1w} = 919 \pm 27$ msec and $\alpha = 0.95 \pm 0.01$. T_1 in gray matter was found to be $T_{1g} = 1711 \pm 24$ msec, and in the ventricle, $T_{1v} = 3630$ msec. These values are in good agreement to those found in earlier studies (16).

For the estimation of the mean transit time, the perfusion signal as function of the time between inversion and saturation, T_{sat}, is shown in Fig. 3. The mean transit delays found in the individual subjects average to 308 ± 105 msec, where the large standard variation may in part be due to intersubject variations but is to a high degree caused by the low SNR of these measurements that limits the accuracy of the fit. Including a dispersion of the transit time in the model causes only small variations in the expected signal shape.

The results of the perfusion measurements are shown in Fig. 4. Perfusion values in the left and right hemispheres are 15.6 ± 3.2 mL/100 g/min (mean $\pm$ standard deviation over all subjects) and 15.2 ± 4.8 mL/100 g/min and are thus identical within the error limits. Gray matter

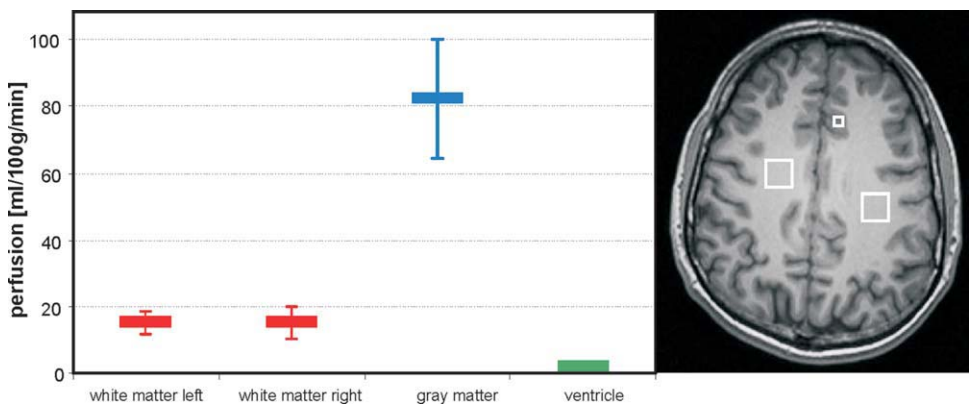

FIG. 4. Perfusion values for four different voxels (positions and sizes on the right). Error bars indicate standard deviation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

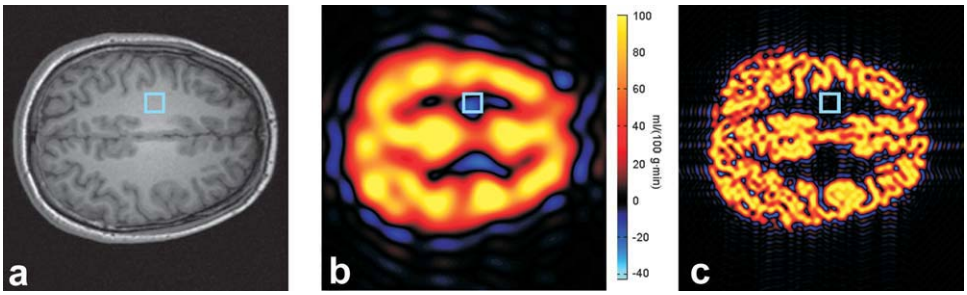

FIG. 5. Simulation results for perfusion imaging with an isotropic resolution of 12.5 mm (b). White matter perfusion is set to zero. The signal is simulated by convoluting the point-spread function with the gray matter mask. The mean value inside the selected white matter mask is −10.4 mL/min/100 g; for voxels that are completely inside white matter regions, the apparent perfusion ranges from −13.4 to +17.1 mL/min/100 g. In a high-resolution dataset ((c), voxel size 3.1 mm), this contamination is reduced to 0.08 mL/min/100 g.

perfusion was found as 83.2 ± 15.2 mL/100 g/min, while ventricle perfusion was, with a measured value of 1.4 mL/100 g/min, equal to zero within the measurement accuracy. This demonstrates the absence of effects of an imperfect inversion slice profile, which would cause considerable overestimation of the perfusion values. The gray matter value may be affected by residual contributions from white matter or cerebrospinal fluid that may be contained in the selected voxels. Because much care was used to position the voxels, this effect is expected to be small.

No changes in the quantitative results are caused when the transit time dispersion is included. The difference in the quantification between the two models is only 0.2% and thus far below measurement accuracy.

The repeated measurements in the same volunteers and the same voxels resulted in a mean intrasubject standard deviation of 2.8 mL/100 g/min, which is only slightly smaller than the intersubject error of 3.2 mL/100 g/min for the left hemispherical white matter perfusion.

Errors caused by inaccuracies in the values found for the transit delay and T_{1t} have only limited effect: Variations of these values within the error margins cause a maximum change of the left-hemispheric perfusion value of 1.9 mL/100 g/min.

DISCUSSION

The measurements shown here demonstrate the capability of the presented technique to measure white matter perfusion quantitatively, with a high accuracy. The values obtained for white matter are close to literature values: Positron Emission Tomography (PET) data from the same brain region found a value of 17 ± 2 mL/100 g/min for white and 95 ± 13 mL/100 g/min for gray matter at rest (17); other studies show similar values (18,19). The gray/white matter ratio is with a value of 5.3, also in the expected range.

The highly accurate measurement of white matter perfusion is possible due to a dedicated sequence design with special consideration of the particular properties of white matter perfusion measurements, as described in (4):

- The low inherent SNR of the scarcely perfused white matter was accounted for by using large voxel sizes and by applying spectroscopic techniques for acquisition and postprocessing.
- Partial-volume effects were avoided by using a highly selective spectroscopic localization technique with outer volume suppression.
- The problem of long and inhomogeneous transit delays was addressed by using a technique that allows moving the edge of the tagging slice very close to the voxel of interest.

Increasing the SNR of a perfusion imaging technique by increasing the voxel dimensions to a size similar to that used here is not possible due to restrictions caused by the point spread function: In Fig. 5, the signal obtained from gray matter perfusion is plotted, assuming a mean perfusion of 80 mL/min/100 g in gray matter and zero everywhere else. Using a spatial resolution of 12.5 mm^2 (16 voxels in a field of view of 200 mm) results in a perfusion value of −10.4 mL/min/100 g for the indicated white matter voxel, which adds to the actual white matter perfusion. This contamination is due to the point-spread function of the measurement and is avoided by the spectroscopic approach shown here.

The main issue affecting the accuracy of the quantitative perfusion values is the transit delay, which is known to be long and inhomogeneous in white matter. Its quantification is difficult because the SNR is still low and the resulting values are subject to relatively large uncertainty. In addition, it might vary between regions and subjects, especially in the case of pathologies. Individual determination of the transit delay for each subject is usually not possible since the measurement takes a long time and may not yield sufficient signal; only by averaging over several subjects can the transit time be determined accurately enough. While this may set a limit to the achievable precision of the quantification, the effect is eased by the relatively small influence of transit delay changes on the calculated perfusion value. Changing the value of 308 msec used here in the reconstruction by one third causes a change in the perfusion value by only 9%. This effect may, however, pose a strong limitation on the quantification accuracy in patients with pathologies that influence the blood flow.

An additional factor that might affect the quantification, namely the dispersion of the transit delay due to different pathways, has been shown to cause no significant change in the perfusion value.

By giving up on the spatial resolution for the sake of sensitivity, it is possible to obtain quantitative perfusion data from a white matter voxel with high accuracy. The spectroscopic approach further improves the SNR efficiency. The values obtained show low standard deviations and agree with literature values determined with other techniques.

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