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Improved Pseudo-Continuous Arterial Spin Labeling for Mapping Brain Perfusion

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Abstract

Purpose—To investigate arterial spin labeling (ASL) methods for improved brain perfusion mapping. Previously, Pseudo-continuous arterial spin labeling (pCASL) was developed to overcome limitations inherent with conventional continuous arterial spin labeling (CASL), but the control scan (null pulse) in the original method for pCASL perturbs the equilibrium magnetization, diminishing the ASL signal. Here, a new modification of pCASL, termed mpCASL is reported, in which the perturbation caused by the null pulse is reduced and perfusion mapping improved.

Materials and Methods—Improvements with mpCASL are demonstrated using numerical simulations and experiments. ASL signal intensity as well as contrast and reproducibility of *in-vivo* brain perfusion images were measured in four volunteers who had MRI scans at 4 Tesla and the data compared across the labeling methods.

Results—Perfusion maps with mpCASL showed, on average, higher ASL signal intensity and higher image contrast than those from CASL or pCASL. Furthermore, mpCASL yielded better reproducibility in repeat scans than the other methods.

Conclusion—The experimental results are consistent with the hypothesis that the new null pulse of mpCASL leads to improved brain perfusion images.

Keywords

MR Perfusion imaging; Arterial spin labeling; Alzheimer's disease

INTRODUCTION

Arterial spin labeling (ASL) MRI is an entirely non-invasive method to measure *in-vivo* cerebral perfusion imaging. The technique (1–4) has gained considerable interest for studies of various brain disorders, including neurodegenerative diseases such as Alzheimer's disease (5, 6), other dementias (7, 8), and chronic and acute cerebrovascular diseases (9, 10) as well as for functional studies of the brain (10). Labeling of the arterial blood can be accomplished with a number of different strategies. The most common methods are continuous arterial

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spin labeling (CASL), and pulsed ASL (PASL). CASL uses a long radiofrequency (RF) pulse of several seconds duration to adiabatically invert the spins in arterial blood as the blood flows through a particular slice (1, 2) containing a large artery (e.g. internal carotid artery) that feeds the tissue of interest (e.g. brain). PASL employs a short RF pulse of a few milliseconds duration to label a particular plug of arterial blood passing through the labeling slice (3, 4). A signal proportional to brain perfusion is obtained by measuring the difference between two experiments, one using an inversion pulse for spin labeling and another using a so-called null pulse which should match the power and magnetization transfer (MT) characteristics of the inversion pulse without perturbing the equilibrium spin magnetization. Ideally, the labeling pulse should fully invert the magnetization to induce a label, while the null pulse should not perturb the equivalent magnetization to be used as the control pulse. Theoretical and experimental studies demonstrated that CASL provides more efficient spin labeling (11–14) and higher signal yield than PASL (13–14). However, the advantage of CASL is offset by a range of technical complications, including the need for a long continuous RF pulse and compensation of magnetization transfer (MT) effects which can restrict applications especially at high magnetic fields. More recently, a new approach to CASL, termed pseudo-continuous arterial spin labeling or pulsed continuous arterial spin labeling (pCASL) (15), was introduced (15–17) that eased the technical restrictions of CASL. In pCASL, continuous labeling is achieved by a train of rapidly repeating low tip RF pulses and alternating sign (bipolar) magnetic field gradients which is also suitable for MR systems that do not have continuous RF capabilities. Moreover, it has been shown that pCASL can achieve better compensation of adverse MT effects than CASL (15–17). It has been argued that the pCASL inversion pulse is adiabatic (15, 17) because of its immunity to the inhomogeneity of the B₁ field. Although our simulations show that the pCASL inversion sequence does have considerable immunity to B₁ inhomogeneity, the mechanism for this is not adiabatic (see below).

However, pCASL also has limitations. For example, as originally proposed (15), the null pulse is achieved by consecutive RF pulses with alternating 0° and 180° phase shifts in an attempt to avoid any significant perturbation of equilibrium magnetization. Although this scheme works well for static spins, the simulations herein (see below) indicate that the effect of the null pulse can perturb the magnetization of flowing spins and thus diminish the resulting ASL signal. The perturbation results due to the fact that flowing spins accumulate phase as they flow through the inversion slice, causing the null pulse to generate cumulative tipping.

To avoid cumulative tipping in pCASL, a null pulse with a frequency offset in addition to the alternating phase shift was previously described by Jahng et al. (18). Simulations indicated that this modification, here termed as modified pseudo-continuous arterial spin labeling (mpCASL), reduced the perturbation of the equilibrium magnetization, while mirroring the power and MT characteristics of the labeling pulse used in pCASL. However, this refinement has neither been evaluated experimentally nor directly compared with CASL or pCASL experiments.

The main goal of this study was to develop and implement mpCASL on a high field MRI scanner (4 Tesla) and quantitatively compare mpCASL to both CASL and pCASL for *in-vivo* perfusion imaging. Specifically, we aimed to quantitatively compare brain perfusion maps obtained with the various labeling methods in terms of ASL signal intensity, image contrast, and also in terms of measurement reproducibility.

MATERIALS AND METHODS

Simulations

For clarity, we first describe the labeling experiment (inversion pulse) which is the same for pCASL and mpCASL. We then describe the modifications in the pCASL control experiment (null pulse) used to create the mpCASL method. We use the convention that the frequency offset is negative for a positive coordinate offset in a positive gradient field.

Inversion Pulse—Spin labeling (inversion of magnetization) is achieved by applying a train of low tip angle selective RF pulses in the presence of magnetic field gradients with alternating polarity. In addition, the duration of the magnetic field gradient lobes of one polarity is made slightly longer than the duration of the other to achieve progressive spin inversion, whereas the duration of the RF pulse is always kept the same (15). If the inversion were to take place at magnet iso-center, the inversion pulses would all be at the same frequency, and would be applied at the same phase. In other words, the pulses would all have the same phase relationship to a fictitious transverse spin at iso-center that was acted on by the gradients, but not by the RF pulses. When the inversion is not at iso-center, successive RF pulses are applied at frequencies $f = f_0$ and $f = -f_0$ during the negative and positive gradient lobes, respectively. Assume, for example, that the duration of the positive magnetic field gradient lobe is t_0 , where t_0 is the RF pulse duration, and that of the negative lobe is $t_0 + 2\delta t$ (see Fig. 1a). Time segments of inversion and null pulses and the corresponding magnetic field gradients are shown in Fig. 1, depicting an inversion pulse in (a), the corresponding null pulse of pCASL in (b) and the modified null pulse version of mpCASL in (c). The blue and red lines indicate the real and imaginary components of the RF pulses. The panels at the bottom in Fig. 1 depict the phases of each RF pulse. The arrows highlight the difference in the phase between the conventional and modified null pulse.

The initial phases of the pulses are adjusted to maintain a constant phase relationship between the RF and a fictitious spin at the center of the inversion slice. Thus, the phase of successive RF pulses is a function of f_0 , t_0 and the extra duration of the negative gradient, $2\delta t$. Hence, for RF pulses applied during the negative gradient lobes (i.e., pulses with odd numbering $n = 1, 3, 5, \dots$), the phase is:

$$\varphi_- = (n - 1)\Delta\varphi, \quad [1a]$$

where $\Delta\varphi = 2\pi f_0 \delta t$ and the initial phase is assumed to be zero. For RF pulses applied during the positive gradient lobes (i.e., pulse numbers $n = 2, 4, 6, \dots$), the phase is:

$$\varphi_+ = \varphi_0 + (n - 1)\Delta\varphi. \quad [1b]$$

where $\varphi_0 = 2\pi f_0 t_0$.

The principle of operation of the inversion pulse is depicted in Fig. 2, which shows the action of the RF pulses on a kernel of magnetization (microscopic plug of arterial blood) approaching the middle of the inversion slice. It is assumed in this figure that the RF pulses are applied along the x' axis and that the excess gradient causes a net precession of the magnetization about the unit sphere. Fig. 2a indicates that if the magnetization approaches the middle of the slice with a less than 90 degree tip, the effect of the RF pulses is to rotate the magnetization towards the y' axis, where subsequent RF pulses create further tipping of the magnetization. Conversely, Fig. 2b indicates that if the magnetization approaches the middle of the slice with a tip of more than 90 degrees, the effect of the RF pulses is to rotate

the magnetization towards the $-y'$ axis, where subsequent RF pulses reduce the tip angle of the magnetization. In this way, the magnetization is guided to an approximately 90 degree tip at the center of the inversion slice over a range of RF pulse amplitudes and flow rates. By symmetry, the spins continue to inversion as they flow through the second half of the inversion slice (not illustrated). An animation of the action of the inversion pulse train is available in the supplementary material.

Null Pulses—In contrast to the inversion pulse, the duration of both gradient lobe polarities of the null pulse are kept equal at $\tau = t_0 + \delta t$, so that the average gradient is zero. Consequently, null pulses applied with negative magnetic field gradients always have phase, $\varphi_- = 0$, and those applied with positive magnetic field gradients have the phase $\varphi_+ = \varphi_0 - \pi$ (Fig. 1b). Alternatively, the pulses applied with the positive magnetic field gradients may be viewed as positive versions of the pulses applied with negative field gradients, with phase $\varphi_+ = \varphi_0$. The principle of operation is that the second pulse undoes the tip generated by the first pulse, resulting in no net tip. In the presence of flow, however, spins will move between consecutive RF pulses by a distance $\delta z = v \Delta t$ where v is the blood flow velocity and Δt is the RF pulse separation. Hence, a magnetic field gradient of magnitude g will induce a small phase shift ($\delta\varphi = \delta\omega \Delta t = \gamma g v \Delta t^2/2$) as a function of flow velocity and RF pulse spacing. The phase shift prevents the second pulse from exactly undoing the tip produced by the first pulse, with the result that the tip error accumulates over the entire duration of RF pulses, resulting in a net tipping of the flowing spins and consequently degrading the perfusion signal. The effect of the null pulse train is depicted in Fig. 3a, in which the position of a kernel of magnetization from the flowing spins following each pair of pulses is depicted as a dot on the unit sphere, and the trajectory of the magnetization over the unit sphere during a pulse pair near the middle of the pulse train is also shown. An animation of the trajectory of the flowing magnetization is available in the supplementary material.

In the proposed version of mpCASL, the RF null pulses are shifted slightly off resonance, by an amount ε , to break the coherence of the residual tipping of the spins due to flow. In more detail, the successive null RF pulses are applied at frequencies $f = f_0 + \varepsilon$ and $f = -f_0 + \varepsilon$, so that the tip errors do not accumulate and spin magnetization is largely preserved in the presence of flow, leading to the improvement of perfusion signal. The phases of the alternate null pulses in mpCASL applied with negative gradients (i.e., pulses with odd numbers $n = 1, 3, 5 \dots$) are accordingly:

$$\varphi_- = (n - 1)(\varphi_{0\varepsilon} + \Delta\varphi_{0\varepsilon}), \quad [2a]$$

where the initial phase is again zero, $\varphi_{0\varepsilon} = 2\pi\varepsilon t_0$, $\Delta\varphi_{0\varepsilon} = 2\pi\varepsilon\Delta t$ and Δt is the separation time between the successive RF pulses (Fig. 1c). For the null pulses applied with positive gradients (i.e., pulse numbers $n=2, 4, 6, \dots$), we have accordingly:

$$\varphi_+ = \varphi_0 + (n - 1)(\varphi_{0\varepsilon} + \Delta\varphi_{0\varepsilon}) - \pi. \quad [2b]$$

where $\varphi_0 = 2\pi f_0 t_0$.

We empirically found $\varepsilon = 200$ Hz is effective in achieving the null pulse condition for a large range of blood flow velocities. The action of the new null pulse is shown in Fig. 3b. In contrast to the null pulses, which have alternating RF phases, the inversion pulses, serving an entirely different mechanism for labeling, have a continuous RF phase in presence of alternating field gradients, resulting in a net inversion of the spin magnetization.

Simulations of the spin magnetization profiles in presence of constant blood flow velocity in the range of 0 – 500 mm/sec were carried out using the Bloch equations, including spin-lattice and spin-spin relaxation of human blood at 4T (i.e., $T_1=1500\text{ms}$; $T_2=150\text{ms}$) and 1s transit time for spins flowing from the inversion slice to the imaging slices. The spin labeling was simulated using the actual experimental parameters (See below). The spin magnetization profiles for inversion and null pulses of both pCASL and mpCASL were simulated, and the perfusion signal of each version, ΔM_z (defined as the difference between inversion and null pulse magnetizations) assuming an equilibrium magnetization M_z of 1, were compared over a range of blood flow velocities. The simulations were performed in Matlab 7.0.4 using the MatPulse simulation program (19).

Pulse Sequence Implementation

The pCASL and mpCASL pulse sequences were developed in-house using the Siemens Integrated Developments Environment for Applications (IDEA), whereas the sequence of CASL was originally provided to us by Dr. Wang, University of Pennsylvania. Each RF pulse in pCASL and mpCASL was 600 μs long, had a field strength of $B_1=5\mu\text{T}$ and was amplitude modulated with a Hanning function. The RF pulses were applied in the presence of bipolar magnetic field gradients of 6 mT/m magnitude and 100 μs rise/fall times. For labeling, the top hats of the bipolar magnetic field gradients were alternated between 720 μs and 600 μs long and for the control scan were set equal to 660 μs in both pCASL and mpCASL. In addition, an offset frequency of 200 Hz (determined empirically as mentioned above) was added to the null pulse of mpCASL whereas the null pulse of pCASL was applied at resonance, as originally described (15). To avoid technical limitations of the RF power transmitter, such as distortions from the active gating, the train of 1200 short RF pulses for 1.03 second total duration for labeling had to be divided into the 20 blocks of 60 RF pulses per block. Variable durations from 1–3s for labeling were achieved by increasing the number of blocks of RF pulses. For comparison, continuous labeling (CASL) was also performed using the parameters described in reference (20). In particular, the CASL pulses were applied for 1.2 seconds, had a magnetic field strength of $B_1=3.5\mu\text{T}$ in the presence of a constant magnetic field gradient of 2 mT/m.

Data Acquisition

Imaging Parameters—CASL, pCASL or mpCASL were each incorporated into the same echo-planar imaging (EPI) sequence to map brain perfusion. All experiments were performed on a 4T MRI medical scanner (Medspec Bruker/Siemens) using a single housing birdcage transmit and 8 channel receiver head array coil. The parameters for imaging and reconstruction were kept identical for each labeling method of CASL, pCASL and mpCASL, while RF and gradients were optimized for each labeling method. Specifically, the parameters for image acquisition were: 5200ms repetition time, 9ms echo time, $3.8 \times 3.8\text{ mm}^2$ inplane resolution, 64×60 matrix size, 6/8 partial Fourier encoding and 2894 Hz/pixel bandwidth. The bandwidth was optimized for EPI to minimize geometrical distortions due to magnetic susceptibility effects. No parallel acquisitions or other manipulation of the raw data, such as signal filtering, were used for these ASL experiments. Forty control and 40 labeling scans were acquired in an interleaved manner and averaged to boost the signal-to-noise ratio. Sixteen slices, each 5 mm thick with 1.2 mm inter-slice gap were acquired, covering most regions of the cerebrum. The 1mm thick labeling slice was located 80 mm inferior to the central imaging slice, approximately at the level of the carotid and vertebrae arteries ascending into the circle of Willis. The distance of the labeling slice to the proximal and distal image slice was 30 mm and 130mm, respectively. The labeling duration was 1.2 s followed by a 1.0 s post labeling delay before the perfusion signal was acquired. The specific absorption rate (SAR) differed marginally across the methods and was 10% higher

with CASL compared to the two other methods. The scan time of the whole sequence was about 7 minutes.

For processing, the labeling and control images were co-registered using affine transformations with six degrees of freedom to account for movement between scans and then subtracted from each other to obtain perfusion weighted images. The SPM5 statistical parametric mapping program (Wellcome Department of Cognitive Neurology, London, England) was used for all image processing steps.

Subjects—Seven healthy human subjects (four women, three men, mean age 30 ± 6 years; age range, 23–38 years) were scanned. Labeling parameters were optimized for each ASL method first on a group of 3 subjects, while the imaging part of the sequence was identical across the methods. For reproducibility measurements another four subjects (two women, two men, mean age 29 ± 5 years; age range, 24–35 years) were scanned twice (each subject remained inside the magnet between the pair of scans). For image analysis (mean ASL signal, signal-to-noise ratio, and contrast), values from the two scans of each subject were averaged to eliminate bias toward the first or second scan. The volunteers were asked to refrain from caffeine on the day of their scan and to not fall asleep during the acquisition to achieve comparable conditions for brain perfusion among the subjects. All subjects provided written informed consent before participating in the study which was approved by the Committees of Human Research at UCSF and VA Medical Center, San Francisco.

Statistics

To compare mpCASL, pCASL and CASL, we evaluated perfusion mean signal intensity, signal-to-noise ratio, uniformity of the ASL signal across the brain, image contrast, and repeat scanning reproducibility of ASL measurements.

Image Analysis—Statistical analysis of the perfusion maps was performed slice by slice over the cerebrum, while regions other than brain, such as cerebrospinal fluid (CSF) spaces and areas outside the brain, were masked out by visually setting a lower threshold for perfusion intensity.

The image statistics included: ASL mean signal intensity (MSI), signal-to-noise ratio (SNR), uniformity of the ASL signal across the slices, and image contrast across the pixels. MSI was measured by averaging image intensities over the brain region. SNR was measured by dividing MSI by background noise, which was determined by measuring the image intensity in regions outside the brain in the perfusion weighted image. Signal uniformity was determined by normalizing average MSI over all slices to the standard deviation of MSI across the slices. Finally, image contrast was determined according to definitions set forth by Haralick (21) for image texture analysis. Accordingly, we first discretized the image intensities into 20 clusters to reduce the dimensionality of the analysis using a k-means cluster algorithm (21). Then the co-occurrence matrix of intensities across neighboring voxels was computed along eight angular directions (i.e., 0° , 45° , 90° , 135° , 180° , 225° , 270° and 315°) in the image plane. The measures along the eight directions were then averaged to compute contrast according to (21, 22):

$$CONTRAST = \sum_{i=0}^{N_i-1} \sum_{j=0}^{N_j-1} \{(i - j)^2 C(i, j)\}. \quad [3]$$

Here, $C(i, j)$ represents the value of the co-occurrence matrix, i, j are the discretized intensity levels and N is the total number of pixels. Contrast increases as a function of greater

intensity level differences. The computations were performed using an in-house software written in python, utilizing the SciPy package (23).

We predicted that MSI would increase for both pCASL and mpCASL relative to CASL as a result of better labeling efficiency. Moreover, we expected that MSI would increase more for mpCASL than for pCASL due to the improved version of the null pulse. We also predicted that higher signal yield of mpCASL would overall increase the SNR since we did not expect a significant change in background noise across the different ASL methods. With regard to image contrast, we expected that mpCASL would lead to higher contrast values compared to pCASL and CASL as a result of the increased perfusion signal. To determine if differences in these measures between the labeling methods were significant given the variability between subjects, we performed non-parametric Wilcoxon rank tests using an $\alpha = 0.05$ as the threshold of statistical significance.

Reproducibility—Reproducibility of each perfusion method was examined in four subjects who were scanned twice while remaining in the magnet. Reproducibility was defined in terms of the variance in MSI between repeat measurements (see the definition in the legend of the last figure). We predicted that mpCASL – in addition to higher MSI values - will also provide better reproducibility than pCASL and CASL due to a better signal-to-noise ratio and greater signal uniformity across the brain.

RESULTS

Simulations

Simulations of the spin magnetization for inversion and null pulses are shown in Fig. 4, separately for pCASL and mpCASL, without (Fig. 4a and b) and with (Fig. 4c and d) consideration of spin-lattice and spin-spin relaxation effects and for a blood flow velocity of 200mm/s. The magnetization profiles of pCASL and mpCASL inversion pulses, which are identical per definition, are displayed in Fig. 4a and c. The magnetization profiles of the corresponding null pulses are indicated for pCASL and mpCASL (Fig. 4b and d). As shown, the null pulse of mpCASL retains almost complete equilibrium magnetization in contrast to the null pulse of pCASL, which reduces the magnetization by more than 30%. The effects of T1 and T2 relaxation are mostly observed in the spin magnetization from the inversion pulses, as expected, causing an incomplete inversion whereas the magnetization immediately following the null pulses was almost independent of T1 and T2.

Simulations of the variations of the perfusion signal, ΔM_z , as a function of constant arterial flow velocity are depicted in Fig. 5, separately for mpCASL and pCASL. This implies that mpCASL should achieve in practice a greater perfusion signal than pCASL over a wide range of velocities. In particular, within the range of 100 – 200 mm/s, corresponding to the blood velocity in carotid and vertebrae arteries of humans (24), mpCASL would be expected to yield as much as 30% more signal than pCASL.

In-vivo Experiments

Representative perfusion maps from two subjects using (a) CASL, (b) pCASL or (c) mpCASL for labeling are displayed in Fig. 6 and results from comparison are summarized in Table 1, represented as mean values and maximum-minimum value range. This shows that mpCASL yielded on average higher MSI values for the perfusion maps than pCASL ($p = 0.04$) or CASL ($p = 0.04$), as predicted. The mpCASL also achieved higher SNR values than pCASL ($p = 0.03$) and CASL ($p = 0.04$). Furthermore, mpCASL resulted in greater uniformity of ASL signal across the slices than pCASL ($p = 0.02$) or CASL ($p = 0.04$), as expected.

Moreover, mpCASL yielded a higher contrast for perfusion maps than pCASL ($p = 0.008$) or CASL ($p = 0.004$).

Measurement reproducibility is depicted in Fig. 7, separately for each labeling method. This shows that mpCASL achieved significantly better reproducibility than both CASL and pCASL while pCASL and CASL reached similar reproducibility levels.

DISCUSSION

We have three main findings: First, we showed using simulations that the null pulse of mpCASL preserves equilibrium magnetization better than the original version of pCASL over a wide range of blood flow velocities, leading to a larger perfusion signal. Second, we verified this improvement experimentally on volunteers, demonstrating that mean signal intensity in perfusion maps increased significantly with mpCASL compared to pCASL or CASL. In addition, we showed that contrast in perfusion maps also improved significantly with mpCASL. Third, we showed that mpCASL improves measurement reproducibility. Taken together, these findings suggest that mpCASL provides a substantial improvement for perfusion measurements in human brain.

The concept behind the null pulse of pCASL is that, for each pair of null pulses, the second pulse undoes the tip produced by the first pulse. However, as discussed above, the presence of flow produces phase shifts which prevent the second pulse from exactly undoing the tip produced by the first pulse. We introduce a scheme for the null pulse in which the phase difference between each pair of pulses remains small, while the phase difference over more than a few pairs of pulse grows fairly large, as desired. Thus, although the second pulse still does not exactly undue the tip of the first pulse, the tip errors are not cumulative, and a reasonable null pulse is achieved.

Other reports (16, 17, 25) also addressed shortcomings of the original pCASL scheme. Simulations of the null pulse in original pCASL scheme performed by the authors in (16, 17) did not show perturbation of the magnetization as is shown herein. However, both Dai et al. (16) and Wong (25) used pulses applied to every other gradient lobe, deviating from our proposed pulse design. For the null pulse, this lengthened the time between pulses, so that, under conditions of moderate flow, the phase difference between each pair of pulses remained small, but the phase difference over more than a few pairs of pulse was fairly large, as desired. Thus, under these conditions, our simulations agree with those by Dai et al. and Wong that a reasonable null pulse is achieved (results not shown). On the other hand, the previous simulation of the inversion pulse reported in (16) appears similar to our simulation result in Fig. 4, as would be expected since the inversion pulse is identical in pCASL and mpCASL. Differences between mpCASL and the other approaches reported in references (16, 17, 25) need to be further explored in experimental settings. It should be noted that our proposed version of the null pulse was designed to avoid differences in phase accrual between the arterial spins and the RF pulses as the slice position is changed. In addition, our simulations indicate that the mechanism for inversion is not adiabatic, as initially assumed (14, 15), but results from the combined action of the RF and gradient pulses as depicted in Fig. 2.

Our experimental results of a significant global increase of the perfusion signal with mpCASL are consistent with our simulations that shifting the RF frequency of the null pulses slightly off resonance preserves equilibrium magnetization. Besides, the experimental results indicating an average ASL signal increase of roughly 25% with mpCASL compared to pCASL are close to the predicted signal gain of up to 30% based on our simulations.

The global signal increase with mpCASL and overall increase in the signal-to-noise ratio in brain perfusion maps resulting in a significantly better image contrast implies mpCASL has advantage over other methods for the detection of local alterations of perfusion. This is particularly important for perfusion studies of focal brain disorders, such as small brain lesions and local strokes, as well as for functional imaging studies using arterial spin labeling. Moreover, mpCASL yielded a more uniform ASL signal across the slices than the other methods. This observation is consistent with the improved ASL signal intensity of perfusion measurements using mpCASL and can be also explained by the greater immunity of mpCASL to the labeling offset and transit time of blood flow between labeling slice and imaging slices. Finally, we also showed that mpCASL provided better measurement reproducibility than pCASL and CASL. Since reproducibility of repeat scans should be governed primarily by instrumental noise but not physiological variability, the improvement in reproducibility with mpCASL can be explained by its better labeling consistency. This suggests that the gain in signal intensity with mpCASL can be utilized to improve the power of perfusion measurements in brain.

A few limitations of our study ought to be mentioned: Inhomogeneity of the B_1 magnetic field can diminish the advantages of mpCASL, though simulations have indicated that mpCASL is relatively insensitive to B_1 field variations within a certain range. The impact of B_1 -field variations on the effectiveness of mpCASL needs to be further explored experimentally. Another limitation is that the additional frequency offset of the null pulse in mpCASL, despite being small, might induce an imbalance in MT between inversion and null pulses that could lead to artifacts and complications in quantifying blood flow. An alternative would be to replace the coherent frequency offset of the null pulse by small random phase offsets between pairs of pulses, which would break the phase accumulation while equalizing MT effects with the inversion pulse. More studies are warranted to investigate MT effects in our version of mpCASL.

In conclusion, simulations and experiments indicate mpCASL yields a stronger perfusion signal than pCASL and CASL and therefore should improve perfusion images in the human brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Arterial spin labeling pulse sequence methods, as diagrammed as RF pulse shapes, magnetic field gradient waveforms, and RF phases (top to bottom, respectively). The real and imaginary components of the RF pulses are shown in blue and red, respectively. The inversion pulse of mpCASL and pCASL is depicted in (a). The null pulse of pCASL is depicted in (b) and the null pulse of mpCASL is shown in (c). The arrows indicate the phase offset in the null pulse of mpCASL.

Figure 2.

The operation of the RF inversion pulse on spin magnetization approaching the middle of the inversion slice with a tip angle of less than (a) and greater than (b) 90 degrees. The orange triangle represents the oscillation range of the magnetization induced by the bipolar gradients, while the curved arrows indicate the rotations induced by the RF pulses.

Figure 3.

The effect of the RF null pulse train on the spin magnetization using (a) the null pulse of the original pCASL and (b) the modified null pulse of the mpCASL; each dot on the unit sphere shows the position of a kernel of magnetization from the flowing spins following each pair of pulses, and the green line is the trajectory of the magnetization over the unit sphere accumulated at the time of a pulse pair occurring near the middle of the pulse train.

Figure 4.

Simulated longitudinal magnetization profiles of flowing spins, flowing through the inversion slice (10 mm thick with slice center at $z=0$) towards the imaging slice. Simulations are without (a, b) and with (c, d) consideration of relaxation effects ($T_1=1500\text{ms}$ and $T_2=150\text{ms}$), and assume a flow velocity of 200 mm/s. The magnetization profiles correspond to applications of inversion pulses (a, c) and null pulses (b, d). The inversion pulse results are the same for pCASL and mpCASL. The horizontal axis shows the position of the flowing spins through the inversion slice.

Figure 5. Simulations of the perfusion signal yield (ΔM_z) as a function of flow velocity for pCASL ($\blacktriangle$) and mpCASL ($\blacklozenge$), including the relaxation effects ($T_1=1500\text{ms}$ and $T_2=150\text{ms}$) and assuming an equilibrium magnetization $M_z=1$.

Figure 6.

Representative perfusion-weighted images from two subjects (top, bottom), using (a) CASL, (b) pCASL or (c) mpCASL. Perfusion images were provided using 40 control and 40 label scans. The total scan time for each ASL scan was 7 minutes. The images are from the 1st study of repeat scanning. The calibration strip shows the ASL signal intensity.

Figure 7.

Reproducibility of perfusion measurements from repeat scans averaged over four subjects. $\text{Var}_{\text{diff}}(\text{MSI})$ is the variance of difference score in MSI between repeat 1 N scans where the

variance of difference score is computed as $\frac{1}{N-1} \sum_{k=2}^N (\text{MSI}_k - \text{MSI}_1)^2$, and N is the number of scans.

The error bars indicates the variation between the subjects.

Table 1

Summary of analysis of the perfusion images acquired using the three ASL methods

Methods/Features	MSI	SNR	Uniformity	Contrast
CASL	0.73 (0.47– 1.03)	3.48 (2.24 – 4.90)	0.83 (0.57– 0.98)	168 (159 – 173)
pCASL	0.79 (0.56 – 0.92)	3.04 (2.15 – 3.53)	0.71 (0.63 – 0.84)	181 (169 – 201)
mpCASL	1.00 ^a (0.75 – 1.10)	4.54 ^b (3.41 – 4.99)	1.29 ^c (0.90 – 1.78)	198 ^d (191– 202)

Means and (minimum - maximum) values of the mean value across the four subjects.

MSI = mean signal intensity, where ASL signal intensity is defined as $\Delta M_Z/M_Z$.^aP=0.04 vs. pCASL and CASL;^bP=0.03 vs. pCASL and P=0.04 vs. CASL;^cP=0.02 vs. pCASL and P=0.04 vs. CASL;^dP=0.008 vs. pCASL and P=0.004 vs. CASL.