Evaluation of cerebral blood flow using multi-phase pseudo continuous arterial spin labeling

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The arterial spin labeling (ASL) methods have been widely used for evaluating of cerebral blood flow (CBF) in magnetic resonance imaging (MRI) [1-7]. At present, there are several ASL methods which are different way of applying the radio frequency (RF) pulse; pulsed arterial spin labeling (PASL) [3, 4], continuous arterial spin labeling (CASL) [5], and pseudo continuous arterial spin labeling (pCASL) [2, 6, 7]. The pCASL method has been widely used for evaluating the cerebral blood flow (CBF) because it has higher labeling efficiency [8] of the flow blood in these methods. The ASL methods are needed to set the post labeling delay (PLD) which is the time to wait for the labeling blood from below the imaging plane. Because the hemodynamic status cannot be estimated in each patient, quantitative values of the blood flow may not be accurate. The multi-phase sequence with the PASL method, which can collect data in multiple time phases, has reported [9] in the evaluation of the renal blood flow regardless of the hemodynamics of the subject. However, the evaluating the CBF using multi-phase sequence with the pCASL method has not been reported. The purpose of this study is to evaluate the CBF value using the transit-time map obtained from the multi-phase pCASL method at 3-tesla MRI.
Methods and Materials

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Patient population

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Twelve patients who underwent both 3-tesla MRI and single photon emission computed tomography (SPECT) with iodine-123-N-isopropyl-p-iodoamphetamine ($^{123}$I-IMP) were investigated. These patients had no previous history of vascular stenosis on any side. This study was approved by the institutional review boards of our institution.

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MRI data acquisition

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To obtain the CBF with ASL (ASL-CBF), the magnetic resonance (MR) images were obtained with a 3-tesla whole-body scanner (AchievaTX; Philips Medical Systems, Best, The Netherlands) using an 8-channel head coil. Two different kinds of imaging sequence were acquired. One was the pCASL method with the fixed PLD at 1525 ms (fixed-PLD pCASL) for calculating the ASL-CBF and the other was the multi-phase pCASL method for correcting the ASL-CBF with fixed-PLD pCASL. The imaging parameters for the fixed-PLD pCASL with the two-dimensional single-shot echo planar imaging (EPI# were following: repetition time (TR), 4500 ms; echo time (TE), 15 ms; flip angle (FA), 9°; number of signal average (NSA), 30; slice thickness, 5 mm; slice gap, 0.5 mm; EPI factor, 35; sensitivity encoding (SENSE) factor, 2.5; field of view (FOV), 240 mm; image matrix, 80×80; number of slices, 25; label duration, 1625 ms; PLD, 1525 ms; background suppression, which consisted of a saturation pulse immediately before labeling and inversion pulses at 1710 and 2860 ms after the saturation pulse; scan time, 4:39. The imaging parameters for the multi-phase pCASL with the two-dimensional single-shot echo planar imaging (EPI# were following: TR, 200 ms; TE, 9.5 ms; FA, 15°; NSA, 30; slice thickness, 8 mm; slice gap, 25 mm; EPI factor, 27; SENSE factor, 2.5; FOV, 240 mm; image matrix, 80×80; number of slices, 5; label duration, 1000 ms; PLD, 11 ms; cycle duration, 4500 ms; scan time, 2:16. These two sequences were oriented along the plane parallel to the anterior commissure and posterior commissure (AC-PC) line. The position of labeling plane was 20 mm below the lowest imaging slices in two methods. In the multi-phase pCASL sequence, the center of the slice was located on the AC-PC line.
To obtain the CBF with $^{123}$I-IMP (IMP-CBF), SPECT data were acquired from 20 to 40 min after the tracer injection, using a triple-head #-camera (GCA-9300/DI; Toshiba) equipped with low-energy, high-resolution fanbeam collimators. The energy settings were 160-keV peak with 24% width for the main window. The matrix size was 128 × 128 pixels. The images were reconstructed using the filtered backprojection method. The data were preprocessed using a Butterworth filter with a cutoff frequency of 0.10 cycle per pixel and a power factor of 8. Attenuation correction was performed using the method of Chang [10]. The attenuation coefficient was set at 0.10 per cm. The imaging resolution was about 10-mm full width at half maximum after reconstruction. Quantitative blood flow was determined by using the $^{123}$I-IMP injection and single-scan autoradiographic (ARG) technique [11]. The $^{123}$I-IMP-ARG method is based on the 2-compartment model for tracer kinetics. The method used a standard arterial input calibrated by the radioactivity of a single arterial whole-blood sample, a standard lipophilic fraction of $^{123}$I-IMP in whole blood, and a fixed distribution volume of $^{123}$I-IMP (41 mL/mL). That is, 222 MBq (6 mCi) $^{123}$I-IMP were infused into the antecubital vein at a constant infusion rate for 1 min. At 10 min after the beginning of the $^{123}$I-IMP infusion, one arterial blood sample was taken and its whole-blood radioactivity concentration was counted using a well counter that was cross-calibrated to a SPECT scanner. A single SPECT scan was obtained at a midscan time of 30 min after $^{123}$I-IMP injection. The duration of the SPECT scan was 20 min.

CBF calculation with MRI (without correction)

To obtain the ASL-CBF without correction (ASL-CBF(default)), the control and label images obtained with the fixed-PLD pCASL sequence were the output in the digital imaging and communication in medicine (DICOM) format, and the CBF calculation was done with the MATLAB software (Mathworks, Natick, MA, USA) on a personal computer. The CBF (ml/100mL/min) was calculated using the following equation (1) [12]:

\[
\text{CBF} = \frac{6000}{2 \times \# \times \# \times \#_{\text{inv}} \times T_{1\text{blood}} \times M_{\text{ASL}}/M_{0\text{CSF}} \times \exp((\text{delay} + \text{slice-time}(z-1))/T_{1\text{blood}}) \times \exp(TE/T2^*)}{...}(1)
\]

where \# is the water content of blood (assumed to be 0.76[13]), \# is the labeling efficiency (assumed to be assumed to be 0.85[8]), \#_{\text{inv}} is correction for the loss of perfusion signal.
due to the two global inversion pulses for the background suppression (#\textit{inv} is assumed to be 0.83\textsuperscript{[14]}), $T_{1\text{blood}}$ is assumed to be 1680 ms\textsuperscript{[15]}, #\textit{M}_{\text{ASL}} is the difference in signal intensity between control and label images with the fixed-PLD pCASL sequence, #\textit{M}_{\text{CSF}} is the equilibrium signal intensity of cerebrospinal fluid (CSF) calculated from the control image, corrected for scaling factors and amplifier differences with the ASL sequence, delay is the imaging delay, slice-time is the readout duration of a single slice, $z$ is the number of the particular slice, TE is the echo time, and $T2^*$ is the transversal relaxation rate of arterial blood (assumed to be 50 ms\textsuperscript{[16]}).

CBF calculation with MRI (with correction)

To obtain the ASL-CBF with correction (ASL-CBF (corrected)), the control and label images obtained with the multi-phase pCASL sequence were the output in the DICOM format, and the CBF calculation was done with the Image J software (NIH Image, Bethesda, MD, USA) and the MATLAB software on a personal computer. The process of the calculation to the ASL-CBF (corrected) was shown the following (Fig.1):

(i) The image binarization was applied for control images to identify the contour of the brain as a mask image.

(ii) The subtraction between control and label images was applied to each time phase (Fig.2).

(iii) A sixth-order polynomial fitting was applied on the subtracted signal intensity to pixel by pixel for each phase. The peak transit time was calculated from the subtracted signal intensity of the fitting curve on each pixel. The median filter was used to average the neighbor pixels. The filtered images were multiplied to the mask images as to the transit time images. The transit time images could mean the peak time that the labeling blood reached at the imaging slices.

(iv) The corrected ASL-CBF (ASL-CBF (corrected)) was calculated by applying the transit time to the "delay-time" of the equation (1) on each pixel.

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Data analysis
The CBF was evaluated with three of the five slices which were the cerebellum, basal ganglia and higher cortex level in the multi-phase pCASL sequence. In comparison of the CBF, the slice level with both the IMP-CBF and the ASL-CBF (default) were used the same level with ASL-CBF (corrected). The regions of interest (ROIs) were drawn on the brain at each slice level (Fig.3). A total 22 segments of three slices per patient were evaluated. Data were presented as mean ± standard deviation.

(I) Patient-based analysis: To compare the CBF, the mean CBF of all segments per patient were measured. The mean transit time of all segments per patient was measured.

(II) Slice level-based analysis: To compare the CBF in each slice level, the mean CBF in each slice level was measured. The coefficient of determination ($R^2$) was calculated to determine a linear correlation between the IMP-CBF and the ASL-CBF (default), the IMP-CBF and the ASL-CBF (corrected), respectively.

(III) Segment-based analysis: To compare the CBF in all segments, the mean CBF in all segments was measured.

Statistical analysis

In comparison of the mean CBF in patient-based and slice level-based analysis, Steel's test was applied that the IMP-CBF was used as a control with a significance level of 5% ($P < 0.05$). The coefficient of determination was calculated to determine a linear correlation between IMP-CBF and ASL-CBF with and without correction of arterial transit time. All statistical analyses were performed with JMP software (version 10; SAS Institute Inc., Cary, NC, USA).
Fig. 1: The process of the calculation to the ASL-CBF (corrected)

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**Fig. 2:** Images of multi-phase pCASL sequence

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**Fig. 3:** An illustration of the region of interests

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Results

A total of 264 segments in the twelve patients were evaluated. Figure 4 demonstrated an example of a patient of the CBF and the transit time images.

(I) **Patient-based analysis:** The mean IMP-CBF, ASL-CBF (default), ASL-CBF (corrected) and transit time were 28.4 ± 5.5, 29.6 ± 9.4, 23.0 ± 11.8 [ml/min/100g] and 1977.5 ± 191.8 [ms], respectively. There were no significant differences between IMP-CBF and ASL-CBF (default), IMP-CBF and ASL-CBF (corrected) (P=0.2677, 0.9945, respectively) (Fig.5).

(II) **Slice level-based analysis:** Table 1 showed the mean CBF and the transit time. The coefficient of determination between the IMP-CBF and the ASL-CBF (default), the IMP-CBF and the ASL-CBF (corrected) was at the cerebellum level $R^2 = 0.0301 (P=0.4175)$ and 0.0042 ($P=0.7646$), at the basal ganglia level $R^2 = 0.0165 (P=0.1245)$ and 0.1113 ($P=0.6914$), at the higher cortex level $R^2 = 0.0382 (P=0.0563)$ and 0.0507 ($P=0.0274$), respectively. Figure 6 showed the CBF at each slice level. The basal ganglia and higher cortex level between the IMP-CBF and the ASL-CBF (default) showed the significant difference. However, there was no significant difference between the IMP-CBF and the ASL-CBF (corrected).

(III) **Segment-based analysis:** Figure 7 showed the mean CBF at each segment. The segment number 16, 17, 21 and 22 showed significant differences between the IMP-CBF and the ASL-CBF (default). These segments between the IMP-CBF and the ASL-CBF (corrected) showed no significant differences. All other segments showed no significant differences between the IMP-CBF and the ASL-CBF (default), the IMP-CBF and the ASL-CBF (corrected).
Fig. 4: The CBF images and transit-time map

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Fig. 5: Comparison of the mean CBF at each method

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Fig. 6: Comparison of the CBF at each slice level

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Table 1: The mean CBF and transit time at each slice level

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Fig. 7: Comparison of the CBF at each segment

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Conclusion

We evaluated the ASL-CBF using the transit time images which were obtained from the multi-phase pCASL method. The ASL-CBF without correction of the arterial transit time was showed lower CBF than the IMP-CBF. However, the ASL-CBF with correction of the arterial transit time showed higher CBF than without correction. As a result, the correction of the arterial transit time using the transit time images was useful to assign the proper arterial transit time to the equation of the ASL-CBF. This new correction method using the multi-phase pCASL sequence in MRI evaluations of the CBF can eliminate the dependence on subject hemodynamics, and it enables the calculation of the CBF to be evaluated at the time at which the maximum amount of labeled blood has reached to the brain.

In conclusion, The ASL-CBF value could be corrected by using the transit time images obtained from multi-phase pCASL method.
References


