Published in final edited form as:

J Magn Reson Imaging. 2015 October ; 42(4): 1126–1133. doi:10.1002/jmri.24866.

Optimization of phase-contrast MRI for the quantification of whole-brain cerebral blood flow

Shin-Lei Peng, PhD^{1,2,3}, Pan Su, BS^{1,2,4}, Fu-Nien Wang, PhD³, Yan Cao, PhD⁵, Rong Zhang, PhD⁶, Hanzhang Lu, PhD^{1,2,4}, and Peiying Liu, PhD^{1,2}

¹Department of Radiology, Johns Hopkins University, Baltimore, MD 21287, USA

²Advanced Imaging Research Center, UT Southwestern Medical Center, Dallas, TX 75390, USA

³Department of Biomedical Engineering and Environmental Sciences, National Tsing Hua University, Hsinchu, Taiwan

⁴Biomedical Engineering Graduate Program, UT Southwestern Medical Center, Dallas, TX 75390, USA

⁵Department of Mathematical Sciences, University of Texas at Dallas, Richardson, TX 75080, USA

⁶Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, TX 75231, USA

Abstract

Purpose—Whole-brain cerebral blood flow (CBF) measured by phase-contrast MRI (PC-MRI) provides an important index for brain function. This work aimed to optimize the PC-MRI imaging protocol for accurate CBF measurements.

Materials and Methods—Two studies were performed on a 3 Tesla system. In Study 1 (N=12), we optimized in-plane resolution of PC-MRI acquisition for CBF quantification by considering accuracy, precision, and scan duration. In Study 2 (N=7), we assessed the detrimental effect of non-perpendicular imaging slice orientation on CBF quantification. Both One-way ANOVA with repeated measurement and Friedman test were used to examine the effects of resolution and angulation on CBF quantification. Additionally, we evaluated the inter-rater reliability in PC-MRI data processing.

Results—Our results showed that CBF measurement with 0.7mm resolution could be overestimated by up to 13.3% when compared to 0.4mm resolution. Moreover, CBF could also be overestimated by up to 18.8% when the slice orientation is deviated by 30° from the ideal angulation. However, within 10° of the ideal slice orientation, estimated CBF was not significantly different from each other “(p=0.23 and 0.45 for internal carotid artery and vertebral artery, respectively). Inter-rater difference was <3%.

Conclusion—For fast and accurate quantification of whole-brain CBF with PC-MRI, we recommend the use of an imaging resolution of 0.5mm and a slice orientation that is less than 10° from vessel's axial plane.

Keywords

Cerebral blood flow; phase-contrast MRI; partial voluming effect; blood flow quantification; flow velocity

INTRODUCTION

Cerebral blood flow (CBF), which denotes blood supply to the brain at a given time, is an important physiological parameter for probing cerebral hemodynamics and brain function. CBF provides important information in the understanding of early brain development (1,2), normal aging (3,4), and a variety of diseases such as Alzheimer's disease (5), Parkinson's disease (6), diabetes (7), cerebrovascular diseases (8–10), drug addiction (11,12), and mental disorders (13,14).

CBF can be measured by different imaging methods. Positron emission tomography (PET) with the infusion of ^{15}O -labeled water is considered the gold standard for in vivo CBF quantification (15,16). However, PET-CBF measurement requires an on-site cyclotron and arterial blood sampling, and therefore is not widely available. MR perfusion imaging using dynamic susceptibility contrast (DSC) techniques or arterial spin labeling (ASL) can also provide CBF maps of the brain. But the absolute CBF quantification in DSC MRI and ASL MRI could be confounded by factors such as arterial input function (17), labeling efficiency (18) and assumptions of tissue/blood T1 (19). Unlike ^{15}O -PET, DSC MRI and ASL MRI, Phase-Contrast MRI (PC-MRI) is a noninvasive MRI technique for quantitative flow measurements without the needs of exogenous tracers or assumptions associated with complex models (20,21).

PC-MRI utilizes the phase of an image to encode the velocity of flowing spins (22) and has been validated for quantitative flow measurements (20,21). By measuring the flow flux at the main feeding arteries of the brain (Fig. 1), including bilateral internal carotid arteries (ICAs) and vertebral arteries (VAs), one can quantify whole-brain CBF noninvasively (1,3,11,23). Its simplicity and accuracy in absolute CBF quantification as well as the relatively short scan duration have made PC-MRI increasingly popular in clinic and research applications. One of the major applications of PC-MRI is that, by combining with the measurement of arterial and venous oxygenation, a highly desirable index of cerebral oxygen metabolism, cerebral metabolic rate of oxygen (CMRO_2), can be estimated (1,3,11,23–25). Another important application is that the whole-brain CBF measured by PC-MRI can be used to calibrate other CBF mapping methods including DSC MRI (26) and ASL MRI (27), alleviating confounding factors during absolute quantification in these methods. Moreover, with recent advances in simultaneous PET-MR systems, PC-MRI can potentially be used to calibrate relative CBF maps obtained by PET, eliminating the need for dynamic arterial sampling during the PET scan.

Therefore, optimizing the PC-MRI protocol for accurate quantification of whole-brain CBF is a critical step towards its wider applications in CBF mapping and CMRO₂ estimation. The present study aims to address two technical issues in PC-MRI. One potential issue of the PC-MRI acquisition is that the measured velocity map is susceptible to partial voluming, which could lead to biases in CBF estimation. In this regard, higher imaging resolution is expected to provide a more accurate CBF measurement. However, higher spatial resolution is usually associated with lower sensitivity and longer scan duration. Therefore, an optimal tradeoff between accuracy and time-efficiency needs to be determined for a practical PC-MRI protocol. Another potential issue of the PC-MRI acquisition is that the measured flow might be biased due to imperfect slice positioning. Although it is known that the imaging slice in PC-MRI should be perpendicular to the vessel orientation, in practice this is sometimes difficult to ensure. When the imaging slice is not perpendicular to the vessel orientation, partial voluming problems might arise and lead to inaccurate CBF measurement. It is therefore important to understand and quantify the estimation bias of CBF in order to avoid or accounted for the effect of non-perpendicular slice positioning.

The present work aims to optimize and standardize the PC-MRI protocol for whole-brain CBF quantification.

MATERIALS AND METHODS

General

Experiments were performed on a 3 Tesla MRI scanner (Philips Healthcare, Best, The Netherlands) using an 8-channel receive-only head coil. The body coil was used for radio frequency transmission. Foam padding was placed around the head to minimize motion during MRI scan acquisition. The protocol was approved by the local Institutional Review Board. A total of 19 subjects (12 males, 7 females; 19–56 years old) participated in this study. All subjects gave informed written consent before participation.

Study 1

The goal of this study was to investigate the effect of in-plane resolution on CBF quantification. Resolution values of 0.4, 0.5, 0.6 and 0.7 mm were evaluated. Twelve subjects (8 males, 19–56 years) were scanned. For each subject, a 3D time-of-flight (TOF) angiogram was first performed to visualize the feeding arteries of the brain which is necessary for PC MRI slice positioning (Fig. 1a). Imaging parameters of the TOF angiogram were: TR/TE/flip angle=20ms/3.45ms/18°, FOV=160×160×70.5 mm³, voxel size=1.0×1.0×1.5 mm³, one 60 mm saturation slab positioned above the imaging slab, number of slices=47, with the top slice positioned right below the bottom of pons. Next, each subject underwent two MRI sessions with a 5min break between the sessions. The first session focused on left ICA and the second session focused on left VA. Due to time constraints, left ICA and left VA were chosen as the representative of the ICAs and VAs, respectively. The CBF measure was performed using two PC-MRI scans targeting for the two feeding arteries, respectively, at the level of foramen magnum where the arteries enter the skull (Fig. 1b) (23). The exact positioning of the PC-MRI scans was determined automatically using an algorithm that has been reported earlier (28). Briefly, the algorithm

segmented out the targeted artery using the results of the 3D TOF angiogram. The center of the imaging slice was determined as the center of the artery at the level of foramen magnum. The angulation of the imaging slice was then determined such that it is perpendicular to the targeted artery at this location. This computerized positioning minimizes the operator dependence and assures the perpendicularity of the imaging slices to the targeted arteries. Following the angiogram, PC-MRI scans were performed. The PC-MRI sequence followed that has been validated previously (21,29) which is based on bipolar field gradient to encode flowing spins with gradient-echo acquisition using the shortest TR and TE possible. For image reconstruction, the velocity map image was computed from the phase difference between two scans with opposite signs of bipolar gradients. Four spatial resolutions were examined, with multiple repetitions for each resolution in a randomized order. The resolutions we examined are within the range of resolutions that have been reported in literature comparing PC-MRI with Transcranial Doppler (TCD)(30–32). The scan durations of each scan were 22.1, 14.8, 10.7 and 8.5 sec for the resolution of 0.4, 0.5, 0.6 and 0.7 mm, respectively. The numbers of repetition were 11, 8, 7 and 6 for the resolution of 0.4, 0.5, 0.6 and 0.7 mm, respectively, assuring sufficient signal-to-noise (SNR) at each resolution. For easy comparison, the reconstructed images used identical voxel size ($0.3 \times 0.3 \times 5 \text{ mm}^3$) for all resolutions. Other imaging parameters of the PC-MRI scans were: single slice, FOV= $200 \times 200 \times 5 \text{ mm}^3$, maximum $V_{\text{ENC}} = 40 \text{ cm/s}$ in the through-plane direction. Here, a smaller V_{ENC} was used to increase SNR of voxels near the edge of the arteries which have slow flow velocity. Since small V_{ENC} causes phase wrapping in the voxels with flow velocity higher than V_{ENC} (usually at the center of ICAs), velocity aliasing correction (33) was performed before further analysis when needed.

Each PC-MRI scan generated three images, an anatomic image, a magnitude image (or called complex difference image), and a velocity map. Data processing of PC-MRI followed previously reported method (23,28). Briefly, the rater was instructed to manually draw an ROI on the magnitude image by tracing the boundary of the targeted artery based on the brightness of the voxels without including adjacent vessels. The blood velocity can then be converted to CBF by integrating over the artery ROIs (26). The resulted CBF of each artery was written in the unit of ml/min, i.e., blood influx per unit time. The whole-brain total CBF was obtained as the sum of CBF of all four feeding arteries. To account for brain size differences, the total CBF (in ml/min) can be further normalized to the parenchyma volume of the brain to obtain a unit volume CBF (in ml/100g/min). But since we aim to compare CBF quantification within each subject, only CBF in ml/min was evaluated in this work

CBF values of the left ICA and left VA were obtained for each resolution and each repetition. Then for each artery, the test-retest reproducibility at each resolution was measured by Coefficient of Variation (CoV) calculated as:

$$CoV_j = \frac{1}{I} \sum_i \frac{SD_k(CBF_{ijk})}{Mean_k(CBF_{ijk})}$$

Where CBF_{ijk} represents the k^{th} repetition of CBF measurement of Subject $\#i$ ($i = 1, 2, \dots, I$) with resolution j ($j = 0.4, 0.5, 0.6$ and 0.7). SD_k and $Mean_k$ stand for the standard deviation

and average of CBF across repetitions, respectively. Note that the CoV is expected to contain both the random measurement noise and CBF physiologic variations. Additionally, cross-sectional area of the targeted artery was also calculated.

To compare data across resolutions, one-way ANOVA tests with repeated measures of resolution were performed on mean CBF, CoV of CBF, and artery area. If a resolution-effect was observed in the ANOVA analysis, paired t-tests among the resolutions were conducted. In order to make no assumption about the probability distribution of the data set, the non-parametric statistical test, Friedman test (34), was used to test the resolution-effect as well. A $p < 0.05$ is considered statistically significant.

Study 2

In this study, we investigated how slice orientation would affect CBF quantification. The ideal orientation of a PC-MRI scan is to have the imaging slice perpendicular to the main direction of flow (33). When the imaging slice is not perpendicular to the blood vessel, i.e., with an angulation from the ideal orientation, a bias in CBF estimation may be present. To systematically evaluate the bias caused by imperfect slice orientation, we varied the angulation of the imaging slice from 0° to 30° at 5° step, with 0° represents the ideal positioning where the imaging slice is perpendicular to the targeted artery. As in Study 1, the imaging slice of 0° was determined automatically using a computerized algorithm that has been reported earlier (28). Then the imaging slices of all other angulations were determined automatically by rotating the norm vector of the 0° slice along a random direction to the targeted angulations. Seven subjects (4 males, 24–49 years) participated in this study. The MRI session started with a 3D TOF angiogram, similar to Study 1. The ideal orientation of left ICA and left VA were automatically determined for each subject by the computerized algorithm. Then a total of 28 PC-MRI scans (7 angulations $\times$ 4 repetitions) were performed on left ICA in random order. Next, the 28 PC-MRI scans were also performed on left VA. The optimal in-plane resolution determined from Study 1 was used. Other imaging parameters were identical to those used in Study 1.

Mean CBF value, CoV, and artery area from each slice angulation were obtained following the data processing in Study 1. To compare the difference among imaging slice angulations, one-way ANOVA tests with repeated measures of angulation were performed on mean CBF, CoV and artery area of left ICA and left VA, respectively. If an angulation-effect was observed in the ANOVA analysis, each angulation was compared to 0° using paired t-test, to identify which angulations are different from the perpendicular positioning. Similar to Study 1, the non-parametric statistical test, Friedman test (34), was also used to test the angulation-effect. A $p < 0.05$ is considered statistically significant.

Additionally, as the data processing involves manual ROI selection, inter-rater reliability of CBF quantification was evaluated by having two raters (SLP and PS, each with one-year experience of PC-MRI ROI drawing) independently analyze the same datasets of Study 1 and Study 2. The agreements between the CBF values obtained by the two raters were evaluated with the Bland-Altman method (35,36).

RESULTS

Study 1

In Study 1, PC-MRI were performed on the left ICA and left VA with in-plane resolutions of 0.4, 0.5, 0.6 and 0.7 mm, respectively. One representative set of left ICA images are shown in Fig. 2a. One-way ANOVA analysis showed that, the imaging resolution has a significant effect on CBF values for left ICA (Fig. 2b, $p=0.021$). Paired t-tests revealed that left ICA CBF obtained with 0.7mm resolution was significantly higher than that obtained with 0.5 mm resolution ($p=0.03$) and 0.6 mm resolution ($p=0.05$), showing a significant CBF overestimation by 5.5% and 3.5%, respectively. This resolution effect was found to be more pronounced for VA (Fig. 2e, $p<0.001$ using ANOVA analysis). In post-hoc pairwise comparisons, CBF of left VA was significantly different between any two resolutions ($p<0.05$ for all pairwise comparisons). The resolution of 0.5mm, 0.6mm and 0.7mm respectively showed a significant CBF overestimation by 3.4% ($p=0.01$), 7.5% ($p=0.002$) and 13.3% ($p=0.0002$) when compared to that from resolution of 0.4mm.

For the measured CBF in both left ICA and left VA, the CoV tended to be slightly greater at higher spatial resolutions, as shown in Fig. 2c and 2f. However, one-way ANOVA analysis showed that, the main effect of resolution on CoV did not reach a significance level ($p=0.43$ and 0.18 for left ICA and left VA, respectively), due to large inter-subject variations.

Arterial cross-sectional area measured on the image was found to be significantly dependent on spatial resolutions for both left ICA (Fig. 2d, $P<0.001$, using ANOVA analysis) and left VA (Fig. 2g, $p<0.001$, using ANOVA analysis). Post hoc pair wise comparisons showed that the differences between any pair of resolutions were statistically significant for both left ICA ($p<0.05$) and left VA ($p<0.001$).

Non-parametric Friedman test was used to compare data across resolution as well. By using the Friedman test, the imaging resolution dependence on CBF values for ICA part showed a trend but did not reach a significant level ($p=0.14$). For VA part, the resolution effect was significant ($p<0.001$). The main effect of resolution on CoV was not significant for both ICA and VA ($p=0.73$ and $p=0.42$, respectively). Arterial cross-sectional area measured on the image was found to be significantly dependent on spatial resolutions for both left ICA ($p<0.001$) and left VA ($P<0.001$).

Since lower resolution is associated with a greater degree of partial voluming, CBF measured at higher resolution is expected to be closer to the true value. However, CBF measured at higher resolution could be confounded by lower SNR and larger CoV, and its measurement time is also longer. Therefore, to reach a tradeoff between accuracy, precision and time-cost, we recommend the spatial resolution of 0.5mm for PC-MRI, and this was subsequently used in Study 2.

Study 2

In Study 2, PC-MRI scans with 0.5mm in-plane resolution were performed on left ICA and VA, respectively, with the angulation of the imaging slice varying between 0° and 30° at 5° step from the perpendicular plane of the targeted artery. Magnitude images of left ICA

obtained with the 7 different angulations from a representative subject are illustrated in Fig. 3a. It can be seen that as the angulation increases (i.e., less perpendicular to the artery), the shape of the artery changes from round to ovoid, suggesting a greater extent of partial voluming.

Mean CBF value, CoV, and artery area of the left ICA and VA are shown in Fig. 3b–g. As expected, the angulation of the imaging slice has a significant effect on the measured area of the left ICA (Fig. 3d, $p < 0.001$, using ANOVA analysis) and left VA (Fig. 3g, $p < 0.001$, using ANOVA analysis), as the artery area increases with the angulation. Moreover, the angulation also showed a significant effect on the CBF for both left ICA (Fig. 3b, $p < 0.001$, using ANOVA analysis) and left VA (Fig. 3e, $p < 0.01$, using ANOVA analysis), with larger angulation leading to greater CBF overestimation. This is because of the limited spatial resolution, partial voluming effect would lead to an overestimation in CBF quantification when the PC-MRI imaging slice is not perpendicular to the flow direction. Compared to the ideal, perpendicular orientation (i.e., angulation of 0°), the angulations of 20° , 25° and 30° showed a significant CBF overestimation by 9.27% ($p = 0.006$), 8.88% ($p = 0.01$) and 18.8% ($p = 0.002$), respectively, in left ICA. In left VA, the angulations of 15° , 20° , 25° and 30° showed a significant CBF overestimation by 10.1% ($p = 0.009$), 12.3% ($p = 0.005$), 13.2% ($p = 0.009$) and 15.4% ($p = 0.02$), respectively. No significant CBF difference was found when the slice angulation was within 10° from the ideal orientation, for both left ICA and left VA. Thus, it appears that PC-MRI can tolerate certain degree of slice orientation imperfection. When the angulation from perpendicular position was 10° or less, the resulted CBF was comparable to that obtained with a perpendicular slice for both ICAs and VAs. ANOVA analysis showed that the CoV of the PC-MRI scans was independent of the slice angulation for both left ICA ($p = 0.44$, Fig. 3c) and left VA ($p = 0.82$, Fig. 3f).

Non-parametric Friedman test was used to compare data across angulation as well. By using the Friedman test, the angulation dependence on CBF values for both left ICA and left VA was significant ($p < 0.001$ and $p < 0.01$, respectively). The main effect of angulation on CoV did not reach a significance level for both ICA and VA ($p = 0.11$ and $p = 0.92$, respectively). Arterial cross-sectional area measured on the image was found to be significantly dependent on angulation for both left ICA ($p < 0.001$) and left VA ($P < 0.001$).

Evaluation of inter-rater reliability

Because the CBF difference between the two raters would increase as the CBF values increase, a logarithmic transformation was applied to the CBF measurements to remove this relationship for fair comparison across subjects and across the two arteries (36,37). Fig. 4 shows the Bland-Altman plots using log transformed CBF measurements for the left ICA and VA of the Study 1 and Study 2. In Study 1 (Fig. 4a–b), the geometric mean ratios of left ICA and left VA by the two raters was 1.001 and 0.999, respectively. In ICA, the CBF values obtained by the two raters differed by 0.2% on average with a 95% confidence interval of $[-1.1\%, 1.4\%]$. In VA, the inter-rater difference was 0.01% on average with a 95% confidence interval of $[-4.9\%, 4.9\%]$. In study 2 (Fig. 4c–d), the geometric mean ratios of left ICA and left VA by the two raters was 0.995 and 0.977, respectively. In ICA, the CBF values obtained by the two raters differed by -0.45% on average with a 95%

confidence interval of $[-4.6\%, 3.7\%]$. In VA, the inter-rater difference was -2.4% on average with a 95% confidence interval of $[-9.6\%, 4.9\%]$. Our results demonstrated that there is a close agreement in CBF quantification between raters. Moreover, the rater-effect is not a major contribution to the uncertainty in CBF quantification since CBF variation caused by different raters were smaller than the variations cause by physiologic fluctuation and measurement noise, i.e., CoV of CBF quantification.

DISCUSSION

The present study aims to optimize phase-contrast MRI protocol for the quantification of whole-brain CBF. Two studies were conducted to achieve this goal. Firstly, by evaluating different in-plane resolutions, we suggested that the spatial resolution of 0.5mm provides a good tradeoff between accuracy, precision and scan duration in PC-MRI. Secondly, we have demonstrated that non-perpendicular positioning of the imaging slice on the targeted artery could result in an overestimation in CBF. But if the slice orientation is within 10° of the ideal angulation, the bias is negligible. In addition, we explored the rater-effect on CBF quantification, given that there are manual ROI drawing involved in PC-MRI data processing. Our results showed that the rater-induced CBF difference is less than 3%.

The main challenge of the PC-MRI acquisition is the partial voluming effect, arising at the edge of a vessel lumen where the voxels contain signals from both moving spins and stationary tissue. Given the limited resolution of the acquired image, partial voxels (containing part of the blood vessel) is considered as full voxels in the vessel ROI, which will lead to an overestimation in the cross-sectional area of the vessel and thus in CBF values calculated as integration of flow velocity within the cross-sectional area (38). The limited spatial resolution and non-perpendicularity between the imaging slice and flow direction are significant contributors to the partial voluming effect (33). In Study 1, we evaluated the spatial resolution induced partial voluming effect on CBF measurements. Our data demonstrated an overestimation of CBF and artery area in PC-MRI scans acquired at low resolutions. Moreover, this CBF overestimation caused by low resolution was found to be more pronounced in VAs than in ICAs, suggesting that CBF quantifications of smaller vessels are more likely to be affected by the resolution-induced partial voluming effect. This is because the ratio of partial voxels in all vessel voxels is higher in smaller vessels than in large vessels.

Although higher resolution indicates smaller partial voluming effect and thus more accurate CBF measurements, it is not necessary that higher resolution is always better. Because of the lower SNR, high resolution may cause underestimation of CBF at the edge voxels where flow velocity is small. Our results also showed that the measurement precision, indicated by CoV, tends to be higher in PC-MRI scans acquired with higher resolution, although this effect didn't reach statistical significance. Another concern is that high spatial resolution is usually achieved at a cost of scan duration. Therefore, considering the tradeoff among accuracy, precision and time-cost, we recommend 0.5mm (scan duration=15sec) as the optimal resolution for CBF quantification using PC-MRI. At this resolution, for a typical arterial vessel with a diameter of 3.5~5mm, one would have about 45~90 voxels in the region of interest.

With the proposed spatial resolution of 0.5mm, the CoV of CBF measurements were $6.7 \pm 2.5\%$ and $6.8 \pm 3.2\%$ for ICA and VA, respectively. Previous test-retest reliability studies have reported that the CoV of CBF measured by PET was 8.4% (39) and that measured by pseudo-continuous arterial spin labeling (pCASL) was 3.5%–7.5% (40). So the precision of PC-MRI with 0.5mm precision is generally comparable to other CBF techniques. In terms of scan time, a total of 2.5 min is needed to quantify whole brain CBF using the optimized PC-MRI, including 1.5min for TOF angiogram and 1 min for four PC-MRI scans of four feeding arteries at the level of foramen magnum. For comparison, the scan time for PET and pCASL were respectively 20 min and 5.3 min. Therefore, although the measured CBF is lack of spatial information, PC-MRI using our optimized measurement scheme and imaging resolution could serve as a reliable and efficient way to quantify whole brain CBF.

The findings from the present study need to be interpreted in the context of its limitations. First, the optimal PC-MRI parameters proposed in this work for whole brain CBF quantification have not applied to large-scale studies. In Study 1, the resolution dependence effect on the CBF of ICA is a trend if the non-parametric test was used. Therefore, a larger-scaled study could be performed in future to improve the statistic power and assess the feasibility of the optimized protocol in a large population. Second, a comparison study between PC-MRI using our optimized protocol and other established techniques, such as ^{15}O -PET or TCD, would validate the accuracy and reliability of our protocol. Third, for the targeted artery ROI selection, only manual ROI selection was performed in this work. Although our results showed small inter-rater variability in tracing the boundary of the arteries on the PC-MRI images, the rater's skill and experience may affect the accuracy of the PC-MRI results. In future studies, we will work on a rater-independent automatic segmentation method to extract the cross-sectional area of the arteries.

In conclusion, this work showed that PC-MRI scans applied on major feeding arteries of the brain with a spatial resolution of 0.5 mm could serve as an optimal protocol for the quantification of whole-brain CBF. Although lacking spatial specificity, this method provides a non-invasive (i.e., no need for exogenous tracers), accurate (not dependent on model assumptions), and fast (<3min) measurement of whole-brain CBF, which could be used in clinical applications to evaluate cerebral hemodynamics and to calibrate other regional CBF mapping techniques.

Acknowledgments

Grant sponsors: NIH R01 MH084021 (to HL), NIH R01 NS067015 (to HL), NIH R01 AG042753 (to HL), and NIH R21 NS085634 (to PL).

References

1. Liu P, Huang H, Rollins N, et al. Quantitative assessment of global cerebral metabolic rate of oxygen (CMRO₂) in neonates using MRI. *NMR Biomed.* 2014; 27:332–340. [PubMed: 24399806]
2. Varela M, Groves AM, Arichi T, Hajnal JV. Mean cerebral blood flow measurements using phase contrast MRI in the first year of life. *NMR Biomed.* 2012; 25:1063–1072. [PubMed: 22290659]
3. Peng SL, Dumas JA, Park DC, et al. Age-related increase of resting metabolic rate in the human brain. *NeuroImage.* 2014; 98:176–183. [PubMed: 24814209]

4. Chen JJ, Rosas HD, Salat DH. Age-associated reductions in cerebral blood flow are independent from regional atrophy. *NeuroImage*. 2011; 55:468–478. [PubMed: 21167947]
5. Nishimura T, Hashikawa K, Fukuyama H, et al. Decreased cerebral blood flow and prognosis of Alzheimer's disease: A multicenter HMPAO-SPECT study. *Ann Nucl Med*. 2007; 21:15–23. [PubMed: 17373332]
6. Derejko M, Slawek J, Wieczorek D, Brockhuis B, Dubaniewicz M, Lass P. Regional cerebral blood flow in Parkinson's disease as an indicator of cognitive impairment. *Nucl Med Commun*. 2006; 27:945–951. [PubMed: 17088679]
7. Kaplar M, Paragh G, Erdei A, et al. Changes in Cerebral Blood Flow Detected by SPECT in Type 1 and Type 2 Diabetic Patients. *J Nucl Med*. 2009; 50:1993–1998. [PubMed: 19910437]
8. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke - A systematic review. *Stroke*. 2006; 37:1334–1339. [PubMed: 16574919]
9. Donahue MJ, Dethrage LM, Faraco CC, et al. Routine Clinical Evaluation of Cerebrovascular Reserve Capacity Using Carbogen in Patients With Intracranial Stenosis. *Stroke*. 2014; 45:2335–2341. [PubMed: 24938845]
10. Siero JC, Hartkamp NS, Donahue MJ, et al. Neuronal activation induced BOLD and CBF responses upon acetazolamide administration in patients with steno-occlusive artery disease. *NeuroImage*. 2014; 1016/j.neuroimage.2014.09.033
11. Liu P, Lu H, Filbey FM, Tamminga CA, Cao Y, Adinoff B. MRI assessment of cerebral oxygen metabolism in cocaine-addicted individuals: hypoactivity and dose dependence. *NMR Biomed*. 2014; 27:726–732. [PubMed: 24757009]
12. Volkow ND, Mullani N, Gould KL, Adler S, Krajewski K. Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. *Br J Psychiatry*. 1988; 152:641–648. [PubMed: 3262397]
13. Lask B, Gordon I, Christie D, Frampton I, Chowdhury U, Watkins B. Functional neuroimaging in early-onset anorexia nervosa. *Int J Eat Disord*. 2005; 37 (Suppl):S49–51. discussion S87–49. [PubMed: 15852320]
14. Pinkham A, Loughhead J, Ruparel K, et al. Resting quantitative cerebral blood flow in schizophrenia measured by pulsed arterial spin labeling perfusion MRI. *Psychiatry Res*. 2011; 194:64–72. [PubMed: 21831608]
15. Ostergaard L, Johannsen P, Host-Poulsen P, et al. Cerebral blood flow measurements by magnetic resonance imaging bolus tracking: Comparison with [O-15]H₂O positron emission tomography in humans. *J Cerebr Blood F Met*. 1998; 18:935–940.
16. Mintun MA, Raichle ME, Martin WR, Herscovitch P. Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. *J Nucl Med*. 1984; 25:177–187. [PubMed: 6610032]
17. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. 1. Mathematical approach and statistical analysis. *Magn Reson Med*. 1996; 36:715–725. [PubMed: 8916022]
18. Wu WC, St Lawrence KS, Licht DJ, Wang DJ. Quantification issues in arterial spin labeling perfusion magnetic resonance imaging. *Top Magn Reson Imaging*. 2010; 21:65–73. [PubMed: 21613872]
19. Buxton RB, Frank LR, Wong EC, Siewert B, Warach S, Edelman RR. A general kinetic model for quantitative perfusion imaging with arterial spin labeling. *Magn Reson Med*. 1998; 40:383–396. [PubMed: 9727941]
20. Bakker CJ, Hoogeveen RM, Viergever MA. Construction of a protocol for measuring blood flow by two-dimensional phase-contrast MRA. *J Magn Reson Imaging*. 1999; 9:119–127. [PubMed: 10030659]
21. Evans AJ, Iwai F, Grist TA, et al. Magnetic resonance imaging of blood flow with a phase subtraction technique. In vitro and in vivo validation. *Invest Radiol*. 1993; 28:109–115.
22. Haccke, E.; Brown, R.; Thompson, M.; Venkatesan, R. Magnetic resonance imaging: Physical principles and sequence design. New York, NY: Wiley-Liss; 1999. MR angiography and flow quantification.

23. Liu P, Xu F, Lu H. Test-retest reproducibility of a rapid method to measure brain oxygen metabolism. *Magn Reson Med*. 2013; 69:675–681. [PubMed: 22517498]
24. Jain V, Langham MC, Wehrli FW. MRI estimation of global brain oxygen consumption rate. *J Cerebr Blood F Met*. 2010; 30:1598–1607.
25. Jain V, Buckley EM, Licht DJ, et al. Cerebral oxygen metabolism in neonates with congenital heart disease quantified by MRI and optics. *J Cerebr Blood F Met*. 2014; 34:380–388.
26. Aslan S, Xu F, Wang PL, et al. Estimation of labeling efficiency in pseudocontinuous arterial spin labeling. *Magn Reson Med*. 2010; 63:765–771. [PubMed: 20187183]
27. Bonekamp D, Degaonkar M, Barker PB. Quantitative cerebral blood flow in dynamic susceptibility contrast MRI using total cerebral flow from phase contrast magnetic resonance angiography. *Magn Reson Med*. 2011; 66:57–66. [PubMed: 21287594]
28. Liu P, Lu H, Filbey FM, et al. Automatic and reproducible positioning of phase-contrast MRI for the quantification of global cerebral blood flow. *PLoS One*. 2014; 9:e95721. [PubMed: 24787742]
29. Zananiri FV, Jackson PC, Goddard PR, Davies ER, Wells PN. An evaluation of the accuracy of flow measurements using magnetic resonance imaging (MRI). *J Med Eng Technol*. 1991; 15:170–176. [PubMed: 1800748]
30. Lotz J, Doker R, Noeske R, et al. In vitro validation of phase-contrast flow measurements at 3 T in comparison to 1.5 T: precision, accuracy, and signal-to-noise ratios. *J Magn Reson Imaging*. 2005; 21:604–610. [PubMed: 15834905]
31. Meckel S, Leitner L, Bonati LH, et al. Intracranial artery velocity measurement using 4D PC MRI at 3 T: comparison with transcranial ultrasound techniques and 2D PC MRI. *Neuroradiology*. 2013; 55:389–398. [PubMed: 23143179]
32. Coverdale NS, Gati JS, Opalevych O, Perrotta A, Shoemaker JK. Cerebral blood flow velocity underestimates cerebral blood flow during modest hypercapnia and hypocapnia. *J Appl Physiol*. 2014; 117:1090–1096. [PubMed: 25012027]
33. Lotz J, Meier C, Leppert A, Galanski M. Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation. *Radiographics*. 2002; 22:651–671. [PubMed: 12006694]
34. Friedman M. The use of ranks to avoid the assumption of normality implicit in the analysis of variance. *J Am Stat Assoc*. 1937; 32:675–701.
35. Bland JM, Altman DG. Statistical Methods for Assessing Agreement between Two Methods of Clinical Measurement. *Lancet*. 1986; 1:307–310. [PubMed: 2868172]
36. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res*. 1999; 8:135–160. [PubMed: 10501650]
37. Bland JM, Altman DG. Transformations, means, and confidence intervals. *Brit Med J*. 1996; 312:1079–1079. [PubMed: 8616417]
38. Bernstein, M.; King, K.; Zhou, X. *Handbook of MRI pulse sequences*. Elsevier; 2004.
39. Coles JP, Fryer TD, Bradley PG, et al. Intersubject variability and reproducibility of O-15 PET studies. *J Cerebr Blood F Met*. 2006; 26:48–57.
40. Chen YF, Wang DJJ, Detre JA. Test-Retest Reliability of Arterial Spin Labeling With Common Labeling Strategies. *J Magn Reson Imaging*. 2011; 33:940–949. [PubMed: 21448961]

Figure 1.

Illustration of the positions of the MRI scans and representative images. (a) Slice position of the 3D TOF angiogram scan for visualization of the brain's feeding arteries. (b) Example of PC-MRI slice positions on the maximum-intensity-projection (MIP) image from TOF angiogram. The red bars indicate the slice positioning of PC MRI at the level of foramen magnum for two representative feeding arteries, left internal carotid artery (LICA) and left vertebral artery (LVA). (c) The corresponding two phase images from the two feeding arteries positioned at the level of foramen magnum.

Figure 2.

Effect of spatial resolution on PC-MRI results. (a) Magnitude images of left ICA with four different in-plane resolutions from a representative subject. Red lines indicate the voxels included in the artery ROI. (b)–(d) Mean CBF, CoV, and artery area obtained at different spatial resolution for left ICA (N=12). (e)–(g) Mean CBF, CoV, and artery area obtained at different spatial resolution for left VA (N=12). Error bars indicate standard errors (*: p<0.05, **: p<0.01).

Figure 3.

Effect of non-perpendicular slice orientation on PC-MRI results. (a) Magnitude images of left ICA with seven different slice angulations from a representative subject. Red lines indicate the voxels included in the artery ROI. (b)–(d) Mean CBF, CoV, and artery area obtained at different angulations for left ICA (N=7). (e)–(g) Mean CBF, CoV, and artery area obtained at different angulations for left VA (N=7). Error bars indicated standard errors (*: $p < 0.05$, **: $p < 0.01$, comparing to 0° angulation).

Figure 4.

Comparisons of CBF values obtained by two different raters. (a–b) Bland-Altman plots between two raters using loge transformed CBF measurements for left ICA and left VA obtained in study 1 (N=12, with 4 resolutions for each subject). Each color represents the data points from one resolution. (c–d) Bland-Altman plots between two raters using loge transformed CBF measurements for left ICA and left VA obtained in study 2 (N=7, with 7 angulations for each subject). Each color represents the data points from one angulation. For all the Bland-Altman plots, the solid line indicates the mean difference between two measurements. The dashed lines indicate the 95% confidence interval. Each dot represents data from one artery of one subject.