Temporal and Spatial Variances in Arterial Spin-Labeling Are Inversely Related to Large-Artery Blood Velocity

A.D. Robertson, G. Matta, V.S. Basile, S.E. Black, C.K. Macgowan, J.A. Detre, and B.J. MacIntosh

ABSTRACT

BACKGROUND AND PURPOSE: The relationship between extracranial large-artery characteristics and arterial spin-labeling MR imaging may influence the quality of arterial spin-labeling–CBF images for older adults with and without vascular pathology. We hypothesized that extracranial arterial blood velocity can explain between-person differences in arterial spin-labeling data systematically across clinical populations.

MATERIALS AND METHODS: We performed consecutive pseudocontinuous arterial spin-labeling and phase-contrast MR imaging on 82 individuals (20–88 years of age, 50% women), including healthy young adults, healthy older adults, and older adults with cerebral small vessel disease or chronic stroke infarcts. We examined associations between extracranial phase-contrast hemodynamics and intracranial arterial spin-labeling characteristics, which were defined by labeling efficiency, temporal signal-to-noise ratio, and spatial coefficient of variation.

RESULTS: Large-artery blood velocity was inversely associated with labeling efficiency ($P = .007$), temporal SNR ($P < .001$), and spatial coefficient of variation ($P = .05$) of arterial spin-labeling, after accounting for age, sex, and group. Correction for labeling efficiency on an individual basis led to additional group differences in GM-CBF compared to correction using a constant labeling efficiency.

CONCLUSIONS: Between-subject arterial spin-labeling variance was partially explained by extracranial velocity but not cross-sectional area. Choosing arterial spin-labeling timing parameters with on-line knowledge of blood velocity may improve CBF quantification.

ABBREVIATIONS: ASL = arterial spin-labeling; CoV = coefficient of variation; PC = phase contrast; WMH = white matter hyperintensities

Quantitative CBF is a valuable measure to track pathophysiologic changes in cerebrovascular function and brain metabolism. Two noninvasive MR imaging–based techniques, which capture distinct hemodynamic features, are arterial spin-labeling (ASL) and phase-contrast (PC) imaging. ASL measures regional CBF with tissue-level precision, using magnetized arterial blood water as an endogenous tracer. PC imaging, by comparison, quantifies whole-brain CBF with a bipolar gradient to induce phase shifts proportional to blood velocity within the carotid and vertebral arteries. Among the factors that influence ASL, CBF quantification is most sensitive to labeling efficiency and the equilibrium magnetization of arterial blood. In practice, labeling efficiency is assumed constant (eg, 0.85). Field inhomogeneity and nonlinear effects of blood velocity, however, contribute individual variability. Studies that have empirically estimated labeling efficiency by normalizing pseudocontinuous ASL-based whole-brain CBF to that measured with PC imaging report individual labeling efficiencies ranging from 0.7 to 1.1. Recent work in a large middle-aged cohort, however, has questioned the validity of this normalization method due to substan-
tial variability within individual measurements.\textsuperscript{11} Rather than incorporating PC-based CBF as a normalization factor, corresponding knowledge of PC-based metrics, such as blood velocity, may be beneficial for planning ASL protocols because many labeling and acquisition parameters are timing-based.

Simulated and empiric ASL data suggest that labeling efficiency is highest for blood velocities of \(-10\) cm/s.\textsuperscript{8} These studies reflect hemodynamics in healthy adults, leaving questions regarding the reliability of ASL in patients with vascular pathology. Aging, cerebrovascular risk factors, and stroke status are associated with larger cross-sectional areas and slower, more pulsatile blood velocity within the large arteries.\textsuperscript{12,13} Such changes occurring in proximity to the ASL labeling plane may confound CBF quantification in these clinical cohorts. For instance, age is associated with a decreased signal-to-noise ratio, due, in part, to increased variability between individual control-tag difference images.\textsuperscript{14} Arterial transit time is another velocity-sensitive hemodynamic characteristic associated with aging\textsuperscript{15} and the presence of white matter hyperintensities (WMH).\textsuperscript{16} Prolonged transit time is visualized by localized regions of hyperintense ASL signal, contributing to greater spatial variance in whole-brain CBF.\textsuperscript{17} To expand our understanding of the relationship between large-artery characteristics and CBF estimates, we compared ASL and PC in individuals across a range of age and vascular pathology. We hypothesized that large-artery blood velocity would be inversely related to labeling efficiency, temporal SNR, and spatial variance in ASL.

**MATERIALS AND METHODS**

**Participants and Protocol**

Participants were recruited into 4 groups: 1) healthy young adults (younger than 40 years); 2) healthy older adults (50 years or older); 3) older adults with WMH of presumed vascular origin; and 4) older adults with chronic stroke infarcts (older than 3 months post-stroke). Exclusion criteria included the presence of dementia, a genetic predisposition to WMH, and extracranial arterial occlusion by localized regions of hyperintense ASL signal, contributing to greater spatial variance in whole-brain CBF.\textsuperscript{17} To expand our understanding of the relationship between large-artery characteristics and CBF estimates, we compared ASL and PC in individuals across a range of age and vascular pathology. We hypothesized that large-artery blood velocity would be inversely related to labeling efficiency, temporal SNR, and spatial variance in ASL.

**MR Imaging Acquisition**

We completed neuroimaging with a 3T MR imaging system (Achieva; Philips Healthcare, Best, the Netherlands) with a body coil transmitter and an 8-channel head coil receiver. Structural imaging included high-resolution T1 (TR/TE = 9.5/2.3 ms, flip angle = 8°, voxel dimensions = 0.9 \times 0.7 \times 1.2 mm\textsuperscript{3}, FOV = 240 \times 191 \times 168 mm\textsuperscript{3}) and FLAIR (TR/TE/TI = 9000/125/2800 ms, flip angle = 90°, voxel dimensions = 0.4 \times 0.4 \times 3 mm\textsuperscript{3}, FOV = 240 \times 240 \times 156 mm\textsuperscript{3}) acquisitions. Two 2D acquisitions independently quantified CBF: PC to measure large-artery blood flow and ASL to measure tissue-level CBF. The PC acquisition captured a single 5-mm section perpendicular to the extracranial internal carotid artery, with cardiac synchronization (finger pulse gating, single cardiac phase [acquisition delay = 250 ms, acquisition window = 500 ms], TR/TE = 20/9.1 ms, flip angle = 15°, maximum velocity encoding = 100 cm/s, voxel dimensions = 0.5 \times 0.5 mm\textsuperscript{2}, FOV = 150 \times 150 mm\textsuperscript{2}). Pseudocontinuous labeling for the ASL scan used a train of radiofrequency pulses (duration = 0.5 ms, flip angle = 18°, interpulse pause = 0.5 ms) with a balanced gradient scheme for 1650 ms and occurred at a position identical to that of the PC acquisition. Thirty control and tag ASL volume pairs were acquired by single-shot echo-planar imaging (TR/TE = 4000/9.6 ms, flip angle = 90°, in-plane resolution = 3 \times 3 mm\textsuperscript{3}, FOV = 192 \times 192 mm\textsuperscript{2}, section thickness = 5 mm, number of sections = 18 [no gap], postlabel delay = 1600 ms at the first section and ascending for subsequent sections).

We did not select background suppression to maximize the detectability of deleterious individual-difference images that were spurious due to head motion. A proton density–weighter reference volume was acquired to estimate the equilibrium magnetization and extract a receiver coil sensitivity profile (TR = 10 seconds, but otherwise identical to ASL parameters). We prioritized the frontal cortices and subcortical tissue when setting the ASL FOV, leaving inconsistent coverage of the cerebellum and the most superior cerebrum. PC and ASL scan durations were 1.5 and 4.5 minutes, respectively. The 2 acquisitions were run sequentially, and the order was varied between participants.

**MR Imaging Processing**

Images were processed with the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Brain extraction\textsuperscript{18} and segmentation\textsuperscript{19} tools isolated GM and WM from the T1WI. Brain mass was estimated on the basis of tissue densities of 1.03 g/mL for GM and 1.04 g/mL for WM.\textsuperscript{20} In-house software,\textsuperscript{21} combined with manual editing, segmented WMH from the FLAIR image. Stroke lesions were identified by CSF segmentation from the T1WI, manual editing, and confirmation against the FLAIR image. WMH and infarct volumes were normalized to an intracranial capacity of 1300 mL. Older adults with a normalized hyperintensity burden of \(\geq 10\) mL across periventricular and deep brain regions were assigned to the WMH group.

Internal carotid and vertebral artery masks were isolated from the PC magnitude image by using FSL segmentation software and manual editing. Interrater reliability of this method was excellent (Cronbach \(\alpha >0.99\) for the internal carotid artery and \(>0.95\) for the vertebral artery between 1 experienced and 2 novice raters). These masks represent the cross-sectional area of each artery, and they were overlaid onto the PC phase image to compute mean blood velocity. Arterial blood flow is the product of area and mean velocity, and PC-CBF was calculated as the sum of flow through all 4 arteries, normalized to brain mass. Peak blood velocity was taken as the highest velocity signal from a voxel in the center of the vessel lumen.

ASL-CBF was calculated from the mean of the control-tag difference images. To maximize image quality, we systematically removed individual-difference images with high relative head motion before CBF calculation, as previously described.\textsuperscript{14} The remaining difference images underwent in-plane spatial smoothing by using a Gaussian kernel of 5-mm full width at half maximum, section-by-section adjustment for incremental postlabel delay, and calibration to absolute CBF units with a proton density–weighted image.\textsuperscript{3} The T1 relaxation time for arterial blood was set at 1.65 seconds for all participants. Calibration to absolute CBF units at this stage did not correct for labeling efficiency. Images with intravascular artifacts were retained. Although intravas-
circular artifacts are suggestive of prolonged arterial transit time, CBF calculations over the whole brain should remain valid in the absence of crushing gradients.3

We calculated 4 ASL variables to compare against extracranial hemodynamics: 1) GM-CBF, 2) individual labeling efficiency equal to the ratio between ASL-based and PC-based whole-brain CBF, 3) temporal SNR equal to the ratio between the mean and the SD of the individual-difference images, and 4) spatial coefficient of variation (CoV) equal to the ratio between ASL-based and PC-based whole-brain hemodynamics: 1) GM-CBF, 2) individual labeling efficiency with the calculated labeling efficiency.

Statistical Analysis

CBF, mean blood velocity, and cross-sectional area were compared between groups by ANOVA. We assessed the associations of mean blood velocity and cross-sectional area with GM-CBF, individual labeling efficiency, temporal SNR, and spatial CoV by linear regressions, adjusting for age, sex, and group. To account for between-vessel differences in area and velocity, we calculated flow-weighted measures in which the influence of each artery on the pooled variables was proportional to the contribution of that vessel to whole-brain CBF. Differences between whole-brain ASL-CBF and PC-CBF were characterized in a paired analysis by ratio and mean difference. Finally, we compared GM-CBF with ASL-CBF and PC-CBF accounted for a significant proportion of the between-person variance in ASL-CBF (r² = 0.40, P < .001), though technique differences were evident. Intermodality analyses suggested that ASL-CBF was systematically lower than PC-CBF (r = −2.6, P = .01), and this difference was greater in WMH than in stroke or healthy older adults groups (Table 2). The ASL-CBF to PC-CBF ratio (ie, individual labeling efficiency) ranged from 0.48 to 1.60 across our entire sample. A group effect was observed (F = 4.3, P = .008), with the ratio being lower in WMH than in stroke and healthy older adults groups.

RESULTS

Large-artery characteristics and whole-brain hemodynamics from 82 participants (n = 15 young, 22 healthy older, 15 with WMH, and 30 with stroke) are reported in Table 1. In WMH, the normalized hyperintensity volume ranged from 0.03 to 98.2 mL. Group differences in velocity, but not cross-sectional area, were observed (Fig 1). Although the fraction of whole-brain CBF contributed by each extracranial artery was similar across groups, greater within-group variability was observed in older adults with vascular pathology (Fig 1, lower panel).

Labeling Efficiency

PC-CBF accounted for a significant proportion of the between-person variance in ASL-CBF (r² = 0.40, P < .001), though technique differences were evident. Intermodality analyses suggested that ASL-CBF was systematically lower than PC-CBF (r = −2.6, P = .01), and this difference was greater in WMH than in stroke or healthy older adults groups (Table 2). The ASL-CBF to PC-CBF ratio (ie, individual labeling efficiency) ranged from 0.48 to 1.60 across our entire sample. A group effect was observed (F = 4.3, P = .008), with the ratio being lower in WMH than in stroke and healthy older adults groups.

FIG 1. Vascular characteristics of the bilateral (left and right) internal carotid (LICA and RICA) and vertebral arteries (LVA and RVA) for each group. Panel 3 shows the relative contribution to total CBF by each vessel.
Our current findings contrast with ASL simulations. Whereas the previous findings were under the assumption of constant flow profiles, our PC implementation averaged velocities over the cardiac cycle; consequently, the velocity estimates more closely reflect data from previous work.5 However, label efficiency variance was high for low velocities; thus, we are unable to provide empirical support for the theorized inverted U-shaped profile.7-9 Notably, features of ASL variance, namely temporal SNR and spatial CoV, were independently associated with mean blood velocity but not cross-sectional area in regression analyses. Reduced temporal SNR at a low velocity contributed to the increased variance of labeling efficiency within this range. These results reaffirm that hemodynamics at the labeling plane are an important consideration for CBF quantification in ASL, especially in older adults with cerebrovascular disease.

Previous work estimated ASL labeling efficiency based on PC,7-9 though the validity of this method has recently come under scrutiny.11 Our current findings contrast with ASL simulations that posited a direct association between velocity and labeling efficiency below peak velocities of 20 cm/s.7-9 Whereas the previous findings were under the assumption of constant flow profiles, our PC implementation averaged velocities over the cardiac cycle; consequently, the velocity estimates more closely reflect data from Aslan et al,8 who found an inverse association between velocity and labeling efficiency above 10 cm/s. ASL signal intensity and transit delays have been shown to vary as a function of the cardiac cycle,22 so dissimilar relationships between mean and peak veloc-
At acquisition, ASL signal is dependent on the arterial transit time. We observed that slower velocity was related to greater spatial CoV of the perfusion-weighted image, which is consistent with greater macrovascular signal at the time of acquisition. Real-time monitoring of blood velocity before ASL planning may help mitigate these indices of ASL variance in 2 ways: First, acquiring additional tag and control volumes in individuals with low velocity would improve signal-to-noise ratio. Second, prescribing postlabel delay based on arterial blood velocity may help to distinguish aspects of arterial transit time that separate slower flow velocity from collateral or tortuous pathways.

The GM-CBF values observed here are consistent with those in other studies involving younger adults, healthy older adults, and individuals with chronic stroke. Older adults with WMH, however, exhibited lower GM-CBF than previously reported. Calibration of the GM-CBF to individual labeling efficiency on the basis of PC altered the sensitivity to distinguish clinical groups. With PC-based calibration, we noted GM-CBF differences between healthy young and older adults and between healthy older adults and those with stroke, which were not apparent with a constant labeling efficiency for all participants. Longitudinal relaxation time was held constant across all groups in our estimation of CBF with ASL. Age- and sex-dependent variability in blood T1 may have partially contributed to group differences in global ASL signal. The change in group differences following calibration to PC-CBF, which is independent of blood T1 effects, may be partially due to correction for group differences in longitudinal relaxation. Nevertheless, these results raise important questions about the consideration of labeling efficiency and the design of ASL protocols for CBF quantification in clinical cohorts with altered large-artery velocity profiles.

Despite these proposed links between blood velocity and ASL, a large proportion of the variance remains unexplained in this study. In several cases, the calculated labeling efficiency exceeded 1.0, which is an implausible finding. We implemented gated cardiac PC-MRI to capture velocity data at a single phase in the cardiac cycle on the basis of a 500-ms acquisition window that was optimized for a range of R-R intervals centered at 1000 ms. Heart rate variability could shift this acquisition window to favor the diastolic phase of the cardiac cycle, which would influence the PC-CBF calculation and contribute to a higher ratio between ASL-CBF and PC-CBF. Vessel segmentation and partial volume errors related to vertebral artery tortuosity and smaller arterial caliber may have reduced PC-CBF accuracy. Another consideration is the ASL volume coverage. Whereas PC-CBF reflects whole-brain flow, the ASL FOV did not encapsulate the entire global ASL signal.

### Table 3: Linear regression parameters for the association of extracranial mean blood velocity and cross-sectional area with ASL characteristics

| Model      | Independent Variables | β    | 95% CI     | T-Statistic | P Value |
|------------|-----------------------|------|------------|-------------|---------|
| GM-CBF    | Area (cm²)            | 46.5 | (8.2–84.7) | 2.03        | .046    |
| Adjusted R² = 0.43 | Velocity (cm/s)     | 1.5  | (0.8–2.3)  | 3.42        | .001    |
| ASL-CBF-PC-CBF | Area (cm²)          | −0.79| (−1.58–0.01)| −1.65       | .103    |
| Adjusted R² = 0.21 | Velocity (cm/s)    | −0.02| (−0.04–0.00)| −2.78       | .007    |
| GM-temporal SNR | Area (cm²)         | 1.78 | (0.24–3.32)| 1.93        | .058    |
| Adjusted R² = 0.47 | Velocity (cm/s)    | 0.07 | (0.04–0.10)| 3.99        | <.001   |
| GM-spatial CoV | Area (cm²)          | −0.11| (−0.61–0.39)| −0.36       | .720    |
| Adjusted R² = 0.31 | Velocity (cm/s)    | −0.01| (−0.02–0.00)| −2.01       | .048    |

*All models were adjusted for age, sex, and group. GM-CBF is uncorrected for labeling efficiency.

**FIG 3.** GM-CBF between groups calculated with 2 labeling efficiency estimates. White bars incorporate a constant labeling efficiency (ie, 0.85), and gray bars incorporate individual labeling efficiency based on the ASL-to-PC ratio for whole-brain CBF. Post hoc group comparisons are indicated at P < .05 for differences from the young group (asterisk) and differences from old group (dagger) within the same calibration technique.
brain for all participants. Anatomic variability in the circle of Wil- 

lis (ie, distal to PC imaging) may also contribute to a mismatch

between upstream and downstream flow measurements.34

These discrepancies may have contributed to a portion of

the unexplained variance between ASL-CBF and PC-CBF and em- 

phasize the need for caution when comparing ASL-CBF directly

with PC-CBF.11 Of note, our ASL protocol did not incorporate

background suppression or involve 3D acquisition, which are

now consensus guidelines for clinical ASL.3 Two main reasons for

these preferences were the following: 1) Study development pre- 

dated the consensus article, and 2) a parallel objective of the data

acquisition was to address deleterious head motion, which is

more easily approached with multiple 2D sections as opposed to 3D

readouts. Recently, a sequence that measures artery-specific label

efficiency, thereby improving ASL-CBF accuracy, has been pro-

posed and validated.35 Comparison of PC-CBF with ASL-CBF

using this calibration method may facilitate investigation into the

impact of age- and disease-related increases in hemodynamic

pulsatility on ASL after controlling for effects on label efficiency.

CONCLUSIONS

The current study compared characteristics from ASL- and PC- 
based cerebral perfusion imaging in adults with and without

vascular disease. Mean blood velocity through the ASL labeling plane

was inversely related to labeling efficiency, as well as ASL temporal

and spatial variance. These associations suggest that velocity im-

pacts ASL at both the labeling and acquisition stages. ASL plan-

ning based on real-time velocity monitoring (eg, number of

control/tag pairs, postlabel delay) may help optimize the signal-

to-noise ratio and minimize the effect of arterial transit time on

CBF maps.

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ing for the Child Health and Development Institute (nonprofit Huntington dis-

ease research entity, Ironwood Pharmaceuticals company); I review grants for 

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Grants Pending: National Institutes of Health, Comments: I am a co-investigator

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