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Arterial Spin-Labeling Parameters and Their Associations with Risk Factors, Cerebral Small-Vessel Disease, and Etiologic Subtypes of Cognitive Impairment and Dementia

B. Gyanwali, C.S. Tan, J. Petr, L.L.T. Escobosa, H. Vrooman, C. Chen, H.J. Mutsaerts, and S. Hilal



ABSTRACT

BACKGROUND AND PURPOSE: Cerebral small-vessel disease may alter cerebral blood flow (CBF) leading to brain changes and, hence, cognitive impairment and dementia. CBF and the spatial coefficient of variation can be measured quantitatively by arterial spin-labeling. We aimed to investigate the associations of demographics, vascular risk factors, location, and severity of cerebral small-vessel disease as well as the etiologic subtypes of cognitive impairment and dementia with CBF and the spatial coefficient of variation.

MATERIALS AND METHODS: Three hundred ninety patients with a diagnosis of no cognitive impairment, cognitive impairment no dementia, vascular cognitive impairment no dementia, Alzheimer disease, and vascular dementia were recruited from the memory clinic. Cerebral microbleeds and lacunes were categorized into strictly lobar, strictly deep, and mixed-location and enlarged perivascular spaces into the centrum semiovale and basal ganglia. Total and region-specific white matter hyperintensity volumes were segmented using FreeSurfer. CBF ($n = 333$) and the spatial coefficient of variation ($n = 390$) were analyzed with ExploreASL from 2D-EPI pseudocontinuous arterial spin-labeling images in white matter (WM) and gray matter (GM). To analyze the effect of demographic and vascular risk factors as well as the location and severity of cerebral small-vessel disease markers on arterial spin-labeling parameters, we constructed linear regression models, whereas logistic regression models were used to determine the association between arterial spin-labeling parameters and cognitive impairment no dementia, vascular cognitive impairment no dementia, Alzheimer disease, and vascular dementia.

RESULTS: Increasing age, male sex, hypertension, hyperlipidemia, history of heart disease, and smoking were associated with lower CBF and a higher spatial coefficient of variation. Higher numbers of lacunes and cerebral microbleeds were associated with lower CBF and a higher spatial coefficient of variation. Location-specific analysis showed mixed-location lacunes and cerebral microbleeds were associated with lower CBF. Higher total, anterior, and posterior white matter hyperintensity volumes were associated with a higher spatial coefficient of variation. No association was observed between enlarged perivascular spaces and arterial spin-labeling parameters. A higher spatial coefficient of variation was associated with the diagnosis of vascular cognitive impairment no dementia, Alzheimer's disease, and vascular dementia.

CONCLUSIONS: Reduced CBF and an increased spatial coefficient of variation were associated with cerebral small-vessel disease, and more specifically lacunes, whereas cerebral microbleeds and white matter hyperintensities were associated with WM-CBF and GM spatial coefficient of variation. The spatial coefficient of variation was associated with cognitive impairment and dementia, suggesting that hypoperfusion might be the key underlying mechanism for vascular brain damage.

ABBREVIATIONS: AD = Alzheimer's disease; ASL = arterial spin-labeling; ATT = arterial transit time; CIND = cognitive impairment no dementia; CMB = cerebral microbleed; NCI = no cognitive impairment; ePVS = enlarged perivascular spaces; PLD = post-labeling delay; sCoV = spatial coefficient of variation; SVD = cerebral small-vessel disease; VaD = vascular dementia; VCIND = vascular CIND; WMH = white matter hyperintensities

CBF ensures a constant delivery of oxygen and nutrients to brain tissue.¹ Recently, the assessment of CBF has become a common clinical investigation to evaluate vascular brain damage,² owing to the noninvasive and quantitative measurement by

arterial spin-labeling (ASL).¹ Reduced CBF has been linked with normal aging³ and systemic vascular risk factors such as

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hypertension, hyperlipidemia, and diabetes⁴ and may manifest as cerebral small-vessel disease (SVD).⁵

SVD such as lacunes, white matter hyperintensities (WMH), cerebral microbleeds (CMBs), and enlarged perivascular spaces (ePVS) have been attributed to cerebral ischemia and hypoperfusion.^{6,7} Previous studies used ASL to demonstrate the association between reduced CBF with the presence and severity of WMH,⁸ an increased number of CMBs,^{9,10} and lacunar infarcts.^{11,12} However, the most important risk factors of hypoperfusion and how it contributes to SVD and cognitive impairment remain inconclusive. No studies have yet examined the association of ePVS with CBF parameters. Furthermore, the relationship between the location and severity of SVD with CBF in gray matter (GM) and white matter (WM) as measured by ASL has not yet been elucidated.

Reduced CBF due to vascular disease might be related to Alzheimer's disease (AD) as well as its preclinical stages, ie, mild cognitive impairment or cognitive impairment no dementia (CIND).^{13,14} Previous ASL studies have focused on mild cognitive impairment and AD, showing marked CBF reduction in the cortical area,¹⁴ with very limited studies on vascular CIND (VCIND) and vascular dementia (VaD).^{14,15} This limitation is mainly attributed to vascular artifacts commonly encountered in the elderly, making it difficult to quantify CBF with the commonly used single post-labeling delay (PLD) ASL.¹⁶ The spatial coefficient of variation (sCoV) of ASL images has been recently proposed to quantify the presence of vascular artifacts to overcome this issue.¹⁶ While abnormality in the sCoV cannot be interpreted as abnormal CBF, a higher sCoV was shown to correlate with arterial transit time (ATT), age, and sex,¹⁶ making it a potential proxy marker of vessel insufficiency. The sCoV can thus be used to quantify perfusion-related changes in combination with CBF and allow studying the ASL data in populations in which CBF alone is not conclusive. Previous research has mostly focused on the white American and European populations, with limited research on Southeast Asians, who have a higher prevalence of vascular risk factors, SVD, cognitive impairment, and dementia.¹⁷

We first aimed to determine the association between demographic and vascular risk factors as well as the location and severity of SVD with ASL perfusion parameters (GM-CBF, WM-CBF, GM-sCoV, and WM-sCoV). Second, we aimed to analyze the association of ASL parameters with etiologic subtypes of cognitive impairment and dementia: CIND, VCIND, AD, and VaD in a memory clinic population.

MATERIALS AND METHODS

Study Population

This study drew patients from a memory clinic of National University Hospital, Singapore, with the following diagnostic categories: no cognitive impairment (NCI), CIND, and dementia. The diagnosis of cognitive impairment was based on the clinical presentation as well as detailed neuropsychological assessments following the recommendation of the National Institute of Neurologic Disorders and Stroke and the Canadian Stroke Network (Online Supplemental Data).

From August 2010 to November 2017, a total of 579 participants were recruited who underwent clinical, physical, and neuropsychological assessments along with a 3T brain MR imaging

at the National University of Singapore. Of 579 participants, 12 did not undergo MR imaging, and 52 had no ASL sequence, leaving 515 patients for ASL analysis.

Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board. Written informed consent was obtained from all patients before their participation in this study.

Demographics and Vascular Risk Factors

A detailed questionnaire was administered to all participants to document age, sex, race, and education. Any history of hypertension, hyperlipidemia, and type 2 diabetes mellitus was noted and verified by medical records. A history of stroke was ascertained by a questionnaire and confirmed from medical records. A history of heart disease was defined as a previous diagnosis of myocardial infarction, congestive heart failure, atrial fibrillation, or intervention procedures such as angioplasty or stent placement. Smoking was categorized as "ever" versus "never."

Neuroimaging

MR imaging was performed at the National University of Singapore Clinical Imaging Research Center using a 3T Magnetom Trio, a Tim system (Siemens) with a 32-channel head coil. The standardized neuroimaging protocol in this study included 3D T1-weighted, T2-weighted, FLAIR, and SWI sequences.

MR imaging markers of SVD (CMBs, lacunes, ePVS) were defined on the basis of the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria.¹⁸ Quantitative MR imaging analyses for WMH volume were performed using FreeSurfer, Version 5.1.0 (<http://surfer.nmr.mgh.harvard.edu>) on T1-weighted images (Online Supplemental Data).

ASL Parameters. Pseudocontinuous ASL was acquired with a 2D gradient-echo echo-planar imaging readout with the following parameters: voxel size = $3 \times 3 \times 5$ mm³, 24 slices, labeling duration = 1656 ms, initial PLD = 1500 ms, section readout time = 49.94 ms leading to a PLD range of 1500–2649 ms across all slices or a mean PLD of 2074 ms, TR/TE = 4000/9 ms, and generalized autocalibrating partially parallel acquisitions factor = 3. Two ASL volumes of 23 control-label pairs were acquired with a 1-hour interval and were concatenated into 1 ASL time-series to decrease physiologic fluctuations. ASL image-processing was performed with ExploreASL software (<https://github.com/ExploreASL/ExploreASL>) (default settings without hematocrit correction) based on SPM (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>) and Matlab (MathWorks).¹⁹ From the CBF map, we acquired 4 ASL parameters: GM-CBF, WM-CBF, GM-sCoV, and WM-sCoV. CBF reflects perfusion in milliliters of blood/100-g tissue/min and was calculated in total GM and WM regions of interest (ROIs). sCoV, which was shown to serve as a proxy for ATT, was defined as the SD of ASL signal/mean ASL signal within an ROI. We performed quality assessment of the ASL scans blinded to the clinical diagnosis. On the basis of visual assessment, 515 scans were classified into 1 of the 4 categories:

- Unusable scans that were incomplete, had labeling errors, or severe motion artifacts ($n = 125$)
- Angiography scans with dominant vascular artifacts and no or minimal tissue perfusion contrast ($n = 57$)

- Acceptable scans with minor (vascular) artifacts and reasonable tissue perfusion contrast ($n = 166$)
- Good artifact-free scans with tissue perfusion contrast ($n = 167$).

For the sCoV analysis, we used a total of 390 patients, including scans with angiography and acceptable and good scans. For the CBF analysis, the 57 patients who had an angiography-like ASL scan were excluded, resulting in 333 patients for the CBF analysis.

Statistical Analysis

In this study, CMBs, lacunes, WMH volume, and ePVS were treated as counts and categoric variables. For categoric data, we classified CMBs as 0, 1, 2–4, >4; lacunes as 0, 1, ≥ 2 and by their location (strictly lobar, strictly deep, and mixed-location); and ePVS as ≤ 10 , 11–20, >20 and by location (centrum semiovale and basal ganglia). WMH volumes were logarithmically (log) transformed due to skewed distribution and were divided into tertiles (the first tertile was used as a reference) and by location (anterior and posterior).

For linear regression analysis, the log transformation of ASL parameter data (GM-CBF, WM-CBF, GM-sCoV, and WM-sCoV) was performed to ensure a normal distribution. Log-transformed ASL data were then standardized by dividing each variable by its SD. ASL data were used as continuous data (CBF: 1 SD unit decrease in 10 log; and sCoV: 1 SD unit increase in 10 log). Post-logarithmic transformation normality tests revealed normal distribution for most of the variables. To analyze the relationship between CBF (log GM-CBF) and sCoV (log GM-sCoV), we performed a Pearson correlation analysis. Finally, to analyze the effect of demographic and vascular risk factors on ASL parameters, we constructed linear regression models with the mean difference (β) and 95% CI. All models were first adjusted for age and sex and subsequently for hypertension, hyperlipidemia, diabetes, history of heart disease, history of stroke, and smoking. The same regression models were then conducted to analyze the association between location and severity of SVD markers with ASL parameters. In regression analyses, SVD markers were treated as determinants, and ASL parameters, as outcomes. We repeated these analyses for the 3 diagnostic groups: ie, NCI, CIND, and dementia.

Logistic regression models with ORs and 95% CIs were used to determine the association between ASL parameters and CIND, VCIND, AD, and VaD (NCI was used as the reference group). Models were adjusted for age, sex, education, and vascular risk factors. Results were considered significant at $P < .05$.

RESULTS

Baseline Characteristics

The characteristics of the study participants in CBF ($n = 333$) and sCoV ($n = 390$) analyses are shown in the Online Supplemental Data. There was a high prevalence of vascular risk factors and SVD in participants. In this study, we excluded 189 participants with ASL labeling errors or severe motion artifacts or no MR images. Excluded participants were significantly older, less educated, had a higher burden of vascular risk factors, and had dementia (Online Supplemental Data). Furthermore, those participants in whom CBF could not be measured ($n = 570$) were older (75 years versus 73 years), a significant number of participants were men (8.7% versus

42.0%), had a history of heart disease (31.6% versus 11.4%) and higher burden of cardiovascular risk factors, and more had dementia (47.4% versus 24.0%) compared with those in whom CMB could be measured ($n = 333$) (data not shown). We analyzed the correlation between GM-sCoV and GM-CBF in 333 subjects (with both CBF and sCoV data), and there was a negative correlation between log GM-CBF and log GM-sCoV ($r = -0.767$, $R^2 = 0.588$, $P < .001$) (data not shown).

WM-sCoV

The results for the association between WM-sCoV and demographics, vascular factors, SVD, and etiologic subtypes of cognitive impairment and dementia are shown in the Online Supplemental Data. However, WM-sCoV was associated with age, sex, vascular risk factors, and SVD in this study, and we did not further discuss these findings because the results were similar to the GM-sCoV results and did not add further insight into our findings. Furthermore, ASL measurements have a higher SNR and higher accuracy in GM compared with WM because CBF is higher and ATT is shorter in GM than in WM;^{16,20} hence, our findings with respect to WM-sCoV may not be accurate.

Determinants of ASL Parameters

Among demographic and vascular risk factors, older age and male sex were associated with significant changes in all 3 ASL parameters (lower GM-CBF and WM-CBF, and higher GM-sCoV), whereas hyperlipidemia was associated with reduced GM-CBF; smoking, with a lower mean WM-CBF; and hypertension and a history of heart disease, with higher GM-sCoV. Moreover, there was borderline significance with smoking and higher GM-sCoV (Online Supplemental Data).

Location and Severity of SVD and ASL Parameters

An increased severity of lacunes was associated with changes in all 3 ASL parameters: lower GM-CBF, a comparable decrease in WM-CBF, and higher mean GM-sCoV. Similarly, the presence of ≥ 2 lacunes was associated with higher mean GM-sCoV. The increased severity of CMBs as well as the presence of >4 CMBs were associated with lower mean WM-CBF and higher mean GM-sCoV, but lower mean GM-CBF did not reach statistical significance. Similarly, total WMH volume and second and third tertiles of WMH volumes were associated with higher mean GM-sCoV. In addition, WMH volume in the third tertile was also associated with lower mean WM-CBF. However, the severity of ePVS was not associated with ASL parameters. Stratifying ePVS into ≤ 10 ePVS, 11–20 ePVS, and >20 ePVS also did not show any significant association (Online Supplemental Data).

An increased number of mixed-location lacunes were associated with lower GM- and WM-CBF and higher GM-sCoV. Similarly, an increased number of mixed-location CMBs were associated with lower WM-CBF and higher GM-sCoV, but not with GM-CBF. Higher volumes of anterior and posterior WMHs were associated with lower WM-CBF and higher GM-sCoV. WMH volumes in the anterior and posterior regions were not associated with lower GM-CBF. In contrast, ePVS in the centrum semiovale and basal ganglia were not associated with any of the 3 ASL parameters (Online Supplemental Data).

Stratified analysis among participants with NCI, CIND, and dementia also showed similar associations (Online Supplemental Data).

ASL Parameters with Etiologic Subtypes of Cognitive Impairment and Dementia

Lower GM-CBF was associated with AD, whereas lower WM-CBF was associated with CIND. There was borderline significance of lower WM-CBF with AD. Lower GM- and WM-CBF were not associated with the diagnosis of VCIND and VaD. By contrast, higher GM-sCoV was associated with VCIND, AD, and VaD, but not CIND (Online Supplemental Data).

DISCUSSION

In this study, we found that increasing age, male sex, hyperlipidemia, and smoking were associated with lower CBF, whereas increasing age, male sex, hypertension, and a history of heart disease were associated with higher GM-sCoV. With respect to SVD, increased severity of lacunes and mixed-location lacunes were associated with reduced CBF. Similarly, an increased severity of CMBs, specifically mixed-location CMBs, and total WMH volume including anterior and posterior regions were associated with lower WM-CBF and higher GM-sCoV. Higher GM-sCoV was associated with etiologic subtypes of cognitive impairment and dementia.

The association of increasing age with hypoperfusion is in line with findings in previous studies. Age was previously associated with endothelial dysfunction and vascular remodeling, leading to chronic hypoperfusion²¹ and impaired cerebral autoregulation, causing several hemodynamic changes in the brain.²² The tortuosity of cerebral microvascular vessels was found to be increased in the elderly compared with young adults²³ and was associated with reduced CBF.²⁴ Most of the tortuous arteries are found in the WM of the brain,²⁴ which may explain the lower WM-CBF in this study. Similarly, we found that men had more cerebral hypoperfusion compared to women, suggesting differences in brain structure, chemistry, and function.²⁴ Estrogen is found to be protective against ischemia.²⁶ Moreover, women tend to have smaller brain volume, higher cerebral metabolic rate, higher resting CBF, and lower vascular risk factors compared with men.²⁵

Hypoperfusion due to hypertension can result from increased vessel stiffness due to atherosclerosis, disturbed hemodynamic flow patterns, and increased vascular resistance.²⁷ Hypertension can damage brain endothelial cells, which produce the vasodilator nitric oxide, contributing to cerebral hypoperfusion and hence higher GM-sCoV in our study.²⁸ Similarly, hyperlipidemia has been considered an important risk factor for decreased cerebral perfusion.²⁹ High levels of blood cholesterol and triglycerides lead to the accumulation of fatty deposits in the walls of arteries, resulting in narrowing of the lumen and reducing the supply of blood to the brain.³⁰ Smoking, on the other hand, increases the formation of plaque in blood vessels, which narrows the lumen of the blood vessels.³¹ Furthermore, nicotine causes blood vessels to constrict and also stimulates the release of catecholamines and other free radicals, which injure arterial endothelium, promote atherogenesis, and eventually reduce CBF.³² It has been shown that heart diseases such as myocardial infarction, congestive heart failure, and atrial fibrillation decrease cardiac output and reduce

cerebral perfusion.³³ A previous study has shown that patients with heart disease are at increased risk of atrial thrombogenicity and cardioembolism, leading to ischemic brain disease.³⁴

We found that SVD such as lacunes and CMBs was associated with lower WM-CBF and higher GM-sCoV, whereas total WMH volume was only associated with higher GM-sCoV. This finding could be because SVD markers are the consequence of cerebral amyloid angiopathy (CAA) and hypertensive arteriopathy. Lower CBF and higher sCoV due to SVD in this study may be due to amyloid deposition in the blood vessels and arteriosclerosis, which contributes to narrowing of the vessel lumen, leading to hypoperfusion.⁶ Such reduced cerebral perfusion may lead to tissue damage, infarction, and additionally CMBs.³⁵

We found that mixed-location lacunes and CMBs and WMH located in the anterior and posterior regions were associated with a lower CBF and higher sCoV. This finding can be because mixed lacunes and mixed CMBs represent mixed pathology, so patients with both CAA and hypertensive arteriopathy are more susceptible to cerebral ischemia and may exhibit mixed-location SVD on MR imaging.⁶ By contrast, the location and severity of ePVS were not associated with ASL parameters. As ePVS are considered an early MR imaging marker of SVD,^{36,37} we speculate that our study population might be already in the more advanced stage of the disease, which may explain the lack of association between the location and severity of ePVS with ASL parameters. Furthermore, it has been shown that perivascular spaces are present in abundance throughout the healthy brain³⁸ and may, thus, represent a nonpathologic process of aging with no contribution to hypoperfusion. As perivascular spaces are the fluid-filled spaces surrounding the penetrating vessels, responsible for regulating the immune response and drainage of interstitial fluids,³⁸ they are unlikely to affect cerebral perfusion.

We found that increased GM-sCoV was associated with the diagnoses of VCIND, AD, and VaD. These results indicate involvement of increased ATT and might reflect a reduction in the blood supply due to SVD, reduced neuronal activity, and cerebral atrophy.³⁹ It is further shown that hypoperfusion induces neurovascular dysfunction, triggering amyloid aggregation in the brain leading to cognitive impairment and dementia.⁴⁰ Accumulation of amyloid- β in the brain parenchyma and in the cerebral blood vessels starts decades before the onset of clinical symptoms of AD, implying that an early ischemic insult might initiate the disease process.⁴¹ This possibility might explain the increased sCoV in our patients with VCIND and reduced CBF in patients with CIND, causing speculation that GM- and WM-CBF alone may not be reliable indicators of disease at the later stage. These results suggest that chronic vascular hypoperfusion could contribute to neuronal damage, cognitive impairment, and dementia; hence, the sCoV of ASL could be a marker of disease severity.

Moreover, higher sCoV was linked with increased ATT.¹⁶ At the same time, WM-CBF is known to be difficult to measure, and ASL measurements are known to underestimate WM-CBF for a longer ATT, especially in deep WM.²⁰ However, we have observed that an increase in the sCoV was not necessarily connected with a decrease in WM-CBF or at least not a larger decrease than in GM-CBF.¹⁹ It has been shown that measuring significant WM signal is possible, though this might be difficult with standard PLD and

acquisition duration in deep WM, and delayed ATT can manifest itself as lower CBF on ASL measurements, even though the perfusion might be intact.⁴² A similar observation was made using healthy volunteers and very long breath-holds. A hypercapnic state leads to reduction of ATT, making the ATT/PLD combination much more favorable for measuring CBF than in normal settings that lead to a higher increase in WM-CBF than in GM-CBF, showing the important role of a short ATT in CBF measurement in WM with ASL.⁴³ Similarly, a decrease in WM-CBF was not always explained by an increase in the sCoV.¹⁹ This finding leads us to an assumption that despite needing to be interpreted with care, real WM-CBF differences can be observed in our data. Similarly, certain redistributions between the macro- and microvascular compartments can be detected with the sCoV changes without being really reflected by changes in GM- or WM-CBF. Taken together, despite the WM-CBF measurement with ASL being difficult and absolute CBF values not being fully reliable, WM-CBF can still yield interesting information.

In our current study, there was negative correlation between CBF and sCoV in 333 subjects (with both CBF and sCoV data). This is partially correct because those 333 scans were labeled as good and acceptable. However, in this study, there are also another 57 scans labeled as angiography with scans with dominant vascular artifacts, and no-or-minimal tissue perfusion contrast when calculated CBF cannot be reliable. Analyzing the sCoV allows us to include more data in this study, especially when the study population is older adults with a higher burden of cerebrovascular disease. Thus, we believe that the sCoV is a good proxy parameter of global cerebrovascular health when CBF cannot be used interchangeably with sCoV.

The limitations of this study are, first, that ASL image quality can be affected by older age and dementia because these patients often find it difficult to stay still inside the scanner. To minimize this bias, we excluded those scans labeled as angiography and unusable. Furthermore, individuals who were more ill were excluded from the study, possibly affecting both the group analysis and individual clinical findings. Second, because this is a cross-sectional study, we cannot prove that SVD and a decrease in CBF or an increase in the sCoV across time caused hypoperfusion or vice versa. Future longitudinal studies are needed to understand the cause-effect relation between hypoperfusion and SVD. Third, in this study, not all participants underwent a brain PET scan to confirm the presence of amyloid or tau pathology; hence, the participants with AD could be considered as having probable AD. Finally, WM-CBF is difficult to measure with ASL, especially for longer ATTs.²⁰ However, we observed that an increase in the sCoV, associated with increased ATT,¹⁶ was not necessarily connected with a decrease in WM-CBF.¹⁹ We, therefore, assume that some true WM-CBF differences might be observed in our data.

CONCLUSIONS

In this study, we found that a higher sCoV of ASL images was associated with cognitive impairment and dementia, as well as with lacunes, WMH, and CMB, but not with ePVS. Our findings suggest that SVD may induce brain changes via vascular insufficiency, implying that chronic hypoperfusion may increase the

risk for neuronal injury and neurodegeneration. Hence, sCoV of ASL images may be a useful indicator of vascular brain damage.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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