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RESEARCH ARTICLE

Lower cerebral blood flow predicts cognitive decline in patients with vascular cognitive impairment

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Abstract

INTRODUCTION: Chronic cerebral hypoperfusion is one of the assumed pathophysiological mechanisms underlying vascular cognitive impairment (VCI). We investigated the association between baseline cerebral blood flow (CBF) and cognitive decline after 2 years in patients with VCI and reference participants.

METHODS: One hundred eighty-one participants (mean age 66.3 ± 7.4 years, 43.6% women) underwent arterial spin labeling (ASL) magnetic resonance imaging (MRI) and neuropsychological assessment at baseline and at 2-year follow-up. We determined the association between baseline global and lobar CBF and cognitive decline with multivariable regression analysis.

RESULTS: Lower global CBF at baseline was associated with more global cognitive decline in VCI and reference participants. This association was most profound in the domain of attention/psychomotor speed. Lower temporal and frontal CBF at baseline were associated with more cognitive decline in memory.

DISCUSSION: Our study supports the role of hypoperfusion in the pathophysiological and clinical progression of VCI.

KEYWORDS
arterial spin labeling, cerebral blood flow, cerebral perfusion, cognitive function, vascular cognitive impairment

Highlights

- Impaired cerebral blood flow (CBF) at baseline is associated with faster cognitive decline in VCI and normal aging.
- Our results suggest that low CBF precedes and contributes to the development of vascular cognitive impairment.
- CBF determined by ASL might be used as a biomarker to monitor disease progression or treatment responses in VCI.

1 | BACKGROUND

Vascular cognitive impairment (VCI) refers to impairment in at least one cognitive domain, attributable to vascular brain injury. It ranges from mild cognitive impairment to end stage dementia.[1] In recent years, attention has been shifting to even earlier stages, that is, subjective cognitive impairment. This term refers to cognitive complaints without objective cognitive impairment in neuropsychological assessment[2] and is associated with an increased risk for future cognitive decline.[3,4]

Although the exact pathophysiological mechanisms in VCI remain largely unknown, chronic cerebral hypoperfusion is thought to be one of the key factors.[5] Cerebral blood flow (CBF) can be measured quantitatively at the tissue level using arterial spin labeling (ASL) magnetic resonance imaging (MRI), which is a non-invasive imaging technique that uses the contrast effect of magnetically labeled inflowing blood to measure cerebral perfusion.[6] Reduced CBF has repeatedly been demonstrated in patients with VCI compared to healthy controls.[7–10] Furthermore, CBF is negatively related to the severity of white matter hyperintensities (WMHs), an important imaging marker of vascular brain injury,[11] and the existence of a so-called CBF penumbra (ie, lower CBF surrounding WMHs) has previously been demonstrated to be associated with future WMH expansion.[12] WMHs have repeatedly been associated with cognitive deficits, and progression of WMH load is associated with further cognitive decline.[13] Cross-sectional studies investigating the direct association between CBF and cognitive function in patients with VCI have yielded inconsistent results,[14–16] while longitudinal studies are sparse.

Establishing the effects of reduced CBF on early stages of cognitive decline is crucial for the understanding of the causal role of hypoperfusion in the etiology of VCI. In this longitudinal study, we aimed to investigate the association between baseline CBF, measured with ASL imaging, and cognitive decline after 2 years in patients with cognitive complaints and vascular brain injury on MRI (ie, possible VCI), as well as age-matched reference participants.

2 | METHODS

2.1 | Study population

We studied participants of the Heart-Brain Connection (HBC) study, a prospective multicenter observational cohort study. The rationale and methodology have been described elsewhere.[17] In brief, the study focuses on relationships between the hemodynamic status of heart and brain and cognitive impairment. Participants were enrolled between September 2014 and September 2017. Follow-up visits took place between September 2016 and November 2019. For the current study, we included all patients with possible VCI and reference participants with available ASL imaging at baseline and neuropsychological testing at baseline and at 2-year follow-up. Inclusion criteria for both possible VCI and reference participants included age 50 years or older and ability to undergo cognitive testing and other study procedures, including MRI. Possible VCI was defined as cognitive complaints regardless of the severity of cognitive impairment (ie, total spectrum of subjective cognitive decline to mild dementia), combined with moderate to severe vascular brain injury on MRI (defined as WMH Fazekas score >1 and/or [lacunar] infarcts and/or intracerebral [micro-]hemorrhages[18]), or mild vascular brain injury (defined as WMH Fazekas score 1) with the presence of vascular risk factors, and with a Mini-Mental State Examination (MMSE)[19] score of ≥20. Reference participants had no history of VCI. All group-specific inclusion and exclusion criteria have been described in detail elsewhere.[17] Patients with possible VCI were recruited from memory and neurology outpatient clinics. Reference participants were recruited via advertisements and among spouses of patients. Participants were recruited at four sites in the Netherlands: Leiden University Medical Center (LUMC) in Leiden, Maastricht University Medical Center (MUMC) in Maastricht, University Medical Center Utrecht (UMCU) in Utrecht, and VU University Medical Center (VUMC) in Amsterdam. The study was performed according to the Helsinki Declaration and was approved by the medical ethics committee of LUMC. All participants provided written informed consent.

2.2 | Brain MRI acquisition

All brain MRI scans were acquired on Philips Ingenia, Achieva, and Gemini 3T MRI scanners (Philips, Best, the Netherlands). The standardized MRI protocols included three-dimensional (3D) T1-weighted, T2 fluid-attenuated inversion recovery (FLAIR) and susceptibility-weighted imaging (SWI).[17] CBF was measured with pseudo-continuous ASL (pCASL) (multislice two-dimensional echo planar imaging (EPI) acquisition with background suppression; labeling duration = 1800 ms, post-labeling delay = 1800 ms; single-shot EPI readout; pixel size = 3 × 3 mm; slice thickness 7 mm).[20]

2.3 | MRI analysis

For each patient, infarcts and other pathologies that potentially affect automatic tissue segmentation were annotated by a neuroradiologist and manually segmented by trained students. Software by Quantib BV was used to segment WMH on FLAIR scans. The automated Iris pipeline[21] was used for brain tissue segmentation using the 3D T1-weighted images (SPM8; Statistical Parametric Mapping, London, UK). From these segmentations, volumes in milliliters (ml) of total brain gray matter (GM), white matter (WM), cerebrospinal fluid, and WMHs were computed. Subsequently, total brain volume and WMH volume were normalized to the intracranial volume to calculate relative brain volume and relative WMH volume.

pCASL data were processed using the automated Iris pipeline for CBF quantification.[20] Quantification of ASL data into CBF maps was based on a single-compartment model after the subtraction of labeled images from control images according to the recommended approach.[19] To scale the signal intensities of the subtracted ASL images to absolute CBF units, a separately acquired proton density weighted image (M0) was used. The quantification further included motion correction of the raw ASL data[22] and additional partial volume correction (PVC).[23] CBF was quantified in normal-appearing GM (NAGM) only. To obtain the NAGM mask for each participant, the infarct/pathology masks were removed from the GM mask. Subsequently, PVC-uncorrected ASL images of all patients were visually inspected.[20] Participants with suboptimal quality of ASL images (ie, motion artifacts, incomplete ASL sequence, or labeling errors) and participants with ASL images with dominant vascular artifacts and little tissue perfusion signal were excluded. The regions of interest (ROIs) were defined using a multiatlas approach. This involved the registration of 30 manually labeled T1W images, each containing 83 ROIs, to the patients' T1 images. This involved the registration of 30 manually labeled T1W images, each containing 83 ROIs to the patients' T1 images.[24,25] In our analyses, we combined these ROIs to obtain mean CBF values of the frontal, parietal, temporal, and occipital brain lobes.

2.4 | Neuropsychological assessment

We performed a standardized neuropsychological assessment, based on the Dutch Parelsnoer Initiative,[26] at baseline and at two-year follow-up. The neuropsychological assessment has been described in detail elsewhere.[17] Briefly, we used the MMSE[19] for cognitive screening. In addition, we examined four cognitive domains: memory, language, attention and psychomotor speed, and executive functioning. To examine memory, we performed the Visual Association Test (VAT)[27] Part A and the total immediate recall, delayed recall, and recognition of the Rey Auditory Verbal Learning Test (RAVLT).[28,29] To asses language, we used the VAT naming test and 1-min animal fluency.[30] To examine attention and psychomotor speed, we performed the Trail Making Test (TMT) Part A,[31] Stroop Color Word Test (SCWT) card I and II,[32–34] Letter Digit Substitution Test (LDST),[35] and Forward Digit Span.[36] For the assessment of executive functioning we used the index score of TMT part B/part A, the SCWT interference score (card 3/[card 1 + card 2]/2), and Backward Digit span.[36] In participants where the TMT-B was aborted ($n = 6$ at baseline, $n = 10$ at follow-up), TMT-B was estimated by multiplying the time needed to complete TMT-A with the mean B/A index. All neuropsychological test scores were standardized into z-scores using the reference participants as the reference group. Subsequently, z-scores of the individual tests at baseline were subtracted from z-scores of the corresponding individual tests at 2-year follow-up, resulting in a change z-score for each individual test. Cognitive change compound scores were determined by averaging the change z-scores of all tests within one domain. In addition, a score for global cognitive change was constructed by calculating the mean change score across all four cognitive domains. Negative change scores indicate cognitive decline, whereas positive change scores indicate improved cognitive performance.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed regarding the association between cerebral blood flow (CBF) and cognitive impairment in vascular cognitive impairment (VCI). We cite several cross-sectional studies; however, these have generated conflicting results. Longitudinal studies are sparse.
2. **Interpretation**: We found that lower CBF at baseline was associated with faster cognitive decline at 2-year follow-up in VCI patients and controls, supporting the role of hypoperfusion in the pathophysiological and clinical progression of VCI. However, effect sizes were quite small, suggesting other factors probably also play a role in the development of cognitive impairment.
3. **Future directions**: Future longitudinal studies should investigate multiple assumed pathophysiological mechanisms underlying VCI (eg, hypoperfusion, blood-brain barrier leakage, inflammation) simultaneously to unravel the sequence and relative importance of events.

2.5 | General and health characteristics

History of previous stroke and transient ischemic attack (TIA) and the presence of cardiovascular risk factors (ie, hypertension, hypercholesterolemia, and diabetes mellitus) were obtained from self-reported medical history and medication use. Smoking status was defined as never, former, or current. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Level of education was classified according to the system of Verhage.[37]

2.6 | Statistical analyses

Characteristics of the study population were presented as mean ± standard deviation (SD), as median [interquartile range], or as number of participants (percentages). Independent sample *t* tests and Pearson X^2 were performed to compare groups when appropriate. Paired sample *t* tests were used to compare raw neuropsychological test scores at baseline and at follow-up.

To examine the associations between CBF at baseline and cognitive decline, we used multivariable linear regression analysis, with the compound change scores of the different cognitive domains as dependent variable and CBF as independent variable (separate models for each cognitive domain). We corrected for age, sex, educational level, participant group, study center, baseline relative WMH volume, and baseline brain atrophy (relative brain volume). Analyses were performed in the pooled sample of possible VCI and reference participants. Effect modification by participant group (possible VCI or reference participant) was assessed by including interaction terms (participant group × CBF) in the analyses. Extreme values visualized on scatterplots were checked for validity, and measures for influential outliers (eg, Cook's distance, studentized residuals) were evaluated. Furthermore, to study results robustness (ie, to verify that results were not solely influenced by few participants with extreme values), bootstrapping was performed. A thousand bootstrap samples were drawn with replacement from the original sample, and the standardized point estimates with 95% percentile confidence interval and corresponding *p* value were extracted.[38] Given that the possible VCI group was composed of both patients with subjective cognitive impairment (cognitive complaints but without formal cognitive impairment), as well as patients with formal cognitive impairment, subgroup analysis was performed in patients with possible VCI.

As a secondary analysis, we repeated linear regression analysis with regional CBF (CBF in the frontal, parietal, temporal, and occipital lobes) as the independent variable to investigate whether the association between CBF and cognitive decline was determined by global or regional hypoperfusion. All analyses were performed with SPSS software (version 28.0; IBM, Chicago, IL, USA). A *p* value <0.05 was considered statistically significant. To account for multiple testing, a false discovery rate of 10% was applied.[39]

3 | RESULTS

3.1 | Characteristics of study population

At baseline, 295 participants were included, of whom 166 were patients with possible VCI and 129 were reference participants. Baseline ASL scans were not acquired in 15 participants and not suitable for analysis in 18 participants. An additional 14 participants were excluded due to suboptimal quality of ASL scans or dominant vascular artifacts with little tissue perfusion. During follow-up, nine participants died and 59 participants were no longer willing or unable to participate (30.8% and 23.3% drop-out during follow-up in the VCI group and the reference group, respectively). This resulted in a study population of 181 participants, which included 92 patients with possible VCI and 89 reference participants who completed the follow-up neuropsychological assessment after a mean follow-up of 25.3 ± 2.1 months and were included in this analysis (Figure S1). Compared with participants included in the analysis, excluded participants were older (mean age 69.6 vs 66.3 years, $p < .001$), scored lower on the MMSE at baseline (mean score 27.5 vs 28.3, *p* .007), and had higher baseline WMH volume (median WMH volume 8.4 vs 1.6 ml, $p < .001$); Table S1 in the supplementary information.

Table 1 presents detailed characteristics of the study population, in total and per participant group. Compared with the reference group, patients with possible VCI more often had cardiovascular risk factors and more often had a history of TIA or stroke. Furthermore, patients with possible VCI had a lower score on the MMSE at baseline, higher relative WMH volume, lower relative brain volume, and lower CBF than reference participants. Mean cognitive test scores on all individual tests and domain scores at baseline and follow-up are presented in Table S2. Based on neuropsychological assessment at baseline, 64.1% of patients with possible VCI had subjective cognitive impairment (cognitive complaints but without formal cognitive impairment), 19.6% had minor cognitive impairment (one cognitive domain impaired), and 16.3% had major cognitive impairment (two or more cognitive domains impaired).

3.2 | Global CBF and cognitive decline

Table 2 presents the adjusted associations between global CBF and cognitive decline (unadjusted results can be found in Table S3, scatterplots can be found in Figure S2). After correction for age, sex, educational level, participant group, study center, baseline relative WMH volume, and baseline relative brain volume, a lower CBF at baseline was associated with more global cognitive decline (standardized beta [St-β] 0.172 [95% confidence interval (CI) 0.019–0.344], $p = .026$). This association was most profound in the domain of attention/psychomotor speed (St-β 0.227 [95% CI 0.071–0.397], $p = .004$). These results remained significant after correction for multiple testing. We found no associations between whole-brain CBF and cognitive decline in the other cognitive domains. After adjusting for

TABLE 1 Characteristics of study population.

Characteristic	Total (*N* = 181)	VCI (*N* = 92)	Reference participants (*N* = 89)	*p* value
General characteristics				
Age [years]	66.3 ± 7.4	67.0 ± 7.9	65.5 ± 6.9	.184
Sex [*n*, (% women)]	79 (43.6)	37 (40.2)	42 (47.2)	.344
BMI [kg/m^2]	26.5 ± 3.7	26.5 ± 3.8	26.5 ± 3.6	.943
Diabetes mellitus [*n*, (%)]	14 (7.7)	12 (13.0)	2 (2.2)	.010
Hypertension [*n*, (%)]	85 (47.0)	65 (70.7)	20 (22.5)	<.001
Hypercholesterolemia [*n*, (%)]	95 (52.5)	73 (79.3)	22 (24.7)	<.001
Smoking, never/former/current (*n* [%])	60/97/24 (33.1/53.6/13.3)	20/55/17 (21.7/59.8/18.5)	40/42/7 (44.9/47.2/7.9)	.002
History of stroke (*n* [%])	38 (21.0)	38 (41.3)	0 (0)	<.001
History of TIA (*n* [%])	26 (14.4)	23 (25.0)	3 (3.4)	<.001
Education, score	5.3 ± 1.2	5.2 ± 1.3	5.4 ± 1.1	.335
Baseline MMSE	28.3 ± 1.8	27.8 ± 1.2	28.8 ± 1.2	<.001
Brain MRI				
WMH volume (ml)	1.63 [6.38]	5.47 [14.30]	0.43 [1.54]	<.001
Relative WMH volume (% of ICV)	0.11 [0.44]	0.39 [1.08]	0.03 [0.11]	<.001
Brain volume (ml)	1061.3 ± 108.0	1045.7 ± 115.9	1077.5 ± 97.3	.048
Relative brain volume (% of ICV)	75.9 ± 4.7	74.7 ± 5.0	77.1 ± 3.9	<.001
Global CBF[a] (ml/100 g/min)	53.9 ± 11.0	51.7 ± 10.6	56.2 ± 11.0	.006
Frontal lobe CBF[a] (ml/100 g/min)	55.9 ± 10.6	54.1 ± 10.5	57.7 ± 10.5	.020
Temporal lobe CBF[a] [ml/100 g/min]	50.1 ± 10.7	48.0 ± 9.5	52.2 ± 11.5	.008
Parietal lobe CBF[a] (ml/100 g/min)	54.8 ± 11.1	53.2 ± 11.0	56.4 ± 11.1	.055
Occipital lobe CBF[a] (ml/100 g/min)	54.9 ± 12.0	53.5 ± 12.3	56.3 ± 11.5	.124
Cognitive functioning				
Global cognitive functioning change score[b]	0.005 ± 0.602	−0.051 ± 0.815	0.063 ± 0.219	<.001
Memory change score[b]	0.186 ± 1.081	0.125 ± 1.404	0.249 ± 0.587	.001
Attention/psychomotor speed change score[b]	−0.052 ± 0.798	−0.151 ± 1.068	0.050 ± 0.318	<.001
Language change score[b]	−0.112 ± 0.953	−0.172 ± 1.281	−0.050 ± 0.392	.004
Executive functioning change score[b]	−0.001 ± 0.597	−0.007 ± 0.689	0.005 ± 0.489	.056

Note: Data are presented as means ± standard deviation, or median (interquartile range) or number of participants (percentages).
Abbreviations: BMI, body mass index; CBF, cerebral blood flow; ICV, intracranial volume; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack; VCI, vascular cognitive impairment; WMH, white matter hyperintensity.
[a]CBF values represent partial volume corrected CBF values.
[b]Cognitive functioning change scores indicate change z-scores, negative change scores indicate cognitive decline, whereas positive change scores indicate improved cognitive performance.

multiple testing, we found no significant interaction between global CBF and participant group (results not shown). The standardized point estimates, 95% percentile CIs, and *p* values that resulted from the bootstrap procedure are presented in Table S4. Results remained similar after bootstrapping.

The results of subgroup analysis in the possible VCI group can be found in Table S5. Effect sizes of the association between baseline CBF and cognitive decline were greater in patients with formal cognitive impairment in comparison with patients with only subjective cognitive impairment. In neither of the subgroups did the association reach statistical significance; however, analyses were performed in small sample sizes (*N* = 59 participants with subjective cognitive impairment, and *N* = 33 participants with formal cognitive impairment).

3.3 | Regional CBF and cognitive decline

Adjusted associations between regional CBF (in the frontal, parietal, temporal, and occipital lobes) and cognitive decline are shown in Table 3 (unadjusted results can be found in Table S6). A lower

TABLE 2 Associations between global cerebral blood flow and cognitive change.

Cognitive domain	Adjusted[a] St-β (95% CI)	*p* value
Global cognitive function	0.172 (0.019 to 0.344)	.026[b]
Memory	0.158 (0.000 to 0.326)	.054
Attention/psychomotor speed	0.227 (0.071 to 0.397)	.004[b]
Language	0.039 (−0.130 to 0.221)	.619
Executive functioning	0.043 (−0.151 to 0.237)	.611

Note: St-β values represent standardized regression coefficients. Negative cognitive change scores indicate cognitive decline (change z-scores were calculated by subtracting z-scores at baseline from z-scores at follow-up).
Abbreviation: CI, confidence interval.
[a]Adjusted for age, sex, educational level, participant group, study center, baseline relative WMH volume, and baseline relative brain volume.
[b]Remained significant after testing for multiple comparisons.

TABLE 3 Associations between regional brain cerebral blood flow and cognitive change.

Cognitive domain	Region	Adjusted St-β[a] (95% CI)	*p* value
Global cognitive function	Frontal	0.164 (0.018 to 0.310)	.026[b]
	Parietal	0.162 (0.018 to 0.306)	.032[b]
	Temporal	0.210 (0.053 to 0.350)	.006[b]
	Occipital	0.172 (0.019 to 0.306)	.029[b]
Memory	Frontal	0.183 (0.029 to 0.327)	.018[b]
	Parietal	0.156 (0.000 to 0.312)	.050
	Temporal	0.200 (0.040 to 0.360)	.014[b]
	Occipital	0.110 (−0.055 to 0.275)	.187
Attention/ pyschomotor speed	Frontal	0.200 (0.053 to 0.347)	.008[b]
	Parietal	0.189 (0.041 to 0.324)	.015[b]
	Temporal	0.254 (0.107 to 0.401)	.001[b]
	Occipital	0.167 (0.015 to 0.334)	.040[b]
Language	Frontal	0.009 (−0.117 to 0.126)	.906
	Parietal	0.043 (−0.097 to 0.183)	.574
	Temporal	0.035 (−0.128 to 0.198)	.654
	Occipital	0.116 (−0.039 to 0.284)	.147
Executive functioning	Frontal	0.049 (−0.098 to 0.196)	.546
	Parietal	0.046 (−0.138 to 0.253)	.555
	Temporal	0.088 (−0.070 to 0.246)	.300
	Occipital	0.088 (−0.088 to 0.286)	.310

Note: β values represent standardized regression coefficients. Negative cognitive change scores indicate cognitive decline (change z-scores were calculated by subtracting z-scores at baseline from z-scores at follow-up).
Abbreviation: CI, confidence interval.
[a]Adjusted for age, sex, educational level, participant group, study center, baseline relative WMH volume, and baseline relative brain volume.
[b]Remained significant after testing for multiple comparisons.

CBF in all brain regions was associated with more global cognitive decline and more cognitive decline in attention/psychomotor speed. Additionally, lower temporal and frontal CBF were associated with more cognitive decline in the memory domain. After adjusting for multiple testing, we found no significant interaction between regional CBF and participant group (results not shown). The standardized point estimates, 95% CIs, and *p* values that resulted from the bootstrap procedure are presented in Table S7. Results remained similar after bootstrapping.

4 | DISCUSSION

This study demonstrates that lower baseline global CBF, determined by ASL, was associated with more global cognitive decline in patients with possible VCI and reference participants. This association was most profound in the domain of attention/psychomotor speed. Additionally, regional CBF in the temporal and frontal lobes were particularly associated with cognitive decline in memory.

Longitudinal studies on the association between CBF and cognitive decline in patients with VCI and healthy aging are sparse. One study, which included patients with mild cognitive impairment independent of underlying pathology (VCI or neurodegenerative disease), showed that patients who clinically converted to dementia after two years had lower baseline CBF.[40] In patients with stroke, baseline CBF could also predict the development of dementia.[16] Another study showed an association between baseline CBF and change in MMSE score after three years in hypertensive patients with cerebral small vessel disease.[41] Our results, revealing an association between lower baseline CBF and more cognitive decline after two years in patients with possible VCI and reference participants, are in line with these previous findings. However, a study in community-dwelling elderly did not find an association between CBF and cognitive decline at six- to eight-year follow-up.[42] Differences in the composition of the study population, the use of a more extensive cognitive test battery (which is more sensitive for the detection of cognitive decline), and differences in the analysis of ASL scans could explain why we found an association between baseline CBF and cognitive decline, whereas the previous study did not.

As a secondary aim, we investigated whether the association between CBF and cognitive decline was determined by global or regional hypoperfusion. We demonstrated that both global cognitive decline and cognitive decline in attention/psychomotor speed were determined by global cerebral hypoperfusion. This is in line with previous studies showing that CBF reduction in patients with VCI was widespread, in contrast to CBF reduction patterns in patients with Alzheimer's disease (AD), in which selective CBF reductions were found in specific brains areas.[7] However, we also found an association between temporal and frontal, but not global, CBF and cognitive decline in memory. This suggests that cognitive decline in memory is dependent specifically on regional temporal and frontal CBF, which is not surprising considering the important role of the medial temporal lobe and frontal lobe in memory.[43,44] This is also in line with previous studies reporting that hippocampal perfusion correlates with memory performance in mild cognitive impairment[45,46] and that CBF in the left inferior frontal gyrus correlates with memory function in patients with subjective cognitive impairment.[47] Nonetheless, this a

noticeable finding since previous studies suggested that global, rather than regional, CBF reductions were most important for cognitive decline in VCI.[7,16,41] However, most prior studies did not determine CBF in multiple brain regions or did not assess multiple cognitive domains, which could have prevented the uncovering of an association between regional CBF and cognitive decline in specific cognitive domains. Future studies in VCI should therefore include assessment of CBF in multiple brain regions, as well as assessment of multiple cognitive domains.

It remains a matter of debate whether cerebral hypoperfusion precedes structural vascular brain damage and contributes to cognitive decline or whether hypoperfusion reflects a diminished metabolic demand by damaged tissue. Our observation that lower baseline CBF is associated with cognitive decline over two years suggests that low CBF precedes and contributes to the development of VCI. This is also supported by other studies showing that changes in CBF occur prior to clinical symptoms[48] and studies that have revealed increased oxygen extraction from the blood within WMH.[49,50] However, in subgroup analysis, we found bigger effect sizes in patients with formal cognitive impairment compared with patients with subjective cognitive impairment, who are at an earlier disease stage. Nonetheless, a possible explanation for this finding could be that patients who already had formal cognitive impairment at baseline were more prone to actually undergo further cognitive decline within the short follow-up period of two years. Although we did find an association between baseline CBF and cognitive decline, the observed effect sizes are quite small. This suggests that other factors probably also play an important role in the development of cognitive impairment. Possible other drivers for cognitive impairment in these patients are, for example, blood-brain barrier dysfunction[51] or co-occurrence of AD pathology.[52] The limited changes in cognitive scores over two years' time in the study population could also have contributed to small effect sizes.

Although we demonstrated an association between baseline CBF and cognitive decline in this study, we did not find a cross-sectional association between CBF and cognitive functioning within the HBC study.[15] This difference might imply that CBF and cognitive function are associated in a time-related manner. If cerebral hypoperfusion indeed plays a role in the early pathophysiological stages of VCI, then reduced CBF precedes the loss of brain tissue integrity, which accumulates and then eventually leads to a worsening of cognitive function at later stages.

In this study, we assessed CBF using ASL MRI. Its advantages include its ability to assess CBF quantitatively, its non-invasive and patient-friendly nature as there is no need for contrast agent or radioactive tracers, and its concomitant integration with structural brain scans. However, certain limitations need to be acknowledged. First, we used a delay time of 1.8 s, which reflects the timing of the first acquired slice, whereas each subsequent slice was acquired with an increase in delay of 35 ms. Although this is in line with recommendations of the consensus paper on ASL,[20] it can still result in an underestimation of CBF due to a possible delayed transit time, especially in patients with possible VCI, who had a high prevalence of cardiovascular risk factors. Although participants with clearly prolonged transit time based on visual inspection were excluded, this might have led to an underestimation of the observed associations and a lower sensitivity to detect associations. Future studies could perform multiple post-labeling delay ASL to overcome this issue.[48] Second, CBF was only quantified in GM, as the signal of ASL is particularly low and noisy in WM due to the longer transit time and lower perfusion compared to GM.[53] However, in VCI, blood flow may be affected in both GM and WM,[54] with a tendency toward extensive CBF changes in the NAWM in the proximity of WMHs.[55] Furthermore, we measured CBF in resting state, whereas previous studies suggested that CBF in resting state could still be preserved or compensated in early stages of disease.[56] These aspects might also have led to lower sensitivity and underestimation of observed associations.

A few other limitations of the study must be considered. First, we cannot exclude selection bias, as excluded participants due to missing baseline ASL or follow-up neuropsychological assessment were older and had lower baseline MMSE scores and higher baseline WMH volumes compared to our study population. However, the smaller sample size at follow-up with less severely diseased patients most likely resulted in an underestimation of the found associations. Second, sampling bias cannot be excluded, as in the reference group we included spouses of patients, but on average only 20% in all centers. Third, patients with VCI were not included based on established VCI criteria,[57] as we also included patients who had subjective cognitive complaints without objective cognitive impairment. However, patients with cognitive decline as a result of vascular brain injury may not always develop cognitive deficits that are severe enough to be classified as mild cognitive impairment. No strict method exists for separating people with these subtler cognitive changes from people who complain but actually have no change in cognitive performance at all. Additionally, the severity of cognitive impairment does not always correspond to vascular brain damage burden. Moreover, patients with subjective cognitive complaints have a higher risk of future cognitive decline,[3,4] and interest in research on VCI is shifting toward earlier stages with subjective cognitive impairment. Fourth, because AD-specific markers (eg, amyloid and tau status) were not assessed, it is not clear whether neurodegenerative pathology, besides vascular pathology, contributed to cognitive decline in the study population. Fifth, the results of this study might not be broadly generalizable to other races as the majority of our study population was Caucasian. Finally, the follow-up period for cognitive assessment was relatively short, especially since we mainly included patients with early-stage VCI. For the majority of participants this resulted in only limited cognitive decline or stable cognitive function, and some patients even performed better on cognitive tests at follow-up. Nevertheless, we were still able to demonstrate associations between baseline CBF and cognitive decline. Despite these limitations, the strengths of our study include its longitudinal design, the large cohort of patients with possible VCI and reference participants, the use of contrast-agent-free state-of-the-art imaging, and the use of an extensive standardized neuropsychological test battery enabling us to examine four different cognitive domains.

5 | CONCLUSION

In conclusion, this longitudinal study showed that lower CBF at baseline was associated with cognitive decline in VCI and normal aging, independent of age, sex, educational level, WMH volume, and brain atrophy. Whereas decline in attention/psychomotor speed and global cognitive decline were associated with global hypoperfusion, decline in memory was especially associated with lower perfusion in the temporal and frontal lobes. Our findings provide more insight into the role of hypoperfusion in the pathophysiology and progression of VCI. More research investigating the complex interplay between different pathophysiological processes, including hypoperfusion, that play a role in cognitive decline in VCI is needed to unravel the exact sequence and relative importance of events. This is essential for the identification of new therapeutic targets and early recognition of patients with an increased risk for cognitive decline. CBF determined by ASL might be used as a biomarker to monitor disease progression or treatment responses in VCI in the future.

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CONFLICT OF INTEREST STATEMENT

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided written informed consent.

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REFERENCES

1. Dichgans M, Leys D. Vascular cognitive impairment. *Circ Res*. 2017;120:573-591.
2. Benedictus MR, van Harten AC, Leeuwis AE, et al. White matter hyperintensities relate to clinical progression in subjective cognitive decline. *Stroke*. 2015;46:2661-2664.
3. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol*. 2020;19:271-278.
4. Pitti H, Diaz-Galvan P, Barroso J, et al. Cerebrovascular damage in subjective cognitive decline: a systematic review and meta-analysis. *Ageing Res Rev*. 2022;82:101757.
5. Yata K, Tomimoto H. Chronic cerebral hypoperfusion and dementia. *Neurol Clin Neurosci*. 2014;2:129-134.
6. Haller S, Zaharchuk G, Thomas DL, Lovblad KO, Barkhof F, Golay X. Arterial spin labeling perfusion of the brain: emerging clinical applications. *Radiology*. 2016;281:337-356.
7. Mokhber N, Shariatzadeh A, Avan A, et al. Cerebral blood flow changes during aging process and in cognitive disorders: a review. *Neuroradiol J*. 2021;34:300-307.
8. Kato H, Yoshikawa T, Oku N, et al. Statistical parametric analysis of cerebral blood flow in vascular dementia with small-vessel disease using Tc-HMPAO SPECT. *Cerebrovasc Dis*. 2008;26:556-562.
9. Schuff N, Matsumoto S, Kmiecik J, et al. Cerebral blood flow in ischemic vascular dementia and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance imaging. *Alzheimers Dement*. 2009;5:454-462.
10. Shim YS, Yang DW, Kim BS, Shon YM, Chung YA. Comparison of regional cerebral blood flow in two subsets of subcortical ischemic vascular dementia: statistical parametric mapping analysis of SPECT. *J Neurol Sci*. 2006;250:85-91.
11. Shi Y, Thrippleton MJ, Makin SD, et al. Cerebral blood flow in small vessel disease: a systematic review and meta-analysis. *J Cereb Blood Flow Metab*. 2016;36:1653-1667.
12. Promjunyakul N, Lahna D, Kaye JA, et al. Characterizing the white matter hyperintensity penumbra with cerebral blood flow measures. *Neuroimage Clin*. 2015;8:224-229.
13. Grau-Olivares M, Arboix A. Mild cognitive impairment in stroke patients with ischemic cerebral small-vessel disease: a forerunner of vascular dementia? *Expert Rev Neurother*. 2009;9:1201-1217.
14. Sun Y, Cao W, Ding W, et al. Cerebral blood flow alterations as assessed by 3D ASL in cognitive impairment in patients with subcortical vascular cognitive impairment: a marker for disease severity. *Front Aging Neurosci*. 2016;8:211.
15. Leeuwis AE, Hooghiemstra AM, Bron EE, et al. Cerebral blood flow and cognitive functioning in patients with disorders along the heart-brain axis: cerebral blood flow and the heart-brain axis. *Alzheimers Dement*. 2020;6:e12034.
16. Firbank MJ, He J, Blamire AM, et al. Cerebral blood flow by arterial spin labeling in poststroke dementia. *Neurology*. 2011;76:1478-1484.
17. Hooghiemstra AM, Bertens AS, Leeuwis AE, et al. The missing link in the pathophysiology of vascular cognitive impairment: design of the heart-brain study. *Cerebrovasc Dis Extra*. 2017;7:140-152.
18. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822-838.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
20. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med*. 2015;73:102-116.
21. Bron EE, Steketee RM, Houston GC, et al. Diagnostic classification of arterial spin labeling and structural MRI in presenile early stage dementia. *Hum Brain Mapp*. 2014;35:4916-4931.
22. Huizinga W, Poot DH, Guyader JM, et al. PCA-based groupwise image registration for quantitative MRI. *Med Image Anal*. 2016;29:65-78.
23. Asllani I, Borogovac A, Brown TR. Regression algorithm correcting for partial volume effects in arterial spin labeling MRI. *Magn Reson Med*. 2008;60:1362-1371.
24. Hammers A, Allom R, Koepp MJ, et al. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Hum Brain Mapp*. 2003;19:224-247.
25. Gousias IS, Rueckert D, Heckemann RA, et al. Automatic segmentation of brain MRIs of 2-year-olds into 83 regions of interest. *Neuroimage*. 2008;40:672-684.

26. Aalten P, Ramakers IH, Biessels GJ, et al. The Dutch Parelsnoer Institute–Neurodegenerative diseases; methods, design and baseline results. *BMC Neurol*. 2014;14:254.
27. Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry*. 2002;73:126-133.
28. Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc*. 2005;11:290-302.
29. Rey A. *L'examen Clinique En Psychologie*. Presses universitaires de France; 1958.
30. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the animal, profession and letter M naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc*. 2006;12:80-89.
31. Reitan RM. The relation of the trail making test to organic brain damage. *J Consult Psychol*. 1955;19:393-394.
32. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment*. 2006;13:62-79.
33. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643-662.
34. Hammes J. *De Stroop Kleur-Woord Test: Handleiding*. Swets & Zeitlinger; 1971.
35. van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24-81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. *J Clin Exp Neuropsychol*. 2006;28:998-1009.
36. Wechsler D. *Wechsler Memory Scale - 3rd edition: Administration and Scoring Manual*. The Psychological Corporation; 1997.
37. Verhage F. *Intelligentie en Leeftijd; Onderzoek Bij Nederlanders van Twaalf Tot Zevenenzeventig Jaar*. Van Gorcum; 1964.
38. Cheung SF, Pesigan IJA, Vong WN. DIY bootstrapping: getting the nonparametric bootstrap confidence interval in SPSS for any statistics or function of statistics (when this bootstrapping is appropriate). *Behav Res Methods*. 2023;55:474-490.
39. Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I. Controlling the false discovery rate in behavior genetics research. *Behav Brain Res*. 2011;125:279-284.
40. Edman A, Edenbrandt L, Fredén-Lindqvist J, Nilsson M, Wallin A. Asymmetric cerebral blood flow in patients with mild cognitive impairment: possible relationship to further cognitive deterioration. *Dement Geriatr Cogn Dis Extra*. 2011;1:228-236.
41. Kitagawa K, Oku N, Kimura Y, et al. Relationship between cerebral blood flow and later cognitive decline in hypertensive patients with cerebral small vessel disease. *Hypertension Res*. 2009;32:816-820.
42. Abdulrahman H, Hafdi M, Mutsaerts H, et al. Cerebral perfusion and the risk of cognitive decline and dementia in community dwelling older people. *Cereb Circ Cogn Behav*. 2022;3:100125.
43. Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. *Annu Rev Neurosci*. 2007;30:123-152.
44. Fletcher PC, Henson RN. Frontal lobes and human memory: insights from functional neuroimaging. *Brain*. 2001;124:849-881.
45. Bangen KJ, Restom K, Liu TT, et al. Assessment of Alzheimer's disease risk with functional magnetic resonance imaging: an arterial spin labeling study. *J Alzheimers Dis*. 2012;31(suppl 3):S59-S74.
46. Westerberg C, Mayes A, Florczak SM, et al. Distinct medial temporal contributions to different forms of recognition in amnestic mild cognitive impairment and Alzheimer's disease. *Neuropsychologia*. 2013;51:2450-2461.
47. Niwa F, Kondo M, Sakurada K, Nakagawa M, Imanishi J, Mizuno T. Regional cerebral blood flow in [123]I-IMP single-photon emission computed tomography and the wechsler memory scale-revised in nondemented elderly subjects with subjective cognitive impairment. *Intern Med*. 2016;55:3571-3578.
48. Huang D, Guo Y, Guan X, et al. Recent advances in arterial spin labeling perfusion MRI in patients with vascular cognitive impairment. *J Cereb Blood Flow Metab*. 2023;43(2):173-184.
49. Yao H, Sadoshima S, Ibayashi S, Kuwabara Y, Ichiya Y, Fujishima M. Leukoaraiosis and dementia in hypertensive patients. *Stroke*. 1992;23:1673-1677.
50. Yamauchi H, Fukuyama H, Yamaguchi S, Miyoshi T, Kimura J, Konishi J. High-intensity area in the deep white matter indicating hemodynamic compromise in internal carotid artery occlusive disorders. *Arch Neurol*. 1991;48:1067-1071.
51. Kerkhofs D, Wong SM, Zhang E, et al. Blood-brain barrier leakage at baseline and cognitive decline in cerebral small vessel disease: a 2-year follow-up study. *Geroscience*. 2021;43:1643-1652.
52. Chui HC, Ramirez-Gomez L. Clinical and imaging features of mixed Alzheimer and vascular pathologies. *Alzheimers Res Ther*. 2015;7:21.
53. van Osch MJ, Teeuwisse WM, van Walderveen MA, Hendrikse J, Kies DA, van Buchem MA. Can arterial spin labeling detect white matter perfusion signal? *Magn Reson Med*. 2009;62:165-173.
54. Tohgi H, Yonezawa H, Takahashi S, et al. Cerebral blood flow and oxygen metabolism in senile dementia of Alzheimer's type and vascular dementia with deep white matter changes. *Neuroradiology*. 1998;40:131-137.
55. Wong SM, Jansen JFA, Zhang CE, et al. Blood-brain barrier impairment and hypoperfusion are linked in cerebral small vessel disease. *Neurology*. 2019;92:e1669-e1677.
56. Ostergaard L, Engedal TS, Moreton F, et al. Cerebral small vessel disease: capillary pathways to stroke and cognitive decline. *J Cereb Blood Flow Metab*. 2016;36:302-325.
57. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord*. 2014;28:206-218.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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