Lower cardiac index levels relate to lower cerebral blood flow in older adults

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ABSTRACT

Objective: To assess cross-sectionally whether lower cardiac index relates to lower resting cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) among older adults.

Methods: Vanderbilt Memory & Aging Project participants free of stroke, dementia, and heart failure were studied ($n = 314$, age 73 ± 7 years, 59% male, 39% with mild cognitive impairment). Cardiac index (liters per minute per meter squared) was quantified from echocardiography. Resting CBF (milliliters per 100 grams per minute) and hypercapnia-induced CVR were quantified from pseudo-continuous arterial spin-labeling MRI. Linear regressions with ordinary least-square estimates related cardiac index to regional CBF, with adjustment for age, education, race/ethnicity, Framingham Stroke Risk Profile score (systolic blood pressure, antihypertensive medication use, diabetes mellitus, current cigarette smoking, left ventricular hypertrophy, prevalent cardiovascular disease [CVD], atrial fibrillation), APOE $\epsilon 4$ status, cognitive diagnosis, and regional tissue volume.

Results: Lower cardiac index corresponded to lower resting CBF in the left ($\beta = 2.4$, $p = 0.001$) and right ($\beta = 2.5$, $p = 0.001$) temporal lobes. Results were similar when participants with prevalent CVD and atrial fibrillation were excluded (left temporal lobe $\beta = 2.3$, $p = 0.003$; right temporal lobe $\beta = 2.5$, $p = 0.003$). Cardiac index was unrelated to CBF in other regions assessed ($p > 0.25$) and CVR in all regions ($p > 0.05$). In secondary cardiac index $\times$ cognitive diagnosis interaction models, cardiac index and CBF associations were present only in cognitively normal participants and affected a majority of regions assessed with effects strongest in the left ($p < 0.0001$) and right ($p < 0.0001$) temporal lobes.

Conclusions: Among older adults without stroke, dementia, or heart failure, systemic blood flow correlates with cerebral CBF in the temporal lobe, independently of prevalent CVD, but not CVR. *Neurology*® 2017;89:2327-2334

GLOSSARY

CBF = cerebral blood flow; **CI** = confidence interval; **CVD** = cardiovascular disease; **CVR** = cerebrovascular reactivity; **FSRP** = Framingham Stroke Risk Profile; **MCI** = mild cognitive impairment; **NC** = normal cognition; **pCASL** = pseudo-continuous arterial spin labeling; **ROI** = region of interest.

Given metabolic demands, the brain disproportionately receives 12% of cardiac output despite accounting for 2% of total body weight.¹ Among older adults, subclinical cardiac output reductions are linked to poorer cognitive performance,² smaller brain volume,³ white matter hyperintensities,⁴ and incident dementia, including Alzheimer disease.⁵ Mechanisms underlying these associations remain elusive. One possible pathway is that subclinical reductions in cardiac output disrupt cerebral blood flow (CBF) homeostasis.

In animal models, cardiac output reductions correspond to lower CBF,⁶ especially when cerebrovascular injury is present.⁷ Vascular risk factor and cardiovascular disease (CVD) prevalence increases with age,⁸ corresponding to compromises in cerebral circulation control mechanisms.⁹ Lower cardiac output coupled with an aging vasculature may affect static CBF

Supplemental data
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autoregulation in older adults by reducing the ability of distal microvasculature to increase cerebral blood volume to maintain CBF in the presence of cerebral perfusion pressure reductions.¹⁰

Among older adults without clinical dementia, stroke, or heart failure, we assess whether cardiac index (cardiac output/body surface area) relates to resting CBF or hypercapnia-induced cerebrovascular reactivity (CVR). By capturing resting CBF in sequence with CVR, we simultaneously evaluate multiple CBF autoregulatory processes. On the basis of prior work,^{2,3,5} we hypothesize that lower cardiac index will correspond to reduced CBF and reactivity throughout the brain.

METHODS Study cohort. The Vanderbilt Memory & Aging Project is a longitudinal study investigating vascular health and brain aging, enriched for mild cognitive impairment (MCI).¹¹ Inclusion required that participants be ≥ 60 years of age, speak English, have adequate auditory and visual acuity, and have a reliable study partner. At eligibility, participants underwent medical history and record review, clinical interview (including functional questionnaire and Clinical Dementia Rating¹² with the informant), and neuropsychological assessment. Participants were

excluded for a cognitive diagnosis other than normal cognition (NC), early MCI,¹³ or MCI¹¹; MRI contraindication; history of neurologic disease (e.g., stroke); heart failure; major psychiatric illness; head injury with loss of consciousness > 5 minutes; and systemic or terminal illness affecting follow-up examination participation. At enrollment, participants completed a comprehensive evaluation, including (but not limited to) fasting blood draw, physical examination, clinical interview, medication review, neuropsychological assessment, echocardiogram, and multimodal brain MRI. Participants were excluded from the current study for missing covariate or brain MRI data (figure 1).

Standard protocol approvals, registrations, and participant consents. The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Written informed consent was obtained before data collection.

Echocardiogram. Standard 2-dimensional, M-mode, and Doppler transthoracic echocardiography was performed by a single research sonographer at the Vanderbilt University Medical Center Clinical Research Center on a Philips IE33 cardiac ultrasound machine (Philips Medical, Andover, MD). Digital images with measurements were confirmed by board-certified cardiologists (D.K.G., L.A.M.) blinded to clinical information using commercially available software (HeartLab; AGFA Healthcare, Greenville, SC).

Image acquisition and quantification were performed according to American Society of Echocardiography guidelines.¹⁴ Left ventricular volume was calculated by the biplane Simpson method. Stroke volume was calculated from the left ventricular outflow tract velocity-time integral and diameter. Cardiac output was calculated as stroke volume times heart rate. Final measurements were from a single cardiac cycle for participants in normal sinus rhythm or the average of 3 cardiac cycles for participants in atrial fibrillation. Cardiac output was indexed to body surface area (cardiac index in liters per minute per meter squared).

Brain MRI. Participants were scanned at the Vanderbilt University Institute of Imaging Science on a 3T Philips Achieva system (Best, the Netherlands) using 8-channel SENSE reception. T1-weighted magnetization-prepared rapid gradient echo (isotropic spatial resolution = 1 mm) images were postprocessed with an established Multi-Atlas Segmentation pipeline¹⁵ with parcellation of 10 regions of interest (ROIs), including right and left hemispheres, right and left frontal lobes, right and left temporal lobes, right and left parietal lobes, and right and left occipital lobes.

Pseudo-continuous arterial spin labeling (pCASL; postlabeling delay 1.525 seconds, spatial resolution $3 \times 3 \times 7$ mm, repetition time/echo time 4,000/13 milliseconds) assessed CBF (mL blood/100 g tissue/min) with a reproducible protocol.^{16,17} Data were corrected for motion and baseline drift with the Functional MRI of the Brain Linear Image Registration Tool. Additional postprocessing was completed with MATLAB (MathWorks, Inc, Natick, MA). Whole-brain CBF maps were generated with a sliding window approach. Images were slice-time corrected and converted to absolute CBF units following recommended guidelines.¹⁸ The separately acquired M_0 image (same geometry but with repetition time 20 seconds) was coregistered to the structural T1-weighted map and fitted to a standard Montreal Neurologic Institute template.¹⁹ Transformation matrices were applied to the CBF maps. Region-specific mean resting CBF values were calculated for gray matter ROIs described above.

The pCASL acquisition was repeated with identical parameters during a hypercapnic stimulus to evaluate CVR. A custom nonbreathing face mask delivered 5% CO_2 and 95% medical-grade room air (hypercapnic normoxia). End-tidal CO_2

Figure 1 Study inclusion and exclusion details

Missing data categories are mutually exclusive. Missing covariate data include 1 participant missing left ventricular hypertrophy data and 1 participant missing atrial fibrillation data. Missing ASL challenge data (affecting CVR calculations) include participants unable to wear the nonbreathing mask or for whom the nonbreathing mask did not fit properly. Interaction and stratified results for resting CBF models included 164 participants with NC and 124 with MCI. Interaction and stratified results for CVR models included 120 participants with NC and 85 with MCI. ASL = arterial spin labeling; CBF = cerebral blood flow; CVD = cardiovascular disease; CVR = cerebrovascular reactivity; MCI = mild cognitive impairment; NC = normal cognition.

Table 1 Participant characteristics

	Total sample (n = 314)
Demographics and health characteristics	
Age, y	73 ± 7
Male, %	59
White non-Hispanic, %	86
Education, y	16 ± 3
Cognitive diagnosis, % MCI	39
Montreal Cognitive Assessment score, total	25 ± 3
APOE ε4 carriers, %	34
Cardiac index, L · min ⁻¹ · m ⁻²	2.6 ± 0.6
Framingham Stroke Risk Profile score, ^a total	12.5 ± 4.1
Systolic blood pressure, mm Hg	143 ± 18
Antihypertensive medication use, %	54
Diabetes mellitus, %	18
Current cigarette smoking, %	2
Prevalent CVD, ^b %	3
Atrial fibrillation, ^b %	6
Left ventricular hypertrophy, %	4
ΔEtcO ₂ ^c	7 ± 3
Resting CBF, mL · 100 g⁻¹ · min⁻¹	
Left hemisphere	37 ± 7
Right hemisphere	37 ± 7
Left frontal lobe	37 ± 8
Right frontal lobe	37 ± 8
Left temporal lobe	35 ± 8
Right temporal lobe	36 ± 8
Left parietal lobe	40 ± 10
Right parietal lobe	39 ± 10
Left occipital lobe	35 ± 10
Right occipital lobe	36 ± 10
Cerebrovascular reactivity,^d % change	
Left hemisphere	2.2 ± 1.6
Right hemisphere	2.3 ± 1.6
Left frontal lobe	2.4 ± 2.0
Right frontal lobe	2.5 ± 1.9
Left temporal lobe	1.9 ± 1.6
Right temporal lobe	2.0 ± 1.8
Left parietal lobe	2.4 ± 2.2

Continued

Table 1 Continued

	Total sample (n = 314)
Right parietal lobe	2.3 ± 2.0
Left occipital lobe	2.9 ± 2.1
Right occipital lobe	2.7 ± 1.9

Abbreviations: CBF = cerebral blood flow; CVD = cardiovascular disease; EtcO₂ = end-tidal CO₂; MCI = mild cognitive impairment.

Cerebrovascular reactivity calculated as (ΔCBF/CBF₀)/ΔEtcO₂.

Values denoted as mean ± SD or frequency.

^aA modified score was included in statistical models, which excluded points assigned to age (6.5 ± 3.0).

^bNine participants met criteria for prevalent CVD, 17 participants met criteria for atrial fibrillation, and 1 participant met criteria for both, resulting in a total of 27 participants with prevalent CVD, atrial fibrillation, or both conditions.

^cΔEtcO₂ = challenge EtcO₂ – resting EtcO₂.

^dData based on n = 221 participants with usable challenge CBF data, including n = 201 participants free of prevalent CVD or atrial fibrillation and n = 20 participants with prevalent CVD or atrial fibrillation.

and arterial oxygen saturation were recorded. The first 4 scan volumes during the challenge were removed from processing to allow blood gases to equilibrate. CVR was calculated as percentage change in CBF (from resting CBF due to the induced hypercapnia) normalized by the end-tidal CO₂ change (millimeters of mercury). Region-specific mean CVR values were calculated for the 10 gray matter ROIs described above.

Analytical plan. Systolic blood pressure was the mean of 2 measurements. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, hemoglobin A_{1c} ≥6.5%, or oral hypoglycemic or insulin medication use. Medication review determined antihypertensive medication use. Left ventricular hypertrophy was defined on echocardiogram (left ventricle mass index >115 g/m² in men, >95 g/m² in women). Self-report atrial fibrillation was corroborated by any one of the following sources: echocardiogram, documented prior procedure/ablation for atrial fibrillation, or medication use for atrial fibrillation. Current cigarette smoking (yes/no within the year before baseline) was ascertained by self-report. Self-reported prevalent CVD with supporting medical record evidence included coronary heart disease, angina, or myocardial infarction (heart failure was a parent study exclusion). Framingham Stroke Risk Profile (FSRP) score was calculated by applying points by sex for age, systolic blood pressure, antihypertensive medication use, diabetes mellitus, current cigarette smoking, left ventricular hypertrophy, CVD, and atrial fibrillation.²⁰ APOE genotyping was performed on whole-blood samples. APOE ε4 carrier (APOEε4) status was defined as positive (ε2/ε4, ε3/ε4, ε4/ε4) or negative (ε2/ε2, ε2/ε3, ε3/ε3).

Before analyses, data inspection revealed no evidence of non-linear effects. Linear regression models with ordinary least-square estimates related cardiac index to resting CBF values and CVR in all gray matter ROIs, including the right and left hemisphere, right and left frontal lobes, right and left temporal lobes, right and left parietal lobes, and right and left occipital lobes. Regions were examined by hemisphere because of asymmetric differences

in older cohorts.²¹ Models were adjusted for age, modified FSRP score (excluding points for age), race/ethnicity, education, *APOE4*, cognitive diagnosis (NC, early MCI, MCI), and corresponding gray matter ROI to account for CBF reductions due to tissue volume loss (e.g., total gray matter in the left temporal lobe was a covariate for left temporal lobe CBF). To determine whether effects were driven by participants with cognitive impairment, secondary models restricting the sample to participants with NC or MCI tested a cardiac index $\times$ diagnosis interaction and then stratified by diagnosis (NC, MCI). These models excluded participants with early MCI because of the small sample size. Sensitivity analyses were performed with the exclusion of participants with atrial fibrillation and prevalent CVD. Significance was set a priori at $p < 0.05$. Analyses were conducted with R 3.1.2 (www.r-project.org).

RESULTS Participant characteristics. Participants included 314 adults 60 to 92 years of age (73 ± 7 years); 59% were men; and 86% self-identified as non-Hispanic white. Table 1 gives total sample characteristics, and table e-1 at Neurology.org gives characteristics by cognitive diagnosis. Figure 2 provides an illustration of mean resting CBF and

challenge CBF maps for participants in the lowest vs highest cardiac index quartile. Participants completing the challenge were more likely female ($p < 0.001$) and had a lower education level ($p < 0.001$) but were comparable in age ($p = 0.48$), race/ethnicity ($p = 0.65$), cognitive diagnosis ($p = 0.41$), *APOE4* ($p = 0.79$), and FSRP score ($p = 0.95$) compared to participants not completing the challenge. Cardiac index was unrelated to end-tidal CO_2 during rest ($p = 0.55$) or challenge ($p = 0.20$) conditions.

Cardiac index and resting CBF. Cardiac index was associated with CBF in the left ($p = 0.001$) and right ($p = 0.001$) temporal lobes. Figure 3 provides an illustration. The left temporal lobe CBF was lower on average by $2.4 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ per 1-unit decrease in cardiac index (defined as 0.6 L/m^2), a magnitude similar to the mean decrease in left temporal lobe CBF with an increase in age of >15 years. The right temporal lobe CBF was lower on average by $2.5 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ per 1-unit decrease in cardiac index, a magnitude equivalent to >20 years of advancing age. Cardiac index was unrelated to CBF in the remaining regions ($p > 0.10$, table 2). In sensitivity analyses excluding participants with atrial fibrillation or prevalent CVD, associations persisted between cardiac index and CBF in the left ($\beta = 2.3$, 95% confidence interval [CI] $0.8\text{--}3.9$, $p = 0.003$) and right ($\beta = 2.5$, 95% CI $0.9\text{--}4.2$, $p = 0.003$) temporal lobes. Null findings persisted in the remaining regions ($p > 0.20$).

In secondary models, the cardiac index $\times$ diagnosis interaction was associated with CBF in the right hemisphere ($\beta = -3.1$, $p = 0.027$), right parietal lobe ($\beta = -3.9$, $p = 0.048$), and right occipital lobe ($\beta = -3.8$, $p = 0.046$). The interaction term was modestly associated with CBF in several additional regions, including the left hemisphere ($p = 0.063$), right frontal lobe ($p = 0.066$), left temporal lobe ($p = 0.07$), and left parietal lobe ($p = 0.08$). Stratified results revealed that associations were exclusively found in participants with NC and present in nearly all regions, although the largest effects were in the left ($p = 0.00004$) and right ($p = 0.0002$, table e-2) temporal lobes.

Cardiac index and CVR. Cardiac index was modestly associated with CVR in the left ($p = 0.06$) and right ($p = 0.05$) occipital lobes. Cardiac index was unrelated to CVR for the remaining regions assessed ($p > 0.08$, table 2). In sensitivity analyses excluding participants with atrial fibrillation or prevalent CVD, cardiac index related to CVR in the left ($\beta = 0.6$, 95% CI $0.1\text{--}1.1$, $p = 0.02$) and right ($\beta = 0.5$, 95% CI $<0.1\text{--}0.9$, $p = 0.04$) occipital lobes. The remaining sensitivity models were similar to primary models ($p > 0.05$).

Figure 2 Resting CBF (A and B) and challenge CBF (C and D) maps for participants in the lowest and highest quartiles of cardiac index

Low and high cardiac index images were created with the unadjusted group mean image of the Memory & Aging Project participants with CBF analyses ($n = 314$) or cerebrovascular reactivity analyses ($n = 221$) in the lowest or highest cardiac index quartile. For illustration purposes only. CBF = cerebral blood flow.

Figure 3 Cardiac index and resting CBF in the (A) left and (B) right temporal lobes for total sample

Solid black line reflects unadjusted values of CBF outcomes (y-axis) corresponding to cardiac index (x-axis). Shading reflects 95% confidence interval. CBF = cerebral blood flow.

In secondary models, the cardiac index $\times$ diagnosis interaction was unrelated to CVR ($p > 0.23$). Stratified results were similarly null ($p > 0.11$, table e-2).

DISCUSSION Among community-dwelling older adults, lower cardiac index was associated with lower resting CBF in the cerebral gray matter, especially the temporal lobes. With the use of comprehensive imaging methods for quantifying systemic and cerebral hemodynamics, associations were statistically independent of key covariates, including vascular risk factors, prevalent CVD, atrial fibrillation, and atrophy. The magnitude of effects for the right and left temporal lobes corresponded to 15 to 20 years of advancing age despite the absence of clinical dementia and stroke in the cohort. Furthermore, associations appeared strongest among participants with NC.

One prior study of 31 nonsmokers free of vascular disease found no association between cardiac index and CBF.²² Methodologic differences may account for the inconsistency in results presented here. For example, the prior work may have been underpowered to detect effects observed here because our cohort was 10 times larger. Alternatively, the prior work used a high-velocity encoding gradient, which may have incorrectly estimated slower flowing blood near the vessel perimeter. The current findings are among the first to document a concurrent association linking cardiac index to cerebral gray matter CBF among aging humans, adding to a growing body of research highlighting the importance of systemic hemodynamics in brain health.^{2–5,23,24}

The mechanism linking systemic blood flow and resting CBF is unclear. A complex autoregulatory

control system maintains constant blood supply to the brain in both resting (static) and acute (dynamic) conditions. The dynamic autoregulatory capacity of CBF (in response to rapid cerebral perfusion pressure changes) generally remains intact in aging adults.^{25,26} Dynamic studies may be less generalizable to static autoregulation, reflecting the steady-state (resting) association between arterial blood pressure and CBF. First, dynamic autoregulation studies rely on experimental manipulation of arterial blood supply to simulate acute orthostatic hypotension (e.g., abrupt postural movements, rapid thigh cuff deflation). Second, CBF is typically estimated with transcranial Doppler quantifying flow velocity in the large arterial supply rather than cerebral tissue perfusion. Such approaches are susceptible to methodologic heterogeneity, especially with concomitant cerebrovascular disease.^{27,28} Therefore, the dynamic autoregulation literature may not fully address the complex myogenic, metabolic, and neurogenic mechanisms involved in cerebral autoregulation.

Patients with heart failure experience CBF reductions^{29,30} that normalize after transplantation,³¹ suggesting that mechanisms underlying static cerebral autoregulation may be compromised with severe cardiac dysfunction.^{29,30} In the absence of heart failure (like the cohort here), these mechanisms may be less effective in elders with a lifetime exposure to suboptimal vascular risk factors.³² Such exposure contributes to compromised vascular compliance³³ and blood-brain barrier integrity.³⁴ These subtle compromises may account for our results suggesting that autoregulatory mechanisms are vulnerable in aging, even before the onset of cognitive impairment, an important observation for the field.

Table 2 Cardiac index, CBF, and CVR

	Total sample (n = 314)		
	β	95% CI	p Value
Resting CBF			
Left hemisphere	0.82	−0.48 to 2.11	0.22
Right hemisphere	1.09	−0.22 to 2.40	0.10
Left frontal lobe	0.67	−0.81 to 2.15	0.38
Right frontal lobe	0.83	−0.64 to 2.30	0.27
Left temporal lobe	2.41	0.96 to 3.86	0.001
Right temporal lobe	2.51	0.98 to 4.04	0.001
Left parietal lobe	−0.59	−2.53 to 1.35	0.55
Right parietal lobe	−0.57	−2.42 to 1.28	0.54
Left occipital lobe	0.91	−0.92 to 2.73	0.33
Right occipital lobe	0.80	−1.05 to 2.64	0.40
CVR			
Left hemisphere	0.26	−0.11 to 0.63	0.16
Right hemisphere	0.10	−0.26 to 0.46	0.59
Left frontal lobe	0.30	−0.16 to 0.75	0.21
Right frontal lobe	0.11	−0.32 to 0.54	0.62
Left temporal lobe	0.17	−0.20 to 0.54	0.37
Right temporal lobe	−0.03	−0.45 to 0.38	0.87
Left parietal lobe	0.44	−0.05 to 0.92	0.08
Right parietal lobe	0.22	−0.23 to 0.67	0.33
Left occipital lobe	0.46	−0.02 to 0.93	0.06
Right occipital lobe	0.43	−0.001 to 0.87	0.05

Abbreviations: CBF = cerebral blood flow; CI = confidence interval; CVR = cerebrovascular reactivity.

Given our cross-sectional methods, our findings could also be explained by a third variable unaccounted for in our analyses, creating an epiphenomenon or reverse causation between cardiac index and CBF. One possibility is compromise to the sympathetic nervous system responsible for hemodynamic control throughout the body,³⁵ such as angiotensin II signaling dysfunction, could affect systemic fluid homeostasis, blood volume, and cerebral circulation.³⁶ Future research examining potential mechanisms is warranted, especially research using longitudinal methods.

Cardiac index and resting CBF associations were localized to the temporal lobes in the entire cohort. In stratified models, the associations were strongest in the participants with NC and more anatomically diffuse with the largest effects in the temporal lobes. The temporal lobes may be especially vulnerable because of a less extensive network of collateral blood flow sources.³⁷ Alternatively, the pCASL perfusion signal may be slice dependent in multislice echo-planar imaging acquisitions (as used here), yielding

lower label decay and shorter postlabeling delays in bottom slices (e.g., temporal lobe) relative to top slices when images are acquired in ascending order.³⁸ Incrementing the postlabeling delay time in a slice-dependent fashion during postprocessing accounts for this effect, and visual inspection of quantified CBF maps revealed no evidence of signal decay. Another possibility is that age-related CBF changes account for the pattern because age-dependent breakdown of the blood-brain barrier has been recently reported in the human hippocampus,³⁴ where Alzheimer disease pathology first evolves.³⁹ We previously reported that lower cardiac index levels correspond to an increased risk of incident dementia, especially Alzheimer disease.⁵ Therefore, subtle compromises in static autoregulatory mechanisms within the cerebral microcirculation may have age-related regional variability or early pathologic changes, placing temporal structures at greatest risk.

We observed differences between cardiac index and resting CBF vs CVR. In sensitivity analyses, lower cardiac index related to less reactivity in the posterior cortex, but results were not significant in primary models or stratified results. Furthermore, cardiac index is unrelated to end-tidal CO₂ during resting and challenge conditions. Our results suggest a mismatch between significant resting CBF and null CVR across different cardiac index values, offering an interesting perspective regarding the effect of peripheral vascular health on cerebrovascular functioning. Collectively, results suggest that the CBF observation may be attributable to alterations in tissue physiology rather than a fundamental impairment in vascular compliance. However, other factors may contribute to these null reactivity results, including insufficient power (with fewer participants in the reactivity analyses because of difficulties wearing the nonbreathing mask). Alternatively, it is plausible that the vascular challenge investigated here (5% CO₂) was insufficient to exhaust cerebrovascular reserve. A different finding might be possible with a larger stimulus (6%–10% CO₂), although these stimuli are less comfortable for participants and atypical in most CVR studies. Another explanation is that cardiac function was captured by echocardiogram in a separate session, so it is unknown whether cardiac output changed in response to the vasodilatory challenge. Lower cardiac index may affect static cerebrovascular function even when dynamic autoregulatory processes remain intact, but our results require replication to confirm the absence of association between cardiac index and CVR.

Our study has several strengths, including using a well-established method for noninvasively assessing cerebral perfusion, evaluating different perfusion conditions, and using a vasodilatory stimulus (CO₂) to assess CVR. Additional strengths include comprehensive

ascertainment of potential confounders, a reliable imaging technique for quantifying cardiac output (reflecting the clinical standard), stringent quality control procedures, and use of a core laboratory for processing cardiac and CBF measurements by technicians who were clinically blinded.

Despite these strengths, several limitations should be considered. First, results are cross-sectional and cannot speak to causality, raising the possibility of reverse causation. Longitudinal studies are needed to understand the temporal nature of associations reported here. Second, our sample included predominantly white, well-educated, healthy older adults. Generalizability to other races, ethnicities, ages, or adults with poorer health is unknown. We speculate that in a less healthy cohort with greater vascular risk factors or more compromised cardiac function, the associations reported here would likely be stronger. Future research is needed to test this hypothesis. Third, partial volume effects inherent to the pCASL technique may have affected our CBF estimates. We previously reported that lower cardiac index is associated with smaller brain volume,³ so we adjusted for regional co-occurring atrophy using a multi-atlas approach to improve segmentation accuracy and to minimize partial volume effects. Nevertheless, it is possible that partial volume effects confounded results. Another limitation is that reactivity models were based on a smaller sample ($n = 221$) because some participants were unable to wear the face mask. In addition, cerebral hemodynamic abnormalities in MCI could drive spurious results.⁴⁰ However, our primary observations remained significant when analyses were restricted to a carefully characterized sample of cognitively normal older adults, suggesting that hemodynamic abnormalities in MCI did not account for our findings. Finally, multiple comparisons could result in false-positive findings. Bonferroni-corrected results (corrected $\alpha = 0.005$) would still suggest that lower cardiac index is associated with lower CBF in the temporal lobes, particularly among participants with NC. Nevertheless, our results require replication.

Among older adults free of clinical stroke, dementia, and heart failure, lower cardiac index relates to poorer CBF, especially in the temporal lobes, independently of concurrent cardiovascular risk factors, CVD, or atrial fibrillation. Associations appear strongest among participants with NC. Further investigation into mechanisms linking cardiac index and regional CBF is warranted to identify primary prevention targets or therapeutic interventions.

AUTHOR CONTRIBUTIONS

Angela L. Jefferson: study concept and design, acquisition of data, analysis and interpretation of data, study supervision, manuscript composition. Dandan Liu: analysis and interpretation of data, manuscript

composition. Deepak K. Gupta: acquisition of data, manuscript composition. Kimberly R. Pechman: analysis and interpretation of data, study supervision, manuscript composition. Jennifer M. Watchmaker: analysis and interpretation of data. Elizabeth A. Gordon: analysis and interpretation of data, study supervision, manuscript composition. Swati Rane: acquisition of data, analysis and interpretation of data, manuscript composition. Susan P. Bell and Lisa A. Mendes: acquisition of data, analysis and interpretation of data. L. Taylor Davis: analysis and interpretation of data, manuscript composition. Katherine A. Gifford: study concept and design, acquisition of data, analysis and interpretation of data, study supervision, manuscript composition. Timothy J. Hohman: acquisition of data, analysis and interpretation of data, study supervision, manuscript composition. Thomas J. Wang: analysis and interpretation of data. Manus J. Donahue: study concept and design, acquisition of data, analysis and interpretation of data, study supervision, manuscript composition.

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DISCLOSURE

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