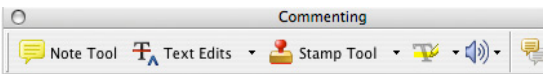
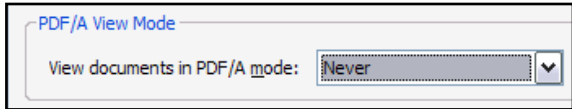
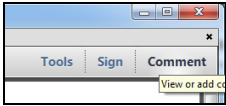
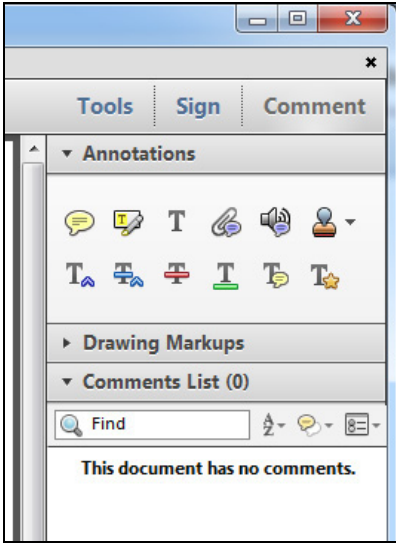


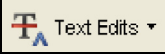


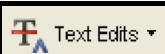

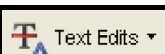





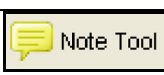

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^aDivision of Behavioral Medicine, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina

^bDivision of Geriatric Behavioral Health, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina

^cDuke Institute for Brain Sciences, Duke University, Durham, North Carolina

^dDuke Brain Imaging and Analysis Center, Duke University, Durham, North Carolina

^eDuke Center for Cognitive Neuroscience, Duke University, Durham, North Carolina

^fDepartment of Radiology, Duke University Medical Center, Durham, North Carolina

^gDivision of Neuroanesthesiology, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina

^hDivision of Neurocritical Care, Department of Neurology, Duke University Medical Center, Durham, North Carolina

ⁱDivision of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina

^jDivision of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina

^kDuke Clinical Research Institute, Durham, North Carolina

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Longitudinal Changes in Regional Cerebral Perfusion and Cognition After Cardiac Operation

^{Q1} Patrick J. Smith, PhD, MPH,* ^{Q14} Jeffrey N. Browndyke, PhD,* ^{Q14} Zachary A. Monge, MA, ^{Q14} Todd B. Harshbarger, PhD, ^{Q14} Michael L. James, MD, ^{Q14} Jeffrey G. Gaca, MD, ^{Q14} John H. Alexander, MD, MHS, ^{Q14} Miles M. Berger, MD, PhD, ^{Q14} Mark F. Newman, MD, ^{Q2} Carmelo A. Milano, MD, and ^{Q2} Joseph P. Mathew, MD, MHSc, MBA, for the Neurologic Outcomes Research Group (NORG)

Division of Behavioral Medicine, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina; Division of Geriatric Behavioral Health, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina; Duke Institute for Brain Sciences, Duke University, Durham, North Carolina; Duke Brain Imaging and Analysis Center, Duke University, Durham, North Carolina; Duke Center for Cognitive Neuroscience, Duke University, Durham, North Carolina; Department of Radiology, Duke University Medical Center, Durham, North Carolina; Division of Neuroanesthesiology, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; Division of Neurocritical Care, Department of Neurology, Duke University Medical Center, Durham, North Carolina; Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina; Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina; Duke Clinical Research Institute, Durham, North Carolina; and Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina

^{Q4} **Background.** Cardiac operation has been associated with increased risk of postoperative cognitive decline, as well as dementia risk in the general population. Few studies, however, have examined the impact of coronary revascularization or valve replacement or repair operation on longitudinal cerebral perfusion changes or their association with cognitive function.

Methods. We examined longitudinal changes in cerebral perfusion among 54 individuals with cardiac disease; 27 undergoing cardiac operation and 27 matched control patients. Arterial spin labeling magnetic resonance perfusion imaging was used to quantify cerebral blood flow within the anterior communicating artery, middle cerebral artery (MCA), and posterior communicating artery vascular territories before operation and postoperatively at 6 weeks and 1 year. Cognitive performance was examined during the same intervals by using a battery of tests that tapped memory, executive, information processing and upper extremity motor functions.

Repeated measures, mixed models were used to examine for perfusion changes and the association between perfusion changes and cognition.

Results. Significant postoperative increases in perfusion were observed at 6 weeks within the MCA vascular territory after cardiac operation ($p = 0.035$ for interaction). Perfusion changes were most notable in distal territories of the MCA and posterior communicating artery at 6 weeks, with no additional changes at 1 year. Postoperative increases in MCA perfusion at 6 weeks were associated with improved psychomotor speed ($\beta = 0.35$, $p = 0.016$), whereas no important differences were found between the groups in vascular territory perfusion and cognition at 1 year.

Conclusions. Cardiac operation is associated with important short-term increases in MCA perfusion with associated improvements in psychomotor speed.

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^{Q5} ^{Q6} Coronary artery bypass grafting (CABG) remains one of the primary treatment methods for individuals with severe coronary disease in the United States [2] and one of the primary sources of disability and mortality in the United States [3]. Although an extensive literature base has examined the relative merits of CABG, the

impact of CABG or valve operation on changes in cognitive and cerebral function remains a source of controversy [4]. Postoperative cognitive decline has been observed in more than 20% of individuals undergoing cardiac operation [5-7], and the extent to which these cognitive changes may be attributable to individual

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*Drs Smith and Browndyke are co-first authors.

^{Q3} Address correspondence to Dr Smith, Duke University Medical Center, Box 3119, DUMC South, Trent Dr, Durham, NC; email: patrick.j.smith@dm.duke.edu

The Supplemental Tables can be viewed in the online version of this article [<https://doi.org/10.1016/j.athoracsur.2018.07.056>] on <http://www.annalsthoracicsurgery.org>.

differences [8, 9] or surgical techniques [10] remains unclear.

Despite the wide range of studies that examined cognitive changes after cardiac operation [5–7,11], few studies have characterized changes in cerebral perfusion after CABG [12, 13] or valve replacement or repair, and no studies have done so using a matched control group with coronary artery disease (CAD). Because individual differences in underlying CAD explain a substantial amount of postoperative cognitive change [11, 14], matched control studies that used individuals with CAD and CAD risk factors are important in delineating the relating influence of cardiac operation versus underlying CAD on cognitive changes [15]. We therefore examined for longitudinal changes in regional cerebral perfusion and cognition in a sample of patients undergoing CABG or valve replacement or repair compared with CAD-matched control participants.

Patients and Methods

The Duke University Medical Center Institutional Review Board approved the study protocol. All enrolled participants provided informed consent before participation. Details of our recruitment and inclusion criteria have been previously reported [16]. Participants were prospectively identified and included individuals aged 60 years or older scheduled to undergo CABG or valve replacement or repair operation with cardiopulmonary bypass. A nonsurgical control group comprised of individuals with CAD was used as a comparator. Individuals in the control group were identified/recruited from a cardiology clinic and were considered to have CAD if they had experienced a prior myocardial infarction or had evidence of CAD by cardiac catheterization. Participants with a history of cortical stroke were excluded. Because of logistical constraints, we were unable to subselect specific control participants on an individual basis for the purposes of matching. Therefore, to provide the most representative sample, we enrolled both control participants and surgical patients who met our detailed inclusion and exclusion criteria. Enrolled participants were assessed at three time points: baseline (for the surgical patients, just before operation) and 6 weeks and 1 year after baseline. Details about neurocognitive and neuroimaging assessment, measurement, and processing are reported in Supplemental Table 1.

Data Analysis

Changes in perfusion measured by arterial spin labeling were analyzed by using a three-way, repeated measures, mixed models, in which data were incorporated from all participants across all time points with the use of Proc Mixed (SAS Institute, Cary, NC). To minimize the number of statistical tests while optimally using the available sample size, we adopted a gatekeeper approach in which we first tested for changes within each vascular territory (anterior communicating artery [ACA], middle cerebral artery [MCA], and posterior communicating artery [PCA]) [17]. If the test for changes in the territory was

important, uncorrected follow-up testing was conducted in a secondary, explanatory step, to determine which territories may have contributed to the observed effect. Analyses of perfusion changes are presented in units of millimeter per 100 g per minute throughout the results. Baseline total gray matter atrophy, sex, and territory hemisphere (left versus right) served as adjustment variables in all analyses, with time and surgical group (surgical versus control) as the predictors of interest. For analyses of cognitive change, reliable change indices were grouped by cognitive domain, providing a mean change in z score that served as the outcome. Because of our small sample size, cognitive subtests were grouped a priori based on prior clinical guidelines [18]. Domains included verbal memory, visual memory, executive function, and psychomotor speed. See Supplemental document for specific neuropsychological tests used for each cognitive domain. Analyses of perfusion and changes in cognitive function were conducted by using age, education, sex, and surgical group as covariates with changes in perfusion as the predictor of interest. Model assumptions about linearity and independence were assessed and found to be acceptable.

Results

Demographic and background characteristics are presented in Table 1. Fifty-one individuals provided baseline and 6-week assessments. Ten individuals dropped out between 6 weeks and 1 year. Participants who did not complete 1-year follow-up assessments did not differ from other participants in any background, demographic, or neuroimaging variables (all p values ≥ 0.461). As shown in Table 1, participants in the control group were more likely to be men and white. Among participants who had valve replacement, 10 underwent aortic valve repair or replacement (9 replacements, 1 repair) and 8 underwent mitral valve repair or replacement (4 replacements, 4 repairs).

Changes in Perfusion Measured by Arterial Spin Labeling

Examination of changes in perfusion was conducted by territory (ACA, MCA, and PCA). Results indicated that there was a main effect of time for total ACA perfusion ($p < 0.001$), but there was no evidence that changes varied as a function of group ($p = 0.457$ for interaction).

Examination of changes in MCA perfusion revealed a time-by-group interaction ($p = 0.035$), such that perfusion was lower among surgical participants than among control participants before operation, but subsequently improved and were not different after operation at 6-week or 1-year follow-up (Fig 1). As shown in Supplemental Table 2, changes were most evident in the middle and distal MCA subregions, suggesting that more distal perfusion zones within the MCA showed the greatest changes (Fig 2). Follow-up analyses within the surgical cohort only demonstrated a significant increase in MCA perfusion from baseline to after treatment (52.5 mL \cdot 100 g⁻¹ \cdot min⁻¹ versus 58.5 mL \cdot 100 g⁻¹ \cdot min⁻¹, $p = 0.07$).

Table 1. Background and Demographic Characteristics of the Sample

Variable	Surgical Patients (n = 27)	Control Participants (n = 27)
Age, years	67.4 ± 7.4	67.7 ± 7.6
Sex, male ^a	13 (48)	24 (89)
White ^a	23 (85)	27 (100)
Years of education	15.5 ± 3.2	15.9 ± 2.4
History of CVD	4 (15)	6 (22)
History of diabetes	8 (30)	7 (26)
History of hypertension	22 (81)	20 (74)
Left ventricular ejection fraction	55.7 ± 8.7	...
NYHA class		
0	9 (33)	...
1	2 (7)	...
2	11 (41)	...
3	5 (19)	...
No. of coronary grafts		
0	18 (67)	...
1	1 (4)	...
2	4 (15)	...
3	2 (7)	...
4	2 (7)	...
Surgical procedure		
VR	18 (67)	...
CABG	6 (22)	...
CABG + VR	3 (11)	...
Mean pump CPB time, minutes	158.1 ± 61.6	...
Mean cross-clamp time, minutes	84.3 ± 45.9	...

^a Statistically different between the surgical and control groups at baseline, $p < 0.05$.

Variables are mean ± SD or n (%).

^{b11} CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; CVD = cardiovascular disease; NYHA = New York Heart Association; VR = value replacement or repair.

^{b12} ^b Statistically different between the surgical and control groups at baseline, $p < 0.10$.

^c Statistically different between the surgical and control groups at baseline, $p < 0.01$.

$p = 0.011$), such that baseline MCA perfusion differences between groups ($56.6 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ versus $49.7 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, $p = 0.013$) were attenuated after operation ($59.4 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ versus $55.7 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, $p = 0.161$).

Examination of changes in PCA perfusion revealed a time-by-group interaction trend ($p = 0.087$), such that perfusion was lower among surgical participants before operation than among control participants, but subsequently improved and were not different at 6 weeks and 1 year. As shown in Supplemental Table 2, changes were most evident in the most distal PCA perfusion zone. Similar to the pattern observed in the MCA, PCA perfusion increased from baseline after operation in the

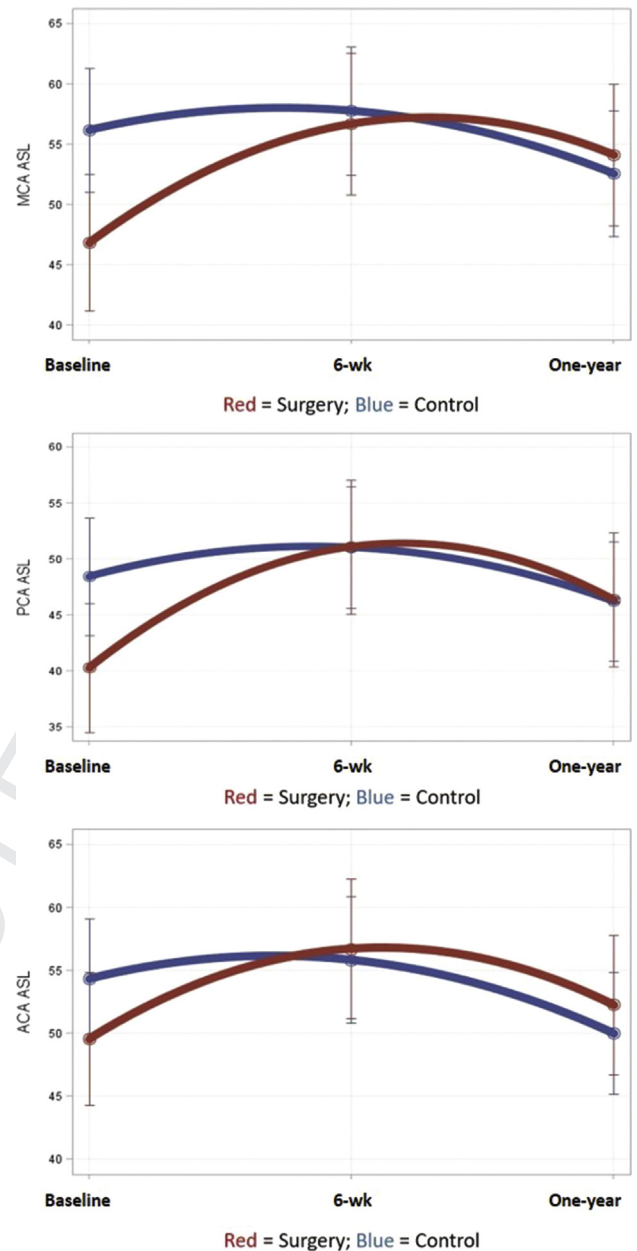
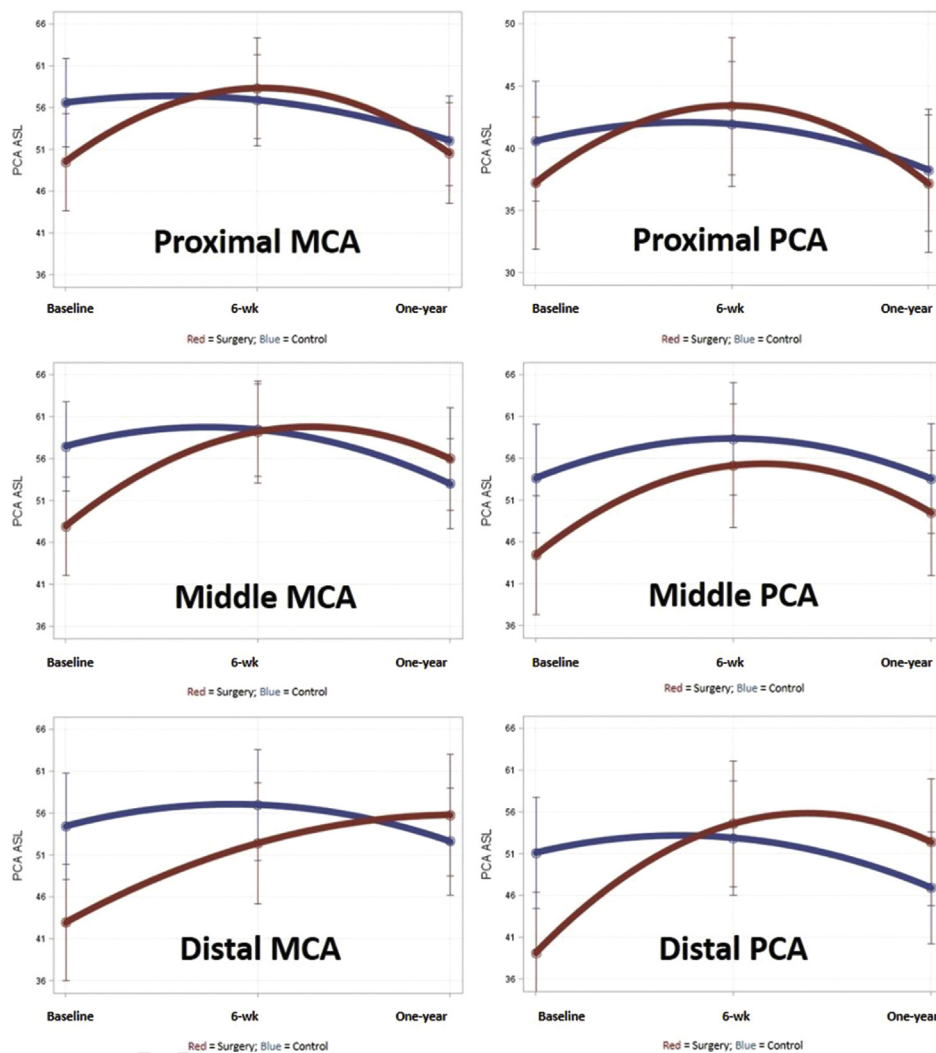


Fig 1. Changes in perfusion by vascular territory. Significant time by surgical interactions were observed within the middle cerebral artery (MCA) ($p = 0.011$) and posterior communicating artery (PCA) ($p = 0.039$) territories, with weaker, nonsignificant changes in the anterior communicating artery (ACA) territories ($p = 0.164$). (ASL = arterial spin labeling.)

surgical group ($44.9 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ versus $52.9 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, $p < 0.001$), tended to be lower among surgical patients relative to control participants at baseline ($47.9 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ versus $43.0 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, $p = 0.072$), and this difference was attenuated after operation ($51.7 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ versus $50.2 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, $p = 0.500$). Finally, examination of ACA perfusion changes revealed that ACA perfusion levels increased from baseline after operation in the

Fig 2. Changes in individuals subregions within the middle cerebral artery (MCA) and posterior communicating artery (PCA) territories. As shown, changes were most evident in subregions 9 ($p < 0.001$), 5 ($p = 0.007$), 6 ($p = 0.011$), and 4 ($p = 0.090$). (ASL = arterial spin labeling.)



to $57.5 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ (SE 12.4) after operation and then tended to drop at the follow-up assessment ($51.2 \pm 10.1 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$), without significant differences between the surgical and control groups ($p = 0.457$).

Perfusion and Cognition

In exploratory analyses of changes in perfusion and changes in cognitive performance, we examined changes in total MCA and PCA perfusion as predictors of cognitive change. Results revealed that increased MCA perfusion was associated with improved psychomotor speed ($\beta = 0.35$, $p = 0.016$) (Fig 3) but was not associated with verbal memory ($\beta = 0.10$, $p = 0.514$), visual memory ($\beta = 0.16$, $p = 0.281$), or executive function ($\beta = 0.00$, $p = 0.968$). Similarly, increased PCA perfusion trended with improved psychomotor speed ($\beta = 0.27$, $p = 0.076$) but was not associated with verbal memory ($\beta = 0.13$, $p = 0.402$), visual memory ($\beta = 0.07$, $p = 0.658$), or executive function ($\beta = -0.06$, $p = 0.686$). Finally, increases in ACA perfusion tended to be associated with verbal memory improvements ($\beta = 0.26$, $p = 0.085$) but were

not associated with visual memory ($\beta = 0.12$, $p = 0.444$), executive function ($\beta = 0.00$, $p = 0.967$), or psychomotor speed ($\beta = 0.06$, $p = 0.693$).

Comment

Results from the present study suggest that cardiac operation is associated with improved perfusion across several brain regions postoperatively at 6 weeks, with associated improvements in tests of psychomotor speed. These results extend previous studies by demonstrating changes in cerebral perfusion in cardiac surgical patients compared with a CAD-matched control group [12, 19, 20], suggesting that the observed associations were not entirely due to underlying cardiovascular disease. In addition, the present study uses longitudinal neuroimaging up to 1 year after the operation, suggesting that the observed pattern of findings were not transient.

Reduced cerebral perfusion has been associated with a greater risk of cognitive impairment and dementia. In a sample from the Rotterdam Study of 4,759 individuals

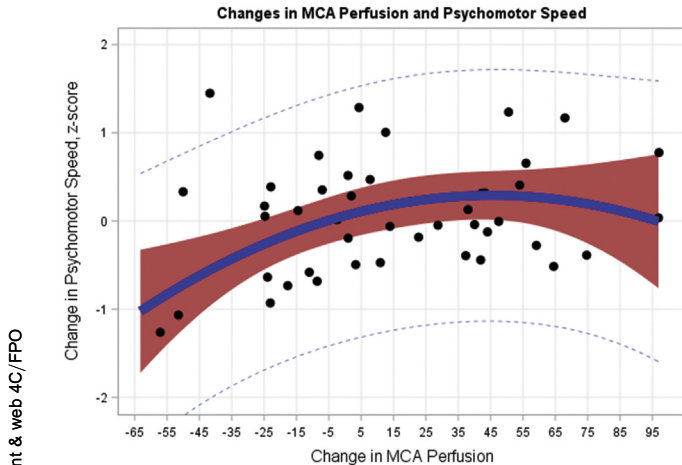


Fig 3. Changes in middle cerebral artery (MCA) perfusion and psychomotor speed.

without dementia at baseline, Wolters and colleagues [21] found that lower cerebral perfusion was associated with greater risk of dementia, independent of stroke. In addition, results were similar when analyses were limited to individuals who had dementia because of Alzheimer's disease specifically, suggesting that the observed association was not due to vascular dementia only, although the association between hypoperfusion and dementia was greater among individuals with more severe white matter hyperintensities. Finally, lower baseline perfusion was associated with accelerated cognitive decline, and this association remained robust after eliminating individuals with incident dementia, suggesting that lower perfusion was predictive of insidious declines among preclinical patients.

Several previous studies have examined changes in cerebral perfusion after cardiac operation, although most have focused on CABG [12, 19]. Individuals undergoing CABG have been shown to have lower perfusion compared with age-matched control participants when assessed preoperatively [20]. In a sample of 82 consecutively enrolled CABG patients, Moraca and colleagues [20] found that 75% of patients undergoing CABG exhibited impairments in perfusion compared with published age-matched control participants and that greater age additionally predicted greater perfusion abnormalities. Efimova and colleagues [12] examined changes in perfusion and cognition in 22 CABG patients evaluated 10 to 14 days after operation and again after 6 months, finding that early reductions in perfusion were associated with altered psychomotor speed. In addition, in an examination of 813 patients undergoing off-pump CABG, Xu and colleagues [13] found that poorer perfusion was independently predictive of neurologic complications, including cerebral infarction, encephalopathy, delirium, and postoperative cognitive dysfunction. Although relatively fewer studies have examined regional changes in perfusion and alterations in cognitive function, Hshieh and colleagues [22] examined this association in 146 older

adults undergoing elective operation, demonstrating associations between perfusion in the posterior cingulate and precuneus with performance on tests of memory, visual attention, and general cognition. Of note, although our small sample size precludes formal analyses of CABG versus valve operation, our findings are particularly important in that they demonstrate improved perfusion and neurocognition in a sample with numerous individuals undergoing valve replacement or repair, who are at greater risk of adverse cerebral events because of cardioembolic or air entry into the cerebral circulation [23, 24].

Although numerous studies have demonstrated an association between lower levels of resting perfusion and poorer cognition, particularly on speed-dependent indices [25], few have examined changes in regional perfusion and cognitive change. Our finding that improved MCA perfusion was associated with increased processing speed is consistent with prior studies demonstrating that exercise-induced MCA perfusion is associated with improved processing speed [26, 27]. In addition, poorer perfusion in brain regions supported by MCA subsidiary vasculature has been associated with lower processing speed among individuals with mild Alzheimer's disease [28] and carotid disease [29], suggesting that MCA-perfused structures (eg, posterior cingulate) may be particularly important for information processing efficiency.

Lower cerebral perfusion may affect brain outcomes through several mechanistic pathways. Numerous studies have suggested that hypoxia induces transcription factors that lead to increased expression of proinflammatory cytokines [30, 31] and subsequent microglial activation [32]. Lower perfusion has also been associated with reduced β -amyloid clearance in animal models, as well as correlated with amyloid burden in human samples [33]. Hypoperfusion has also been implicated in the pathogenesis of small-vessel, microvascular disease [34] as well as endothelial dysfunction [35] and increased blood-brain barrier permeability [36–38]. Although few studies have examined the impact of cardiothoracic intervention on cerebral perfusion, existing studies suggest that improvements to cardiac output may result in distal improvements in cerebral perfusion [39]. It is also possible that increased levels of circulating catecholamines could cause hyperdynamic circulatory changes [40].

The present study must be viewed with several limitations in mind. First, although this is the largest sample, to our knowledge, to have examined changes in regional perfusion after CABG versus matched control participants, our sample size was nevertheless small. Second, our follow-up was limited to 1 year, and we are therefore unable to provide any additional inference to the impact of perfusion changes on long-term cognitive outcomes. However, we also note that few other studies have used longitudinal follow-up and none, to our knowledge, beyond 6 months [12]. Third, we were unable to fully account for potential differences in medication burden or duration for cardiovascular disease or alterations in

left ventricular ejection fraction, because these data were not systematically collected for all participants. In addition, we found no association between baseline left ventricular ejection fraction and either MCA ($p = 0.220$) or PCA ($p = 0.469$) perfusion levels, and perfusion changes within the surgical group in these brain regions were not associated with left ventricular ejection fraction levels at baseline ($p = 0.595$). Fourth, although we obtained cognitive performance data across multiple domains, we were limited in that we only assessed selected cognitive domains. Future studies may benefit from a more extensive cognitive test battery to further elucidate potential associations between changes in perfusion and cognitive performance. Finally, it should be noted that the present analyses relied heavily on comparisons of individuals undergoing valve replacement with CAD patients.

In conclusion, our data suggest that cardiac operation may improve cerebral perfusion within several brain regions and that improved perfusion is associated with modest benefits in cognitive performance. Our data extend previous findings demonstrating that coronary intervention may help improve cerebral perfusion outcomes [21, 36]. Future studies should attempt to examine individual differences in perfusion response after cardiac operation, as well as intraoperative characteristics predictive of perfusion change.

Uncited Reference

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