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Association Between Endothelial Function and Cognitive Performance in Patients With Coronary Artery Disease During Cardiac Rehabilitation

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ABSTRACT

Objective: Subtle cognitive deficits indicating early neural risk are common in the clinical presentation of coronary artery disease (CAD). Although deterioration may be mitigated by exercise, cognitive response to exercise is heterogeneous. Vasculopathy including endothelial dysfunction is a hallmark of CAD and may play an important role in impairing neural adaptation to exercise. This study aimed to assess peripheral measurements of endothelial function as predictors of cognitive performance in CAD participants undertaking cardiac rehabilitation (CR).

Methods: CAD patients ($N = 64$) undergoing CR were recruited for this prospective observational study. Neuropsychological and endothelial function assessments were performed at baseline and after 3 months of CR. Z-scores for overall cognitive performance and specific cognitive domains (verbal and visuospatial memory, processing speed, and executive function) were calculated. Endothelial function was measured by the reactive hyperemia index (RHI) using peripheral arterial tonometry. Cross-sectional and longitudinal associations between RHI and overall cognition were assessed using linear regressions and mixed models, respectively. Domain-specific associations were also explored.

Results: Although lower RHI was not associated with overall cognition at baseline ($b = 0.26, p = .10$), an increased RHI was significantly associated with an improvement in overall cognition ($b = 0.55, p = .030$) over 3 months. Lower RHI was associated with poorer verbal memory ($\beta = 0.28, p = .027$) at baseline and an increased RHI over 3 months was associated with an improvement in processing speed ($b = 0.42, p = .033$).

Conclusions: RHI may be a clinically useful predictor of cognitive change and might provide insight into the etiology of cognitive dysfunction in patients with CAD.

Key words: cognition, coronary artery disease, endothelial function, exercise.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality and morbidity worldwide (1). An underrecognized but particularly important symptom of CAD is cognitive impairment; CAD patients show specific disruptions in multiple cognitive domains (2) and are at an increased risk of mild cognitive impairment, vascular cognitive impairment (VCI), and dementia (3). Cognitive performance is particularly critical in CAD where subtle deficits are predictive of poorer outcomes including physical disability (4), interference with secondary prevention (5), and mortality (6). Although exercise is increasingly recognized as a

promising intervention to increase brain volumes (7) and improve cognitive performance (8), there is wide variability in response (9), suggesting a need to explore predictors of cognitive response to exercise in CAD.

BMI = body mass index, **CAD** = coronary artery disease, **CVLT-II** = California Verbal Learning Test 2nd Ed., **FMD** = flow-mediated dilation, **CR** = cardiac rehabilitation, **PAT** = peripheral arterial tonometry, **RHI** = reactive hyperemia index, **SD** = standard deviation, **VCI** = vascular cognitive impairment, **VO_{2peak}** = peak oxygen uptake per minute

SDC Supplemental Content

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The etiological and clinical role of vascular disease in cognitive decline and risk of dementia is increasingly being investigated. Vasculopathy, a hallmark of CAD, includes endothelial dysfunction, which can be detected noninvasively. The vascular endothelium not only regulates vascular tone and permeability through expression and activation of nitric oxide and other bioactive substances, but is also critically linked to atherosclerotic plaque formation (10). Participants with cardiovascular disease or risk factors show impaired endothelium-dependent vasomotor responses and attenuated vascular nitric oxide bioavailability (11). Endothelial dysfunction has been associated with cerebrovascular damage represented by white matter hyperintensities, lacunar infarctions, brain atrophy, and brain hypoperfusion providing compelling mechanistic grounds for the relationship between CAD and cognitive decline (12,13). Accordingly, mainly cross-sectional associations between markers of poor endothelial function, cerebrovascular damage, and poor cognitive performance suggest that peripheral markers may be reflective of cerebrovascular changes (14). However, the clinical utility of peripheral measurements of endothelial function as prospective predictors of early cognitive changes remains unclear, especially in those with CAD, an at-risk population.

Most studies assessing endothelial function have used brachial artery flow-mediated dilation (FMD) (15). The present study aimed to assess microvascular endothelial function measured by reactive hyperemia index (RHI) using the novel non-operator dependent fingertip pulse amplitude tonometry, as a cross-sectional predictor of overall cognitive function, and explore associations with specific cognitive domains including verbal memory, visuospatial memory, processing speed, and executive function. Because exercise-induced cognitive improvement may rely on processes such as neurogenesis and angiogenesis, which are dependent on the vascular endothelium (16), poorer vascular health may be an important barrier to neural adaptation to exercise and cognitive improvement after exercise in those with CAD. Therefore, the present study also aimed to assess RHI as a prospective predictor of cognitive response to exercise in CAD participants undertaking a 3-month cardiac rehabilitation (CR) program.

METHODS

Participants

Institutional research ethics boards at Sunnybrook Health Sciences Centre and the Toronto Rehabilitation Institute at University Health Network approved this study. Written informed consent was obtained from all study participants before study participation. Patients with CAD (myocardial infarction; angiographic evidence showing $\geq 50\%$ blockage in at least one major coronary artery; percutaneous coronary intervention; or coronary artery bypass graft surgery) were recruited at entry into a CR program between May 2012 and June 2015. Participants were excluded based on previously diagnosed neurodegenerative illness including all-cause dementia, active cancer, surgery planned within 12 months, schizophrenia, bipolar affective disorder, and substance abuse. Participants with standardized Mini Mental Status Examination (17) of 24 or less were excluded because significant cognitive impairment would preclude participants from participating in the CR program independently and from completing the cognitive testing.

Demographic and clinical characteristics, as well as a detailed medical history for eligible participants who provided written informed consent, were collected from patient interviews. Cardiac diagnoses, concomitant

medications, vascular risk factors, and anthropometrics were obtained from patient charts at the Toronto Rehabilitation Institute. Body mass index (BMI) was calculated per standard definition [mass (kilogram)/(height (meter)²)].

CR Program

Participants attended exercise visits that included an aerobic walk or walk/jog and resistance training once a week for 3 months under the supervision of exercise and medical specialists. Participants were also expected to independently exercise at home for at least 4 days of the week. Cardiopulmonary fitness was assessed at entry into CR and at 3 months using the peak oxygen uptake per minute (VO_{2peak}) obtained during a symptom-limited graded exercise test.

Cognitive Testing

A standardized battery of tests recommended by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (18) for the investigation of VCI was used to assess cognitive performance. All cognitive testing was performed by a trained researcher at a standardized time (0930 (30) minutes) and participants refrained from eating or drinking any caffeine-containing beverages for at least 4 hours before testing. Verbal memory was assessed using the verbal learning (recall of a word list for 5 learning trials), short delay free recall (recall of a word list after an interfering list), and long delay free recall (recall of a word list after 20 minutes) outcomes of the California Verbal Learning Test 2nd Edition (CVLT-II) (18). Visuospatial memory was assessed using the visual learning and delayed recall outcomes of the Brief Visuospatial Memory Test-Revised (19). Measures of processing speed included the Trail-Making Test Part A (20) and the Digit Symbol-Coding task, a measure of complex attention and psychomotor speed from the Wechsler Adult Intelligence Scale 3rd Edition (21). Executive function was evaluated using the Trail-Making Test Part B (20) and Stroop Color-Word Interference Test (22).

For each cognitive task, a Z-score was determined from published age and sex and education-matched normative data derived using samples of healthy older patients (23–26). Z-scores of related tests were summed to reflect performance in a cognitive domain and avoid multiple comparisons. Z-scores from the three CVLT-II outcomes (verbal learning, short and long delayed recalls) were summed to represent verbal memory. For visuospatial memory, Z-scores for the two Brief Visuospatial Memory Test-Revised outcomes (visual learning and delayed recall) were summed. For processing speed, the Z-scores for the Trail-Making Test Part A and Digit Symbol-Coding task were summed, whereas the Z-scores of the Trail-Making Test Part B and Stroop Test were summed to represent executive function. Cognitive domain Z-scores were then standardized using the mean and standard deviation (SD) within each domain. Overall cognitive performance score was calculated by summing the four domain-specific Z-scores and standardized using the sample mean and standard deviation (27). A higher Z-score was reflective of better cognitive performance.

Endothelial Function

Endothelial function was assessed using fingertip peripheral arterial tonometry (PAT) (EndoPAT; Itamar Medical, Israel). Measurements were performed in a fasting condition. Participants were given 5 minutes to acclimatize in a dimly lit temperature controlled room. With the participants in a supine position, probes with inflatable neoprene membranes and transducers were mounted on the index fingers of both hands, and the digital pulse amplitude was observed until it was stable. After a baseline assessment of approximately 5 minutes, the brachial artery of the nondominant arm was occluded by inflating a blood pressure cuff to 60 mm Hg above systolic blood pressure not less than 200 mm Hg and not greater than 300 mm Hg for 5 minutes. PAT signals were recorded for at least 5 minutes after cuff release and postocclusion hyperemia. Endothelial function was represented by the RHI, which was calculated as the post- to preocclusion ratio of average pulse wave amplitude in the occluded arm,

relative to the same ratio in the control arm, corrected for baseline vascular tone. An RHI of 1.67 or less indicated vascular endothelial dysfunction.

To date, Endo-PAT2000 is the only device with a Food and Drug Administration indication for assessing endothelial function (28–30). This automated, operator-independent technique has 82% sensitivity and 77% specificity for the diagnosis of coronary artery endothelial dysfunction based on the intracoronary acetylcholine challenge method, the criterion standard for the assessment for endothelial function (28). Significant correlations and receiver-operating curve analysis in a sample of CAD patients have also shown that PAT is comparable with FMD in measuring endothelial function (31). PAT is noninvasive and more feasible and cost-effective than FMD because of limited access and increased cost associated with ultrasound devices and technicians. In addition, the PAT technique uses the contralateral arm as an internal control that can be used to correct for any systemic changes during the test (28), in distinction with FMD. The PAT-derived RHI has also previously showed robust reproducibility (intraclass correlation = 0.74) in adults with metabolic syndrome (32).

Statistical Analysis

Continuous variables were summarized as means and SDs, and categorical variables were summarized as percentages. Relationships between VO_{2peak} , overall cognition score, and domain-specific Z-scores at baseline and during CR, were assessed by Pearson correlations and bivariate mixed models, respectively.

Linear regressions were conducted to investigate the association between RHI and overall cognition score at baseline. Next, multivariate mixed models were used to assess the association between change in RHI and change in overall cognition during CR. Mixed models evaluate the overall effects across time in repeated measures data and are robust and flexible in dealing with missing data (33). Similarly to the main analyses, associations between RHI and individual cognitive domain Z-scores were explored using linear regressions and associations between change in specific cognitive domains and change in RHI during CR were explored using multivariate mixed models. Covariates for all analyses, including age, sex, years of education, smoking history, and VO_{2peak} were chosen a priori based on established associations with cognition and RHI. Linear regressions were performed using SPSS statistical software (Version 23.0; IBM, Armonk, NY) and multivariate mixed model analyses were conducted using the MIXED procedure in SAS University Edition statistical software (SAS Institute Inc, NC). All analyses were considered significant at a two-tailed $p < .05$.

Sample Size

A linear regression analysis was proposed to assess the relationship between RHI (independent) and verbal memory domain Z-scores (primary dependent) at baseline. Assuming a mean SD of 0.69 in RHI (mean (SD) RHI = 0.02 (0.69), $n = 31$) and an SD of 3.41 in verbal memory domain Z-scores (mean (SD) CVLT-II composite Z-score = 1.50 (3.41), $n = 115$) based on findings in a pilot sample, a sample size of 42 provided 80% power to detect a 2 SD drop in verbal memory domain Z-scores per unit of RHI. No studies to date

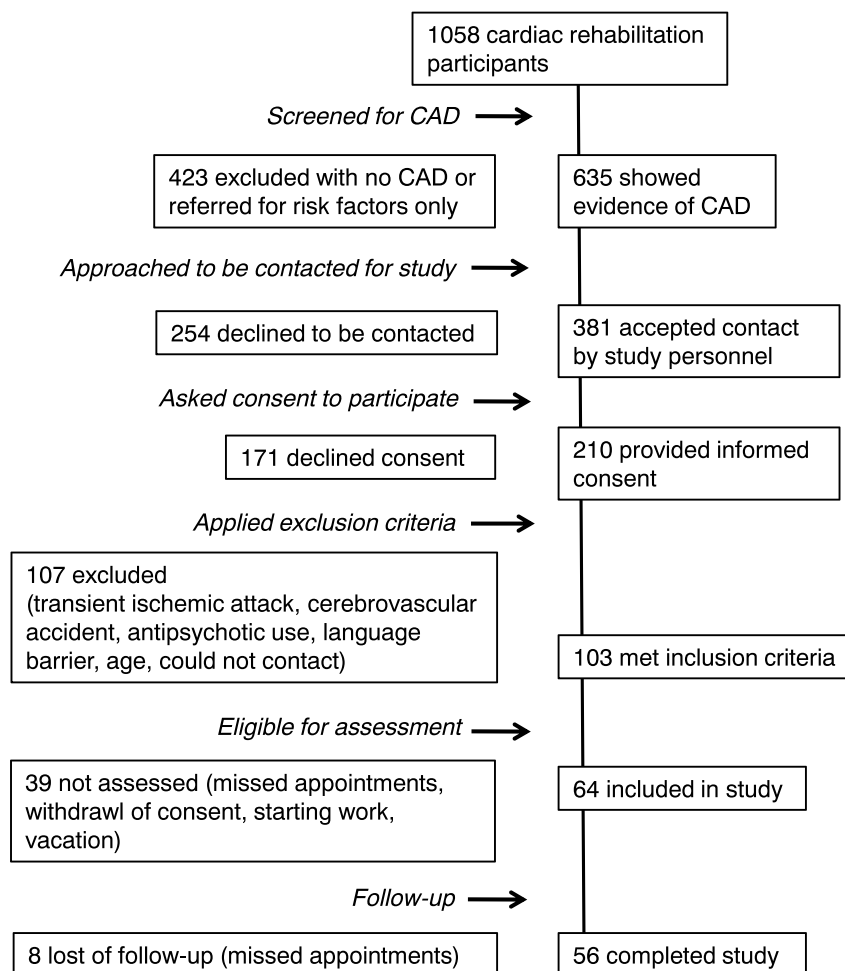


FIGURE 1. Study recruitment process.

TABLE 1. Characteristics of Study Participants ($N = 64$) at Entry and Over 3 Mo of CR

Characteristic	CAD ($N = 64$), M (SD) or n (%)
Sociodemographics	
Age, y	63 (7)
Sex, male	45 (70%)
Ethnicity, white	46 (72%)
Marital status, married	47 (73%)
Years of education, y	16 (3)
Smoking history, smoker or quit smoking	38 (59%)
Lipid profile and HbA1c	
Low density lipoprotein, mmol/L	
Baseline	1.55 (0.61)
3 mo	1.48 (0.54)
High density lipoprotein, mmol/L	
Baseline	1.25 (0.38)
3 mo	1.38 (0.40)
Total cholesterol, mmol/L	
Baseline	3.39 (0.80)
3 mo	3.60 (1.75)
Triglycerides, mmol/L	
Baseline	1.31 (0.62)
3 mo	1.14 (0.51)
Hemoglobin A1c	
Baseline	0.059 (0.008)
3 mo	0.070 (0.080)
Body composition	
Body mass index, kg/m ²	
Baseline	29.2 (5.1)
3 mo	29.4 (4.9)
Body fat percentage	
Baseline	31.7 (12.4)
3 mo	30.9 (9.7)
Waist circumference, cm	
Baseline	99.4 (13.7)
3 mo	100.3 (13.8)
Cardiac history	
Myocardial infarction	33 (52%)
Coronary artery bypass graft surgery	15 (23%)
Stent	47 (73%)
Comorbidities	
Hypertension	57 (89%)
Hypercholesterolemia	62 (97%)
Diabetes	13 (20%)
Depression	16 (25%)
Cardiopulmonary fitness	
VO _{2peak} , ml/kg/min	
Baseline	20.1 (5.4)
3 mo	24.5 (7.2)

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TABLE 1. (Continued)

Characteristic	CAD ($N = 64$), M (SD) or n (%)
Medications	
β -Adrenergic receptor blockers	46 (72%)
Angiotensin-converting enzyme inhibitors	34 (54%)
Antidiabetic	10 (16%)
Platelet inhibitors	57 (89%)
Statin	62 (97%)
Vascular health	
RHI	
Baseline	1.78 (0.44)
3 mo	1.82 (0.43)

CAD = coronary artery disease; SD = standard deviation; VO_{2peak} = peak oxygen consumption; RHI = reactive hyperemia index.

have assessed RHI in longitudinal comparisons. A sample size of 42 is also sufficient to detect a change in slope of 2 units in a repeated measures analysis assessing the relationship between RHI and verbal memory domain Z-scores over 3 months (observations at baseline and 3 months). Assuming a conservative noncompletion rate of 30% (9,34) and to comprehensively adjust for up to five covariates, 60 patients were needed in the study.

RESULTS

Patient Characteristics

The study recruitment process is shown in Figure 1. During the recruitment period, 1058 CAD patients entered the CR program. Of these, 635 patients had evidence of CAD. From the patients who agreed to participate and met inclusion criteria, 64 patients were included in the study. Of those who met study criteria, 39 patients were not assessed because of missed appointments, withdrawal of consent, vacation, and work conflicts. The study sample was similar to a large unselected sample from the center database ($n = 424$) in terms of age (63 (7) versus 64 (10)), sex (70% versus 82% male), years of education (16 (3) versus 16 (3)), cardiac diagnoses, e.g., myocardial infarction (52% versus 49%), BMI (29.2 (5.1) versus 28.5 (5.2)), and fitness level (VO_{2peak} 20.1 (5.4) versus 19.3 (5.7)). Of the patients included in the study, 56 patients completed both visits. RHI measurements were available in 53 participants and overall cognition scores were available in 45 participants at 3-month follow-up.

Demographics and clinical characteristics of all the participants ($N = 64$) are reported in Table 1. The mean lipid profile was in the reference range (low density lipoprotein < 2.50 mmol/L, high density lipoprotein > 0.99, cholesterol < 5.20 mmol/L, triglycerides < 1.70 mmol/L) (35) over 3 months; average plasma glucose concentration (HbA1c < 0.060 desirable) was high despite only 20% of patients with a diagnosis of diabetes. The mean BMI remained in the overweight range (BMI > 25 kg/m²) after 3 months. The mean VO_{2peak} significantly increased over 3 months ($b = 2.20$, $p < .001$).

RHI

As shown in Table 1, RHI at entry into CR indicated normal endothelial function. VO_{2peak} was not associated with RHI at baseline

TABLE 2. Cognitive Test Results and Associations Between Change in Cardiopulmonary Fitness and Change in Overall Cognition Score and Domain-Specific Scores Over 3 Mo of CR in Patients With CAD

Cognitive Domain	Mean Z-Score \pm SD		Association with VO_{2peak} over CR	
	Baseline	3 mo	Estimate (<i>b</i>)	<i>p</i> (<i>p</i> < .05)*
Overall cognition	-0.0004 (1.00)	0.001 (1.00)	0.01	.61
Verbal memory	-0.002 (1.00)	-0.0004 (1.00)	0.001	.93
Visuospatial memory	0.006 (1.00)	-0.09 (1.22)	0.02	.15
Processing speed	0.001 (1.00)	-0.27 (0.75)	0.01	.31
Executive function	0.003 (1.00)	-0.001 (1.00)	0.01	.43

CAD = coronary artery disease; SD = standard deviation; VO_{2peak} = peak oxygen consumption; CR = cardiac rehabilitation.

* Two-tailed significance in unadjusted bivariate mixed models.

($r = 0.11$, $p = .40$). In an unadjusted model, change in RHI ($b = 0.003$, $p = .66$) was not associated with change in VO_{2peak} over CR. Unadjusted associations between RHI, raw cognitive test scores, and all covariates are reported in Table S1 (Supplemental Digital Content, <http://links.lww.com/PSYMED/A526>).

Cognitive Performance

As shown in Table 2, mean overall cognition score and domain-specific Z-scores at entry into CR were in the nonimpaired range (impairment defined by Z-score ≤ 1.5 SDs). Higher VO_{2peak} was not associated with overall cognition or individual cognitive domain Z-scores at baseline. During CR, an increase in VO_{2peak} was not associated with an improvement in overall cognition or specific cognitive domains in unadjusted bivariate associations (Table 2).

Associations Between RHI and Overall Cognition (Primary Outcome)

RHI was not associated with overall cognition at baseline adjusting for age, sex, years of education, smoking history, and VO_{2peak} (Table 3). However, an increase in RHI was significantly associated with an improvement in overall cognition during CR (Table 4). Specifically, a unit increase in RHI over CR was associated with a 0.55 SD improvement in overall cognition over time.

TABLE 3. Associations Between RHI and Cognitive Domains in Patients With CAD

Cognitive Domain	Association with RHI	
	β	<i>p</i> (<i>p</i> < .05)*
Overall cognition	0.26	.10
Verbal memory	0.28	.027*
Visuospatial memory	0.03	.82
Processing speed	0.20	.13
Executive function	0.10	.55

CAD = coronary artery disease; RHI = reactive hyperemia index.

Multiple linear regression analyses controlling for age, sex, years of education, smoking history, and VO_{2peak} were used to determine cross-sectional associations.

* Two-tailed significance.

Associations Between RHI and Individual Cognitive Domains

Lower RHI was significantly associated with poorer verbal memory but not performance in other cognitive domains including visuospatial memory, processing speed, and executive function at baseline adjusting for potential confounders (Table 3). This model suggested that each unit lower in RHI was associated with a 0.65 SD lower in verbal memory performance ($F = 2.94$, $p = .015$, adjusted coefficient of determination (R^2) = 0.16).

During CR, an increase in RHI was significantly associated with improvement in processing speed (Table 4). Specifically, a unit increase in RHI was associated with a 0.42 SD improvement in processing speed over time.

DISCUSSION

The present study assessed the relationships between peripheral measurements of microvascular endothelial function and cognitive performance at entry and after 3 months of CR in patients with CAD. Although RHI was not cross-sectionally associated with overall cognition, an increase in RHI during CR was associated with an improvement in overall cognition. Lower RHI, indicating poorer endothelial function, was significantly associated with poorer verbal memory performance at entry into CR, whereas an increase in RHI over CR was associated with improvement in processing speed. These findings suggest that RHI is a possible predictor of early cognitive changes in patients with CAD.

TABLE 4. Associations Between Change in RHI and Change in Cognitive Domains Over 3 Mo of CR in Patients With CAD

Cognitive Domain	Association with RHI	
	<i>b</i>	<i>p</i> (<i>p</i> < .05)*
Overall cognition	0.55	.030*
Verbal memory	0.36	.093
Visuospatial memory	0.18	.45
Processing speed	0.42	.033*
Executive function	0.48	.061

CAD = coronary artery disease; CR = cardiac rehabilitation; RHI = reactive hyperemia index.

Multivariate mixed models controlling for age, sex, years of education, smoking history, and VO_{2peak} were used to determine longitudinal associations.

* Two-tailed significance.

The role of vascular disease in the pathogenesis of cognitive impairment is an area of keen investigation. Although neurodegeneration is largely considered to underlie cognitive decline and dementia, coexistent or isolated cerebrovascular disease has also been suggested as an important contributor to these changes (3). Previously, FMD, a common proxy for endothelial function, was associated with performance in attention, executive function, and processing speed in hypertensive patients and those with cardiovascular disease (15). Recently, a community-based study reported significant associations between RHI, visuospatial ability, and executive function performance (36). Our findings identify novel associations between RHI and verbal memory in patients with CAD, a population at increased risk of cognitive decline.

Exercise may be protective against cognitive decline because of associations with increases in hippocampal volume (7) and cerebral blood flow (37), which may partly mediate cognitive improvement after exercise. In the present study, cardiopulmonary fitness was not significantly associated with improvement in overall cognition or specific cognitive domains during CR. Associations between cardiopulmonary fitness and cognitive improvement have been inconsistent, and variability in cognitive response to exercise has been reported, particularly in those at high risk of cognitive decline (38), such as those with CAD. Findings from this study reinforce the hypothesis that poor vascular health may be a significant contributor to the variability in cognitive response to exercise.

No study to date has assessed longitudinal relationships between microvascular endothelial function as measured by PAT and cognitive performance. In the present study, an increase in RHI was significantly associated with an improvement in overall cognition and, specifically, processing speed. These findings are consistent with the only other study assessing longitudinal associations between a marker of endothelial function and cognition, in which, lower brachial FMD was significantly associated with a decline in processing speed over 7 years in elderly patients with CAD (39). Present findings are also in accordance with previous associations between FMD and white matter hyperintensities (40) known to be associated with common cognitive deficits consistent with VCI (3). Nitric oxide deficiency underlying peripheral measures of endothelial dysfunction has also been associated with hypoperfusion, which may discriminately damage frontal-subcortical circuits and impair cerebral reactivity (15). This may partly explain the higher prevalence of deficits in processing speed in the study population and a greater magnitude of improvement in this domain compared with memory during CR.

Contrary to previous findings (39), an increase in RHI was not associated with improvement in executive function when adjusting for cardiopulmonary fitness. It is possible that fitness level moderates the effect of endothelial dysfunction on executive function; exercise has been associated with augmented endothelial function (41) and executive function may be the most amenable to the positive effects of exercise (42–44) with greater aerobic capacity associated with better functioning in cognitively at-risk populations (45).

While exercise has been associated with augmented endothelial function, a decrease in endothelial function was not associated with changes in cardiopulmonary fitness in this study. This may be due to several reasons. First, exercise modality may be an important contributor to changes in vascular health. Resistance training may possibly be more beneficial for improvement in vascular

health compared with aerobic exercise (46). Although the CR program in this study consisted of a combination of both aerobic and resistance training, resistance training could not be assessed as an independent predictor of change in vascular health indices because of missing data. Second, improvements in endothelial function may be intimately linked with cardiovascular risk factor modification, such as weight loss, reductions in insulin resistance, or changes in systolic blood pressure (47) after exercise. Consistent with this suggestion, high HbA1c levels and negligible change in body composition measures over CR may explain the lack of association between cardiopulmonary fitness and vascular health observed in this study sample. In addition, changes in vascular health may be influenced by exercise intensity and length of the exercise intervention (48).

Approximately 35% of CAD patients may have cognitive impairment (49). Hence, CAD patients are an ideal population to study associations between vascular disease and cognitive changes because they represent a population with extensive vasculopathy and show subtle early cognitive changes consistent with a preclinical stage (9) when interventions may still be beneficial. This study was strengthened by assessment of temporal relationships between cognitive outcomes, vascular health indices, and effects of exercise, adding to the current literature largely constrained by cross-sectional studies, heterogeneous populations, and methodological differences. In addition, although both FMD and RH-PAT are non-invasive, RH-PAT is advantageous in that it is nonoperator dependent and the contralateral arm serves as an internal control (29). Furthermore, unlike FMD, RHI quantifies the pulsatile volume changes to reactive hyperemia in the microvasculature, which may be more reflective of cerebrovasculature changes (50).

A potential limitation of this study was the use of typical preventative drugs including antihypertensives, aldosterone antagonists, statins, antidiabetic agents, and aspirin, which may have attenuated associations between RHI and cognitive performance (51). Although the study sample was predominantly married white males who were highly educated, it was quite representative of CR participants, which may contribute to the generalizability of the results. Also, data were not available on those who declined to participate in the study to assess recruitment bias but comparison with an unselected sample suggested that the study sample was representative of the CR population. Practice effects may have contributed to the overall improvement in cognitive outcomes; however, a 3-month interval between testing would be expected to minimize such effects on cognitive tests (52). Even though the group as a whole improved, a substantial number of participants (97%) had a decrease on one or more cognitive tests at follow-up despite participation in CR. Subtle changes in cognitive test scores over CR though significant, may not reflect a clinically meaningful change. However, the importance of even subtle changes in cognitive performance in this population has been demonstrated with previous associations with poorer outcomes such as failure to complete CR (5). Future studies should include a control group to determine the independent effects of CAD on the association between RHI and cognition.

In patients with CAD, endothelial dysfunction was significantly associated with poor verbal memory and improvement in endothelial function during CR was significantly associated with improvements in overall cognition and processing speed. These findings suggest that RHI may be of clinical relevance in

cognitively vulnerable populations such as those with CAD. Despite a lack of association with cardiopulmonary fitness, improvements in RHI over CR indicate the importance of lifestyle modifications and pharmacotherapy in modulating vascular health. Assessment of neuroimaging correlates in future studies will further clarify relationships with cognition and facilitate development of vascular health indices as clinically useful predictors of early cognitive changes.

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