RESEARCH ARTICLE

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Subcortical hyperintensities in the cholinergic system are associated with improvements in executive function in older adults with coronary artery disease undergoing cardiac rehabilitation

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Objective: Coronary artery disease (CAD) is frequently accompanied by white matter hyperintensities and executive dysfunction. Because acetylcholine is important in executive function, these symptoms may be exacerbated by subcortical hyperintensities (SH) located in cholinergic (CH) tracts. This study investigated the effects of SH on cognitive changes in CAD patients undergoing a 48-week cardiac rehabilitation program.

Methods: Fifty patients (age 66.5 ± 7.1 years, 84% male) underwent the National Institute of Neurological Disorders and Stroke – Canadian Stroke Network neurocognitive battery at baseline and 48 weeks. Patients underwent a 48-week cardiac program and completed neuroimaging at baseline. Subcortical hyperintensities in CH tracts were measured using Lesion Explorer. Repeated measures general linear models were used to examine interactions between SH and longitudinal cognitive outcomes, controlling for age, education, and max VO_2 change as a measure of fitness.

Results: In patients with SH in CH tracts, there was a significant interaction with the Trail Making Test (TMT) part A and part B over time. Patients without SH improved on average 16.6 and 15.0% on the TMT-A and TMT-B, respectively. Patients with SH on average showed no improvements in either TMT-A or TMT-B over time. There were no significant differences in other cognitive measures.

Conclusion: These results suggest that CAD patients with SH in CH tracts improve less than those without SH in CH tracts, over 48 weeks of cardiac rehabilitation. Thus, SH in CH tracts may contribute to longitudinal cognitive decline following a cardiac event and may represent a vascular risk factor of cognitive decline. © 2017 The Authors. *International Journal of Geriatric Psychiatry* Published by John Wiley & Sons Ltd.

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Introduction

Coronary artery disease (CAD) is a leading cause of disability and is responsible for an estimated 7.4 million deaths per year worldwide (WHO, 2014). An under-recognized symptom of CAD is an increased risk of developing cognitive impairment, especially in executive function domains (Eggermont *et al.,* 2012). Indeed, CAD is a significant risk factor for developing vascular dementia and Alzheimer's disease (AD) in the future (Kovacic *et al.,* 2012).

While the benefits of exercise on cardiac outcomes in CAD have long been known, the potential benefits on delaying cognitive decline or even improving cognitive outcomes are increasingly being recognized (Colcombe and Kramer, 2003; Stanek *et al.,* 2011; Alosco *et al.,* 2014). Indeed, cardiorespiratory fitness ameliorates age-related losses in grey matter (Colcombe *et al.,* 2003). However, the cognitive improvements associated with increasing fitness through cardiac rehabilitation (CR) are heterogeneous (Colcombe and Kramer, 2003) indicating a need to explore the mechanisms that may hinder the cognitive benefits of exercise.

Studies have shown that CAD and its associated cardiovascular risk factors are correlated with damage to the white matter (Schmidt *et al.,* 1992). Disruption of the white matter is typically characterized as white matter hyperintensities (WMH) which are associated with microvascular injuries (Young *et al.,* 2008). Furthermore, the locations of these WMH are important with regards to impairments in different cognitive domains (Yoshita *et al.,* 2006; Biesbroek *et al.,* 2013; Birdsill *et al.,* 2014). More specifically, damage to cholinergic pathways have been shown to be associated with dementia (Swartz *et al.,* 2003). A number of studies in animals and humans of advanced age and AD have found that the severity of abnormalities in the cholinergic tracts correlates with the degree of cognitive decline (Terry and Buccafusco, 2003). Those studies have contributed to the development of the cholinergic hypothesis, stating that a loss of cholinergic function in the central nervous system (CNS) would contribute to cognitive deterioration (Bartus, 2000).

In patients with cerebrovascular risk factors or stroke, subcortical hyperintensities (SH) are common (Schmidt *et al.,* 1992) and are increasingly prevalent with aging (Ylikoski *et al.,* 1995). Subcortical hyperintensities in cholinergic tracts have been associated with memory and executive function deficits in patients with AD and vascular dementia (Behl *et al.,* 2007), executive dysfunction in patients with subcortical ischemic vascular dementia (Kim *et al.,* 2013), and executive function in patients with strokes (Muir *et al.,* 2015). As CAD is a risk factor for developing cerebrovascular disease and stroke (Anderson and Robertson, 2013), and dementia (Viswanathan *et al.,* 2009), SH involving cholinergic projections may be able to explain the cognitive changes observed in the CAD population.

The present study sought to determine whether the presence of SH in cholinergic tracts contributed to the heterogeneity in cognitive response to exercise as seen in patients with CAD undergoing a 48-week CR program. The aim of the study was to explore the neuropathological differences underlying the variation seen in cognitive response to exercise as well as to examine potential neuroimaging biomarkers for cognitive impairment and dementia in a patient population at-risk for future cognitive decline.

Methods

Participants

The Research Ethics Boards at Sunnybrook Health Sciences Centre (SHSC) and University Health Network (UHN) approved this study, and informed consent was obtained from all participants prior to study enrollment.

Eligible patients were 50–80 years could speak and understand English and had evidence of stable CAD (at least one of MI, $\geq$50% blockage in at least one major coronary artery, percutaneous coronary intervention, or coronary artery bypass graft surgery and no hospitalization for cardiac events in the 4 weeks prior). Participants were excluded if they had contraindications to an MRI, psychiatric illnesses other than depression, a diagnosed neurological disorder, or significant cognitive impairment (Mini-Mental Status Examination $<$ 24) (Perry *et al.,* 2000).

All participants were enrolled in a CR program at a standardized time (within 10 weeks) after experiencing an acute coronary syndrome (ACS). The CR program was 48 weeks in duration and was comprised of aerobic and resistance exercises completed under the supervision of exercise and medical specialists. As part of the CR program, participants underwent a peak oxygen uptake (VO_{2peak}) assessment, by exercise stress test, which provides an accurate and reproducible objective measure of cardiopulmonary fitness (Shephard *et al.,* 1968). Following this, participants attended exercise visits once a week that included an aerobic walk or

walk/jog for 36 weeks and then once per month for the remaining 12 weeks. Additionally, participants were expected to exercise independently 5 out of 7 days per week.

Demographics (age, gender, education), cardiac history, vascular risk factors, concomitant medication use, medical/psychiatric comorbidities, and anthropometrics were collected by chart review or during patient interview. Baseline cognitive assessments were performed within 10 days of MRI acquisition.

Cognitive assessments

Cognitive performance was assessed using a battery of tests recommended by the National Institute of Neurological Disorders and the Canadian Stroke Network for vascular cognitive impairment (Hachinski *et al.*, 2006). Executive function and processing speed were assessed using the Digit Symbol Substitution Test (DSST) and the Trail Making Test (TMT). The language domain was assessed using the FAS Verbal Fluency Test and the Animal Naming Test. Verbal memory was assessed using the California Verbal Learning Test—2nd edition (CVLT-II), and visuospatial memory was assessed using the Brief Visuospatial Memory Test—Revised (BVMT-R). Patients were assessed at baseline and at 48 weeks. Cognitive test raters were blinded to the neuroimaging results.

MRI acquisition

All imaging was performed at SHSC in Toronto, Canada on a 3.0 Tesla General Electric Discover MR750 MR scanner. An optimized multimodality imaging protocol was used to acquire high-resolution T1- and proton density (PD)/T2-weighted and fluid attenuated inversion recovery (FLAIR) images.

MRI processing

Structural MRI (T1, T2, and FLAIR) were processed using the SABRE pipeline (Dade *et al.*, 2004). White matter hyperintensities were identified using Lesion Explorer (Ramirez *et al.*, 2011) and further localized to lateral cholinergic projections using the cholinergic hyperintensities projections scale (Bocti *et al.*, 2005). Cholinergic hyperintensities projections scale is a visual rating scale used to determine the severity of WMH in cholinergic pathways using major anatomical landmarks in the axial plane.

Statistical analyses

Independent *T*-tests were used to determine difference in clinical characteristics between those with and without SH in cholinergic tracts. Repeated measures general linear models were used to determine effects of SH in cholinergic tracts over time (i.e. a visit × CH interaction) on changes in cognitive test performance. Statistical models used controlled for age, education, and percent change in VO_{2peak} as a measure of fitness, over 48 weeks of CR.

Post-hoc analysis was performed controlling for anti-cholinergic burden (ACB) due to concomitant medications because ACB was previously associated with executive function in CAD (Lanctot *et al.*, 2014). Because cognitive deficits have been shown to occur following an MI (Gharacholou *et al.*, 2011) or coronary revascularization procedures (Raja *et al.*, 2004), post-hoc analyses were performed to examine the influence of these conditions on the interaction between SH and changes in cognition. All analyses were performed using SPSS statistical software (version 19.0; IBM, Armonk, NY).

Results

Patient characteristics

One hundred and forty-five participants were screened, 124 showed evidence of CAD, 94 accepted contact by study personnel, and 74 provided written informed consent. Ten participants were excluded because of contraindications to MRI or application of the exclusion criteria. Fourteen patients did not return for a 48-week follow-up assessment, resulting in 50 participants included in the final analysis. Overall, the baseline cognitive performance of study participants was within the normal range, except for in six participants who performed at the borderline impaired range on the delayed recall of the BVMT-R, six participants on the TMT-A, four participants on the TMT-B, one participant on the long delayed free recall of the CVLT-II, one participant on the DSST, and one participant on the verbal fluency test, with no participants performing at the borderline impaired range on the animal naming test. At the 48-week follow-up, six participants performed at the borderline impaired range in the BVMT-R, four participants in the TMT-A, two participants in the TMT-B, four

participants in the CVLT-II, one participant on the DSST, one participant in the verbal fluency test, and no participants in the animal naming test.

Cognitive outcomes

Overall, there were significant improvements over 48 weeks of CR in TMT-A ($t(49) = 2.01$, $p = .050$), DSST ($t(49) = 2.05$, $p = .046$), and verbal memory ($t(49) = 3.24$, $p = .002$), but not TMT-B ($t(49) = 1.44$, $p = .155$), visuospatial memory ($t(49) = .58$, $p = .567$), verbal fluency test ($t(49) = 1.30$, $p = .201$), or animal naming test ($t(49) = 1.35$, $p = .182$).

Table 1 shows participant demographics in those with ($n = 24$) and without ($n = 26$) SH in the cholinergic tracts. Coronary artery disease patients with SH were significantly younger than those without SH ($t(48) = -2.375$, $p = 0.022$). The smoking category included current and past smokers, of which only two were current smokers. There were no other differences in demographics and clinical characteristics between the groups. No significant differences in baseline VO_{2peak} were found between the two groups, and all patients improved their VO_{2peak} by an average of 28.0% ($t(49) = 10.95$, $p < .001$) over 48 weeks of CR. There were no significant differences between patients with and without SH in cholinergic tracts at baseline in performance on verbal memory ($F(1,49) = .23$, $p = .63$), visuospatial memory ($F(1,49) = .84$, $p = .36$), DSST ($F(1,49) = .20$, $p = .66$), TMT-A ($F(1,49) = .01$, $p = .93$), TMT-B ($F(1,49) = .59$, $p = .45$), verbal fluency test ($F(1,49) = .62$, $p = .44$), or animal naming test ($F(1,49) < .01$, $p > .99$). Likewise, no significant differences were found between these two groups at 48-week follow-up in performances on verbal memory ($F(1,49) = 1.55$, $p = .22$), visuospatial memory ($F(1,49) = .87$, $p = .36$), DSST ($F(1,49) = .02$, $p = .88$), TMT-A ($F(1,49) = .92$, $p = .34$), TMT-B ($F(1,49) = .32$, $p = .58$), verbal fluency test ($F(1,49) = .86$, $p = .36$), or animal naming test ($F(1,49) = 2.44$, $p = .13$) (Table 2).

Table 1 Participant characteristics and neuroimaging measures at baseline

Characteristic ($n = 50$)	Mean (SD) or % (n)	
Subcortical hyperintensities	Yes ($n = 24$)	No ($n = 26$)
Sociodemographic		
Age (years)*	68.9 (6.3)	64.3 (7.2)
Sex (% male)	83.3 (20)	84.6 (22)
Education (years)	16.4 (3.7)	15.3 (2.7)
Marital status (% married)	75.0 (18)	65.4 (17)
Ethnicity (% Caucasian)	87.5 (21)	88.5 (23)
Vascular risk factors		
Body mass index	28.9 (5.0)	28.3 (3.4)
Hypertension (% yes)	50.0 (12)	53.8 (14)
Hypercholesterolemia	95.8 (23)	100.0 (26)
Diabetes (% yes)	12.5 (3)	11.5 (3)
Smoking (% current or past smoker)	75.0 (18)	50.0 (13)
Cardiac history		
Percutaneous coronary intervention (PCI)	54.2 (13)	46.2 (12)
Coronary artery bypass graft (CABG)	37.5 (9)	50.0 (13)
Myocardial infarction (MI)	33.3 (8)	50.0 (13)
Cardiac rehabilitation baseline		
VO_{2peak}	19.1 (5.8)	18.6 (5.1)

*$t(48) = -2.375$, $p = 0.022$.

Cholinergic subcortical hyperintensities and cognition

The presence of SH in cholinergic tracts was significantly associated with less improvement in TMT-A ($F(1,45) = 4.21$, $p = 0.046$) and TMT-B ($F(1,45) = 5.17$, $p = 0.028$) over 48 weeks of CR. Patients without SH improved on average by 16.6% ($t(25) = 1.919$, $p = .066$) and 15.0% ($t(25) = 2.41$, $p = .024$) in performance on the TMT parts A and B, respectively. Patients with SH on average showed no significant change in TMT-A (3.4%, $t(23) = 0.695$, $p = .494$) or TMT-B (−3.2%, $t(23) = .48$, $p = .632$).

Table 2 Cognitive outcomes at baseline and 48-week follow-up

Cognitive assessment ($n = 50$)	Mean (SD) or % (n)	
Subcortical hyperintensities	Yes ($n = 24$)	No ($n = 26$)
Trail Making Test A—baseline	38.8 (24.5)	39.4 (18.8)
Trail Making Test A—48-week follow-up	37.5 (21.0)	32.8 (12.5)
Trail Making Test B—baseline	83.7 (41.2)	92.9 (44.1)
Trail Making Test B—48-week follow-up	86.3 (58.1)	79.0 (31.7)
Animal Naming—baseline	19.4 (7.2)	19.4 (4.9)
Animal Naming—48-week follow-up	22.1 (7.8)	19.0 (6.1)
FAS Verbal Fluency—baseline	45.6 (16.1)	42.1 (15.0)
FAS Verbal Fluency—48-week follow-up	46.9 (16.3)	42.6 (16.2)
Digit Symbol Substitution Test—baseline	60.3 (15.5)	62.1 (12.5)
Digit Symbol Substitution Test—48-week follow-up	62.8 (17.2)	63.5 (14.9)
CVLT-II—baseline	9.7 (4.0)	10.2 (3.7)
CVLT-II—48-week follow-up	10.4 (4.6)	11.9 (3.4)
BVMT-R—baseline	8.8 (3.4)	9.6 (2.6)
BVMT-R—48-week follow-up	8.6 (3.7)	9.4 (2.6)

There were no significant interactions between the presence of SH in cholinergic tracts and changes in performance over 48 weeks of CR in all other neurocognitive tests assessed: verbal memory ($F(1,45) = 1.33$, $p = .26$), visuospatial memory ($F(1,45) = .09$, $p = .77$), DSST ($F(1,45) < .01$, $p > .99$), verbal fluency test ($F(1,45) < .01$, $p = .98$), and animal naming test ($F(1,45) = 2.94$, $p = .09$).

Post-hoc analyses

Anticholinergic medication burden. Twenty-eight out of 50 participants were on at least one anticholinergic medication: three of the 28 were on two anticholinergic medications, while one of the 28 was on four anticholinergic medications. There was no difference in anticholinergic burden between patients with and without SH ($F(1,40) = .11$, $p = .75$). In a repeated measures general linear model controlling for age, education, percent change in VO_{2peak}, and anticholinergic burden, the interaction between presence of SH and improvements in TMT-A ($F(1,44) = 4.31$, $p = .044$) and TMT-B ($F(1,44) = 6.17$, $p = .017$) remained significant.

Cardiac history. In a repeated measures general linear model controlling for age, education, percent change in VO_{2peak}, and history of MI, the interaction between presence of SH and improvements in TMT-A ($F(1,44) = 4.20$, $p = 0.046$) and TMT-B ($F(1,44) = 4.74$, $p = 0.035$) performances over 48 weeks of CR remains significant. Similarly, in a repeated measures general linear model controlling for age, education, percent change in VO_{2peak}, and history of coronary artery bypass graft surgery, the interaction between presence of SH and improvements in TMT-A ($F(1,44) = 4.28$, $p = 0.045$) and TMT-B ($F(1,44) = 4.75$, $p = 0.035$) performance over 48 weeks of CR remains significant.

Fitness. In a repeated measures general linear model controlling for age, education, and percent change in VO_{2peak}, there was no interaction between the presence of SH and changes in BMI ($F(1,29) = .54$, $p = .47$) or VO_{2peak} ($F(1,29) = .00$, $p = .99$).

Program completion. Patients were considered to be completers of the standardized cardiac program if they attended ≥70% of the supervised weekly classes and completed the weekly exercise records. There was a significant difference in completion versus non-completion of CR between patients with and without SH ($F(1,45) = 4.87$, $p = .03$), with 83.3 and 96.1% completers, respectively. There was no significant difference between completers and non-completers of the program with regards to presence of depression ($F(1,45) = .36$, $p = .55$), diabetes ($F(1,45) = 1.67$, $p = .20$), or hypertension ($F(1,45) = .64$. $p = .43$). There was also no difference between these two groups in baseline cognitive test performance in the TMT-A ($F(1,45) = .01$, $p = .92$), TMT-B ($F(1,45) = .09$, $p = .77$), FAS ($F(1,44) = .81$, $p = .37$), Animal Naming Test ($F(1,44) = .00$, $p > .99$), Digit Symbol ($F(1,44) = 1.11$, $p = .30$), visuospatial memory ($F(1,45) = 0.42$, $p = .52$), and verbal memory ($F(1,45) = .02$, $p = .89$).

Discussion

The findings of this study demonstrated that patients with SH in cholinergic tracts do not improve on tasks of visuomotor speed and working memory subdomains of executive function compared to patients without SH over 48 weeks of CR (Figure 1). TMT-A is a validated, timed measure of psychomotor processing speed and visuospatial abilities, while TMT-B is a measure of working memory and set-shifting abilities (Sanchez-Cubillo *et al.,* 2009). In a study with stroke patients, high SH severity was associated with slower processing speed and more errors in executive set shifting as measured by TMT (Muir *et al.,* 2015). Similar sub-analysis of TMT in this CAD population did not reveal any significant differences between participants with and without SH (TMT-Difference $p = 0.18$, TMT-Quotient $p = .16$, TMT-Proportion $p = 0.16$). The results of these findings may be due to the severity of cerebrovascular disease in the patient populations—patients with CAD only being at higher risk for cerebrovascular disease while patients with stroke have already had a significant cerebrovascular accident. As such, SH in cholinergic tracts may be an important contributor to a patient's cognitive response to exercise interventions. Exercise interventions have the potential to induce neural and vascular plasticity and may have protective effects against abnormal aging. Specifically, executive function has been shown to improve over time with exercise intervention (Colcombe and Kramer, 2003). However, randomized controlled trials of exercise interventions in older individuals have reported variability in cognitive improvements (Ball *et al.,* 2002; Heyn *et al.,* 2004). The sources of this variability are likely not random and may be due to underlying differences in neuropathology.

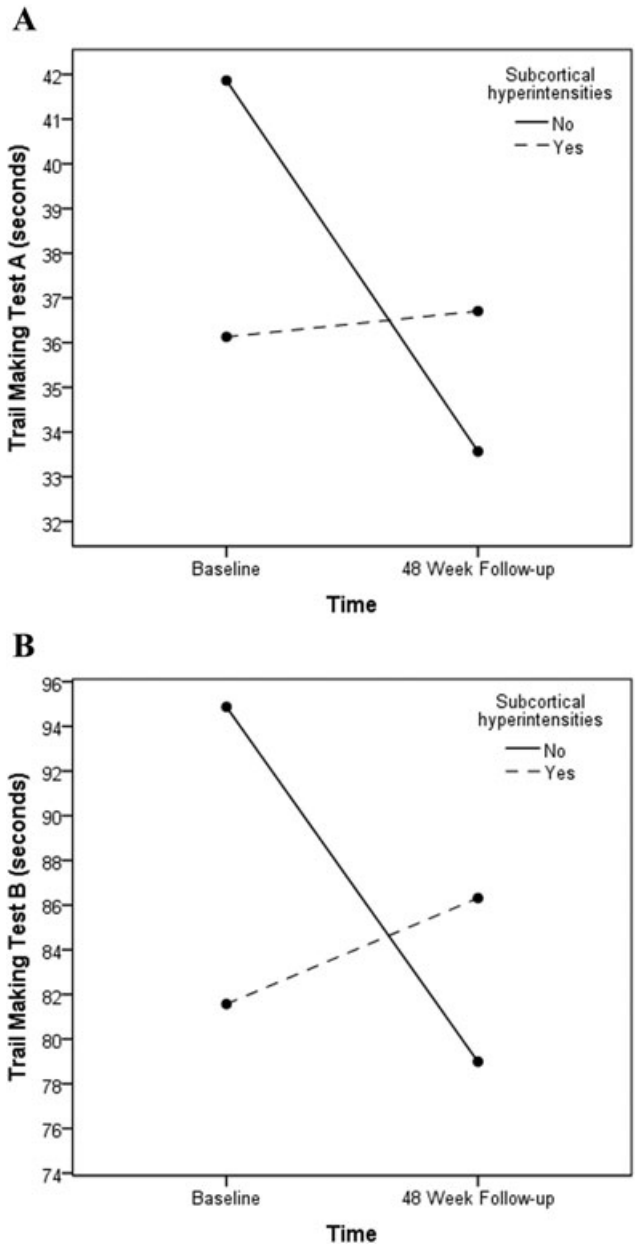

Figure 1 (A) Line graphs showing change in performance on the Trail Making Test A adjusted for age, education, and percent change in VO_{2peak} for participants with subcortical hyperintensities (dashed line) compared to those without (solid line) over 48 weeks of cardiac rehabilitation. Participants without subcortical hyperintensities significantly improved in the performance, while participants with subcortical hyperintensities showed no improvements. (B) Line graphs showing changes in performance on the Trail Making Test B comparing participants with subcortical hyperintensities (dashed line) to those without (solid line) over 48 weeks of cardiac rehabilitation. Participants without subcortical hyperintensities significantly improved in the performance, while participants with subcortical hyperintensities showed no improvements.

Longitudinal studies in patients with dementia have reported a causal relationship between WMH's and dementia severity (Prins and Scheltens, 2015). However, imaging studies investigating SH in cholinergic pathways report that SH localized specifically in these pathways may contribute to cognitive impairment more than total WMH burden (Swartz *et al.*, 2003). It has been suggested that the nucleus basalis-neocortical cholinergic system mediates visual attention (Everitt and Robbins, 1997). In rats, an impaired cholinergic system was associated with deficits in visual attention and working memory performance (Chudasama *et al.*, 2004). Both of these cognitive domains are important in completing the TMT-A and TMT-B tasks (Sanchez-Cubillo *et al.*, 2009).

The presence of SH in cholinergic tracts has shown to be associated with executive function in various populations including those with AD (Behl *et al.*, 2007), vascular dementia (Swartz *et al.*, 2003), stroke (Muir *et al.*, 2015), and Parkinson's disease (Shin *et al.*, 2012). Improvements in executive function in response to cholinergic therapy have been shown to be mitigated by the presence of SH in cholinergic pathways in AD patients (Behl *et al.*, 2007). To date, the association between SH in cholinergic tracts and executive dysfunction has not been shown in those with CAD, despite increased WMH burden in this population (Breteler *et al.*, 1994). In fact, in patients with significant cardiovascular disease, lower cardiac output was associated with greater SH burden (Jefferson *et al.*, 2007).

Despite the presence of SH in cholinergic tracts, there were no significant differences in the performances on the TMT-A and TMT-B between the two groups. This finding can be attributed to the fact that overall, the patients in this study were not cognitively impaired; thus, any differences between the two groups would be too small to detect. The findings demonstrate, however, that already in this relatively cognitively healthy population, SH in cholinergic tracts are associated with a lack of cognitive improvements in executive function over 48 weeks of CR compared to patients without SH.

Finally, the patients without SH were significantly older in this study group compared with those with SH ($p = 0.022$). Over 48 weeks of CR, however, the patients without SH improved in TMT performance, while the patients with SH showed no improvements. This finding suggests that while age is recognized as a significant overall contributor to cognitive health, it does not play a large role in cognitive response to CR.

No significant interactions between the presence of SH in cholinergic tracts and exercise were found in other cognitive tests. The presence of SH in cholinergic tracts was not associated with either verbal or visuospatial memory. There were also no significant findings for the DSST or Verbal Fluency tasks. This finding further supports the concept of different brain regions being responsible for different subdomains of executive function. Indeed, in a factor analysis, verbal fluency tasks loaded heavily towards the language function rather than executive function (Whiteside *et al.,* 2016). Further, while speed of visual scanning is heavily involved in both DSST and TMT, performance in TMT is also dependent on working memory and set-shifting capacity (Sanchez-Cubillo *et al.,* 2009). In this context, the findings of this study suggest that SH in cholinergic tracts may preferentially affect processing speed and set shifting ability necessary for TMT-A and TMT-B, respectively.

Patients with higher WMH volumes were found to be more likely to have cholinergic involvement. However, there is no interaction between global WMH volumes and cognitive response to exercise, whereas there is an interaction between SH in cholinergic tracts and cognitive response. These findings suggest that while global WMH is an important factor in SH in cholinergic tracts, only WMH localized in the cholinergic tracts contribute to differences in cognitive response to exercise.

Several factors should be considered in interpreting this study. The study is limited by the lack of a healthy control group; therefore, the independent contributions of cardiac events and vascular risk factors cannot be examined. However, comparing patients with CAD with and without cholinergic SH allowed assessment specific to whether presence of these SH contributed to a mechanism that has been associated with an increased risk of vascular cognitive impairment. The relatively high level of education of these study participants may have contributed to a cognitive reserve that possibly masked subtle cognitive deficits. The study sample consisted of patients referred to the CR program, which may have introduced a selection bias. However, CR is a standard of care and provided publicly in Canada, potentially reducing the referral bias. In addition, there appeared to be a significant difference in completion versus non-completion between patients with and without SH at 83.3 and 96.1%, respectively. However, interpretation of this finding is limited by the small number of non-completers (n = 5). Similarly, we cannot adequately determine whether completion was significantly associated with baseline characteristics and measures such as cognitive and neuroimaging results or cognitive and CR outcomes in a 48-week follow-up. This rate of completion in our cohort is high, especially because predictors of non-completion such as diabetes were present in this study cohort (Worcester *et al.,* 2004). While standardized guidelines were applied to the exercise program, exercise prescriptions were tailored to each individual participant's baseline fitness; thus, specific exercise intensity and activities may have differed among the participants. These individual exercise intensity and activities were not captured in this study. However, because there was no significant difference between baseline maxVO_2 or BMI, there is unlikely to be a significant difference in exercise intensity or activities between groups. Finally, a total of six cognitive tests were investigated. Given the exploratory nature of this study, statistical corrections for multiple comparisons were not performed. The findings of this study require further research to more fully elucidate the relationship between cognition and the presence of SH in cholinergic tracts.

Coronary artery disease is a significant risk factor for developing AD and vascular dementia; however, the neuropathological mechanisms responsible for progression are not well elucidated. This study provides evidence that the presence of SH in cholinergic tracts may be associated with non-improvements in executive function during CR and may be involved in the pathophysiological process of progression to dementia in an otherwise cognitively healthy, but at-risk population. This study identifies an important neuropathological contributor to differences in cognitive improvements over 48 weeks of CR in patients with CAD and provides a key insight into the mechanisms of CAD-related executive dysfunction.

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Conflict of interest

Calvin Santiago reports no disclosures.

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Key points

- Executive dysfunction is associated with coronary artery disease.
- Cardiac Rehabilitation is associated with improvements in cognitive function, but the response is heterogeneous.
- Subcortical hyperintensities in cholinergic tracts may contribute to the variable cognitive response to cardiac rehabilitation.

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