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

Calvin Santiago1,2, Nathan Herrmann1,3,4, Walter Swardfager4,5, Mahwesh Saleem1,5, Paul I. Oh2, Sandra E. Black4,6,7, Janelle Bradley1 and Krista L. Lanctôt1,2,3,4,5,7

1Neuropsychopharmacology Research Group, Sunnybrook Research Institute, Toronto, Ontario, Canada
2Toronto Rehabilitation Institute, Toronto, Ontario, Canada
3Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
4Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, Ontario, Canada
5Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada
6Department of Medicine (Neurology), Sunnybrook Health Sciences Centre and University of Toronto, Toronto, Ontario, Canada
7Brain Sciences Research Program, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
Correspondence to: K. L. Lanctôt, E-mail: krista.lanctot@sunnybrook.ca

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 VO2 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.

Key words: cerebrovascular disease; vascular dementia; neuroimaging; executive function; cognition; white matter disease

History: Received 01 December 2016; Accepted 24 March 2017; Published online 5 May 2017 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/gps.4729
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 (Kovacíč 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; Alcoso 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, ≥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 (VO2peak) 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 (Bocci 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 VO2peak 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, four participants on the TMT-A, two participants in the TMT-B, four participants 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 \((t(48) = -2.375, p = .022)\). 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\(_{2\text{peak}}\) were found between the two groups, and all patients improved their VO\(_{2\text{peak}}\) 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).

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 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\(_{2\text{peak}}\) | 19.1 (5.8) | 18.6 (6.1) |

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

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 \(\text{VO}_2\text{peak}\), 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 \(\text{VO}_2\text{peak}\), and history of MI, the interaction between presence of SH and improvements in TMT-A \((F(1,44) = 4.20, p = .046)\) and TMT-B \((F(1,44) = 4.74, p = .035)\) performances over 48 weeks of CR remains significant. Similarly, in a repeated measures general linear model controlling for age, education, percent change in \(\text{VO}_2\text{peak}\), and history of coronary artery bypass graft surgery, the interaction between presence of SH and improvements in TMT-A \((F(1,44) = 4.28, p = .045)\) and TMT-B \((F(1,44) = 4.75, p = .035)\) performance over 48 weeks of CR remains significant.

**Fitness.** In a repeated measures general linear model controlling for age, education, and percent change in \(\text{VO}_2\text{peak}\), there was no interaction between the presence of SH and changes in BMI \((F(1,29) = .54, p = .47)\) or \(\text{VO}_2\text{peak} \ (F(1,29) = .00, p = .99)\).

**Program completion.** Patients were considered to be completers of the standardized cardiac program if they attended \(\geq 70\%\) 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 sub-domains 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.
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.

**Figure 1** (A) Line graphs showing change in performance on the Trail Making Test A adjusted for age, education, and percent change in VO$_2$peak 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.
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 maxVO2 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 contributo 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.

**Study funding**

Funding support was provided by: Canadian Institute of Health Research (Lanctot MOP-114913) and the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery.

**Conflict of interest**

Calvin Santiago reports no disclosures.

Nathan Herrmann is supported by peer-reviewed grants from the Alzheimer Society of Canada, Canadian Institute of Health Research, Heart and Stroke Foundation, Ontario Ministry of Health and Long Term Care AFP Provincial Innovation Fund.
and Ontario Brain Institute in addition to research contracts funded by F. Hoffman-La Roche Ltd, and Lundbeck Canada Inc.

Walter Swardfager was supported in part by the Department of Pharmacology and Toxicology, University of Toronto, by the Hurvitz Brain Sciences Program, Sunnybrook Research Institute, by the University Health Network Toronto Rehabilitation Institute, and by the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery.

Mahwesh Saleem was supported by funding from the Alzheimer’s Society of Canada.

Paul I Oh is on the advisory boards for Amgen, Janssen, Pfizer, Astra Zeneca, and Sanofi.

Sandra E Black is supported by peer-reviewed grants from the Canadian Institute of Health Research, Heart and Stroke Foundation, Alzheimer’s Drug Discovery Fund, W. Garfield Weston Foundation, Canada Foundation for Innovation, Ontario Brain Institute, National Institute of Health (USA), Academic Health Science Centres AFP Innovation Fund, University of Toronto Department of Medicine Innovation Fund, Canadian Partnership for Stroke Recovery, contract research funded by Elan Pharma International Ltd, Pfizer Canada, Lundbeck, and Hoffman-La Roche Ltd.

References

Aloso ML, Spitznagel MB, Cohen R, et al. 2014. Cardiac rehabilitation is associated with lasting improvements in cognitive function in older adults with heart failure. *Acta Cardiol* 69: 407–414.

Anderson JT, Robertson NP. 2013. Risk factors and cerebrovascular disease. *J Neurol* 260: 692–694.

Ball K, Berch DB, HelmersKF, et al. Advanced Cognitive Training for, L. & Vital Elderly Study, G. 2002. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA* 288: 2271–2281.

Bartus RT. 2000. On neurodegenerative diseases, models, and treatment strategies: lessons learned and lessons forgotten a generation following the cholinergic hypothesis. *Exp Neurol* 163: 495–529.

Behl P, Bocti C, Swartz RH, et al. 2007. Strategic subcortical hyperintensities in cholinergic pathways and executive function decline in treated Alzheimer patients. *Arch Neurol* 64: 266–272.

Birdell AC, Koschik RL, Janitzis EM, et al. 2014. Regional white matter hyperintensities: aging, Alzheimer’s disease risk, and cognitive function. *Neurobiol Aging* 35: 769–776.

Bocti C, Swartz RH, Gao FQ, et al. 2005. A new visual rating scale to assess strategic white matter hyperintensities within cholinergic pathways in dementia. *Stroke* 36: 2126–2131.

Breteler MM, van Swieten JC, Bots ML, et al. 1994. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology* 44: 1246–1252.

Chudasama Y, Dalley JW, Nathwani F, Bouger P, Robbins TW. 2004. Cholinergic modulation of visual attention and working memory: dissociable effects of basal forebrain 192-IgG-saporin lesions and intraperitoneal infusions of scopolamine. *Learn Mem* 11: 78–86.

Colcombe S, Kramer AF. 2003. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* 14: 125–130.

Colcombe SJ, Erickson KI, Raz N, et al. 2003. Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci* 58: 176–180.

Dade LA, Gao FQ, Kovacevic N, et al. 2004. Semiautomatic brain region extraction: a method of parcellating brain regions from structural magnetic resonance images. *Neuroimage* 22: 1492–1502.

Eggermont LH, de Boer K, Muller M, et al. 2012. Cardiac disease and cognitive impairment: a systematic review, *Heart* 98: 1334–1340.

Everitt BJ, Robbins TW. 1997. Central cholinergic systems and cognition. *Annu Rev Psychol* 48: 649–684.

Gharacholou SM, Reid KJ, Arnold SV, et al. 2011. Cognitive impairment and outcomes in older adult survivors of acute myocardial infarction: findings from the translational research investigating underlying disparities in acute myocardial infarction patients’ health status registry. *Am Heart J* 162: 860–869 e1.

Hachinski V, Iadecola C, Petersen RC, et al. 2006. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke* 37: 2220–2241.

Heyn P, Abreu BC, Ottenbacher KJ. 2004. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch Phys Med Rehabil* 85: 1694–1704.

Jefferson AL, Tate DF, Poppas A, et al. 2007. Lower cardiac output is associated with greater white matter hyperintensities in older adults with cardiovascular disease. *J Am Geriatr Soc* 55: 1044–1048.

Kim HJ, Moon WJ, Han SH. 2013. Differential cholinergic pathway involvement in Alzheimer’s disease and subcortical ischemic vascular dementia. *J Alzheimers Dis* 35: 129–136.

Kovacic JC, Castellano JM, Fuster Y. 2012. The links between complex coronary disease, cerebrovascular disease, and degenerative brain disease. *Ann N Y Acad Sci* 1254: 99–105.

Lancot KL, O’Regan J, Schwartz Y, et al. 2014. Assessing cognitive effects of anti-cholinergic medications in patients with coronary artery disease. *Psychosomatics* 55: 61–68.

Muir RT, Lam B, Hon L, et al. 2015. Trail making test elucidates neural substrates of specific poststroke executive dysfunctions. *Stroke* 46: 2755–2761.

Perry RJ, Watson P, Hodges JR. 2000. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer’s disease: relationship to episodic and semantic memory impairment. *Neuropsychologia* 38: 252–271.

Prins ND, Schelms P. 2015. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* 11: 157–165.

Raja PV, Blumenthal JA, Doraiswamy PM. 2004. Cognitive deficits following coronary artery bypass grafting: prevalence, prognosis, and therapeutic strategies. *CNS Spectr* 9: 763–772.

Ramirez J, Gibson E, Quddus A, et al. 2011. Lesion Explorer: a comprehensive segmentation and parcellation package to obtain regional volumetrics for subcortical hyperintensities and intracranial tissue. *Neuroimage* 54: 963–973.
Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, et al. 2009. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J Int Neuropsychol Soc 15: 438–450.

Schmidt R, Fazekas F, Kleinert G, et al. 1992. Magnetic resonance imaging signal hyperintensities in the deep and subcortical white matter. A comparative study between stroke patients and normal volunteers. Arch Neurol 49: 825–827.

Shephard RJ, Allen C, Benade AJ, et al. 1968. The maximum oxygen intake. An international reference standard of cardiorespiratory fitness. Bull World Health Organ 38: 757–764.

Shin J, Choi S, Lee JH, et al. 2012. Subcortical white matter hyperintensities within the cholinergic pathways of Parkinson’s disease patients according to cognitive status. J Neurol Neurosurg Psychiatry 83: 315–321.

Stanké KM, Gunstad J, Spitznagel MB, et al. 2011. Improvements in cognitive function following cardiac rehabilitation for older adults with cardiovascular disease. Int J Neurosci 121: 86–93.

Swartz RH, Sahlas DJ, Black SE. 2003. Strategic involvement of cholinergic pathways and executive dysfunction: does location of white matter signal hyperintensities matter? J Stroke Cerebrovasc Dis 12: 29–36.

Terry AV Jr, Bacccaflusco JJ. 2003. The cholinergic hypothesis of age and Alzheimer’s disease-related cognitive deficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Ther 306: 821–827.

Viswanathan A, Rocca WA, Tzourio C. 2009. Vascular risk factors and dementia: how to move forward? Neurology 72: 368–374.

Whiteside DM, Kealey T, Semla M, et al. 2016. Verbal fluency: language or executive function measure? Appl Neuropsychol Adult 23: 29–34.

WHO 2014. Global status report on noncommunicable diseases 2014.

Worcester MU, Murphy BM, Mee VK, Roberts SB, Goble AJ. 2004. Cardiac rehabilitation programmes: predictors of non-attendance and drop-out. Eur J Cardiovasc Prev Rehabil 11: 328–335.

Yikoski A, Erkinjuntti T, Raininko R, et al. 1995. White matter hyperintensities on MRI in the neurologically nondiseased elderly: Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. Stroke 26: 1171–1177.

Young VG, Halliday GM, Kril JJ. 2008. Neuropathologic correlates of white matter hyperintensities. Neurology 71: 804–811.