White Matter Microstructural Integrity Is Associated with Executive Function and Processing Speed in Older Adults with Coronary Artery Disease

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Objective: *Coronary artery disease (CAD) is associated with an increased risk of cognitive decline. Although cerebral white matter (WM) damage predicts cognitive function in CAD, conventional neuroimaging measures only partially explain the effect of CAD on cognition. The purpose of this study was to determine if WM microstructural integrity and CAD using diffusion tensor imaging (DTI) correlates with cognitive function in older adults with CAD.* **Methods:** *Forty-nine CAD patients (66 ± 7 years old, 86% male) underwent neurocognitive assessments using the cognitive battery recommended by the National Institute of Neurological Disorders and Stroke–Canadian Stroke Network for the study of vascular cognitive impairment. Composite scores for each cognitive domain were calculated. Microstructural integrity in normal-appearing WM was quantified as fractional anisotropy (FA) using DTI in nine bilateral and two interhemispheric WM tracts from the Johns Hopkins University WM Tractography Atlas. Linear regression models examined associations between FA and cognitive performance, controlling for age, sex, and education, with correction for multiple comparisons using a false discovery rate of 5%.* **Results:** *Executive function was most significantly associated with FA in the left parahippocampal cingulum ($\beta = 0.471$, $t = 3.381$, $df = 44$, $p = 0.002$) and left inferior fronto-occipital fasciculus ($\beta = 0.430$, $t = 2.984$, $df = 44$, $p = 0.005$). FA was not associated with memory in any of the WM tracts examined.* **Conclusion:** *These results suggest that WM microstructural integrity may be an important neural correlate of executive function even in cognitively intact CAD patients. This study suggests WM damage may be relevant to subtle cognitive decline in a population that may have early neural risk for dementia.* (Am J Geriatr Psychiatry 2015; 23:754–763)

Key Words: Cerebrovascular disease, vascular dementia, diffusion tensor imaging, executive function, cognition, white matter disease

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INTRODUCTION

Coronary artery disease (CAD) and associated vascular risk factors are associated with increased risk for cognitive decline and progression to dementia.[1,2] Among the cognitive domains, executive function has been suggested to be particularly vulnerable in those with CAD.[3,4] However, the contributions of CAD and associated cardiovascular risk factors to cognitive decline in healthy aging remain largely under-recognized in clinical care.[5,6] It is important to examine damage to the cerebral white matter (WM) network in this population because WM damage cannot only predict cognitive decline in older adults[7,8] but also future ischemic strokes and myocardial infarction (MI) in CAD patients.[9]

Previous studies have shown that CAD and its associated cardiovascular risk factors are associated with WM damage.[10–12] Disruption of the WM is often characterized as WM hyperintensities (WMHs), which are associated with microvascular injuries[13] and are independently associated with increased risk for cognitive decline and progression to dementia.[14] In a study by Zheng et al.[4], macrostructural neuroimaging measures, including WMH, did not fully explain the effect of CAD on cognition. Controlling for WMH volumes, CAD remained significantly associated with cognition in older community-dwelling adults. Diffusion tensor imaging (DTI) is a sensitive technique thought to detect subtle differences in tissue microstructure, and two measures, fractional anisotropy (FA) and mean diffusivity (MD), have been associated with cognitive performance in other populations. These measures are often used as indices of connectivity in the brain. Specifically, lower FA is thought to reflect axonal injury, whereas higher MD is suggested to represent changes in tract integrity due to demyelination.[15] Therefore, DTI assessment of subtle differences in normal-appearing WM (NAWM) and comparison with cognitive performance in CAD are warranted.

The present study assesses whether higher FA in the major WM tracts is associated with better performance in executive function in patients with CAD. Additionally, the significance of FA in predicting memory performance and the significance of MD were explored. The aim of the study was to determine whether WM integrity in any of the major tracts could explain the variance in cognitive performance in patients with CAD.

METHODS

Participants

This study was approved by Sunnybrook and University Health Network research ethics boards. Written informed patient consent was obtained from all subjects before enrollment into the study. For this cross-sectional study, participants were recruited at entry into a cardiac rehabilitation program. Inclusion criteria were age 50−80 years and evidence of CAD (MI $\geq$ 50% blockage in at least one major coronary artery, percutaneous coronary intervention, or coronary artery bypass graft surgery). Participants were excluded if they had any significant cognitive impairment (Mini-Mental Status Exam <24),[16] neurologic disorders, psychiatric illnesses except for depression, or contraindications to an MRI. In addition to cardiac history, demographic information, concomitant medications, body mass index, and histories of hypertension, dyslipidemia, diabetes mellitus, and smoking were collected.

Cognitive Assessment

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.[17] Executive function and processing speed were assessed using Digit Symbol Substitution Test (DSST), Trail Making Test (TMT) parts A and B, Stroop Dot-Color Test, Stroop Color-Word Interference Test, FAS Verbal Fluency Test, and Animal Naming Test. Verbal memory was assessed using the California Verbal Learning Test, 2nd edition (CVLT-II), which yields a measure of short delay free recall (SDFR) of a word list after 10 minutes and of long delay free recall (LDFR) after 20 minutes. Visuospatial memory was assessed using the Brief Visuospatial Memory Test-Revised (BVMT-R), which yields a measure of total memory recall and of delayed memory recall after 25 minutes. A trained researcher administered the cognitive tests at a standardized time (0930 $\pm$ 30 minutes).