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Neuroimaging and Cardiac Correlates of Cognitive Function among Patients with Cardiac Disease

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Abstract

In the present study, we examined the relationships between whole brain volume (WBV), subcortical hyperintensities (SH), indices of cardiac disease and cognitive function in nondemented cardiac patients with evidence of mild cerebrovascular disease. A total of 27 individuals with evidence of cardiac disease underwent neuropsychological examination, neuroimaging, and cardiac assessment. Cognition was assessed with the Dementia Rating Scale-2 (DRS). WBV and SH were quantified using a semi-automated thresholding program based on MRI. Correlational analyses revealed that WBV predicted performance on the overall DRS score, the attention subscale and the initiation/perseveration scale. SH were significantly associated with performance on the attention subscale, and the initiation/perseveration subscale. Regression analyses revealed that SH accounted for most of the variance in the initiation/perseveration scale, whereas WBV accounted for most of the variance in the attention scale. The only cardiac structural or functional variable related to the neurological indices was aortic diameter, which was strongly related to both neuroimaging variables, as well as performances on the DRS attention and initiation/perseveration subscales. Our results highlight the importance of overall brain parenchyma in determining cognitive status among patients at risk for cognitive decline and suggest that select indices of structural cardiac morphology may be related to the early phases of cerebrovascular disease and cognitive status.

Keywords

Cardiac disease; MRI; Cognition; Neuropsychology; Subcortical hyperintensities

Introduction

Neuroimaging studies have revealed strong relationships between the extent of small-vessel ischemic disease and the magnitude of cognitive impairment among patients that meet research and clinical criteria for vascular dementia (VaD). Using semi-automated quantification techniques and visual rating scales, significant correlations have been reported between total subcortical hyperintensity (SH) volume on magnetic resonance imaging (MRI) and performance on measures of executive functions [1–3]. Similarly, the presence and frequency of small lacunes in the deep grey and white matter is associated with poor performance on measures of abstraction and response initiation among nondemented individuals with mild cognitive impairment [4].

Less information is known about the relationship between whole brain volume (WBV) and neuropsychological function in nondemented individuals with cardiac disease and evidence of at least mild subcortical ischemic disease. Data obtained from large epidemiological studies indicate that decreased brain volume and increased white matter hyperintensities are associated with increased risk for mild cognitive impairment [6–9], though the specific contribution of each neuroimaging index to cognitive dysfunction remains less well-defined. In addition, while many studies have identified relationships between cognitive dysfunction and both increased blood pressure and atherosclerosis [10–12], fewer studies have examined the relationship among specific indices of structural cardiac status and neuroimaging and cognitive parameters.

Aortic arch morphology represents one structural cardiac factor that has a known association with increased risk for ischemic brain infarction. The primary etiology underlying the association is likely the presence of atherosclerotic plaques in the aorta [13–15]. The development of atherosclerotic disease in the aorta is most common among individuals over the age of 60 [16], and the risk of ischemic cerebrovascular disease increases notably in the presence of aortic plaques greater than 4 mm in thickness [13]. Atherosclerotic plaques present in the aorta play a partial role in the diameter of the vessel lumen, which in turn may affect systemic perfusion [17].

The purpose of the present study was to examine the relative contribution of WBV and SH to cognitive function in a sample of nondemented individuals with evidence of cardiac disease and mild ischemic vascular disease. We also examined the relationship between indices of structural cardiac parameters, including aortic diameter, as well as functional measures of cardiac status, including ejection fraction, which have been identified as important correlates of cognitive function among elderly individuals with cardiac disease [18–20]. We predicted that both WBV and SH would independently contribute to cognitive function in this sample, and that both structural and functional cardiac parameters would be associated with cognitive status.

Methods

Subjects

Twenty-seven individuals enrolled in a cardiac rehabilitation project were included in this study. All subjects were participants in a parent study aimed at investigating the development of cerebrovascular disease and cognitive impairment among individuals with cardiac disease. We included all subjects who had undergone neuroimaging at the time of this study. The sample contained individuals with heterogeneous cardiac histories including hypertension (73%); coronary artery bypass graft surgery (33%), and myocardial infarction (67%). According to the patient reports, 21% had undergone percutaneous intervention, 18% had undergone a stent insertion, 9% reported arrhythmias, and 51% had high cholesterol. Additionally, 13% of the sample had a history of diabetes mellitus and 27% reported a history of cancer (none of which involved the central nervous system). One individual reported a history of a transient ischemic attack and no individuals reported having a history of stroke.

The sample had an average age of 68.8 (SD 8.1) years and a mean duration of education of 14.2 (SD 2.8) years. Subjects were included in the study after providing written informed consent approved by the Institutional Review Board of both participating institutions, following a thorough explanation of the study. All subjects received financial compensation for their participation.

Neuropsychological Assessment

A trained research assistant administered the Dementia Rating Scale-2 (DRS) [21] to all research participants. The DRS is a valid and reliable cognitive measure commonly administered to assess cognitive function [21]. The measure consists of five subtests including attention, initiation/perseveration, construction, conceptualization, and memory. A total score is determined for each subtest and for the entire measure. The measure was specifically designed to have a very low floor; however, the subtests of the DRS are sensitive to cognitive changes secondary to mild ischemic vascular disease [4].

Brain MRI and SH Quantification

Brain MRI was obtained with a 1.5-tesla Siemens Magnetom Vision unit. A standard imaging protocol consisting of both sagittal T₁-weighted (TR 500 ms, TE 30 ms) and T₂-weighted (TR/TE = 2,500/80) conventional spin-echo localizer images as well as axial T₁-, T₂-, and FLAIR-weighted (TR/TE = 6,000/105) images was used. The slice thickness for all images was 5 mm with a 2-mm gap. The field of view for the T₁- and FLAIR-weighted images was 240 × 240 mm with a 192 × 256 matrix and one excitation.

SH and periventricular hyperintensities were quantified using the FLAIR images and the software program NIH image. The quantification procedure is a semi-automated program that has been employed previously by our group to examine cerebrovascular disease in geriatric patients and individuals with VaD [1,5,22]. Briefly, the threshold levels were adjusted individually for each subject so that the SH are highlighted based on pixel values. Particular reference was directed to the white matter tracts, periventricular regions, and thalamic and basal ganglia structures. Once the thresholds were set for each individual participant, the values were applied to each slice within the region of interest, and the pixel values were automatically calculated and summed across the slices. WBV was calculated by determining total brain size minus the ventricles.

Cardiac Measures

Complete 2-dimensional transthoracic echocardiograms were performed according to American Society of Echocardiography standards. Four indices were obtained including left aortic wall thickness, aortic root diameter, stroke volume and ejection fraction. Left ventricular wall thickness and aortic root were measured from the 2-dimensional parasternal long-axis view. Stroke volume was calculated based upon biplane volumes: $SV = EDV - ESV/EDV$; where SV = stroke volume, EDV = end-diastolic volume, and ESV = end-systolic volume. The biplane method of discs (or Simpson's rule) calculates volumes from the summation of areas from diameters (discs) of 20 cylinders of equal height; these are apportioned by dividing the chambers' longest length into 20 equal sections. Left ventricular ejection fraction was calculated based upon biplane volumes: $EF = EDV - ESV/EDV$; where EF = ejection fraction.

Data Analyses

Correlations were performed to test the relationships between performance on DRS subscales, MRI indices and stroke volume. Separate stepwise regressions were also performed to examine the independent contribution of WBV and SH on the attention subscale, and the initiation/perseveration subscale.

Results

The mean SH severity was 1,093 (SD = 1,538) and the mean WBV was 152,982 voxels (SD = 18,287). Performances for each subscale and the total score on the DRS are provided in table 1. Conversion of the mean subscale scores to MOANS (Mayo's Older Americans

Normative Studies) age-corrected scores revealed that on average the patient sample was performing within normal limits on the subscales. There was no significant relationship between WBV and SH volume ($r = -0.25$, $p > 0.05$).

Neuroimaging and DRS

Correlation analyses revealed that WBV ($r = 0.47$, $p < 0.05$) and SH ($r = -0.53$, $p < 0.05$) were related to performance on the initiation/perseveration subscale. A stepwise regression analysis revealed that both variables loaded on the subscale [$F(2, 24) = 8.0$, $p < 0.05$], with SH accounting for the majority of variance ($R^2 = 0.24$) and WBV contributing an additional 12% of variance. Both SH ($r = -0.47$, $p < 0.05$) and WBV ($r = 0.55$) also correlated with performance on the attention subscale; however, the regression analyses revealed that WBV accounted for most of the variance ($R^2 = 0.30$), with SH contributing an additional 11% of the variance. Additional analyses revealed that WBV was significantly related to the overall DRS score ($r = 0.51$), accounting for about 30% of the variance in the overall score. Neither WBV nor SH predicted performance on the construction, conceptualization or memory subscales of the DRS.

The two functional cardiac measures were unrelated to the neuroimaging indices or the DRS scores (r values < 0.27). However, there was a relatively strong, but nonsignificant association between ejection fraction and DRS total score ($r = 0.36$), and this association would have been statistically significant with a larger sample size (table 2). Of the two structural cardiac indices (left ventricular wall thickness and aortic root diameter), only aortic root diameter was strongly related to SH total ($r = 0.69$), brain volume (-0.49), DRS total (-0.41), DRS attention (-0.61), and DRS initiation/perseveration ($r = -0.86$).

Discussion

The current study has identified two important findings. First, total brain volume is an important determinant of cognitive function in nondemented individuals with cardiac disease. Even among patients without significant cognitive impairment, total brain volume is associated with overall cognitive function, and performance on specific indices of cognitive status. Total volume of SH, a marker for subcortical ischemic vascular disease, was also associated with performance on a measure of initiation/perseveration and the attention subtest, though WBV was more strongly related to performance on the latter measure. The second important finding, albeit a preliminary result, is that a measure of cardiac morphology (aortic root diameter) was significantly associated with both neuroimaging indices and cognitive function.

Evidence that WBV is strongly related to cognitive function in cardiac patients without dementia is an important finding. Bowler et al. [23] have described a continuum of vascular-mediated cognitive impairment that ranges from 'brain at risk' to dementia. This spectrum has been referred to as vascular cognitive impairment (VCI). The earliest (least severe) end of the spectrum includes individuals with medical conditions that place them at risk for cerebrovascular disease ('brain at risk'), and the other end of the spectrum includes individuals with VaD. Previous studies have reported robust relationships between brain volume and cognitive function among patients that meet criteria for VaD, the most extreme end of the VCI continuum. Our results, however, indicate that the relationship between brain volume and cognition is not unique to patients with dementia. Rather, total brain volume is an important marker of cognitive status even among patients at the initial stages of the VCI continuum. One important question that arises from these findings is whether brain volume serves as a predictor of progression along the continuum of cognitive impairment. That is, do individuals with smaller brain volumes in the 'brain at risk' stage of VCI progress more quickly along the spectrum compared to individuals with larger brain sizes? We have

recently reported [24, 25] that WBV is a strong predictor of progressive cognitive decline among patients with VaD followed over the course of 12 months. Whether or not this relationship also applies to individuals in the earliest stages of the cognitive spectrum has not been determined, but will be an important area of future study.

SH did not relate more strongly to cognitive status in this population. The most parsimonious explanation for this finding is that while all subjects in the study exhibited evidence of at least mild cerebrovascular disease on MRI, the total severity of ischemic disease was not sufficient to significantly impact aspects of cognitive function. In the absence of motor and sensory deficits, these MRI findings might be considered silent infarctions. It is likely that development of severer ischemic vascular disease would result in greater cognitive disturbance and consequently produce more robust relationships between cognition and SH. Previous studies, including those from our lab and the work of others, indicate that higher loads of SH are associated with poorer performance on measures of attention and executive function, including the DRS initiation/perseveration scale. The latter relationship has been observed among individuals with VaD [1], and among nondemented individuals with discrete ischemic lesions in the subcortical white matter [4]. Our results extend these findings to the earliest stages of cerebrovascular involvement.

The second contribution of the study is the observed relationship between aortic root diameter and both neuroimaging variables and cognition. Some caution is warranted in interpreting these data since information was not available for the entire sample, and it is possible that the strength of the correlations would diminish with a larger cohort. Nevertheless, in terms of the cognitive variables, it is interesting that aortic root diameter correlated only with those measures that were themselves associated with the neuroimaging variables, suggesting a possibly larger interaction between cardiac morphology, microvascular disease and cognitive status. This relationship is not without some basis, as aortic root morphology is a known risk factor for brain ischemia [14–17], Aortic root diameter may be a marker for vascular disease as it is most often increased due to hypertension; on the other hand, left ventricular mass and wall thickness have been more reliable markers of cardiovascular risk and end-organ damage from hypertension. This relationship is presumably influenced by the presence of aortic plaques, a pathological entity that was not quantified or assessed in the present study. It is possible that measures of aortic compliance would moderate the relationship between aortic root diameter and SH. In the present study, we did not have available data on aortic compliance, but this, along with more direct measures of atherosclerosis in the aorta, may prove to be important determinants of the earliest phases of cerebrovascular disease in the elderly.

It is interesting that we did not observe significant relationships between stroke volume or ejection fraction and the neuroimaging or cognitive indices. Our results are not very different than the outcomes of previous studies [26, 27], which suggests that the relationship between these functional measures and central nervous system integrity is not straightforward. It is noteworthy that the average ejection fraction in the current study was 63% and none of the participants in the present study had ejection fractions under 40%; it is possible that inclusion of subjects with lower ejection fractions would have resulted in a more robust relationship between these variables [20]. Additional studies will be needed to determine this with greater certainty.

Another caveat to the current findings is related to the high prevalence of hypertension in the current study and the heterogeneous composition of the group in terms of cardiac history. Given the relatively restricted sample size, we were not able to covary for all of these factors, or remove individuals from analyses to examine the influence of aortic root diameter independent of hypertension. As such, it is possible that the relationships observed,

particularly between SH and cognition, are highly influenced by the presence of hypertension. Previous studies have in fact identified strong relationships between these two variables [28–30] and we would expect that hypertension has an important role in the evolution of SH in this population. Identifying the steps in this process will remain an important target of future research.

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Table 1

Performances on the DRS and cutoff scores

DRS subscale	Ischemic patients	MOANS age- and education-corrected scale scores
Total score	138.6 $\pm$ 4.7	10
Attention	35.9 $\pm$ 1.3	10
Initiation/perseveration	36.2 $\pm$ 2.0	10
Construction	5.9 $\pm$ 0.3	10
Conceptualization	36.4 $\pm$ 3.0	10
Memory	23.9 $\pm$ 1.5	9

Results are means $\pm$ SD.

Table 2

Descriptive statistics for the cardiac variables

Cardiac variable	Mean	SD
Ejection fraction	0.63	0.07
Stroke volume, ml	73.52	33.04
Aortic root diameter, cm	3.3	0.47
Left ventricular wall thickness, cm	1.15	0.24