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Cerebral Blood Flow and Neuropsychological Functioning in Elderly Vascular Disease Patients

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Abstract

This study was designed to determine the relationships between PET-based quantitative measures of cerebral blood flow and cerebrovascular reserve and neuropsychological functioning in elderly individuals with atherosclerotic vascular disease. It was hypothesized that cerebrovascular function would be significantly associated with neuropsychological functioning. Results showed that both baseline global cerebral blood flow and cerebrovascular reserve were significantly associated with global neuropsychological functioning, when controlling for age and sex. Cerebrovascular reserve was additionally associated with performance on measures of memory and attention. Additional research is needed to determine whether measures of cerebral blood flow can be used to predict cognitive decline.

INTRODUCTION

There is a vast literature demonstrating the negative effects of vascular disease, and particularly cerebrovascular disease, upon cognition. Indeed, although Alzheimer's disease (AD) remains the leading cause of dementia in the U.S., it has been estimated that cerebrovascular disease is a contributing factor in over half of all cases of dementia, regardless of dementia subtype (Breteler, 2000). The existence of common risk factors, i.e., hypertension, diabetes, obesity, hyperlipidemia and apolipoprotein ε4 genotype, for both Alzheimer's and vascular dementia (Iadecola, 2004; Naderali, Ratcliffe, & Dale, 2009) and the positive effects of the treatment of vascular risk factors on cognitive decline in patients with AD without cerebrovascular disease (Deschaintre, Richard, Leys, & Pasquier, 2009) reinforce the view that in the least, the pathologies are intricately linked. Similarly, atherosclerotic vascular disease (AVD) has been associated with cognitive dysfunction and dementia. However, relatively few studies focus on the earliest stages of this process, prior to the development of significant cognitive decline. Previous studies from our lab have revealed significant relationships between forearm vascular function (a measure of overall vascular health) and global neuropsychological performance (Moser et al., 2004; Moser et al., 2007) as well as initiation and processing speed (Moser et al., 2008) in elderly individuals with AVD. Given the public health significance of both dementia and vascular-related diseases, it is important to gain a better understanding of the relationship between cerebrovascular health and cognition, particularly among individuals who do not yet have

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advanced disease (e.g. stroke, vascular dementia), as early intervention may help prevent or at least attenuate the disease processes.

The purpose of the present study was to examine the relationship between cerebrovascular function as characterized by quantitative measures of cerebral blood flow (gCBF) and cerebrovascular reserve (CVR) and neuropsychological performance in a sample of elderly individuals with atherosclerotic vascular disease who had no history of stroke, cardiac surgery, or dementia diagnosis. It was hypothesized that higher levels of cerebral blood flow would be significantly and positively associated with neuropsychological performance.

METHODS

This research was approved by the University of Iowa Institutional Review Board and all participants provided written informed consent following a thorough discussion of the study.

Participants

Participants were 14 elderly individuals with atherosclerotic vascular disease (10 men, 4 women; Mean age = 68 years, SD = 6; Mean education = 16 years, SD = 4) who were already enrolled in our ongoing program of research on aging, cognition and vascular disease. All participants had an unequivocal diagnosis of AVD with a history of one or more of the following: angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, placement of coronary artery stent, and peripheral vascular disease (claudication). All female participants were post-menopausal and none were on hormone replacement therapy. Exclusion criteria included history of coronary artery bypass grafting, valve replacement, carotid endarterectomy, stroke, head injury with loss of consciousness longer than 30 minutes, other neurological disorder or systemic illness unrelated to vascular disease that was likely to affect cognition, focal neurological sign, diagnosis of dementia, renal disease, hepatic disease, gout, adrenocortical insufficiency, and current or past severe psychiatric illness (e.g. bipolar affective disorder, schizophrenia). Additional exclusion criteria included taking warfarin (due to increased risk of bleeding during placement of an arterial line), taking any medication with known cerebrovascular activity, and known sensitivity to carbonic anhydrase inhibitors or antibacterial sulfonamides, thiazide diuretics, or other sulfonamide-derivative diuretics. Participants were asked to refrain from consuming alcohol for 24 hours prior to the study and caffeine for three hours prior to the study.

Neuropsychological Assessment

All participants underwent a large battery of standardized and well-established neuropsychological tests administered by a trained research assistant under the supervision of a licensed psychologist (D.J.M.). For the purposes of the current study, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess level of neuropsychological functioning (Randolph, 1998). This widely-used battery consists of 12 subtests and yields a Total Scale Score that indicates level of global neuropsychological functioning, in addition to five Index Scores including Immediate Memory, Delayed Memory, Attention, Language and Visuospatial/Constructional.

Assessment of Cerebral Blood Flow and Cerebrovascular Reserve

Participants underwent quantitative [^{15}O]water PET imaging with arterial blood sampling for the determination of global cerebral blood flow (gCBF: mL/min/100mL of tissue) during a simple counting task and during a list recall task. Additionally, gCBF was measured a third time as participants completed the counting task following the administration of the carbonic anhydrase inhibitor acetazolamide (ACZ), in order to assess cerebrovascular reserve, the ability of the brain to increase blood flow when induced to do so. Technical methodology

was implemented as previously described for work at this institution (Boles Ponto, Schultz, Watkins, & Hichwa, 2004; Hichwa, Ponto, & Watkins, 1995; Hurtig et al., 1994; Ponto, Magnotta, Moser, Duff, & Schultz, 2006). Imaging was performed on a Siemens ECAT EXACT HR+ scanner.

Three [^{15}O]water injections (50 mCi per injection) for the measurement of gCBF were performed, two at baseline (i.e., non-vasodilated state) and a third 15 minutes after the intravenous administration of a 1 g bolus of ACZ (Kuwabara, Ichiya, Sasaki, Yoshida, & Masuda, 1995). At baseline, imaging was performed during a simple counting task and during a list recall task, whereas, in the vasodilated state, only the counting task was utilized. The counting task required participants to count “1-2-3, 1-2-3” at an approximate rate of one number per second. In preparation for the memory task, participants were read the Rey Auditory Verbal Learning Test (Rey, 1964) 15-item word list five times. After each presentation of the list, participants were asked to recall aloud as many of the list words as possible. Approximately one hour later, while in the scanner, participants were asked to recall as many of the list words as possible and to continuously recall the list even if it meant having to repeat words they had already stated, until instructed to stop. Participants were instructed to begin the counting or memory task 10 seconds prior to the arrival of the bolus of [^{15}O]water in the brain, and to continue as described for the specified task for the 100 seconds of image acquisition. Arterial blood sampling, using an on-line sampler (Wollenweber, Hichwa, & Ponto, 1997) began simultaneously with the injection of the [^{15}O]water. Activity images were created by summing the forty seconds post-bolus transit and iteratively reconstructing the summed data (2 iterations/8 subsets, zoom = 2.57, Gaussian filter = 5.0 mm). Parametric images were calculated from the activity images and the arterial blood curve using the pixel-wise modeling module of the PMOD software package (PMOD Technologies, Ltd, Zurich, Switzerland, <http://www.pmod.com/technologies/index.html>). Global cerebral blood flow for each of the conditions (baseline counting task, during list recall, after administration of acetazolamide) was determined by averaging all intracerebral pixels excluding ventricular spaces.

Statistical Analysis

Throughout the statistical analysis, gCBF during the simple counting task was used as the measure of “baseline” gCBF. The relationships of baseline gCBF and gCBF during the list recall task to global neuropsychological functioning (RBANS Total Scale Score) were examined using partial correlations, controlling for age and sex. An additional partial correlation was calculated between gCBF during the list recall task and RBANS Total Scale Score while controlling for age, sex, and baseline gCBF. The relationship between CVR and global neuropsychological functioning was examined by calculating the partial correlation between gCBF after administration of acetazolamide and RBANS Total Scale Score, controlling for age, sex, and baseline gCBF. Finally, follow-up partial correlations (controlling for the same variables as above) were calculated between measures of gCBF, CVR, and more specific measures of neuropsychological functioning (the five RBANS Index Scores).

RESULTS

Descriptive statistics for disease-related variables, PET and neuropsychological variables are presented in Tables 1 and 2. As a group, participants performed in the average range with regard to global neuropsychological function (RBANS Total Scale Score) and on all five RBANS Index scores. There was no statistically significant difference observed between measures of gCBF taken during the baseline counting task and the list recall task [$t(13) = -.59, p = .567$]. As expected, there was a significant increase in gCBF after administration of ACZ as compared to during the baseline counting task [$t(13) = -8.50, p < .001$].

Table 3 shows the relationships among baseline gCBF, gCBF during list recall, CVR, and cognition. Specifically, when controlling for age and sex, there were significant and positive relationship between baseline gCBF and RBANS Total Scale Score [partial $r = .581$ ($df = 10$), $p = .047$], and between gCBF during list recall and RBANS Total Scale Score [partial $r = .623$ ($df = 10$), $p = .031$]. However, it should be reiterated here that gCBF did not significantly increase above baseline during the list recall task. Furthermore, the relationship between gCBF during list recall and RBANS Total Scale Score was rendered nonsignificant when controlling for baseline gCBF [partial $r = .467$ ($df = 9$), $p = .148$]. This is discussed later in the manuscript.

With regard to cerebrovascular reserve, it was found that when controlling for age, sex, and baseline gCBF (i.e. while counting), there was a significant relationship between gCBF after administration of ACZ and RBANS Total Scale Score [partial $r = .604$ ($df = 9$), $p = .049$]. Follow-up analyses revealed significant relationships between CVR and two more specific aspects of cognition (RBANS Delayed Memory, Attention Index Scores).

DISCUSSION

In this study of elderly individuals with atherosclerotic vascular disease, baseline gCBF, gCBF during list recall, and CVR (cerebrovascular reactivity to acetazolamide) were all significantly and positively associated with pre-scan performance on a measure of global neuropsychological function. CVR was also significantly associated with performance on more specific pre-scan measures of memory and attention. The measure of gCBF during list recall was not significantly associated with global neuropsychological function when controlling for baseline gCBF.

Although there are very few published studies that have examined the relationship between quantitative gCBF measures and cognition, our findings of significant relationships between gCBF, CVR and neuropsychological status are consistent with expectations based on brain physiology. It is commonly accepted that while the brain accounts for only approximately 3% of body weight, it consumes 20% or more of available oxygen and glucose. Consequently, disrupted perfusion, whether severe and acute or subtle and chronic, would naturally be expected to affect brain function.

It is intriguing, however, that the above relationships between measures of cerebrovascular health and neuropsychological status were evident in this sample of individuals who had atherosclerotic vascular disease, but no history of stroke, cardiac surgery, or dementia diagnosis. These participants, therefore, may have experienced only very mild, if any, vascular cognitive decline. Indeed, as a group, they performed in the average range with regard to global neuropsychological function (RBANS Total Scale Score) and across all five RBANS Index scores. The fact that the above relationships were found speaks not only to the significant association between relatively early-stage vascular disease and neuropsychological status, but also the sensitivity of the methodology employed in this study. We would expect that the relationships between measures of gCBF and cognition would be even stronger in a sample with a greater range of vascular disease severity and cognitive dysfunction.

In a recent study, Kitagawa and co-investigators (Kitagawa et al., 2009) found that, among 27 cognitively intact individuals with hypertension and white matter abnormalities on brain MRI, those showing cognitive decline across a three-year period had significantly lower baseline gCBF values than those who did not show such decline (Mean = 31.2, SD = 2.4 vs. Mean = 42.6, SD = 5.9 mL/min/100g). Interestingly, however, there was not a significant

relationship between gCBF and cognitive status at baseline. Additionally, baseline CVR was found not to be significantly related to cognition at baseline or follow-up.

There are some key differences between the Kitagawa study and the current one. Although both studies found relationships between cognition and gCBF, Kitagawa observed this relationship with cognitive decline across time rather than with baseline cognitive function. These differences could be due to the measures used to assess cognitive function and/or statistical analysis. It is important to note that the Kitagawa study used only the MMSE to assess cognitive function, a very basic assessment tool, whereas, the current investigation utilized the RBANS, an instrument which provides a more comprehensive assessment of neuropsychological status. Specifically, the RBANS assesses memory and attention more thoroughly than does the MMSE, and the RBANS includes a measure of psychomotor processing speed (the Coding subtest, which is incorporated into the Attention Index Score), while the MMSE has no such measure. Given that psychomotor slowing is well known to be associated with cerebrovascular disease (Roman, 2005) it is essential to assess this aspect of cognitive function in studies on the relationship between vascular disease and neuropsychological performance. Furthermore, data analysis in the current study included controlling for age and sex, while neither of these factors was taken into account in the Kitagawa study. In that study, the group of participants who experienced cognitive decline across time consisted entirely of men, while the group that did not experience cognitive decline consisted of only 43% men, underscoring the potential importance of taking sex into account when studying the relationship between vascular disease and cognition. Regardless of the specific differences between the studies, it should be reiterated that both studies found significant relationships between gCBF and cognition in non-demented individuals with vascular disease.

As noted above, the significant relationship observed between gCBF during the list recall task and global neuropsychological function failed to reach statistical significance when controlling for baseline gCBF. It is important to reiterate that gCBF did not increase significantly above baseline during the list recall task. Therefore, the significant relationship that was observed between gCBF during the list recall task and global neuropsychological functioning serves primarily as a within-study replication of the finding that baseline gCBF is associated with global neuropsychological functioning. It does not clarify whether degree of gCBF increase during an in-scanner cognitive task is associated with global neuropsychological functioning.

Regarding limitations of the current study, the sample consisted of relatively highly-educated individuals and, therefore, the above results may not generalize to the larger population of individuals with vascular disease. It is also important to note that this study did not include a healthy elderly comparison group. Lacking this, it remains unclear whether the observed relationships between quantitative measures of gCBF and neuropsychological status are unique to elderly individuals with AVD or whether they also exist as part of the continuum of "normal aging." It should also be noted that the above correlations may give the appearance that CVR correlates more strongly with cognitive function than does baseline gCBF. However, given our sample size, the confidence intervals surrounding these correlations would be expected to be fairly wide and, thus, we lack adequate power to determine whether the correlations are of significantly different magnitude. Additionally, given the cross-sectional nature of the study, we were unable to determine whether our measures of gCBF are predictive of future cognitive decline as observed by Kitagawa (16).

Given the high prevalence of vascular disease, its strong association with neuropsychological dysfunction, and downstream effects on daily functioning and quality of life, it is essential that we gain a clearer understanding of the earliest stages of vascular

cognitive impairment. This cross-sectional study revealed significant and positive relationships between baseline gCBF, CVR and neuropsychological performance in a sample of elderly individuals with atherosclerotic vascular disease, with no history of stroke, cardiac surgery, or dementia diagnosis. Additional longitudinal research is needed to determine the degree to which measures of gCBF and CVR can be used to identify those individuals who are at greatest risk for future vascular-related cognitive decline and/or the development of Alzheimer's disease.

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Table 1

Descriptive Statistics for Vascular Disease-Related Variables

Variable	Mean	SD
Duration of illness (years)	10.29	6.34
Body Mass Index	29.64	5.02
Number of antihypertensive drugs	2.21	1.19
Systolic blood pressure, mm HG	128.00	22.11
Diastolic blood pressure, mm HG	69.93	9.09
Total cholesterol, mg/dl	161.79	42.47
HDL-C, mg/dl	53.50	17.24
LDL-C, mg/dl	88.08	32.21
Triglycerides, mg/dl	111.31	60.10
Glucose, mg/dl	112.29	25.71

Note. Duration of illness = years since first onset of clinically-significant vascular disease symptoms. Number of antihypertensive drugs = number currently prescribed per participant. Participants fasted prior to blood draw. HDL-C = high-density-lipoprotein cholesterol. LDL-C = low-density-lipoprotein cholesterol.

Table 2

Descriptive Statistics for Cerebral Blood Flow and Neuropsychological Data

Variable	Mean	SD	percentile
gCBF during counting task (baseline gCBF)	41.4	5.2	N/A
gCBF during list recall	42.0	5.5	N/A
gCBF after administration of ACZ	59.3	11.1	N/A
RBANS Total Scale Score	102.43	9.40	55
Immediate Memory	102.14	10.40	55
Delayed Memory	101.07	10.42	53
Attention	99.57	8.64	50
Language	101.00	9.72	53
Visuospatial/Constructional	107.14	13.21	68

Note. gCBF = global cerebral blood flow; ACZ = Acetazolamide; All gCBF values are expressed as mL/min/100mL of tissue; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RBANS scores are age-corrected standard scores (normative Mean = 100; SD = 15).

Table 3

Relationships Between Cerebral Blood Flow and Neuropsychological Performance

	Baseline gCBF Partial r	gCBF during list recall Partial r	gCBF after ACZ Partial r
RBANS Total Scale Score	.581 *	.623 *	.604 *
Immediate Memory	.493	.228	.459
Delayed Memory	.219	.389	.625 *
Attention	.465	.805 *	.738 *
Language	.282	.122	-.257
Visuospatial/Constructional	.428	.516	.212

Note.

*
p < .05;

gCBF = global cerebral blood flow; ACZ = Acetazolamide; r values represent partial correlations. Baseline gCBF and gCBF during list recall correlations were calculated controlling for age and sex. gCBF after administration of ACZ correlations were calculated controlling for age, sex, and baseline gCBF.