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Neurobiol Aging. Author manuscript; available in PMC 2009 September 11.

Published in final edited form as:
Neurobiol Aging. 2007 March ; 28(3): 477–483. doi:10.1016/j.neurobiolaging.2006.01.001.

Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients

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Abstract

The present study examines the relationship between systemic hypoperfusion via cardiac output (CO) and neuropsychological performances emphasizing executive function in an aging cohort. Geriatric outpatients with treated, stable cardiovascular disease (CVD) and no history of neurological illness (n = 72, ages 56-85) were administered cognitive measures with an emphasis on executive functioning. Echocardiogram findings were used to stratify participants into two groups: low CO (<4.0 L/min) and normal CO (≥4.0 L/min). Between-group comparisons were made using ANCOVAs adjusting for systolic blood pressure. The low CO group performed significantly worse than the normal CO group on DKEFS Tower Test and DKEFS Trail Making Test. No significant between-group differences were noted for any of the other cognitive indices. Findings suggest that reduced CO is associated with poorer executive functioning among geriatric outpatients with stable CVD, as the cognitive profile emphasizes a relationship between systemic hypoperfusion and problems with sequencing and planning. The executive dysfunction profile may be secondary to reduced blood flow to vulnerable subcortical structures implicated in frontal-subcortical circuitry.

Keywords

Cardiovascular disease; Neuropsychology; Cognition; Executive functioning; Cardiac output; Systemic perfusion; Heart failure

Patients with heart failure are a useful clinical model for examining cognition and perfusion because reductions in cardiac performance, a primary element to heart failure, alter blood flow through the body (systemic perfusion) with corresponding changes in blood flow to the brain (cerebral perfusion). Evidence suggests that there are auto-regulatory mechanisms augmenting blood flow to the brain at the expense of muscle tissue and other organs during critical moments of sudden systemic hypoperfusion (e.g., cardiac arrest; for a review see [24]). However, such auto-regulatory mechanisms may be less effective when hypoperfusion is chronic, and these mechanisms may change as a function of age-associated breakdowns in the vasculature.

The heart failure literature examining systemic hypoper-fusion and cognition has emphasized series of pre- and post-transplant cases. Roman et al. [21], for example, documented impaired

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memory abilities among a cohort of heart transplant candidates, though no impairments were noted in measures of visuoperception, executive functioning, or information-processing speed. Post-transplantation follow-up 1 year later revealed improved memory functioning. However, the heart transplantation literature has been criticized because of the confounding role of patients' pre-transplant poor health status and psychological co-morbidities (e.g., anxiety, depression). For example, Deshields et al. [7] reported significant psychological stress among transplant candidates with improvements in depression, anxiety, and cognitive functioning post transplantation.

One method to avoid confounding variables posed by transplant candidates and recipients is to evaluate patients with reduced cardiac function, who are not yet end-stage, and to focus on blood volume exiting the heart. Some past studies, with mixed results, have examined ejection fraction (EF), a measure of the heart's pumping efficiency, and its relationship to cognition [17]. One explanation for such inconsistent findings is that EF may be a confounded measure of heart pumping efficiency. EF is a measure of stroke volume based on the dimensions of the left ventricle, so in some cases EF may reflect a higher value if there is regurgitation of the aortic or mitral valves. In other cases, EF may reflect a lower value if the left ventricle is dilated.

An alternative measure of cardiac performance free of such confounds is cardiac output (CO). CO is a measure of stroke volume based on forward flow velocities reflecting the amount of blood exiting the heart, as measured by liters per minute (L/min). Differences between EF and CO may be secondary to the regurgitated volume that does not contribute to the net CO or forward flow. Therefore, research focusing on CO may yield more specific findings regarding systemic hypoperfusion, as CO more accurately captures systemic blood flow in contrast to EF.

The purpose of the present study is to examine the relationship between systemic hypoperfusion, as measured by CO, and cognitive functioning with specific emphasis on elements of executive functioning among an older clinical sample with prevalent cardiovascular disease (CVD). Subcortical structures in the brain are particularly susceptible to alterations in blood flow because of the small perforating vessels feeding these structures [15]. These same subcortical structures are implicated in the frontal-subcortical circuitry originally described by Alexander et al. [1], which mediate some elements of executive functioning. Consistent with this model, ischemia and neurocognitive dysfunction associated with frontal-subcortical system compromise has been observed [4] even in healthy elderly cohorts [25]. Thus, the primary aims of the present study are two-fold:

1. To assess the relationship between systemic hypoperfusion and cognition, emphasizing executive functioning among older adults with CVD. We hypothesize that systemic hypoperfusion will be associated with multiple elements of executive dysfunction, including sequencing, inhibition, planning, generation, and working memory. In contrast, we hypothesize that systemic hypoperfusion will not be associated with other non-executive cognitive measures (e.g., learning and memory).
2. To determine if CO, as a measure of systemic perfusion, is more sensitive to cognitive changes in this geriatric population than EF. We hypothesize that low CO will be associated with executive dysfunction, but such associations will not be detectable with EF.

1. Methods

1.1. Participants

Participants consisted of 72 community-dwelling individuals participating in an NIH-supported study (F32-AG022773) examining the effects of systemic hypoperfusion on

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cognition and functional abilities in the elderly. Participants were recruited from local medical centers, rehabilitation programs, private practices, and general advertisements. Inclusion criteria required a documented history of prevalent CVD, such as prior myocardial infarction, heart failure, coronary artery disease, cardiac surgery, or hypertension. Participants were English-speaking and had normal or corrected hearing and vision at the time of testing. Exclusion criteria included any history of traumatic brain injury with loss of consciousness greater than 10 min, neurological disease (e.g., Parkinson's disease, stroke), major psychiatric illness (e.g., schizophrenia), and/or previous drug or alcohol abuse requiring hospitalization.

1.2. Neuropsychological assessment

Neuropsychological measures were selected to reflect tasks sensitive to cognitive functions mediated by frontal-subcortical systems and were intended to cover the heterogeneity of executive functioning in addition to other cognitive measures including learning and memory. The measures were carefully selected so that a range of performance was documented, precluding floor or ceiling effects. Except where specifically noted, lower scores reflect greater cognitive impairment.

Mini-Mental State Examination (*MMSE* [9]) is a measure of overall cognitive functioning and is often used to document dementia severity.

Controlled Oral Word Association (*COWA* [26]) is a test of rapid word generation based on an orthographic cue. Raw scores reflect the total number of words generated across three letters ('F', 'A', 'S') during three separate 60 s trials.

Ruff Figural Fluency Test (*Figural Fluency* [23]) is a test of non-verbal generation of figures. To control for the complexity of designs generated across participants, modified instructions directed individuals to use exactly four lines in their pattern generation. Raw scores reflect the total number of designs generated across three trials, each of which lasts 60 s.

Trail Making Test (*DKEFS subtest* [5]) is sensitive to difficulties with cognitive flexibility and sequencing. Raw scores reflect time to completion with greater scores indicating worse performance.

Paced Auditory Serial Addition Task (*PASAT* [11]) is a task of working memory. Raw scores reflect the average percent of items correct across four separate trials involving different paces of presentation.

Color-Word Interference Test (*DKEFS subtest* [5]) is a modified version of an inhibition task involving suppression of an automatic response (word reading) in favor of a novel response (color naming) first developed by Stroop [27].Raw scores reflect the speed at which participants complete the task. Higher scores denoting worse performance.

Tower Test (*DKEFS subtest* [5]) is a task of planning and problem solving abilities. Raw scores reflect the participant's ability to use the fewest possible moves to reach the target.

Category Fluency (*Animal Naming* [16]) is a test of rapid word generation based on a semantic cue. Raw scores reflect the total number of animals generated during a 60-s trial.

California Verbal Learning Test-II (*CVLT-II* [6]) is a measure of verbal learning, retrieval, and encoding abilities. Raw scores are reflected by four indices, including total number of words recalled across five learning trials (Trials 1-5), an interference condition (List B), and Short Delay Free Recall and Long Delay Free Recall conditions.

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Biber Figure Learning Test-Extended (*BFLT* [10]) is a test assessing non-verbal visuospatial learning, retrieval, and encoding abilities. Raw scores are reflected by four indices, including total number of designs reproduced across five learning trials (Trials 1-5), an interference condition (Distractor List), as well as Short Delay Free Recall and Long Delay Free Recall conditions.

1.3. Psychological assessment

Beck Depression Inventory-II (*BDI-II* [2]) is a validated 21-item self-report questionnaire assessing depression. Respondents are asked to endorse statements characterizing their mood. Scores range between 0 and 63, with scores greater than 14 suggestive of depression.

Medical Outcomes Study SF-36 [30] is a self-report measure of subjective health status. It consists of eight domains summarized into two composite scores, including a Physical Composite Summary (PCS) and a Mental Composite Summary (MCS) that reflect physical and mental quality of life, respectively.

1.4. Cardiovascular assessment

Echocardiogram—A complete, transthoracic echocardiogram was obtained from each participant according to standards put forth by the American Society of Echocardiography. From these data, two indices were derived: left ventricular ejection fraction (LVEF) and CO. LVEF is calculated based upon biplane volumes (i.e., EF=EDV-ESV/EDV×100%, where: 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 of 20 cylinders, discs of equal height, which are apportioned by dividing the chambers longest length into 20 equal sections. This directly assessed area is independent of preconceived ventricular shape and is less sensitive to geometric distortions; it is therefore recommended in patients with coronary artery disease and regional wall motion abnormalities.

CO is the amount of blood in liters per minute that is pumped from the heart to perfuse the systemic circulation. Because the flow is pulsatile, CO is a function of stroke volume and heart rate. Stroke volume can be calculated as the mean velocity of blood flow leaving the left ventricle recorded with Doppler echocardiography multiplied by the area of LV outflow tract measured from the 2D echo image [CO = (TVI×CSA)×HR, where: TVI: time velocity integral, CSA: cross-sectional area, and HR: heart rate]. While this method reflects a non-invasive procedure for obtaining CO, previous research has shown that data generated from such non-invasive procedures strongly correlates with invasive measures of CO [18].

1.5. Procedure

The local IRB approved this study and written informed consent was obtained from all participants prior to testing. Participants were compensated 50 dollars. Cognitive evaluations were conducted in a single session for all participants except one, which required two testing sessions secondary to the participant's time constraints. With respect to the cognitive protocol, it is noteworthy that three participants were unable to complete a single trial of the PASAT, and five participants were able to complete the early PASAT trials but unable to sustain the task in its entirety. Group membership was equally split among these eight participants (i.e., four with low CO, four with normal CO). PASAT data is missing on one participant secondary to examiner error. Therefore, data analyses including the PASAT consist of 63 participants. Cardiovascular assessment was conducted in a single testing session lasting 2 h. Secondary to technical issues, EF data is missing for three participants. Secondary to time constraints, not all participants completed their SF-36 questionnaires, so SF-36 data is available on 50 participants.

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1.6. Data analysis plan

Descriptive statistics were generated to summarize demographic variables (i.e., age and education) as well as global cognitive status and psychological functioning. For the primary analyses, the sample was dichotomized into two groups: low (<4.0, $n = 28$) and normal CO (≥4.0, $n = 44$), and the rationale for this dichotomy was based on a few factors. First, the precedent within the cardiac literature is to identify risks associated with cardiac disease, and such studies rely on dichotomous independent variables. Second, we did not expect any meaningful variations in normal cardiac output that would correspond to changes in cognitive functioning, as cognitive outcomes are relatively static when related to normal CO values. Third, and most clinically relevant, the dichotomization of cardiac output was based on widely accepted cut-offs utilized by cardiologists to identify impaired versus normal cardiac function in clinic. This dichotomization allows our data to be applied in a clinical context.

Differences in vascular related medical history (e.g., hypertension, diabetes) were conducted using chi-square analyses. Significance was set a priori at 0.05.

Between-group comparisons based on CO were conducted utilizing *t*-tests for age, education, BDI-II total score, and both SF-36 composite scores (i.e., MCS, PCS). However, an analysis of covariance (ANCOVA) adjusting for systolic blood pressure was used to test for between-group differences on the MMSE, as previous studies have documented an independent relationship between systolic blood pressure and cognition [8].

Hypothesis testing was conducted via a series of ANCOVAs adjusting for systolic blood pressure [8] for all cognitive measures of interest (i.e., COWA, Figural Fluency, PASAT, DKEFS Trail Making Test, DKEFS Tower Test, DKEFS Color-Word Interference Test, Category Fluency, CVLT-II, BFLT). In light of the a priori hypotheses of differential executive dysfunction for the low CO group in the absence of any memory differences, significance was set at 0.05 for all between-group comparisons.

For the EF analyses, the sample was dichotomized into low (<0.50, $n = 15$) and normal EF (≥0.50, $n = 54$). ANCOVAs were conducted adjusting for systolic blood pressure for all cognitive measures of interest (i.e., COWA, Figural Fluency, PASAT, DKEFS Trail Making Test, DKEFS Tower Test, DKEFS Color-Word Interference Test, Category Fluency, CVLT-II, BFLT). Significance was set at 0.05.

2. Results

2.1. Demographic characteristics

Descriptive statistics for all demographic variables (e.g., age, education, gender) as well as for the MMSE, BDI-II, and SF-36 composite scores were generated (see Table 1). Participants consisted of 39 males and 33 females with a mean age of 69.14 years (S.D. = 7.51) and mean education of 14.32 years (S.D. = 2.91). The sample was comprised of 86.1% non-Hispanic Caucasian participants. Between-group comparisons of the low CO and normal CO groups revealed no significant differences for age ($t_{(70)} = -0.38$, ns), educational level ($t_{(70)} = -0.74$, ns), gender ($x^2 = 2.36$, ns), BDI-II total score ($t_{(67)} = -0.41$, ns), SF-36 PCS ($t_{(48)} = 0.98$, ns), or SF36 MCS ($t_{(48)} = 0.47$, ns). An ANCOVA adjusting for systolic blood pressure revealed no between-group differences on the MMSE ($F_{(1,71)} = 1.72$, ns). In light of the missing SF-36 data, a follow-up independent samples *t*-test was performed to assess whether those participants that completed the SF-36 differed from those that did not. Results suggest no betweengroup difference in global cognitive status (i.e., MMSE) for completers versus non-completers ($t_{(69)} = -1.15$, ns).

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Information pertaining to current relevant medications is provided in Table 2. No between-group differences were observed for medication use for beta blockers ($x^2 = 0.01$, ns), ace inhibitors ($x^2 = 1.24$, ns), nitrates ($x^2 = 1.29$, ns), anticoagulants ($x^2 = 0.16$, ns), statins ($x^2 = 0.01$, ns), digoxins ($x^2 = 2.20$, ns), diuretics ($x^2 = 0.84$, ns), diabetics ($x^2 = 0.82$, ns), or psychotropics ($x^2 = 3.15$, ns). The exception to this was ASA use ($x^2 = 4.33$, $p = 0.04$), for which the normal CO group reported significantly greater use than the low output group (normal CO= 70%, low CO= 44%). Follow-up ANCOVA adjusting for systolic blood pressure revealed no significant difference between ASA users and non-users for global cognitive status ($F_{(1,65)} = 1.35$, ns).

2.2. Medical history and current cardiovascular health

No between-group differences were noted for vascular medical history variables, including angina ($x^2 = 1.47$, ns), arrhythmia ($x^2 = 2.03$, ns), atrial fibrillation ($x^2 = 1.04$, ns), current cigarette smoking ($x^2 = 0.37$, ns), coronary artery bypass ($x^2 = 0.58$, ns), diabetes ($x^2 = 1.67$, ns), family history of heart disease ($x^2 = 1.22$, ns), heart failure ($x^2 = 0.01$, ns), hypercholesterolemia ($x^2 = 0.01$, ns), hypertension ($x^2 = 1.44$, ns), myocardial infarction ($x^2 = 0.02$, ns), valve repair ($x^2 = 0.11$, ns), or valve replacement ($x^2 = 2.32$, ns). Between-group differences were noted for history of cigarette smoking ($x^2 = 4.98$, $p = 0.03$) and stent insertion ($x^2 = 4.62$, $p = 0.03$); however, the normal CO group reported significantly greater frequencies for both items (62.8% and 27.91%, respectively) as compared to the low CO group (35.7% and 7.69%, respectively).

2.3. Cognition and CO

Significant between-group differences emerged for two executive functioning measures, including DKEFS Tower Test ($F_{(1,71)} = 5.34$, $p = 0.02$) and DKEFS Trail Making Test ($F_{(1,71)} = 4.92$, $p = 0.03$). In all cases, the normal CO group performed significantly better than the low CO group. No significant between-group differences emerged for the remaining cognitive measures, including COWA ($F_{(1,71)} = 0.47$, ns), Figural Fluency ($F_{(1,71)} = 0.32$, ns), DKEFS Color-Word Interference Test ($F_{(1,71)} = 0.42$, ns), PASAT ($F_{(1,62)} = 0.53$, ns), Category Fluency ($F_{(1,71)} = 0.74$, ns), CVLT-II Trial 1-5 ($F_{(1,71)} = 1.29$, ns), CVLT-II List B ($F_{(1,71)} = 0.13$, ns), CVLT-II Short Delay ($F_{(1,71)} = 0.07$, ns), CVLT-II Long Delay ($F_{(1,71)} = 0.41$, ns), BFLT Trial 1-5 ($F_{(1,71)} = 0.13$, ns), BFLT Distractor List ($F_{(1,71)} = 0.55$, ns), BFLT Short Delay ($F_{(1,71)} = 1.15$, ns), and BFLT Long Delay ($F_{(1,71)} = 0.56$, ns). Means and standard deviations are provided in Table 3.

In light of the between-group difference for ASA use (i.e., significantly less ASA use for the low CO group as compared to the normal CO group), follow-up ANCOVAs were conducted adjusting for systolic blood pressure for the two executive function measures that yielded significant betweengroup differences for users versus non-users of ASA. Findings revealed no significant difference for both the DKEFS Tower Test ($F_{(1,65)} = 0.81$, ns) and the DKEFS Letter-Number Sequencing ($F_{(1,65)} = 2.85$, ns), suggesting that ASA use is unrelated to performance on these two measures.

2.4. Cognition and EF

When the sample was re-dichotomized into low and normal EF, no significant between-group differences emerged for any of the cognitive measures, including DKEFS Tower Test ($F_{(1,68)} = 0.24$, ns), DKEFS Trail Making Test ($F_{(1,68)} = 0.46$, ns), COWA ($F_{(1,68)} = 4.01$, ns), Figural Fluency ($F_{(1,68)} = 1.94$, ns), DKEFS Color-Word Interference Test ($F_{(1,68)} = 0.01$, ns), PASAT ($F_{(1,58)} = 0.29$, ns), Category Fluency ($F_{(1,68)} = 0.80$, ns), CVLT-II Trial 1-5 ($F_{(1,68)} = 0.16$, ns), CVLT-II List B ($F_{(1,68)} = 0.19$, ns), CVLT-II Short Delay ($F_{(1,68)} = 0.16$, ns), CVLT-II Long Delay ($F_{(1,68)} = 0.01$, ns), BFLT Trial 1-5 ($F_{(1,68)} = 1.75$, ns), BFLT Distractor

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List ($F_{(1,68)}$ = 0.06, ns), BFLT Short Delay ($F_{(1,68)}$ = 2.17, ns), or BFLT Long Delay ($F_{(1,68)}$ = 3.29, ns).

3. Discussion

The present study assessed the relationship between systemic hypoperfusion and neurocognitive functioning among a geriatric cohort with CVD. Consistent with a priori hypotheses, systemic hypoperfusion, as measured by CO, was associated with impairments in some elements of executive function, including sequencing and planning. As expected, reduced CO was not associated with non-verbal visuospatial or verbal memory impairments. The significant findings for some executive function tasks, taken together with the null findings on all memory indices, suggest that systemic hypoperfusion is associated with a particular cognitive profile corresponding to specific brain structures independent of systolic blood pressure. Subcortical structures of the brain are particularly susceptible to the chronic systemic hypoperfusion associated with low CO [15]. We propose that the age-associated breakdown of the cerebrovasculature, taken together with the chronicity of hypoperfusion in these patients, exacerbates these subcortical structures' susceptibility to alterations in perfusion.

There are two possible explanations why some but not all executive function measures were related to CO, including anatomical specificity and measurement sensitivity. The dorsolateral prefrontal cortex has been implicated not only in the performance of tasks involving planning [13] and sequencing [14], but also as an area of regional specialization for one of the three parallel and contiguous circuits linking the prefrontal cortex to subcortical structures [1,22]. The structure of this circuitry allows for deficits associated with the dorsolateral prefrontal cortex to be recapitulated via damage to subcortical structures [22]. Coupled with the fact that subcortical structures are particularly susceptible to alterations in blood flow [15], CO may be uniquely related to planning and sequencing performance because both tasks rely on the integrity of the dorsolateral prefrontal cortex. An alternate explanation that cannot be ruled out is that the planning and sequencing measures are more sensitive to subtle cognitive executive dysfunction associated with reduced systemic perfusion as compared to the other executive function tasks.

Our findings augment the existing literature in two ways. In addition to relating CO to sequencing, which has been reported before [20], we illustrate that reduced CO is associated with multiple elements of executive dysfunction, including planning independent of systolic blood pressure. Furthermore, we extend previous research in this area by focusing on a geriatric sample: a cohort that presents unique issues associated with neurovascular aging [29], chronicity of systemic hypoperfusion, or some combination of these factors.

The present findings relating systemic hypoperfusion to executive dysfunction among an aging cohort have implications for the hypoperfusion model of neurodegenerative disease, as previous studies have reported cerebral hypoperfusion as a risk factor for the evolution of vascular dementia [28]. Our findings suggest that systemic hypoperfusion is associated with cognitive impairment (i.e., executive dysfunction) prior to the clinical onset of a neurodegenerative syndrome, as our sample consisted of older adults free of neurological disease or dementia. Those participants with chronically reduced systemic perfusion may be at increased risk for the development of dementia, an outcome that will be elucidated by longitudinal study of this cohort.

In contrast to the CO findings, EF was not significantly associated with any executive function or memory measure, which is consistent with some previous studies [3,20]. Other studies though have reported relationships between cognition and EF [19,31]. For instance, Zuccala et al. [31] reported a significant association between MMSE and LV dysfunction. Our

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methodology included not only the MMSE but two complex measures assessing multiple components of memory that include acquisition, interference, and retention, none of which were associated with reduced EF. It is noteworthy that between-group comparisons of perceived health status yielded no significant differences for the low and normal EF groups (data not shown). Thus, the discrepancy between our data and those of prior studies may be secondary to confounds associated with the poor health status of end-stage participants used in previous research rather than a specific relationship between cognitive functioning and LV performance based on measures of EF.

Our study is unique in that we focused on a geriatric cohort, which few studies have done before. The exception to this is a study by Zuccala et al. [31], which included a sample of older adults whose mean age was 77 years. The paucity of geriatric research in this area is undoubtedly secondary to the young mortality rate of end-stage heart failure patients. Our study is also unique because of the emphasis of CO as an outcome measure, incorporation of a wider breadth of executive functioning and memory measures, and the exclusion of end-stage heart failure patients awaiting transplant.

Despite the strengths of the current study, there are a couple of limitations that must be considered. First, the demographics of our sample may limit generalizability, as the sample was predominantly college educated and most participants identified themselves as non-Hispanic Caucasian (i.e., 86%). Another noteworthy limitation that must be considered is the lack of a corresponding cerebral perfusion measure to verify the association between systemic perfusion and cerebral blood flow. In the absence of a cerebral blood flow measure, it is difficult to conclude absolutely that the neurocognitive differences are directly attributable to perfusion reductions. Reduced CO is known to be associated with a variety of neurohumoral maladaptive responses that act locally [12] but could also have a broader systemic impact affecting brain function. However, many feasibility factors contribute to the omission of a cerebral perfusion measure, including expense and neuroimaging contraindications that cardiovascular patients pose (i.e., many cardiovascular patients have pacemakers constructed of ferrous metal preventing them from undergoing magnetic resonance imaging (MRI)). If feasible, future studies may wish to include perfusion MRI in conjunction with CO to verify the direct association between cerebral and systemic blood flow and to rule out the possibility that the association reported in our study is secondary to some epiphenomenon.

The present study reported a relationship between systemic hypoperfusion and certain elements of executive functioning, including planning and sequencing, though a similar association with memory was not observed. Findings suggest that chronic systemic hypoperfusion differentially impacts executive functioning among older adults, and this unique relationship may be secondary to the vulnerability of subcortical brain structures to subtle reductions in blood flow.

Acknowledgments

Funding source: This research was supported by F32-AG022773 (ALJ), K12-HD043444 (ALJ), K23-MH065857 (RPH), R01-AG017975 (RAC), and P30-AG013846 (Boston University Alzheimer's Disease Core Center). The authors wish to thank Ms. Kristin MacGregor, Dr. Andrew Freeman, Ms. Kathleen Davis, and Ms. Sarah Yoho for their data collection and coding efforts. We would also like to thank Dr. Daniel Levine and the Rhode Island Hospital Heart Failure Clinic staff for their generous recruitment efforts.

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Table 1

Participant demographic information

Variable	Low CO participants *M* (S.D.)	Normal CO participants *M* (S.D.)
Age (years)	68.71 (8.28)	69.41 (7.06)
Education level (years)	14.00 (2.99)	14.52 (2.87)
MMSE	28.54 (1.58)	28.93 (1.15)
BDI-II	5.19 (6.29)	5.84 (6.34)
Gender (% female)	57.1	38.6
SF-36 PCS	44.81 (10.29)	42.01 (9.70)
SF-36 MCS	54.95 (7.81)	55.91 (6.75)

Note: CO: cardiac output; M: mean; S.D.: standard deviation; MMSE: Mini-Mental State Examination; BDI-II: Beck Depression Inventory-II; SF-36 PCS: SF-36 physical composite summary; SF-36 MCS: SF-36 mental composite summary.

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Table 2

Relevant medication information

Medication	Participants (*n* = 72) % (presence of medication)
Beta Blockers	57.1
Ace Inhibitors	52.9
Nitrates	12.9
ASA	57.1
Anticoagulants	17.1
Statins	70.0
Digoxins	12.5
Diuretics	26.4
Diabetics	11.0
Psychotropics	12.3

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Table 3

Means and standard deviations for cognitive measures

Cognitive measures	Low CO *M* (S.D.)	Normal CO *M* (S.D.)
COWA	40.29 (12.21)	40.09 (9.64)
Figural Fluency	29.25 (9.24)	30.34 (7.95)
Sequencing*	123.00 (89.90)	90.25 (29.54)
Color-Word	68.29 (18.00)	66.50 (16.91)
Tower Test*	15.96 (4.58)	17.95 (3.80)
PASAT	58.03 (19.01)	60.20 (13.58)
Category Fluency	19.64 (5.59)	20.52 (4.69)
CVLT-II Trial 1-5 total	51.79 (11.35)	53.68 (10.33)
CVLT-II List B	5.71 (1.84)	5.48 (1.58)
CVLT-II Short Delay	10.89 (2.91)	10.95 (3.26)
CVLT-II Long Delay	11.14 (2.68)	11.59 (3.43)
BFLT Trial 1-5 total	124.57 (35.37)	124.82 (30.66)
BFLT Distractor List	11.71 (5.11)	9.39 (4.55)
BFLT Short Delay	25.75 (9.40)	27.64 (8.40)
BFLT Long Delay	28.82 (8.33)	29.73 (7.82)

Note: *M*: mean; S.D.: standard deviation; COWA: Controlled Oral Word Association; sequencing: DKEFS Letter-Number Sequencing; Color-Word: DKEFS Color Word Test; Tower Test: DKEFS Tower Test; PASAT: Paced Auditory Serial Addition Task; CVLT-II: California Verbal Learning Test-II; BFLT: Biber Figure Learning Test-Extended.

*Significant between-group difference.