Cerebrovascular Perfusion among Older Adults with and without Cardiovascular Disease

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Abstract

Background and Purpose: Cardiovascular disease (CVD) encompasses a range of disorders that affect health and functioning in older adults. While cognitive declines have been linked to both cardiovascular and cerebral blood perfusion, protective neurovascular mechanisms raise the question whether cerebrovascular perfusion differs as a function of cardiovascular health status. The present study examined whether cerebrovascular perfusion significantly differs between healthy older adults with and without diagnosed CVD. The study also examined whether previously documented sex differences in cerebral perfusion would be replicated.

Methods: Twenty CVD patients without significant heart failure and 39 healthy controls were recruited to undergo a comprehensive assessment including an interview, echocardiogram, and magnetic resonance imaging (MRI). Arterial spin labeling (ASL) was used to quantify cerebral blood perfusion.

Results: Both groups exhibited mean left ventricular ejection fractions that fell within normal limits. In line with previous research, women exhibited significantly higher cerebral perfusion than men. There were no significant group differences in whole brain cerebrovascular perfusion, regional perfusion, or white matter perfusion by patient status after accounting for sex and age.

Conclusions: These findings suggest that the effects of mild CVD on cerebrovascular perfusion are minimal. Future studies are needed to investigate the mechanisms involved in maintaining cerebrovascular perfusion in the context of altered peripheral perfusion determine and to determine whether this finding extends to more acute or severe CVD.

Introduction

Cardiovascular disease (CVD) includes a range of disorders of the circulatory system, from hypertension to heart failure, that have been linked to adverse effects on other functional systems such as cognitive function.[1] CVD diagnoses have also been associated with mild cognitive impairment in domains such as memory, executive function, attention, and psychomotor speed, as well as dementia.[2-4,36]

One possible mechanism for the effect of CVD on cognitive function is cerebral hypoperfusion. Prior literature supports the notion that problems with peripheral perfusion may affect cerebral perfusion and, in turn, impact cognition. For instance, Efimova, Efimova, Triss, and Lishmanov[5] investigated cerebral perfusion in patients with arterial hypertension and found that it was significantly lower among these patients compared to a control group. Decreases in cerebral perfusion, alone, have also been linked to cognitive declines. For example, Kitagawa and colleagues[6] found that cerebral hypoperfusion was associated with cognitive decline on the Mini Mental State Exam (MMSE). Alosco and team[7] found that reduced total cerebral perfusion was correlated with decreased performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) battery composite score, Trail Making Test B, and the MMSE.

Other research suggests that cerebral perfusion is especially relevant among older adults regardless of cardiovascular health, as the aging process leads to declines in cerebral blood flow.[8-9] Stoquart-ElSankari and colleagues[9] observed significantly lower total cerebral blood flow in older adults compared to younger adults. Therefore, cerebral hypoperfusion is a serious clinical concern that is associated with cognitive impairment and neurodegenerative processes in aging and CVD.

Several studies have examined cerebral perfusion in individuals with stroke, Alzheimer's disease and other neurodegenerative diseases.[8,10] Alexopoulos and team[11] examined 19 patients with mild dementia, 24 patients with mild cognitive impairment, and 24 health elderly controls and found

significantly lower perfusion in the patient groups. In another study, 17 patients with Alzheimer's disease and 20 patients with Parkinson's disease dementia were compared to 37 matched controls. Results showed similarity in hypoperfusion levels among the patient groups, which differed compared to controls.[12] Lower cerebral blood flow has been related to more advanced stages of Alzheimer's disease in another study.[13] It has also been reported that cerebral perfusion may decline at a steeper rate with age when it is combined with other vascular risk factors, such as oxidative stress, and it may be a marker of mild cognitive impairment and Alzheimer's disease.[14-15] With this in mind, researchers are utilizing these findings on cerebral perfusion to predict clinical outcomes of Alzheimer's, Stroke, and other disorders with cognitive decline.[8,16-17]

In addition to neurodegenerative disorders, cerebral perfusion has been examined in individuals with chronic fatigue and depression.[18-20] For instance, eleven patients with chronic fatigue syndrome and 10 matched controls participated in a neuroimaging study using arterial spin labeling to assess the relationship between cerebral blood flow and chronic fatigue. Biswal, Kunwar, and Natelson[19] found that the patients exhibited significantly lower global cerebral blood flow than controls, which authors suggest demonstrates a neurological aspect to this illness. Kataoka and team[20] deduced from their study that hypoperfusion in the left prefrontal cortex may be associated with depressive symptoms exhibited by patients with Alzheimer's dementia. Alosco and colleagues[18] reported increased depressive symptoms in older adults with heart failure who exhibited lower cerebral perfusion.

While cognitive declines have been linked to both CVD and cerebral perfusion, it remains unclear whether cerebrovascular perfusion differs as a function of CVD status. As CVD is associated with systemic vascular hypoperfusion, it is plausible that cerebral perfusion would also be compromised among those with CVD. However, autoregulatory mechanisms are thought to protect the brain from systemic vascular dysfunction.[21] Thus, regulation of cerebral blood flow may serve as a protective factor for the brain integrity among individuals with CVD. On the other hand,

autoregulation of brain perfusion in CVD may be compromised by CVD, its associated factors, and other disorders of aging (e.g., hypertension, diabetes, head injury, stroke, tumors, hematoma).[22,35] Therefore, it is possible that CVD also compromises autoregulation of cerebral blood flow, which may be a major mechanism that contributes to cognitive decline in this population.

Another reason to examine the effects of CVD on cerebral perfusion is its putative impact on a widely used functional neuroimaging technique with increasing application in this population, blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI). The BOLD response is measured by detecting changes in capillary oxygenation over time. CVD-related changes in cerebral blood perfusion could alter the validity and reliability of measurement of this signal, which would confound interpretations of the imaging results.[23, 15] Murata and colleagues[24] described the need to take into consideration baseline blood circulation status in individuals with stroke due to its impact on the response.

Arterial spin labeling (ASL) is a non-invasive MRI technique used to assess blood perfusion of the brain. It involves magnetically tagging and tracking water in arterial blood to calculate cerebral blood flow in units of ml of blood/100 ml of tissue/min. Clinical and research applications are well established and substantial scientific literature exists in each.[25] A notable finding of prior ASL studies is sex differences. Specifically, women have significantly greater whole-brain and gray-matter perfusion than men. For example, Parkes, Rashid, Chard, and Tofts[26] measured cerebral perfusion in 19 females and 15 males, ages 20 to 67, using ASL-MRI scans. They found significantly higher perfusion in the whole brain (13% higher) and specifically in grey matter (13% higher) in females compared to males. Liu and colleagues[15] compared perfusion of 20 females and 15 males, ages 23 to 84, using ASL-MRI scans. Their findings showed that women had significantly higher cerebral blood flow values than men (11.7% higher for global grey matter), independent of age. Given these findings, sex differences should be considered when examining perfusion.

It is often assumed that the BOLD or ASL response that underlies fMRI is preserved, even among patients with CVD. It is important to test this assumption and verify the utility of fMRI among patients with CVD and other medical disorders that can affect cerebrovascular function. With rapidly growing experimental and clinical applications, research is needed that explicitly examines cerebrovascular perfusion among populations with known alterations of vascular integrity and subsequent hemodynamic responsivity.

The current study set out to determine whether cerebrovascular perfusion in older adults differed as a function of CVD status. That is, whether or not cerebral blood flow remains intact even amongst those with known cardiovascular pathology. Sex differences were expected and, therefore, examined within this sample to potentially replicate previous findings.

Methods

Participants

Participants included 59 adults over the age of 50 (Mage = 66.68 years ± 9.63; 25 males) who were recruited via advertisements in Rhode Island newspapers and outpatient cardiology clinics (see Table 1). The sample was predominantly Caucasian (95%), with 1 participant who identified as Asian and 2 participants who identified as African American. Participants had an average of 15.98 (± 2.28) years of education.

Twenty of the 59 participants (13 males, 7 females) had been diagnosed with cardiovascular disease (CVD). These patients exhibited cardiac function within normal limits, defined as mean ejection fraction greater than 55% (mean CVD group ejection fraction of 58.25% ± 4.94), and were all receiving treatment for CVD. In terms of New York Heart Association (NYHA) Functional Classification, the 20 CVD participants' medical records showed Class I (6; 30%), Class II (10; 50%), or Class III (4; 20%), with no participant categorized as Class IV. In terms of The American College of Cardiology/American Heart Association Classification, the 20 CVD participants' medical records

indicated classifications of either Stage B (6; 30%) or Stage C (14; 70%). Thus, while we did not explicitly recruit for milder CVD patients, CVD participants were generally healthy, had minimal or mild heart failure, and did not exhibit major functional limitations or heart defect.

Screening included a comprehensive assessment of exclusion criteria. These were insulin-dependent diabetes, non-English speaking, current psychiatric disorders or a history of hospitalization for psychiatric disorders, neurologic disorders (e.g., traumatic brain injury, stroke), and MRI contraindications. None of the participants scored below the clinical cutoff of 25 on the Mini-Mental State Examination (MMSE).[27] The study received approval from appropriate Institutional Review Boards and all participants completed written informed consent. Participants were compensated $150 for their participation in the study.

Procedures

Following screening, individuals who met the study criteria were invited to three separate assessment sessions. The initial session included obtaining a more detailed medical history, demographic information, and administering the MMSE. The second session of the study involved an echocardiogram, which was administered and evaluated by a cardiologist to determine cardiac function (cardiac output and left ventricular ejection fraction). Height and weight were also measured in order to calculate Body Surface Area (BSA) using the standard DuBois and DuBois formula: $BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$. Cardiac index, which is a measure of cardiac output that controls for body size, was calculated by dividing cardiac output by body surface area. In the final session, participants underwent MRI, including acquisition of resting state cerebrovascular perfusion data.

All scans were obtained using a 3 Tesla Siemens TIM Trio scanner equipped with a 32-channel head coil array.

After the initial localizer scan, a 3D T_1-MPRAGE scan with 1mm isotropic resolution was conducted. Parameters for this scan were TR=1900ms, TE=2.98ms, TI=900ms, and readout flip

angle=9°. This provided a 3D T_1 image dataset for gray-white matter segmentation that was used to mask non-gray matter regions. Two three-minute resting state ASL scans were acquired using a PICORE-Q2TIPS technique,[28] which allowed 18 contiguous axial slices. In-plane spatial resolution was $3mm^2$ with a slice thickness of 6mm. Timing parameters for the two resting state scans were TR=2500ms, TI_1=700ms, TI_2=1800ms (inversion to start of the 64^2 echo planar image readout sequence with TE=16ms).

T_1 weighted anatomical volumes were segmented using FreeSurfer,[29-30] which generated white and gray matter segmentations, including cerebral cortical ribbon boundaries. Segmentation thresholds were set such that voxels within the white matter and the cortical ribbon were selected only if they were determined by Statistical Parametric Mapping (SPM5)[31] software to be composed of at least 80% gray matter. Cerebrovascular perfusion was then calculated by averaging perfusion values (ml of blood/100ml of tissue/min) within the segmented white matter and cortical ribbon taking into account water exchange between the vascular and interstitial compartments. Thus, perfusion (f) was calculated on a voxel basis as:

$$f = \frac{\Delta M}{2\alpha q M_0 TI_1 \exp\left(-TI_2 / T_{1a}\right)}$$

Where ΔM is the signal difference between corresponding voxels in labeled and control images, α is the inversion efficiency (0.95 as determined with the scanner manufacturer), q is the factor taking into account the water exchange term for gray matter (0.932 for 3 Tesla and the above acquisition parameters,[32] M_0 is the equilibrium magnetization, $TI_{1,2}$ are the inversion times given above, and T_{1a} is the arterial blood T_1.

Descriptive analyses and group-comparison analyses were planned. Whole brain gray matter cerebrovascular perfusion was our primary variable of interest and group status (patient vs. control) was our primary predictor variable. Additionally, we were interested in perfusion as a function of

participant sex, conducting regression analysis with sex and age entered in the first block and patient status entered in the second block.

Follow-up analyses were conducted to explore possible group differences in white matter, gray matter regions, and at the voxel level. Whole-brain white matter comparisons were identical to the whole-brain gray matter comparisons except values from individual white matter segmentations were averaged. Regional quantifications represented average mean perfusion derived from Desikan atlas regions. Voxel-wise contrasts were accomplished by transforming individual perfusion maps into standard stereotaxic space. An average group map was calculated for each group and an independent samples t-test was conducted to contrast the groups for each voxel with a two tailed significance level of $p<.05$, corrected for multiple comparisons using the False Discovery Rate procedure.[33]

Results

Summary maps of average perfusion transformed into standard stereotaxic space[34] are presented by group in Figure 1. Patterns are consistent with prior literature with a gradient of increasing perfusion from white to gray matter. An independent samples t-test of each voxel revealed no significant group differences.

Group means and standard deviations for whole brain, regional (i.e. in the frontal, temporal, parietal, and occipital lobes), and white matter cerebrovascular perfusion are presented in Table 2. Results were consistent across perfusion analyses with no significant group differences. Patients and controls did not significantly differ on whole brain perfusion [$t(57) = .17$, $p = .867$, $d = 0.04$], frontal lobe perfusion [$t(28.291) = -.41$, $p = .682$, $d = 0.12$], parietal lobe perfusion [$t(57) = .86$, $p = .394$, $d = 0.23$], temporal lobe perfusion [$t(57) = -.31$, $p = .757$, $d = 0.08$], occipital lobe perfusion [$t(27.92) = 1.20$, $p = .241$, $d = 0.35$], or white matter perfusion [$t(57) = -1.90$, $p = .063$, $d = 0.51$].

There were no significant differences between males and females with regard to NYHA [t(39) = -.58, p=.56, d = .18], ejection fractions [t(57) = -.60, p = .548, d = 0.16], age [t(57) = .49, p = .63, d = 0.13], temporal perfusion [t(57) = -1.833, p = .072, d = 0.48], or white matter perfusion [t(57) = -.428, p = .67, d = 0.11]. There were consistent sex differences such that females exhibited greater whole brain perfusion [t(57)= -2.63, p = .011, d = 0.69], greater frontal perfusion [t(57)= -2.209, p = .031, d = 0.57], greater parietal perfusion[t(57)= -3.21, p = .002, d = 0.86], and greater occipital perfusion [t(57)= -2.59, p = .012, d = 0.69] compared to males. Additionally, as expected, participants with CVD exhibited significantly lower left ventricular ejection fractions compared to participants without CVD (58.25% ± 4.94 vs. 60.26% ± 3.43), F(1,57) = 3.33, p = .037, f = 0.4642. While patients had significantly lower ejection fractions than controls, it is important to note that mean ejection fractions were normal in both groups, as patients were being effectively treated.

We examined the whole brain perfusion data utilizing regression analysis with sex and age entered in the first block and patient status entered in the second block. The first model was significant, F(2,56) = 3.40, p = .04, and accounted for 10.8% of the variation in cerebrovascular perfusion. In this model, sex was a significant predictor of perfusion (β = .329, p = .012) but age was not (β = .003, p = .978). The second model was not significant but approached significance, F(3,55) = 2.454, p = .073, and accounted for 11.8% of the variation in perfusion. In this model, similar to the first model, sex was a significant predictor of perfusion (β = .364, p = .009) but age was not (β = -.045, p = .749). In addition, patient status was not a significant predictor of perfusion (β = .117, p = .436).

As the patient and control groups had different sex distributions, we also conducted exploratory sub-group analyses that sex-matched participants across groups rather than controlling for this demographic variable. We utilized a random number generator to select 7 of the 27 females in the control group and 12 of the 13 males in the patient group. This allowed for a subset of data consisting of equal sex distributions for each group: 19 control participants (7 female, 12 male) and 19 patient

participants (7 female, 12 male). Regression analysis (sex and age entered in the first block, patient status entered in the second block) were repeated with this subset dataset. This random selection and regression procedure was repeated five times to yield mean estimates of group effects. We found the same pattern as the primary regression across these iterations. In all five subset analyses, sex was a significant predictor of cerebrovascular perfusion in both the first model (mean β = .425, mean p = .016; βs ranged from .33 to .486; ps ranged from .003 to .046) and the second model (mean β = .431, mean p = .016; βs ranged from .328 to .493; ps ranged from .003 to .049). Consistent with the primary analysis, the subset analyses also showed that age was not a significant predictor of perfusion in either the first model (mean β = -.100, mean p = .459; βs ranged from -.143 to .046; ps ranged from .35 to .774) nor the second model (mean β = -.147, mean p = .426; βs ranged from -.21 to -.025; ps ranged from .233 to .898). Across all five subset analyses, patient group status was not a significant predictor of whole brain cerebrovascular perfusion (mean β = .105, mean p = .562; βs ranged from .065 to .191; ps ranged from .268 to .70).

Because there were significant sex differences in regional perfusion (for frontal, parietal, and occipital lobes), we also conducted the regression and sex-matched sub-analyses described above for each of these regions to assess for potential patient status effects after accounting for sex and age. Consistent with the whole brain perfusion results, patient status with the full dataset was not a significant predictor of frontal perfusion (β = .160, p = .291), parietal perfusion (β = .068, p = .641), or occipital perfusion (β = .071, p = .621). Similarly, across the five sex-matched subset analyses, patient group status was not a significant predictor of frontal perfusion (mean β = .123, mean p = .501; βs ranged from .042 to .198; ps ranged from .258 to .826), parietal perfusion (mean β = .074, mean p = .679; βs ranged from .004 to .148; ps ranged from .372 to .978), or occipital perfusion (mean β = .063, mean p = .628; βs ranged from -.06 to .181; ps ranged from .307 to .863).

Discussion

This study investigated the relationship between cerebrovascular perfusion and CVD status. Findings demonstrated no significant differences between healthy CVD patients and controls on whole brain voxel-wise perfusion cerebrovascular perfusion, mean total and regional gray matter perfusion, or white matter perfusion after accounting for age and sex effects. These results suggest that when mild cardiac pathology is present, cerebrovascular perfusion may not be significantly altered. It is important to note that while participants with CVD had significantly lower left ventricular ejection fractions compared to participants without CVD, participants with CVD had ejection fractions in the normal range and thus, cardiac function was not compromised. These results show that while patients with CVD statistically differed on peripheral perfusion, they did not clinically differ, and this was reflected in lack of significant cerebrovascular perfusion difference between the two groups. This suggests that in a relatively healthy patient group, the brain's integrity may likely remain intact until later in the disease progression. That is, there might be threshold effects at higher levels of CVD impairment, which would be an important question for future studies investigate. This study also found sex differences in cerebrovascular perfusion. Consistent with past literature,[15,26] females exhibited higher whole brain perfusion, frontal perfusion, parietal perfusion, and occipital perfusion than males.

Despite a rapidly growing fMRI research literature on cognitive function among diverse patient populations, relatively little is known about how systemic and cerebrovascular perfusion might affect fMRI. In this study we found no significant between-group perfusion differences by CVD patient status, suggesting that the impact of CVD on fMRI assessment is limited among patients with CVD outside the context of significant heart failure. Thus, the results of this study suggest that fMRI is as valid and reliable a method to utilize with CVD patients who are undergoing effective treatment (e.g., ejection fractions within the normal range) as it is for their non-CVD peers. Nevertheless, careful interpretation of fMRI is warranted moving forward due to possible CVD effects on perfusion

in individuals who are not undergoing CVD treatment, have more severe illness, and/or exhibit additional factors that may influence perfusion (e.g., relevant comorbid diagnoses). Based on the current study, we only discuss perfusion in the context of CVD with normal ejection fraction. Future studies should expand this research to untreated or more severe samples, as it is possible that cerebrovascular perfusion deficits may emerge as CVD severity increases.

Study limitations that should be considered when interpreting the data. First, the size of our sample was small, as we examined 39 control participants and 20 patients. However, we conclude that statistical power was sufficient to detect medium effects, and a medium effect ($f = 0.464$; $d = 0.511$) was expected based upon observed group differences in systemic perfusion (i.e., LVEF). The observed effect for patient group status on perfusion was far from this estimate in both the main analysis ($\beta = .117$, $p = .436$) as well as the subgroup analyses (mean $\beta = .105$, mean $p = .562$). Replication of previously reported sex effects between 25 males and 34 females also suggests sufficient statistical power to detect small to medium effects.[15,26] As previously noted, our patient sample was also limited to mostly mild cases, with no participants falling into the NYHA Class 4 categorization, and only 4 participants falling into the NYHA Class 3 categorization. Future studies that specifically recruit more severe samples would be better positioned to examine how cerebrovascular perfusion may differ among those populations. Our sample also lacked diversity with 95% of the sample identifying as Caucasian. Future studies should aim to recruit participants from more diverse backgrounds. In addition, the sample included more women (34) than men (25), with sex distributions being uneven (e.g., more males than females in the patient group). While we addressed this issue in this study by controlling for sex and conducting subset analyses, future studies should attempt to recruit even distributions of male and female participants across patient and control groups. Given sex differences in CVD prevalence and lifespan of older adults, researchers may need to be especially thoughtful in the design and recruitment for future studies to reach ideal demographic distributions of participants in a timely fashion. Furthermore, the patients in this study were

undergoing effective treatment for CVD. These results could be attributed, in part, to treatment, medication adherence, lack of severity, and overall well-managed status of the CVD patients. Future studies could investigate these relationships between CVD and cerebrovascular perfusion in an untreated patient sample to better understand at what point cerebrovascular perfusion becomes significantly impaired. Next, a longitudinal design may further provide information on these relationships. For example, CVD patients could be given an ASL scan when diagnosed and subsequent scans could take place over time so that cerebrovascular perfusion can be better understood in a within-subjects context that takes into account illness progression and treatment (or non-treatment) over time. Lastly, an additional limitation was that PICORE-Q2TIPS ASL was used including pulsed ASL. While newer PCASL avoids weaknesses associated with pulsed ASL and would increase the sensitivity in detecting group differences, we were limited to already collected sequences and resources. Future research should aim to make use of the newest PCASL to improve upon this limitation.

In conclusion, this study found no significant cerebrovascular perfusion differences between healthy CVD patients with normal cardiac efficiency and healthy controls. The study also replicated previous findings on sex differences in perfusion, finding that females exhibiting higher perfusion compared to males. The results of this study suggest that CVD patients without impairment of cardiac function also have normal cerebrovascular functioning, and thus, they are likely to exhibit normal BOLD response in the context of fMRI imaging. This is a first step in understanding cerebrovascular perfusion in the context of CVD. Future studies examining moderate and severe heart failure in the context of CVD are needed. Additionally, studies of mechanisms involved in maintaining cerebrovascular perfusion in the context of altered peripheral perfusion are needed, including how sex differences associated with cerebrovascular and peripheral perfusion might interact with CVD effects.

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Table 1.

	Cardiac Patients N =20	Non-Patient Controls N=39	Overall N=59	Significance (p value)
Age in years M(SD)	72.50(8.95)	63.69(8.64)	66.68(9.63)	0.001
Sex				0.011
Female	7	27	34	
Male	13	12	25	
Years of Education M (SD)	15.90(2.53)	16.03(2.17)	15.98(2.28)	.670

Demographic Information

N = Sample Size; M = Mean; SD = Standard Deviation

Table 2.

Group Means and Standard Deviations for Whole Brain Cerebrovascular Perfusion, Regional Perfusion, and White Matter Perfusion (ml of blood/100 ml of tissue/min)

Status	N	Whole Brain Perfusion M(SD)	Frontal Lobe Perfusion M(SD)	Parietal Lobe Perfusion M(SD)	Temporal Lobe Perfusion M(SD)	Occipital Lobe Perfusion M(SD)	White Matter Perfusion M(SD)
Control	39	45.09 (5.50)	45.90 (5.91)	50.40 (7.08)	45.94 (6.62)	53.66 (8.43)	31.18 (5.49)
CVD Patient	20	45.14 (7.56)	46.80 (8.70)	48.63 (8.26)	46.56 (8.45)	49.92 (12.64)	34.14 (6.03)
Total	59	45.11 (6.21)	46.20 (6.92)	49.80 (7.48)	46.15 (7.23)	52.39 (10.10)	32.18 (5.80)

N = Sample Size; M = Mean; SD = Standard Deviation

Figure 1. Mean cerebral perfusion by group.

Notes: units are ml of blood/100 ml of tissue/min, slice locations are z = +65 to z = -30 in 5mm increments. Left is left.