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Cerebral Hypoperfusion Is Exaggerated With an Upright Posture in Heart Failure

Impact of Depressed Cardiac Output

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ABSTRACT

OBJECTIVES The purpose of this study was to examine cerebral blood flow (CBF) supine and during upright sitting in HF patients and control subjects to test the hypothesis that patients with HF will have a greater reduction in CBF from supine to seated compared with the control group.

BACKGROUND Reduced CBF has been reported in patients with heart failure (HF). However, previous work has only examined CBF while supine, although an upright posture common to daily living may lead to further reductions.

METHODS In 22 HF patients and 22 age- and sex-matched control subjects, continuous heart rate, mean arterial pressure, and end-tidal carbon dioxide readings were collected while supine and seated upright. Cardiac output was estimated from pulse contour analysis and was corrected for body size (cardiac index). The right internal carotid artery was imaged by using ultrasound to estimate CBF.

RESULTS Heart rate increased less in response to the upright posture in HF patients versus control subjects ($p = 0.006$). Mean arterial pressure was unchanged, whereas end-tidal carbon dioxide decreased in response to position ($p = 0.004$) but did not differ between groups. Cardiac index was lower in patients with HF ($p < 0.001$) and decreased in both groups in response to the upright posture ($p = 0.025$), with a trend for a greater decrease in the HF group ($p = 0.065$). CBF decreased more in response to the upright posture in the HF group than in the control group ($p = 0.007$).

CONCLUSIONS The reduction in CBF was exaggerated in the upright posture in HF patients and may increase the risk for subsequent cognitive impairment. (J Am Coll Cardiol HF 2015;3:168–75) © 2015 by the American College of Cardiology Foundation.

Heart failure (HF) is an independent predictor of cognitive decline (1) that affects ~25% to 50% of patients (2). Cerebral hypoperfusion secondary to impaired cardiac function is believed to contribute to the burden of cognitive impairment. Indeed, when heart function is improved with cardiac transplantation or cardiac resynchronization therapy, improvements in cognition and cerebral blood flow (CBF) have been noted (3–6). Although several studies have reported reduced CBF in patients with HF (7–9), these reports measured CBF only while supine.

Upright positions, a part of normal daily living, are associated with gravity-driven hydrostatic gradients in the body and the translocation of blood to the lower extremities. In generally healthy adults, upright posture is associated with small reductions in CBF. This is a consequence of complex interactions among reductions in local perfusion pressure, cardiac output, and/or arterial partial pressure of carbon

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dioxide, even though mean arterial pressure (MAP) is not reduced in the upright position (10,11). In HF, in which supine cardiac output is already limited, upright posture may increase the vulnerability to cerebral hypoperfusion, thus furthering the risk of chronic ischemia and cognitive impairment.

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The purpose of the present study was to evaluate the cardiovascular and cerebrovascular response to an upright, seated position in HF patients compared with control subjects. We hypothesized a greater CBF decrease in response to the upright position in the HF group compared with the control group and that the decrease would be greatest in those with a lower supine resting cardiac output.

PATIENTS AND METHODS

Twenty-two community-dwelling patients with HF and 22 age- and sex-matched control subjects in generally good health and with no history of HF participated in the study. The HF patients had a clinical diagnosis of HF and exhibited clinical and therapeutic stability for 1 month. Exclusion criteria included cardiac transplant recipients, New York Heart Association functional class IV, stroke within the past 10 years, arterial blood pressure ≥160/90 mm Hg, and documented diagnosis of dementia. The experimental procedures for this study were approved by the Office of Research Ethics at the University of Waterloo (ORE 18543 and 15731) and the Hamilton Integrated Research Ethics Board (HIREB 13-338) in accordance with the Declaration of Helsinki. All participants volunteered freely after reading and signing an informed consent form and were aware of their rights to withdraw from the study at any time.

STUDY DESIGN. This study used a cross-sectional design. Left ventricular ejection fraction and New York Heart Association class were obtained from the medical records of the HF patients. All participants provided a list of recent medications and continued to take these medications according to their normal schedule.

STUDY PROCEDURE. Participants completed the Montreal Cognitive Assessment (MoCA), 2 timed 8-m usual walking speed tests and anthropometric measures (i.e., height, weight, waist/hip ratio). Participants then lay supine on a bed and were instrumented to continuously monitor heart rate, arterial blood pressure, cardiac output, and end-tidal carbon dioxide ($ETCO_2$). An estimate of CBF was obtained with an ultrasound after 10 min (for stabilization). Participants were assisted to a seated position, and the procedure was repeated.

INSTRUMENTATION AND MEASUREMENTS. Montreal Cognitive Assessment. The MoCA is a screening tool for mild cognitive impairment and has been used previously in a population with HF (12,13). Initial testing of the MoCA in a sample of older adults demonstrated a cutoff score of <26/30 for mild cognitive impairment and yielded a sensitivity of 90% and a specificity of 78% (14).

Cardiovascular and Cerebrovascular Assessments. Heart rate (electrocardiogram; ECG Module, Finapres Medical Systems, Amsterdam, the Netherlands) and arterial blood pressure (finger-cuff plethysmography; Finometer Pro, Finapres Medical Systems) were collected beat-to-beat throughout the test. Cardiac output was estimated from the Modelflow algorithm (15) and corrected for body surface area to yield a cardiac index (CI). Total peripheral resistance was calculated as MAP divided by cardiac output. Breath-by-breath exhaled carbon dioxide was sampled through a nasal cannula and analyzed by using infrared spectroscopy (Ohmeda 5200 CO_2 Monitor, Ohmeda, Madison, Wisconsin) to estimate $ETCO_2$ in millimeters of mercury. Measures of heart rate, arterial blood pressure, cardiac output, and $ETCO_2$ were collected at 1 kHz (PowerLab, Chart version 5.5.6, ADInstruments, Colorado Springs, Colorado). Steady state beat-by-beat data were averaged for 1 min after at least 5 min in each posture.

CEREBRAL BLOOD FLOW. CBF was quantified by using extracranial ultrasound measured bilaterally supine (right internal carotid artery [RICA] and left internal carotid artery [LICA]) and unilaterally seated (RICA). An 8- to 12-Hz linear array transducer (L14-6s with M5 system, Mindray, Shenzhen, China) was used to image the internal carotid artery (ICA) 1 to 2 cm distal to the carotid bifurcation to minimize turbulent flow from the carotid bulb. ICA diameter was measured during the diastolic phase by electronic calipers in triplicate and averaged. The Doppler function of the same probe permitted measurement and time-averaging of the mean flow velocity from the ICA. CBF through the ICA was calculated as follows: $CBF = \text{mean flow velocity} \times \pi(\text{diameter}/2)^2$.

STATISTICAL ANALYSIS. Participant and medical characteristics between HF patients and control subjects were compared by using Student *t* tests for continuous variables and *z* tests for categorical variables. Cardiovascular and cerebrovascular baseline

ABBREVIATIONS AND ACRONYMS

CBF = cerebral blood flow

CI = cardiac index

$ETCO_2$ = end-tidal carbon dioxide

HF = heart failure

ICA = internal carotid artery

LICA = left internal carotid artery

MAP = mean arterial pressure

MoCA = Montreal Cognitive Assessment

RICA = right internal carotid artery

supine variables between HF patients and control subjects were also compared by using Student *t* tests. When appropriate due to non-normal distribution of variables, nonparametric Mann-Whitney *U* tests were used. To compare the difference between supine and seated values among the HF patients and control subjects, 2-way repeated measures analysis of variance tests were used. When a significant interaction was detected, Tukey post-hoc tests were applied. A monoexponential 3-parameter nonlinear regression analysis compared how the change in CBF from supine to seated was related to supine CI.

Statistical analyses were performed by using SigmaPlot version 12.5 software (Systat Software Inc., Chicago, Illinois), with statistical significance set at $p < 0.05$ and trends reported for $p \leq 0.10$. Data are presented as mean ± SD for parametric tests, median (interquartile range) for nonparametric tests, and number (%) for categorical variables.

RESULTS

All participants completed the study protocol in its entirety with no requests to stop the procedures early. The anatomic location of the carotid bifurcation was situated too high up the neck on the right side in 4 patients with HF and on the left side in 3 patients with HF to obtain valid ultrasound measurements on the ICA. The sample size was reduced to 18 and 19 for these measures, respectively.

CHARACTERISTICS. In general, the patients with HF ($n = 22$) were mainly older men with a mean left ventricular ejection fraction of 33 ± 11% (4 patients with ≥45%), 63% were New York Heart Association class II, and 27% were New York Heart Association class III. A higher proportion of the HF cohort had diabetes ($p = 0.001$) and a history of smoking ($p < 0.001$) (Table 1). HF patients had a lower education level ($p < 0.001$), lower MoCA scores ($p < 0.001$), and slower gait speeds ($p < 0.001$) compared with control subjects. Patients with HF were more likely to be prescribed the following medications: beta-blockers ($p < 0.001$), angiotensin-converting enzyme inhibitors ($p < 0.001$), diuretics ($p < 0.001$), statins ($p = 0.015$), and clopidogrel ($p = 0.013$) (Table 2). There was a trend for warfarin use ($p = 0.055$) to be higher in the HF group.

BASELINE. Cardiovascular and cerebrovascular variables during the supine baseline posture were compared between the HF patients and control subjects, as shown in Table 3. The HF patients had significantly lower CI ($p < 0.001$) and CBF through the right internal carotid artery (CBF_{RICA}) ($p = 0.046$) compared with the control subjects. No significant differences were detected between CBF_{RICA} and CBF through the LICA in control subjects ($p = 0.718$) or HF patients ($p = 0.292$, data not shown).

TABLE 1 Characteristics of Heart Failure Patients and Control Subjects

	Heart Failure Patients	Control Subjects
Age, yrs	69 ± 9	70 ± 9
Male/female	18/4	18/4
Education, yrs	12.2 ± 4*	16.6 ± 3
History of smoking	17 (77)	4 (18)
History of diabetes	10 (45)*	0
History of atrial fibrillation	4 (18)	0
Pacemaker/ICD	12 (54)*	0
Height, cm	173 ± 10	172 ± 8
Weight, kg	87 ± 20	78 ± 16
BMI, kg/m^2	29 ± 7	26 ± 5
Waist/hip ratio	0.96 ± 0.10	0.91 ± 0.09
Gait speed, m/s	0.98 ± 0.2*	1.34 ± 0.20
MoCA score	24.5 (22.0–27.0)*	28.5 (27.0–29.0)

Values are mean ± SD, n, n (%), or median (interquartile range). *$p < 0.05$.
BMI = body mass index; ICD = implantable cardioverter-defibrillator.

POSTURE. The cardiovascular and cerebrovascular variables in the supine and seated positions in the HF group and control group are presented in Figures 1 and 2, respectively. A significant interaction was identified for heart rate ($p = 0.006$; posture × group) (Figure 1A) such that the increase in response to the seated posture was not as large in the HF group compared with the control group. Total peripheral resistance increased significantly with the upright position ($p = 0.009$; main effect position) (Figure 1C). CI was lower in the HF group ($p < 0.001$; main effect

TABLE 2 Medication Summary

	Heart Failure Patients	Control Subjects
Beta-blocker	22 (100)*	2 (9)
ACE inhibitor	13 (59)*	0
Diuretic	20 (91)*	4 (18)
Angiotensin II receptor antagonist	7 (32)	3 (14)
Calcium channel blocker	3 (14)	0
Nitroglycerin spray	4 (18)	0
Statin	16 (73)*	7 (32)
Alpha$_1$-antagonist	4 (18)	3 (14)
Aspirin	7 (32)	4 (18)
Warfarin	7 (32)†	1 (5)
Clopidogrel	7 (32)*	0
Antidepressant	4 (18)	0

Values are n (%). *$p < 0.05$. †$p \leq 0.10$.
ACE = angiotensin-converting enzyme.

TABLE 3 Baseline Supine Comparisons

	Heart Failure Patients	Control Subjects
Heart rate, beats/min	62.1 ± 10.4*	56.4 ± 10.6
MAP, mm Hg	89.9 ± 11.0	93.7 ± 9.1
TPR, mm Hg/l/min	16.8 (11.4–23.6)	18.4 (15.7–22.1)
Cardiac index, l/min/m^2	3.2 ± 1.5†	5.2 ± 1.3
CBF_{RICA}, ml/min	258 ± 54†	301 ± 69
$ETCO_2$, mm Hg	36.2 ± 5.5	36.7 ± 4.5

Values are mean ± SD or median (interquartile range). *p ≤ 0.10. †p < 0.05.
CBF_{RICA} = cerebral blood flow through the right internal carotid artery; $ETCO_2$ = end-tidal carbon dioxide; MAP = mean arterial pressure.

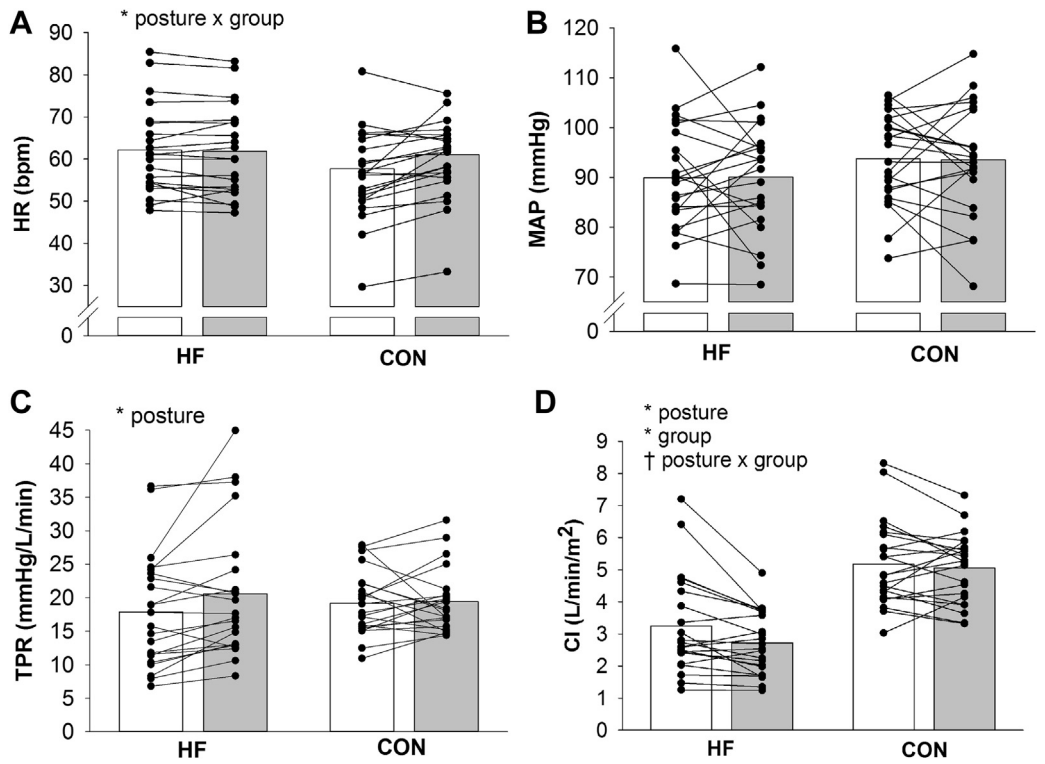
group) and decreased in both groups in response to the upright, seated position (p = 0.025; main effect position). There was a trend for an interaction effect in CI (p = 0.065; posture × group) (Figure 1D) with a greater decrease in the HF patients (-12% in the HF group vs. -0.44% in the control group). The HF group had a greater decrease in CBF_{RICA} (p = 0.007; posture × group) (Figure 2A) in response to the upright, seated position (-15% in the HF group vs. -0.02% in the control group). A significant main effect of position was found for $ETCO_2$ (p = 0.004; main effect position) (Figure 2B) with lower values in the seated position, but no difference between groups was noted.

CBF AND CARDIAC OUTPUT. A nonlinear relationship was found between supine CI and the change in CBF_{RICA} from supine to seated. The lower supine CI resulted in a greater drop in CBF (r^2 = 0.20; p = 0.047) (Figure 3).

DISCUSSION

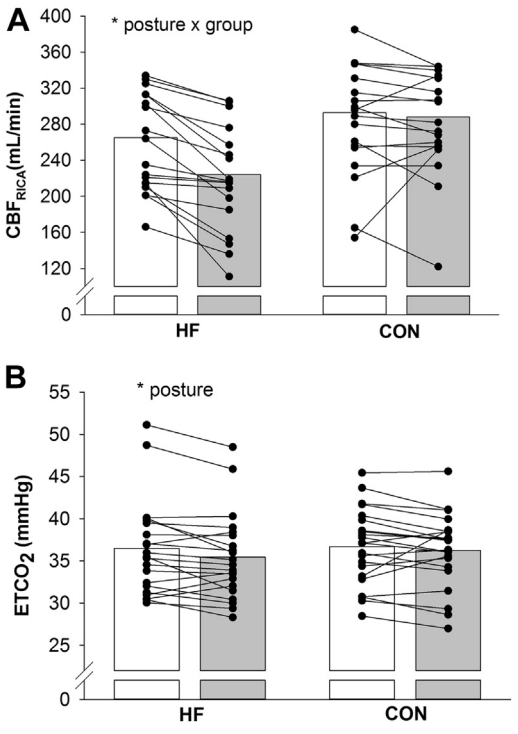
The present study examined the cardiovascular and cerebrovascular response to an upright seated posture in HF patients compared with control subjects and evaluated if supine CI was predictive of the magnitude of drop in CBF. As anticipated based on previous literature (7-9), HF patients had lower

FIGURE 1 Cardiovascular Variables During Different Postures



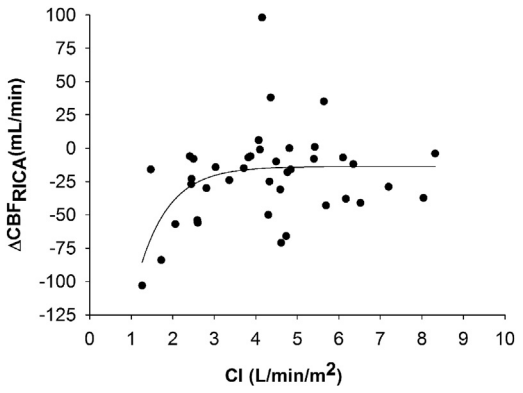
(A) Heart rate (HR), **(B)** mean arterial pressure (MAP), **(C)** total peripheral resistance (TPR), and **(D)** cardiac index (CI) for supine **(open bars)** and seated **(solid bars)** in the control (CON) and heart failure (HF) groups. **Bars** represent mean values, and the **lines** on the graphs connect individual subject values in supine and seated positions. *Statistical significance, p < 0.05. †Statistical trend, p ≤ 0.10. Posture indicates a main effect of posture; group indicates a main effect of group; posture × group indicates an interaction effect between posture and group.

FIGURE 2 Cerebrovascular Variables During Different Postures



(A) Cerebral blood flow through the right internal carotid artery (CBF_{RICA}) and **(B)** end-tidal carbon dioxide ($ETCO_2$) for supine **(open bars)** and seated **(solid bars)** in the control (CON) and heart failure (HF) groups. Symbols as in Figure 1.

FIGURE 3 Cardiac Index and Cerebral Blood Flow



Nonlinear relationship between supine cardiac index (CI) estimated by using the Finometer Pro and the change in cerebral blood flow through the right internal carotid artery (CBF_{RICA}) from supine to seated ($r^2 = 0.20$; $p = 0.047$).

supine values for CI and CBF. Consistent with our hypothesis, the novel data from this study revealed a significant posture × group interaction effect such that CBF_{RICA} had a greater reduction on moving to the upright seated position in the HF group compared with the control group. Furthermore, we found a nonlinear relationship between supine CI and the change in CBF_{RICA} from supine to seated, suggesting a threshold value for CI below which there was a greater drop in CBF_{RICA} on moving to an upright position. Our results suggest that the cerebral hypoperfusion in HF may be greater than previously recognized based solely on supine measurements and that this exaggerated reduction in CBF may contribute to cognitive impairment through chronic ischemia.

The mechanism underlying the greater reduction in CBF in HF was not related to change in MAP with upright posture. Small reductions in $ETCO_2$ values were found with sitting, potentially contributing to some decline in CBF (11); however, there were no differences between groups. In a healthy population, van Lieshout et al. (10) highlighted that brain perfusion relies on cardiac output when moving from supine to standing by illustrating that leg tensing could relieve decreased cardiac output and restore mean flow velocity in the brain. Additional reports have highlighted the reliance of CBF on cardiac output during exercise in HF patients (16). Likewise, beta-receptor blockade limited the cardiac output response to exercise and restricted the increase in mean flow velocity. When heart function was improved, such as with a transplant, cardiac output increased along with CBF (6). Taken together, results from this study along with previous findings suggest a dependency of CBF on cardiac output, especially when cardiac output is lowered. Furthermore, the greater decline in CBF in HF, even though cerebral perfusion pressure was maintained, suggests that cerebrovascular autoregulation might be compromised in the face of limited cardiac output.

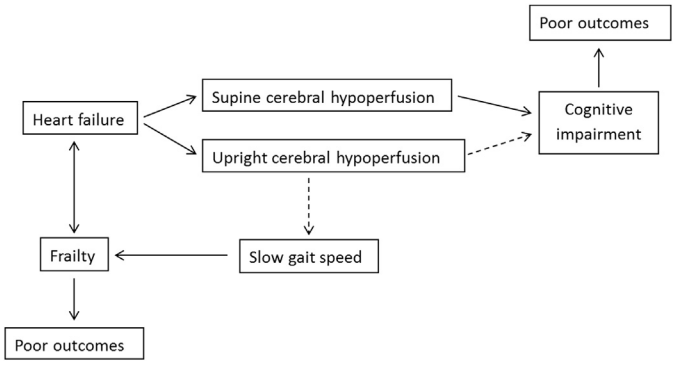
Evidence is mounting that impaired cardiac function, indicated by low cardiac output, may accelerate the effects of normal cerebral aging, including cognitive impairment (17,18). Low cardiac output has also been linked to neuroimaging abnormalities attributable to chronic ischemia, specifically white matter hyperintensities (19). In the Framingham Heart Study, a threshold CI of <2.9 l/min/m^2, measured by using magnetic resonance imaging, was proposed as a potential clinical threshold for abnormal brain changes because significantly lower brain volumes were detected beyond this point (20).

Based on this finding, we investigated whether a lower supine CI was related to a greater drop in CBF from supine to upright sitting and found a significant nonlinear relationship between supine resting CI (estimated from the Finometer Pro) and the absolute reduction in CBF_{RICA} on moving to an upright posture. The decline in CBF_{RICA} with posture change was greatest for estimated CI $<\sim 3$ l/min/m^2. The present results add to existing evidence and support future research investigating how lower CI may accelerate brain aging.

The high prevalence of cognitive impairment in HF has been attributed in part to cerebral hypoperfusion secondary to impaired cardiac function. We found that >60% of the HF patients had some degree of cognitive impairment as detected by a MoCA score <26. This finding is slightly higher than previous research, which documented that 25% to 50% of HF patients experience cognitive deficits (2). Importantly, no formal documentation of cognitive impairment was present in this sample, suggesting that a large portion of mild to moderate cognitive deficits go undetected in a clinical setting. This possibility is concerning given that even mild cognitive deficits may interfere with important self-care practices for HF. In a recent study, poor self-care was an independent risk factor for cardiac events and hospitalizations as well as length of hospital stay (21). Our novel findings suggest that cerebral hypoperfusion is exaggerated in the upright position and thus may further contribute to cognitive decline over time by compromising cerebral perfusion and leading to chronic ischemia in deep cerebral structures and watershed territories.

STUDY LIMITATIONS. A notable limitation of this study is that cardiac output was estimated from the Finometer Pro. The accuracy of the Modelflow algorithm used to estimate cardiac output has been questioned in special populations (22) and with sympathetic activation (23,24); our results should therefore be confirmed by using alternative methods. In the seated position, CBF was only assessed unilaterally on the right side, and assumptions were made regarding bilateral symmetry. In the supine position, CBF_{RICA} and CBF_{LICA} did not differ; therefore, the change to the upright position was presumed to also be the same. The relatively small sample size and cross-sectional nature of this study also must be acknowledged. In addition, our HF group was diverse but reflects the heterogeneity of this population. The effect of medications should also be considered, as most HF patients were on some combination of beta-blocker, angiotensin-converting enzyme inhibitor, and diuretics that may have affected posture response, especially heart rate on sitting. Furthermore, our results should be interpreted with caution because we did not correct for multiple comparisons. However, we analyzed significant differences from the repeated measures analysis of variance tests by using the conservative Tukey test.

FIGURE 4 Relationship Between Cerebral Blood Flow and Frailty



Hypothetical model for the influence of upright cerebral hypoperfusion on poor outcomes acting through slow gait speed and cognitive impairment. **Dashed lines** represent avenues for future investigation.

CONCLUSIONS

This study was, to the best of our knowledge, the first to investigate CBF in a HF population in the upright, seated position. We found that CBF was decreased to a greater extent in HF patients who already had lower supine values compared with age- and sex-matched control subjects. Intermittent reductions in CBF with upright positions during daily living may contribute to cerebral damage, ischemia, and cognitive decline over time. Importantly, cerebral hypoperfusion in HF seems more exaggerated than previously thought, when it was investigated only in supine postures. The CBF decrease from supine to a seated posture seems to be related to impaired cardiac function, as indicated by a low CI with an apparent threshold below which there is a greater decline in CBF. These results are consistent with other studies (18,20,25), which propose that impaired cardiac function below a threshold value may accelerate normal cerebral aging.

PERSPECTIVES

Future work should seek avenues that limit the extent of reductions in upright CBF. An optimal

pharmacological plan should be investigated for maintaining CBF. Physical activity in older adults is beneficial for cardiovascular health and cognitive performance (26). Brain blood flow increases in response to short-term exercise training in previously sedentary seniors (27). In patients with HF, exercise training shows promise to improve cognitive function, although the effect on CBF remains elusive (28).

HF and frailty often coexist in a complex relationship, with each condition exacerbating the other (29). Compared with the control subjects, HF patients in this study had slower gait speeds, a main predictor of frailty (30), and lower MoCA scores, indicating some form of cognitive impairment. The main finding in this study was exaggerated cerebral hypoperfusion in the upright posture, which may act to further impair cognition through chronic ischemia. Furthermore, upright cerebral hypoperfusion may also be contributing to slow gait speeds. Slow gait has been suggested previously as a predictor of cognitive decline (31); however, a common mechanism, cerebral hypoperfusion, may be responsible for both (dashed lines in **Figure 4**). Cognitive impairment and frailty are associated with inadequate patient-centered outcomes such as poor quality of life, loss of independence, morbidity, and mortality (32–35). Therefore, continuing to investigate hypoperfusion in the upright posture and seeking ways to limit the extent of damage could improve the quality of life and outcomes for these patients.

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