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Original Article

Ambulatory Monitoring of Cerebrovascular Responses to Upright Posture and Walking in Older Adults With Heart Failure

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ABSTRACT

Background: Insufficient cardiac output in individuals with heart failure (HF) limits daily functioning and reduces quality of life. Although lower cerebral perfusion, secondary to limitations in cardiac output, has been observed during moderate-intensity efforts, individuals with HF also may be at risk for lower perfusion during even low-intensity ambulatory activities.

Methods: We determined whether HF is associated with an altered cerebrovascular response to low-intensity activities representative of typical challenges of daily living. In this study, we monitored central

RÉSUMÉ

Contexte : Un débit cardiaque insuffisant chez les personnes atteintes d'insuffisance cardiaque limite les activités quotidiennes et affecte la qualité de vie. Par exemple, des efforts d'intensité modérée ont été associés à une perfusion cérébrale affaiblie chez ces personnes. Or, il semble que même des activités ambulatoires de faible intensité soient susceptibles d'avoir les mêmes conséquences.

Méthodologie : Nous voulions déterminer si l'insuffisance cardiaque est associée à une altération de la réponse cérébrovasculaire à des activités de faible intensité qui sont typiques de la vie quotidienne.

Heart failure (HF) is a complex condition related to impairment of contraction or filling of the heart that leads to fatigue and dyspnea even during ambulatory activities of daily living. Possible restrictions in cardiac output ($\dot{Q}$) that coincide with other changes—including elevated activity within the sympathetic and renin-angiotensin-aldosterone systems, interstitial fibrosis, left ventricular hypertrophy and/or dilation, reduced left ventricular contractility,[1] and deficits in skeletal muscle oxygen transport and utilization[2]—could collectively contribute to exercise intolerance. The role of the brain in exercise tolerance of HF patients requires further investigation.[3] Individuals with HF have documented lower cerebral blood flow (CBF) during supine rest,[4,5] with exaggerated reductions in upright postures.[5] Accordingly, concerns have been raised with respect to cerebral autoregulation in HF to maintain CBF across a range of perfusion pressures.[6] Impairments of $\dot{Q}$ and cerebral autoregulation are believed to contribute to lower CBF in individuals with HF as part of the heart-brain axis.[7] Lower CBF might be exacerbated during increased physical demands[8] and could relate to the severe exercise intolerance typically observed in individuals with HF.

Advances in ambulatory monitoring technologies now enable hemodynamic assessment during dynamic real-life scenarios.[9-11] We hypothesized that ambulatory measurements would reveal lower values of cardiac index ($\dot{Q}$i) and lower cerebral perfusion and oxygenation, as measured by middle cerebral artery blood velocity (MCAv) and near infrared spectroscopy (NIRS), at rest, during quiet standing after a posture transition, and during low-intensity over-ground walking in older adults with HF, compared to those in similarly aged controls.

Methodology

Participants

Ten community-dwelling individuals with clinically diagnosed HF (3 women; aged 78 ± 4 years; left ventricular ejection fraction [LVEF] 20%-61%; 8 New York Heart Association [NYHA] class II and 2 NYHA class III), and 13 control participants with no diagnosis of HF (9 women; aged 79 ± 8 years; LVEF 52%-73%) volunteered to participate in

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hemodynamics and middle cerebral artery blood velocity (MCAv) and cerebral tissue oxygenation (near-infrared spectroscopy) in 10 individuals with HF (aged 78 ± 4 years; left ventricular ejection fraction 20%-61%) and 13 similar-aged controls (79 ± 8 years; 52%−73%) during 3 randomized transitions, as follows: (i) supine-to-standing; (ii) sitting-to-slow-paced over-ground walking; and (iii) sitting-to-normal-paced over-ground walking.

Results: Throughout supine, sitting, standing, and both walking conditions, individuals with HF had lower cardiac index and cerebral tissue oxygenation than controls ($P < 0.05$), and MCAv was lower across the range of blood pressure in HF patients ($P = 0.051$) and during walking only ($P = 0.011$). Individuals with HF had an attenuated increase in stroke volume index and cardiac index during normal-paced walking, compared to controls ($P < 0.01$).

Conclusions: The indices of cerebral perfusion from MCAv and cerebral oxygenation were lower during ambulatory activities in individuals with HF; however, relationships between MCAv and blood pressure were not different between those with HF and controls, indicating no difference in static cerebral autoregulation.

Dans le cadre de cette étude, nous avons surveillé l'hémodynamique centrale et la vitesse du sang dans l'artère cérébrale moyenne (VACM), ainsi que l'oxygénation tissulaire cérébrale (par spectroscopie dans le proche infrarouge) chez 10 personnes atteintes d'insuffisance cardiaque (âge : 78 ± 4 ans; fraction d'éjection du ventricule gauche de 20 à 61 %) et 13 témoins d'âge similaire (79 ± 8 ans; de 52 à 73 %) lors de 3 transitions réparties de façon aléatoire, soit : i) de la position couchée à debout; ii) de la position assise à une marche lente et iii) de la position assise à une marche à vitesse normale.

Résultats : En position couchée, assise ou debout et avec les deux vitesses de marche, l'index cardiaque et l'oxygénation tissulaire cérébrale étaient plus faibles chez les personnes atteintes d'insuffisance cardiaque que chez les témoins ($p < 0,05$); la VACM était plus faible dans toutes les plages de pression artérielle chez les personnes atteintes d'insuffisance cardiaque ($p = 0,051$) et durant la marche seulement ($p = 0,011$). Les personnes atteintes d'insuffisance cardiaque présentaient une plus faible augmentation du volume d'éjection systolique et de l'index cardiaque durant la marche à vitesse normale, comparativement aux témoins ($p < 0,01$).

Conclusions : Les indices de la perfusion cérébrale selon la VACM et l'oxygénation cérébrale étaient réduits durant les activités ambulatoires chez les personnes atteintes d'insuffisance cardiaque; cependant, les relations entre la VACM et la pression artérielle n'étaient pas différentes entre les personnes atteintes d'insuffisance cardiaque et les témoins, ce qui indique que l'autorégulation cérébrale statique n'est pas un facteur de différenciation.

this study. Our sample size was based on previous work from our group, identifying differences in the supine-seated CBF response between individuals with HF and controls (alpha = 0.05, beta = 0.20, with an estimated large effect of d = 1.16).[5] The sample was not restrictive on the type of HF, as reduced exercise intolerance is a prominent feature of all HF phenotypes. Exclusion criteria included cardiac transplant recipients, NYHA functional class IV, prior diagnosis of neurologic disease, atrial fibrillation, uncontrolled hypertension (resting blood pressure [BP] ≥ 140/90 mm Hg), diagnosed carotid artery disease, and any acute health condition. Participants were asked to refrain from exercise and alcohol for 24 hours, and from caffeine for 12 hours, prior to testing. Participants arrived by their normal means of transportation for testing at least 2 hours postprandial and were instructed to maintain their normal medication routine prior to participation. The experimental procedures for this study were approved by the Office of Research Ethics at the University of Waterloo (ORE 21025), and in accordance with the Declaration of Helsinki, except for registration in a trial database. All participants volunteered freely after providing informed consent and were able to withdraw from the study at any time.

Protocol overview

Participants completed the Montreal Cognitive Assessment (MoCA) and 2 timed 8-minute walk tests ("as quickly as possible") to quantify their gross characteristics of cognitive and physical functioning, respectively. Subsequently, we assessed cardiac function with participants lying in the left lateral decubitus position after 10 minutes of supine rest. A 5-1 MHz xMATRIX array probe connected to a commercially available ultrasound system (Phillips iE33, Koninklijke Philips Electronics, Amsterdam, Netherlands) was used for all imaging. Left ventricular stroke volume (SV) and LVEF were determined from images taken in the apical 4C and 2C views, calculated using the modified Simpson method.[1] Indices of diastolic function (E/A, E/e') were derived from mitral inflow velocities with the gate positioned at the tip of the mitral valve leaflets, as well as from tissue Doppler imaging of the lateral and septal mitral annulus.

All participants completed 3 randomized, counterbalanced transitions on the same day: (i) supine rest to standing; (ii) seated rest to walking in a controlled indoor hallway at a self-selected slow pace; and (iii) seated rest to walking at a self-selected normal pace. All trials began with a 5-minute rest period and continued for 3 minutes following each transition. Larger ambulatory monitors (e.g., blood pressure unit) were attached to a wheeled walker, which the participants were able to push ahead of them with minimal effort. Each transition included at least 10 minutes of seated rest.

Cardiorespiratory dynamics

Heart rate (HR) and brachial artery BP were assessed using finger photoplethysmography (Portapres Model-2, Finapres Medical Systems, Amsterdam, Netherlands). Reconstructed brachial BP was calibrated to an average of 2 manual BP measurements made during supine rest. Mean BP (MAP) is reported during each condition. For assessment of cerebral autoregulation, MAP in the middle cerebral artery (BP_{MCA}) was estimated by adjusting for the vertical distance between the heart and the transcranial Doppler (TCD) probe.[12] Beat-by-beat SV was estimated using the Modelflow algorithm[13] and calibrated to a simultaneously obtained estimate of supine SV using echocardiography. Beat-by-beat $\dot{Q}$ was

Table 1. Participant characteristics and resting hemodynamics

Characteristic	Control	HF	*P*
Sex, male/female	4/9	7/3	0.100
Age, y	79 ± 8	78 ± 8	0.897
Height, cm	163 ± 12	173 ± 11	**0.043**
Body mass, kg	64.8 ± 15.3	87.3 ± 18.1	**0.004**
BMI, kg/m^2	24.2 ± 4.2	28.8 ± 3.6	**0.012**
Smoking history	1 (8)	8 (80)	**< 0.001**
Walking speed, m/s	1.2 ± 0.3	1.0 ± 0.2	**0.020**
MoCA score	27 (24-28)	25 (22-28)	0.472
Medications			
Beta-blocker	0 (0)	8 (80)	**< 0.001**
ACEi	1 (8)	6 (60)	**0.019**
ARNi	0 (0)	1 (10)	0.435
CCB	1 (8)	3 (30)	0.281
Diuretics			
Loop	0 (0)	6 (60)	**0.002**
Potassium-sparing	0 (0)	2 (20)	0.178
Anticoagulant	0 (0)	5 (50)	**0.007**
Statin	3 (23)	6 (60)	0.102
Nitroglycerin spray	0 (0)	3 (30)	0.068
Cardiac systolic function			
LVEF, %	61 ± 6	45 ± 12	**< 0.001**
SVi, mL/m^2	43 ± 8	31 ± 6	**0.002**
$\dot{Q}$i, L/min per m^2	2.5 ± 0.6	2.0 ± 0.5	**0.004**
Cardiac diastolic function			
E/A	1.1 (0.9-1.4)	1.0 (0.7-1.2)	0.452
E/e'	6.7 ± 1.8	7.2 ± 1.2	0.565

Values are n, mean ± SD, median (IQR), or n (%), unless otherwise indicated. Boldface indicates significance. Hemodynamic and cardiac measurements were made with patient in the left lateral decubitus position.

A, late diastolic peak mitral inflow velocity; ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CCB, calcium-channel blocker; E, early diastolic peak mitral inflow velocity; e', early diastolic peak mitral annular velocity; HF, heart failure; LVEF, left ventricular ejection fraction; MoCA, Montreal cognitive assessment; $\dot{Q}$i, cardiac index; Svi, stroke volume index.

calculated as the product of HR and SV. SV and $\dot{Q}$ were normalized to body surface area (SVi and $\dot{Q}$i, respectively). Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was sampled using a nasal cannula and measured by a stationary infrared spectrometer (5200 CO_2 Monitor, Ohmeda, Madison, WI) during the supine-to-stand trial in 6 controls, and 3 individuals with HF (walking $P_{ET}CO_2$ was not measured in these participants). An ambulatory infrared spectrometer (Capnostream 35, Medtronic, Minneapolis, MN) was used during all trials in the remaining participants. All participants were instructed to breathe through their nose and remain quiet during protocols.

Cerebral hemodynamics and oxygenation

The right middle cerebral artery (MCA) was insonated by a portable TCD ultrasound[14] with a 1.5-MHz motorized probe (TCD-X, Atys Medical, Soucieu-en-Jarrest, France) to measure MCAv. Briefly, the transducer was positioned against the temporal window and secured in place on a glasses frame worn by the participants. An insonation depth between 50 and 60 mm was targeted. Velocity profile, signal strength, and auditory pitch were used to find the MCA, after which the motorized probe established the optimal angle for insonation based on an angled sweep to find the greatest signal intensity. Cerebral tissue saturation index (TSI) was calculated from the ratio of oxygenated to total hemoglobin by spatially-resolved NIRS (PortaLite, Artinis Medical Systems, Elst, Netherlands).[15] The NIRS probe was placed on the forehead, medial and superior to the right eyebrow, and covered by a black band to prevent contamination by ambient light.

Data analysis

Usual walking speed was calculated as the average of the two 8-minute−walk trials. On a beat-by-beat basis, the MCAv waveform was smoothed with a cubic spline function to reduce the influence of signal artifacts (eg, high-frequency spikes and signal dropout). Due to excessive signal noise in some participants, a visual confirmation was performed following smoothing to accept or reject TCD data on a beat-by-beat basis. The visual confirmation process was blinded to avoid assessor bias. Beat-by-beat and breath-by-breath data were time-aligned using a universal timestamp and confirmed using peak-to-peak interval matching for MCAv and BP data, using a custom MATLAB script (version 9.4, MathWorks, Natick, MA). Subsequently, data were interpolated to 1 Hz for averaging across participants. Time zero was defined as the beginning of the transitions. Baseline data were averaged over a 90-second period starting 120 seconds before transition, and the standing/walking timepoint was averaged over the last 30 seconds (ie, 150-180 seconds) of each condition.

Statistical analysis

Statistical analysis was completed using R 3.6.0 (R Core Team, Vienna, Austria). Statistical significance was set a priori at $\alpha = 0.05$. Data were assessed for normality using the Shapiro-Wilk test. For participant characteristics, between-group differences in continuous variables were assessed using either Student's *t*-test or the Mann-Whitney *U* rank sums test for normal and non-normal distributions, respectively. Comparisons for categorical variables were made using Fisher's exact test.

Linear mixed-effects analysis was performed using the "nlme" library to assess the effect of activity (ie, standing/walking) for all cardiovascular, cerebrovascular, and respiratory variables. Group and condition were included as fixed effects, and intercepts for individual participants were included as a random effect. We favoured the simplest models, and thus, when the fixed-effect interaction was nonsignificant, the model without an interaction was interpreted, and interaction-effect *P* values were not reported. In the presence of a significant interaction effect, pairwise contrasts were used to assess between-group differences in each condition, and within-group differences across conditions, corrected for multiple comparisons using Tukey's honestly significant difference method. In tables and text, normally distributed data are presented as mean ± standard deviation (SD), and non-normally distributed variables are presented as median (interquartile range [IQR]).

The relationship between $\dot{Q}$i and walking speed was assessed using a linear mixed-effect model with walking speed assessed as a continuous variable. The interaction effect of speed and group on $\dot{Q}$i was assessed by comparing the linear slope of the estimated marginal means between groups.

Relationships between central hemodynamics (ie, BP_{MCA} and $\dot{Q}$i) with cerebral hemodynamics (ie, mean MCAv) were assessed with repeated measures correlation analyses using the "rmcorr" package. The repeated measures correlation coefficient (r_{rm}) is interpreted similarly to a Pearson's r, in that values

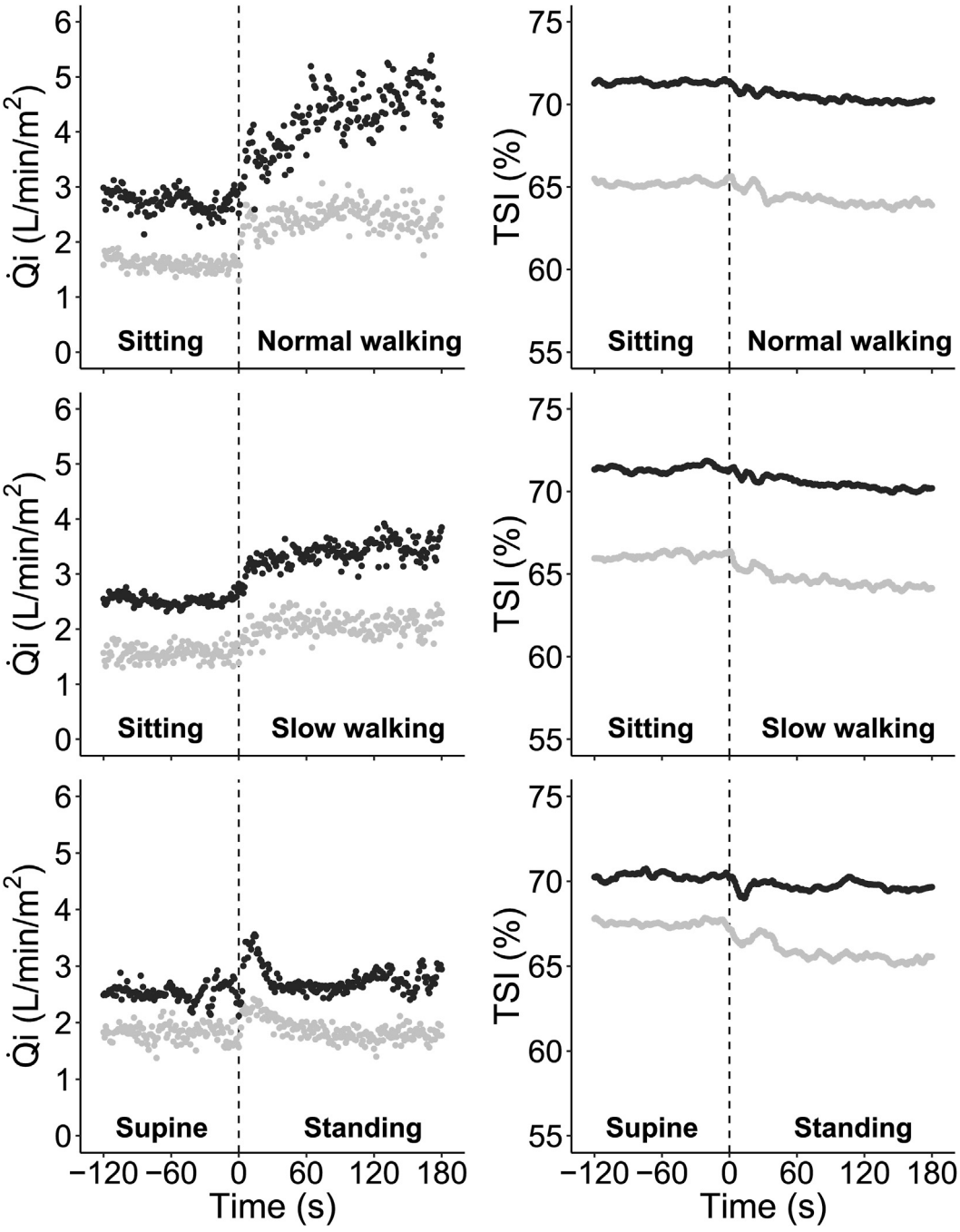

Figure 1. Group-averaged central and cerebral hemodynamic outcomes during simulated activities of daily living. Time series scatterplots of cardiac index ($\dot{Q}i$) and tissue saturation index (TSI) during 3 transition protocols, as follows: sitting to normal-paced walking (**top row**), sitting to slow-paced walking (**middle row**), and supine to standing (**bottom row**). The onset of transition is indicated by a **vertical dashed line** (time = 0 s). Second-by-second group-averaged observations for the controls (**dark grey**) and individuals with heart failure (**light grey**) are shown.

approaching 1.0 indicate both strong relationships among variables, as well as low fit variability between participants. Correlation coefficients were calculated independently for the HF and control groups and are expressed as mean (95% confidence interval [95% CI]). Group differences in the slopes of the MCAv-BP_{MCA} and MCAv-$\dot{Q}i$ relationships were assessed using linear mixed-effect models. A significant interaction for the effects of group and BP_{MCA} (or $\dot{Q}i$) on MCAv would suggest differences in static cerebral autoregulation. $P_{ET}CO_2$ was also considered as a covariate in these models. Finally, cerebral perfusion indices (both MCAv and TSI) were examined as a proportion of $\dot{Q}$ during supine rest and as a function of walking speed using linear mixed-effect models. This analysis assessed within-participant relationships between central and cerebral hemodynamics across walking speeds, and therefore absolute $\dot{Q}$ was preferred over $\dot{Q}i$ on the basis that body surface area correction would not affect the within-participant relationship.

Table 2. Cardiorespiratory and cerebral hemodynamics during supine rest and standing

	Control		HF		
Measurement	Supine	Standing	Supine	Standing	*P*
HR, bpm	60 ± 11	70 ± 11	6 5 ± 8	70 ± 8	G: 0.486 C: **< 0.001**
MAP, mm Hg	93 ± 11	84 ± 11	84 ± 10	74 ± 14	G: **0.014** C: **0.001**
SVi, mL/m^2	43 ± 8	39 ± 10	31 ± 6	27 ± 7	G: **< 0.001** C: **0.010**
$\dot{Q}$i, L/min per m^2	2.5 ± 0.6	2.8 ± 0.7	2.0 ± 0.5	1.8 ± 0.5	G: **< 0.001** C: 0.448
MCAv, cm/s	48 ± 11	43 ± 9	42 ± 6	38 ± 7	G: 0.123 C: **< 0.001**
TSI, %	70 ± 4	70 ± 4	67 ± 6	65 ± 6	G: **0.045** C: **< 0.001**
$P_{ET}CO_2$, mm Hg	37 ± 2	35 ± 4	35 ± 3	33 ± 5	G: 0.090 C: **0.004**

All values are mean ± SD, unless otherwise indicated. values indicate main effects of group (G) and condition (C). Boldface indicates significance.

bpm, beats per minute; HR, heart rate; MAP, mean arterial pressure; MCAv, middle cerebral artery velocity; $P_{ET}CO_2$, partial pressure end-tidal carbon dioxide; $\dot{Q}$i, cardiac index; SVi, stroke volume index. TSI, tissue saturation index.

Results

Participant characteristics

Participants in the HF and control groups were similar in age but differed in height, body mass, body mass index (BMI), smoking history, and medication usage (Table 1). HF was clinically diagnosed with different levels of ejection fraction (reduced, < 40% [HFrEF], n = 2; mid-range, 40%-49 % [HFmEF], n = 4; and preserved (≥ 50% [HFpEF], n = 4). As a group, those with HF had lower resting LVEF, Svi, and $\dot{Q}$I, compared to controls (Table 1).

All participants completed all trials, except for one individual with HF who prematurely stopped the normal-paced walking trial (~90 seconds into walking) due to chest pain. Only data from the supine-to-standing and slow-paced walking transitions were retained for analysis for this participant. Group-averaged responses of key central ($\dot{Q}$i) and cerebral (TSI) hemodynamic outcomes during each condition are displayed in Figure 1.

Supine-to-standing

No interaction between group and condition was observed between supine rest and quiet standing. Compared to controls, individuals with HF had lower MAP, SVi, $\dot{Q}$i, and TSI (group effects $P < 0.05$; Table 2). $P_{ET}CO_2$ was not significantly different between groups (group: $P = 0.090$). Similar responses to standing were observed across groups, including increased HR and decreased MAP, SVi, mean MCAv, TSI, and $P_{ET}CO_2$ (condition effects $P < 0.05$; Table 2).

Sitting-to-slow-paced walking

No differences were observed between 2 seated rest periods prior to the slow- and normal-paced walking (see "Baseline" in Figs. 2 and 3). Walking speed for the slow-paced walking condition did not differ between the control (0.57 ± 0.20 m/s) and the HF (0.45 ± 0.09 m/s; $P = 0.083$) groups. During slow-paced walking, individuals with HF did not have a difference in HR, but they had lower SVi (group: $P < 0.001$), $\dot{Q}$i (group: $P < 0.001$), MCAv (group: $P = 0.006$), and TSI (group: $P = 0.002$; Fig. 2). Slow-paced walking increased HR (condition; $P < 0.001$), SVi (condition: $P = 0.007$), and $\dot{Q}$i (condition: $P < 0.001$), with no changes in MAP (Fig. 2). TSI decreased from baseline to walking (condition: $P < 0.001$) in both groups, and no change occurred in MCAv (condition: $P = 0.093$; Fig. 2). $P_{ET}CO_2$ was not different between groups in sitting or walking (control: 36 ± 3 vs 37 ± 4 mm Hg; HF: 36 ± 4 vs 37 ± 3 mmHg; condition: $P = 0.085$; group: $P = 0.771$).

Sitting-to-normal-paced walking

Walking speed for the normal-paced walking condition was faster in the control group (0.82 ± 0.21 m/s) compared to the HF group (0.68 ± 0.07 m/s; $P = 0.050$). In contrast to slow-paced walking, clear between-group differences were observed in the change from rest to activity during the normal-paced walking condition. HR increased with no difference between group (condition: $P < 0.001$; Fig. 3). Group by condition interaction effects were observed for SVi and $\dot{Q}$i. Individuals with HF had lower SVi and $\dot{Q}$i during sitting ($P = 0.010$ and $P = 0.022$) and walking ($P < 0.001$ and $P < 0.001$). During walking, SVi increased in the control group ($P < 0.001$) but not in the HF group ($P = 0.412$), and although $\dot{Q}$i increased in both the control group ($P < 0.001$) and the HF group ($P = 0.013$), the increase was attenuated in the HF group ($\Delta\dot{Q}$i control: 2.0 ± 0.9 L/min per m^2 vs HF: 0.7 ± 0.3 L/min per m^2; $P = 0.003$). Individuals with HF had lower MAP (group: $P = 0.051$) and TSI (group: $P < 0.001$), which was accompanied by a marginally lower mean MCAv compared to controls (group: $P = 0.056$). TSI decreased during walking (condition: $P = 0.001$), but no differences occurred in $P_{ET}CO_2$ compared to quiet sitting (control: 38 ± 3 vs 38 ± 3 mm Hg; HF: 35 ± 4 vs 37 ± 3 mm Hg; condition: $P = 0.073$).

Cardiac output and walking speed

Participants self-selected the pace during the 2 walking challenges. Significant interactions occurred between group and speed for $\dot{Q}$i (Fig. 4). The slopes relating how $\dot{Q}$i changed in proportion to walking speed were lower in the HF group than in the control group ($P = 0.012$).

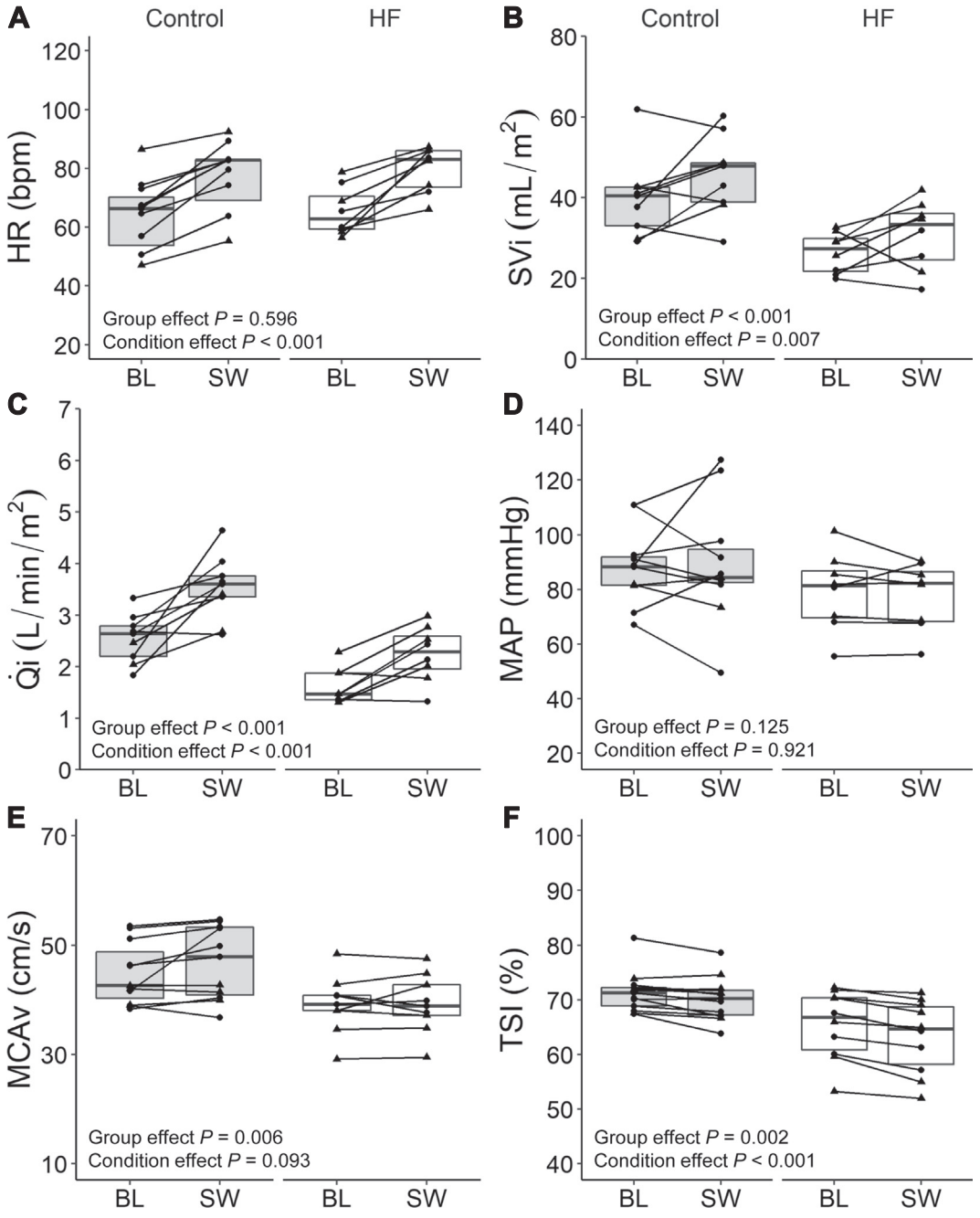

Figure 2. Cardiovascular and cerebrovascular hemodynamics during seated rest and slow-paced walking (SW). Boxplots of (**A**) cardiac index (Q̇i), (**B**) stroke volume index (SVi), (**C**) heart rate (HR), (**D**) mean arterial pressure (MAP), (**E**) middle cerebral artery velocity (MCAv), and (**F**) tissue saturation index (TSI) during seated rest (baseline [BL]) and SW for the control (**grey**) and heart failure (HF; **white**) groups. The line within each box indicates the median; the lower and upper boundaries indicate the 25th and 75th percentiles. Females and males are indicated by **closed circles** and **triangles**, respectively. bpm, beats per minute.

Cerebrovascular regulation

Across the range of BP_{MCA} experienced among the supine rest, seated rest, standing, and walking conditions, a weak-to-moderate relationship between BP_{MCA} and MCAv was observed in the control group (r_{rm} = 0.32 [95% CI 0.12, 0.54]); slope = 0.07 cm/s/mm Hg; P = 0.031), whereas a moderate-to-strong association was observed in individuals with HF (r_{rm} = 0.66 [95% CI 0.39, 0.86]; slope = 0.10 cm/s/mm Hg; $P < 0.001$; Fig. 5). No differences occurred in slopes between groups. MCAv was lower in individuals with HF across the entire range of BP_{MCA} (group: P = 0.051). During walking, MCAv was lower in the HF group than in the control group, and no differences occurred in MCAv between walking speeds and no group-by-speed interaction occurred (Fig. 6). Cerebral perfusion as a proportion of total absolute Q̇ (ie, MCAv/Q̇ and TSI/Q̇) was not different at rest between controls and individuals with HF (MCAv/Q̇:

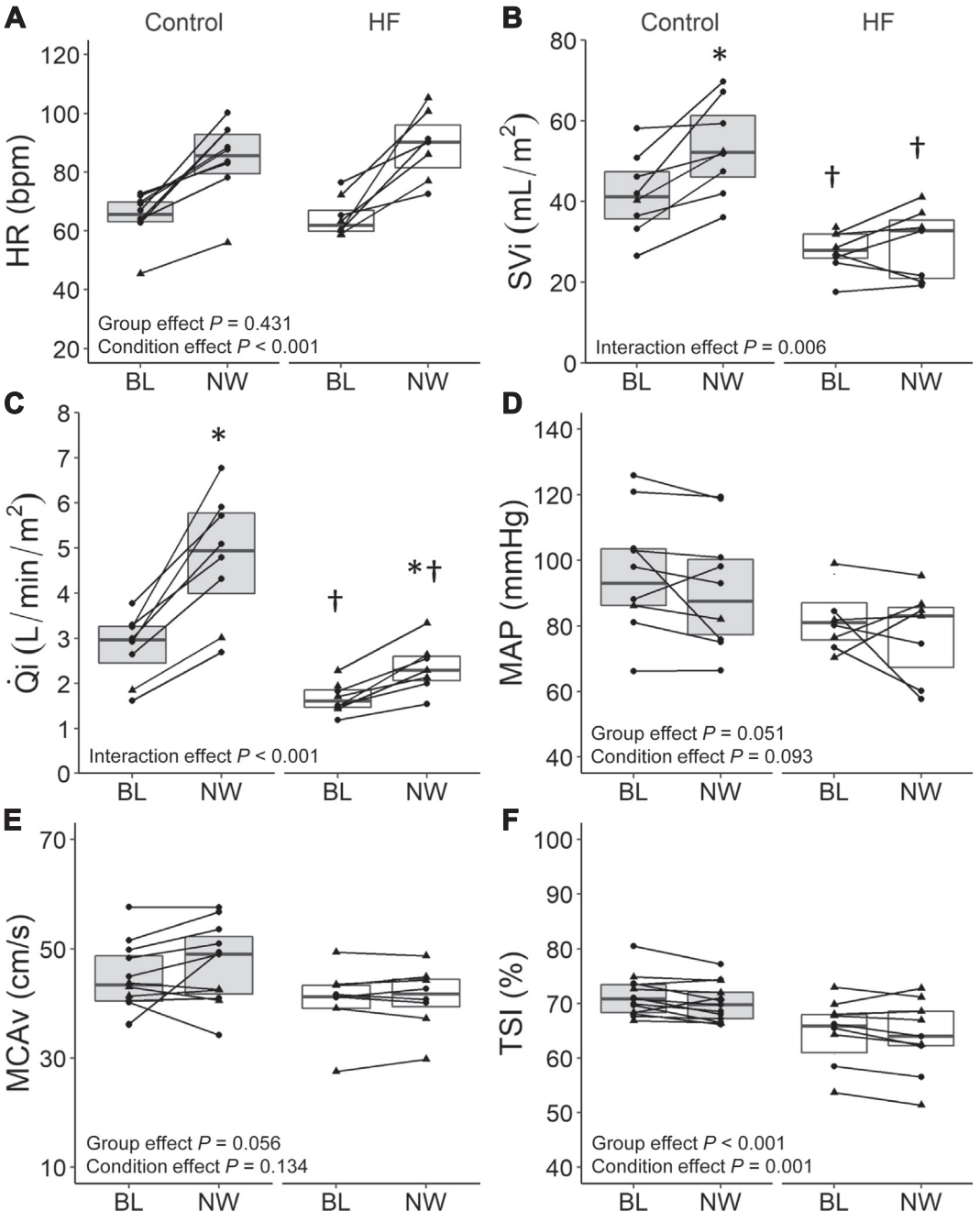

Figure 3. Cardiovascular and cerebrovascular hemodynamics during seated rest and normal-paced walking (NW). Boxplots of (**A**) cardiac index (Q̇i), (**B**) stroke volume index (SVi), (**C**) heart rate (HR), (**D**) mean arterial pressure (MAP), (**E**) middle cerebral artery velocity (MCAv) and (**F**) tissue saturation index (TSI) during seated rest (baseline [BL]) and normal-paced walking (NW) for the control (**grey**) and heart failure (HF; **white**) groups. The line within each box indicates the median; the lower and upper boundaries indicate the 25th and 75th percentiles. Women and men are indicated by **closed circles** and **triangles**, respectively. *Different from BL. †Different from control.

11.7 ± 3.4 vs 10.8 ± 2.1 (cm/s)/(L/min), $P = 0.58$; TSI/Q̇: 16.9 ± 3.5 vs 18.9 ± 4.9 %/L/min, $P = 0.32$).

Discussion

The present study employed ambulatory monitors to track cardiovascular and cerebrovascular responses of community-dwelling older adults with stable HF during low-intensity activities typical of daily life. As hypothesized, older adults with HF had a lower Q̇i and MCAv during any walking speed. Notably, cerebrovascular autoregulation appeared to be intact in HF, as the slope relating MCAv to changes in cerebral perfusion pressure was not different between the HF and control groups. Thus, older adults with HF regulated oxygen delivery to the brain but at a lower overall level.

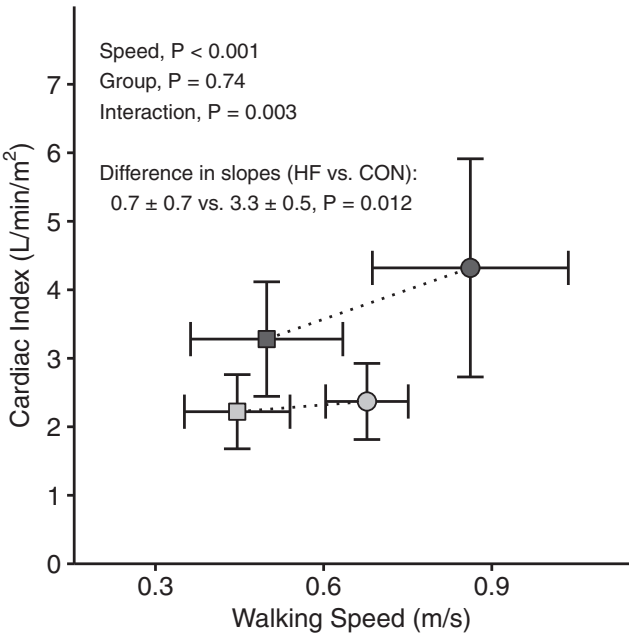

Figure 4. Group responses in the cardiac index ($\dot{Q}i$) response to self-selected slow- and normal-paced walking speeds. Average cardiac indexes during slow-paced (**squares**) and normal-paced (**circles**) walking speeds for the control participants (**black**; n = 13) and individuals with heart failure (HF; **white**; n = 10) are shown. **Error bars** indicate standard deviation in both axes. Main and interaction effects were assessed by linear mixed models. Interaction was assessed post hoc by comparing slopes between groups, reported as estimated marginal means ± standard error. CON, control.

HF is a clinical syndrome in which patients can experience breathlessness and fatigue during normal activities of daily living; working capacity is reduced to typically less than 50% of healthy, aged-matched persons.[16,17] Poor exercise tolerance is associated with compromised skeletal muscle responses[2] and occurs with lower CBF and cerebral oxygenation in HF patients.[18-21] Reduced exercise capacity in our HF participants is probably reflected in the slower self-selected normal walking speed. We extend previous reports of low $\dot{Q}$ during exercise in HF populations[22,23] to report low $\dot{Q}i$ during low-intensity activities reflective of daily physical challenges. The low $\dot{Q}i$ was a consequence of lower SVi. HR was not different between groups, probably because of the low intensity of exercise, even though more HF patients were on beta-blocker medication, and HFpEF participants often exhibit chronotropic incompetence.[24] We did not observe differences in resting cognitive function between groups.

CBF normally increases with exercise intensity up to approximately 70% maximal oxygen consumption.[25] Although overall MCAv was lower in HF patients across all activities, we found no significant effect of activity on MCAv. The absence of an activity effect was likely related to the self-selection of walking paces and large inter-individual variability. These results extend previous research,[5,18,20,21,26] suggesting that lower cerebral perfusion might compromise the ability to perform low-intensity activities of daily living.

Impaired dynamic cerebrovascular autoregulation has been suggested in HF compared to controls at rest[27] and during submaximal handgrip exercise.[8] Here, we assessed static autoregulation from the relative steady-state periods of the activities and found no impairment of cerebrovascular autoregulation through the BP_{MCA} to MCAv relationship in HF. Ogoh et al.[28] found strong effects of altered $\dot{Q}$ on MCAv in younger adults, compared to healthy older adults, and Bronzwaer et al.[29] observed an association between the 2 variables in healthy older adults but not younger adults. Further, lower MCAv has been speculated to be associated with lower $\dot{Q}$ in HF due to elevated sympathetic nerve

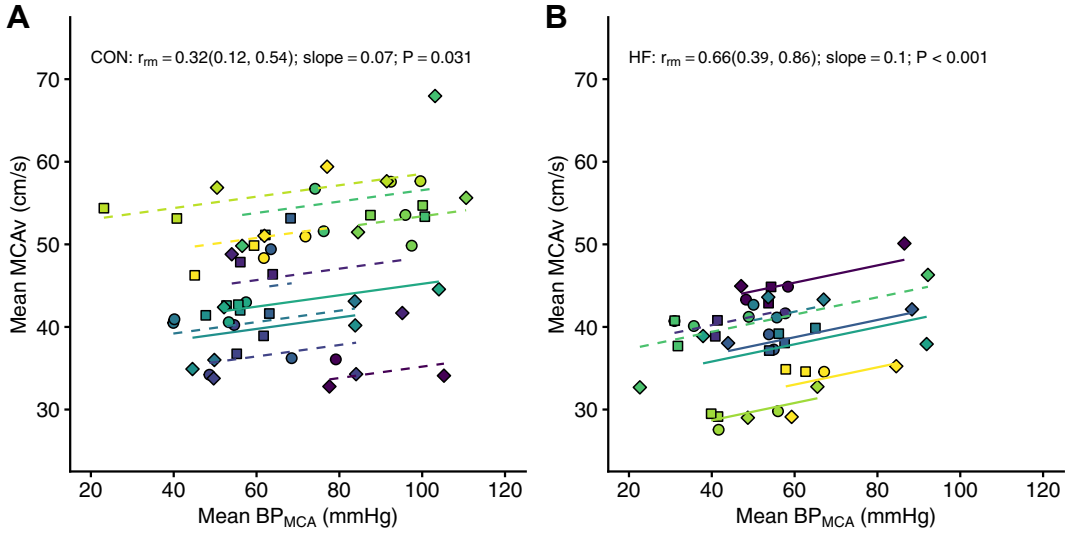

Figure 5. Association between middle cerebral artery velocity (MCAv) and blood pressure at the level of the middle cerebral artery (BP_{MCA}) across all conditions for (**A**) control participants (CON; n = 11) and (**B**) individuals with heart failure (HF; n = 8). Scatterplots show raw data during the supine-to-stand (**diamond**), sit-to-slow walk (**square**), and sit-to-normal walk (**circle**) conditions. Each colour represents a unique participant. The association within each group was assessed by repeated measures correlation (r_{rm}), which fits a constant slope (**lines**) across participants based on an analysis of covariance model and assesses the fit of the raw data to the constant slope (see *Methods* section). Men are indicated by **solid lines** and women by **dashed lines**. The r_{rm} coefficients and 95% confidence intervals are reported.

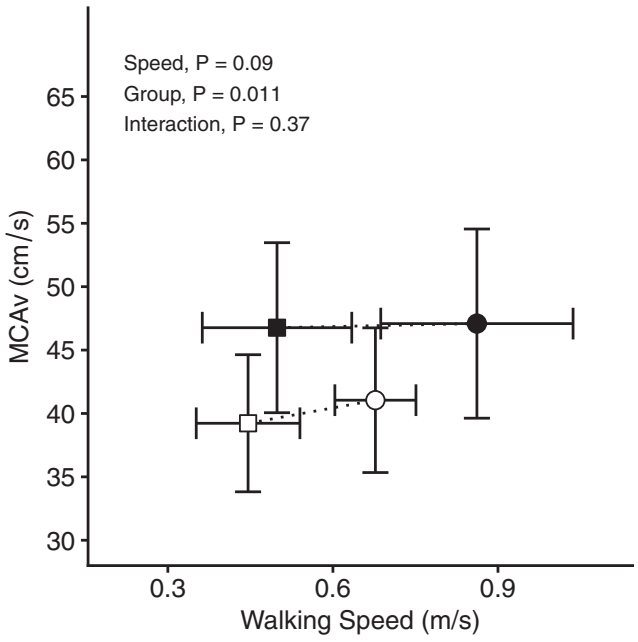

Figure 6. Group responses in the middle cerebral artery velocity (MCAv) response to self-selected slow- and normal-paced walking speeds. Average MCAv during slow-paced (**squares**) and normal-paced (**circles**) walking speeds for the control participants (**black**; n = 13) and individuals with heart failure (**white**; n = 10) are shown. Error bars indicate standard deviation in both axes. Main and interaction effects were assessed by linear mixed models. Interaction was assessed post hoc by comparing slopes between groups, reported as estimated marginal means ± standard error.

activity in the cerebral vasculature.[7] We found no association between changes in $\dot{Q}$i and MCAv in either group; we only found lower overall MCAv in HF patients. Furthermore, MCAv/$\dot{Q}$ and TSI/$\dot{Q}$ ratios were similar between the control and HF groups at rest and responded similarly to low levels of exercise. The absence of an overall relationship between $\dot{Q}$ and MCAv across conditions in the current study could be related to the characteristics of the HF patients in the current study, including factors such as hydration or type and timing of medications, in addition to the relatively small range over which $\dot{Q}$ varied. Dynamic cerebrovascular autoregulation remains a future focus during postural transitions in HF.

Limitations

The participants in the current study volunteered from within the local community and arranged their own transportation to the laboratory, suggestive of a high-functioning group of individuals with HF. Our convenience sample was imbalanced between men and women, limiting generalizability. Further, the small group of HF patients restricted our ability to stratify by HF subtypes, or to account for medications, such as beta-blockers or calcium-channel blockers, both of which may impact the cerebral circulation. We did not assess hydration status that could affect results. Carotid artery stenosis, which might affect cerebral perfusion, was not quantified. A larger controlled trial is required to explore potential differences in cerebrovascular function during activities of daily living. Control participants of both sexes within a similar age range were recruited, but they were not stratified for body size; to address this limitation, outcomes were scaled to body surface area where appropriate. We cannot exclude the possibility of the presence of asymptomatic undiagnosed conditions within these community-dwelling older adults that could have influenced the results.

To monitor cardiovascular and cerebrovascular responses during walking, we employed techniques with some inherent limitations that we acknowledge here. $\dot{Q}$i was estimated by Modelflow analysis of finger arterial blood pressure waveform with a calibration to echocardiography measurements. Although finger waveform might be affected by blood flow distribution during posture transitions,[30] previous observations in young adults suggest that the method can track changes with exercise.[31] Equipment limitations precluded measurement of $P_{ET}CO_2$ in all participants, restricting our ability to explain changes in cerebral perfusion that could occur with hyperventilation in HF.[32] Ambulatory measurements of MCAv[14] were taken to reflect changes in cerebral perfusion during tasks of daily living. Although MCAv is proportional to perfusion, it is dependent on diameter of the MCA, which might be altered in HF or with changes in $P_{ET}CO_2$.[33] In most cases, the MCAv responses tracked alongside those of cerebral oxygenation (ie, TSI). Together, these indices enhance our confidence that MCAv provided an adequate proxy for CBF regulation in this study.

Conclusions

We investigated the hemodynamic response to upright posture and over-ground walking in older adults with HF. Overall, cerebral oxygenation was lower in participants with HF compared to control participants at rest, as well as during standing and walking. Reduced cerebral oxygenation is likely the consequence of the dysregulation of multiple physiological systems, with $\dot{Q}$i being the most prominent in the present study. Static cerebrovascular autoregulation was not different in older adults with HF. Understanding the impact of changes in cardiac function on cerebrovascular physiology might prompt treatment avenues to preserve quality of life in the setting of HF.

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Ethics Statement

The experimental procedures for this study were approved by the Office of Research Ethics at the University of Waterloo (ORE 21025), and in accordance with the Declaration of Helsinki, except for registration in a trial database. All participants volunteered freely after providing informed consent and were able to withdraw from the study at any time.

Patient Consent

The authors confirm that a patient consent form has been obtained for all participants in this study.

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Disclosures

The authors have conflicts of interest to disclose.

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