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Cerebral Blood Flow during Exercise in Heart Failure: Impact of Ventricular Assist Devices

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Abstract

Introduction: In healthy individuals cerebral blood flow (CBF) increases during exercise, but few studies have compared changes in CBF during exercise in patients with heart failure (HF) to healthy controls (CTRL), or assessed the effects of left ventricular assist devices (LVADs). We hypothesised that subjects implanted with LVADs would exhibit impaired cerebrovascular responses to cycle exercise when compared to age- and sex-matched healthy CTRL subjects, but enhanced responses relative to subjects with HF. **Methods:** Internal carotid artery [ICA] blood flow, and intra-cranial middle [MCAv] and posterior cerebral [PCAv] artery velocities were measured continuously using Doppler ultrasound, alongside cardiorespiratory measures at rest and in response to an incremental submaximal cycle ergometer exercise protocol in 9 LVAD participants (58 ± 15 yrs; 87 ± 16 kg; 172 ± 8 cm, 6 ♂), 9 age- and sex-matched subjects with HF (58 ± 8 yrs; 84 ± 11 kg; 177 ± 6 cm), and 9 CTRL (55 ± 14 yrs; 74 ± 16 kg; 168 ± 10 cm). **Results:** At rest, ICA hemodynamics (velocity, shear rate and flow) were greater in CTRLs and LVADs than HF ($p < 0.05$). Higher MCAv ($+5.52 \pm 1.59 \text{ cm.s}^{-1}$, $p = 0.003$) and PCAv ($+5.82 \pm 1.41 \text{ cm.s}^{-1}$, $p = 0.001$) were also observed in LVAD subjects than healthy CTRLs. During exercise, ICA flow increased at all workloads in CTRL, but not in HF or LVAD groups. MCAv increased from baseline in both HF and CTRL participants ($p = 0.0001$), but not in LVAD subjects. Nonetheless, CTRLs and LVADs showed higher MCAv ($p = 0.006$) and PCAv ($p < 0.0001$) values throughout exercise than HF. **Conclusion:** Our findings indicate that LVAD subjects exhibit higher cerebral blood flows at rest and during exercise than matched HF participants, but attenuated brain blood flows during exercise when compared to healthy subjects. Cerebral blood flows should be considered when designing exercise training interventions in patients with HF and LVADs.

Key Words: Cerebral Blood Flow; Heart Failure; Exercise; Ultrasound

Introduction

Exercise tolerance is impaired in heart failure (HF), due to diminished cardiac output, impaired lung function and/or peripheral abnormalities in skeletal muscle and vascular function (1-4). Exercise training, a class 1 recommendation in HF (5), improves functional capacity (6, 7), but impacts on cardiac function are limited and benefits have traditionally been ascribed to improvements in peripheral factors (2, 8). However, recent studies have proposed a potential role for cerebral blood flow as a factor in HF exercise limitation (1-4), although it was concluded in a review on the topic that further research is needed regarding the impacts of exercise on brain perfusion during exercise in HF (2).

Left ventricular assist devices (LVADs) are increasingly used as destination therapy in patients with advanced HF (9). LVADs improve exercise capacity, an effect which may, in part, be due to enhanced cardiac output (3). LVAD implantation also facilitates exercise rehabilitation, which in turn targets the peripheral skeletal muscle and vascular abnormalities which can limit functional capacity (10). A recent experiment by Brassard *et al.*, (3) indicated that increasing LVAD pump speed during submaximal exercise enhanced cerebral perfusion and cardiac output. Furthermore, Jung *et al.* (11) reported a 9% increase in $\text{VO}_{2\text{peak}}$ with elevation in pump speed. However, there are currently no data quantifying and comparing cerebrovascular blood flows in LVADs, HF and matched healthy control subjects during incremental exercise. In the present study we assessed intra-and extra-cranial arterial responses, in both anterior and posterior cerebrovascular circulations, to assess whether LVAD implantation adequately compensates for the demands of exercise in patients with HF. We hypothesised that subjects with implanted LVADs would

exhibit impaired cerebrovascular responses to cycle exercise when compared to age- and sex-matched healthy control (CTRL) subjects, but enhanced responses relative to subjects with HF.

Methods

Participants

Nine participants instrumented with a LVAD (age: 58 ± 15 years; weight: 87 ± 16 kg; height: 172 ± 8 cm, 6♂3♀) and nine age and sex matched HF subjects (HF age: 58 ± 8 years; 84 ± 11 kg; 177 ± 6 cm, 6♂3♀) were recruited from the Advanced Heart Failure Service at Fiona Stanley Hospital (Perth, Western Australia). Nine healthy subjects were contemporaneously recruited to match the age and sex of the LVAD and HF subjects (CTRL; age: 55 ± 14 years; weight: 74 ± 16 kg; height: 168 ± 10 cm, 6♂3♀). All of the LVAD participants recruited were greater than 3 months post implant (76 ± 108 weeks post LVAD implantation; range 12-312 weeks) and had been medically stable for more than 4 weeks prior to participating in the study. The LVAD participants had an average ejection fraction of $26.1 \pm 7.9\%$ (6275 ± 2740 rpm average pump speed). There was a range of continuous (3 Heartmate II, Thoratec Corporation; 2 HVAD, HeartWare) and continuous/semi-pulsatile (4 Heartmate III, Thoratec Corporation) LVAD devices implanted. The HF participants had an average ejection fraction of $25.0 \pm 9.0\%$, with three participants having an ischaemic aetiology, five having a diagnosis of idiopathic dilated cardiomyopathy, and one had hypertrophic cardiomyopathy. The drug regimens for LVADs and HF groups are provided in Table 1. The healthy CTRL group were not taking any medication.

The study was approved by the University of Western Australia's Human Ethics Research Committee as well as the Royal Perth (2015-164) and Fiona Stanley Hospital Ethics Committees. All aspects of the study complied with the ethical principles outlined by the Declaration of Helsinki. The participants were informed of all experimental procedures and associated risks. Participants provided written informed consent before the commencement of the study.

Experimental design

After inclusion, participants were tested in the Cardiac Transplant Unit at the Fiona Stanley Hospital. Participants visited the laboratory on one occasion, in a fasted state (~ 6 hours), having abstained from alcohol, caffeine and vigorous exercise for 24-hours. Upon arrival, participants were instrumented and underwent a 10 min rest period in a semi-recumbent position. Baseline (BL) recordings of the primary outcome measures were then collected during a further 5-minute period of quiet rest. Following BL, subjects performed an incremental exercise test on a recumbent cycle ergometer (Angio imaging ergometer, Lode, Netherlands), with starting workloads of 15 Watts for LVADs and HF, and 45 Watts for CTRLs. The exercise intensity increased by 15-watts every 2 minutes until volitional exhaustion. Cerebrovascular (transcranial Doppler and duplex vascular ultrasound) and cardiorespiratory assessments were continuously collected and compared using the relative workloads (e.g., 20, 40, 60 % of the maximum achievable workload [%Wmax]).

Experimental procedures

Cerebrovascular assessments

Non-invasive insonation via 2MHz transcranial Doppler ultrasound (TCD; Spencer Technologies, Seattle, WA) was used to assess blood velocity in the middle (MCA_v) and posterior (PCA_v) cerebral arteries continuously during exercise by transfixing the probes to a specialized head frame (Marc 600, Spencer Technologies, Seattle, WA). The cerebral arteries were identified and optimised according to their signal depth, waveform and velocities, in keeping with previously published guidelines (12). The MCA_v and PCA_v were continuously sampled at baseline, and throughout the incremental exercise test at 1000Hz via an analogue-to-digital converter (Powerlab, 16/30 ADInstruments, Colorado Springs, CO, USA), and analysed offline using a specialized analytical software package (LabChart 8, ADInstruments, Colorado Springs, CO, USA).

Blood velocity and diameter of the internal carotid artery (ICA) and vertebral arteries (VA) were measured using a 10-15MHz multi-frequency linear array vascular ultrasound (Terason T3200, Teratech, Burlington, MA) (13, 14). The ICA and VA recordings were captured at baseline and ICA recordings were continuously captured throughout the incremental exercise test using identical techniques as previously outline by our research group (15-17). Briefly, blood velocity and diameter of both arteries was measured using a 10-15MHz multi-frequency linear array vascular ultrasound. B-mode imaging was used to measure arterial diameter, while simultaneously captured pulse-wave mode was used to concurrently measure peak blood flow

velocity (14, 18). Diameter and velocity were measured at least 1.5 cm distal to arterial bifurcations to eliminate recordings of turbulent and retrograde flow and non-uniform shear. Care was taken to ensure that the insonation angle (60°) was unchanged throughout each test and there were no alterations of B-mode settings after acquisition of the resting baseline to avoid any artificial changes in arterial wall brightness/thickness. All recordings were made in accordance with our published guidelines (13, 14), with screen capture and storage of video files for offline analysis (18). This analysis involved concurrent determination of arterial diameter and peak blood velocity at 30Hz, using our customized edge detection and wall tracking software which is automated and designed to mitigate observer bias. We have published extensive reproducibility data using this approach (18) and our *within* day coefficient of variation for the assessment of ICA diameter is 1.5% using this technique (19). Blood flow and shear rate were calculated as previously described (15-17, 20). It was not technically possible to capture VA responses during exercise due to the challenges of imaging these vessels during movement in the exercising subjects.

Workloads relative to individual W_{max} were compared at 20, 40 and 60% W_{max} . As exercise intensity and motion artefact increase, the fidelity of the ultrasound data diminishes. Whilst we were very satisfied with data up to 60% W_{max} in all subjects, less subjects had acceptable image quality at the higher workloads. We preferred to adopt a “completers” approach in which all subjects had data at all comparator points. All of the ICA and VA recordings were screen-captured and stored as video files for offline analysis (18). Mean arterial blood pressure (MAP) in CTRLS and HF subjects was assessed using finger-based photoplethysmography (Finometer Pro, Finapres Medical Systems, Amsterdam, the Netherlands) with manual brachial oscillometry

for calibration purposes, whereas MAP was measured using brachial Doppler ultrasound (i.e., Doppler BP) which is considered an adequate surrogate measure in LVAD subjects who do not typically exhibit an adequate pulse for oscillometric approaches (21). This Doppler assessment of BP was recorded for the last 30-40 seconds of each stage at the radial artery. Partial pressure of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$) were assessed from a sample tube connected to the mouthpiece using a gas analyser (ADInstruments, Colorado Springs, CO). All cardiorespiratory variables were sampled continuously throughout the protocol at 1000Hz via an analogue-to-digital converter (Powerlab, 16/30; ADInstruments, Colorado Springs, CO). Breath by breath $\dot{V}O_2$ and minute ventilation ($\dot{V}_E$) were measured via indirect calorimetry (Vyntus CPX, Jaeger, CareFusion, Germany).

Statistics

Statistical and graphing analysis was performed using GraphPad PRISM 6.01 software (GraphPad Software, LaJolla, CA, USA). All data were normally distributed. Analysis of pharmacological intervention comparisons between LVADs and HF subjects was performed using a Fisher's Exact test. All absolute data parameters were compared using 2-way repeated-measures ANOVA, whilst change from baseline scores were compared using a one-way ANOVA. Bonferroni-correction for multiple comparisons were used for all post-hoc analysis of the mean changes from baseline, standard error of the difference and confidence intervals (CI) are provided as indices of variability. Statistical significance was initially assumed at $p < 0.05$. All data are reported in tables and figures are mean $\pm$ SD unless otherwise specified.

Results

Comparison between groups at rest

Cardiorespiratory measures

All cardiorespiratory measures can be found in Table 2. No differences were observed between BL values of VO_2 , or $\text{P}_{\text{ET}}\text{CO}_2$ in LVAD, HF and CTRL groups. In contrast, compared to CTRL, MAP was reduced at rest in LVAD (-14 ± 2 mmHg, $P < 0.0001$) and HF (-24 ± 2 mmHg, $p < 0.0001$). Resting MAP was higher in LVADs than HF subjects ($+10 \pm 2$ mmHg, $p = 0.0003$).

Cerebrovascular measures

Cerebrovascular measures obtained for the internal carotid, as well as middle and posterior cerebral arteries are listed in Table 2. At BL, ICA hemodynamics (velocity, shear stress and flow), as well as velocities in the MCA and PCA, were greater in LVADs (and CTRLs) subjects compared to HF participants (Figures 1 & 2; $p < 0.05$). ICA diameter was reduced in LVAD participants compared with HF and also the CTRLs ($p < 0.05$). Higher levels of MCAv ($+5.52 \pm 1.59$ $\text{cm} \cdot \text{s}^{-1}$, CI=1.68 to 9.36, $p = 0.003$) and PCAv ($+5.82 \pm 1.41$ $\text{cm} \cdot \text{s}^{-1}$, CI=1.85 to 8.69, $p = 0.001$) were observed in LVAD subjects than healthy CTRLs. Blood flow in the VA at BL was not significantly different in CTRL, LVAD or HF participants.

Comparison between groups in response to exercise

Cardiorespiratory measures

Incremental exercise stimulated progressive increases in VO_2 , MAP and P_{ETCO_2} in all groups (Table 2). $\text{VO}_{2\text{peak}}$ values were $12.7 \pm 4.4 \text{ ml.kg.min}^{-1}$ and $13.0 \pm 2.7 \text{ ml.kg.min}^{-1}$ in the HF and LVAD groups, respectively, both significantly lower compared to CTRL ($25.4 \pm 8.3 \text{ ml.kg.min}^{-1}$). Incremental values for % $\text{VO}_{2\text{peak}}$ at each absolute exercise workload (Watts) are included in Table 2, with main effect differences indicating a lower observer value for CTRL compared to HF.

A main effect of group was observed for MAP ($p < 0.0001$) and VO_2 ($p = 0.0008$). Post hoc analysis of the main group effect revealed that MAP was reduced when comparing HF ($-31.0 \pm 6.9 \text{ mmHg}$, CI=13 to 49, $p = 0.001$) to CTRL participants. Similarly VO_2 was lower in HF ($-4.3 \pm 1.2 \text{ ml.kg}^{-1}.\text{min}^{-1}$, CI=1.1 to 7.58) and LVAD ($-5.4 \pm 1.2 \text{ ml.kg}^{-1}.\text{min}^{-1}$, CI=2.2 to 8.6, $p = 0.001$) subjects compared to CTRL. LVAD and HF participants did not differ in terms of group effects for MAP. Interaction effects were observed for both VO_2 and MAP and post hoc analyses revealed that VO_2 and MAP were significantly lower in both LVADs and HF groups, compared to CTRLs, at 20, 40 and 60 % W_{max} (Table 2). No significant main effects for group, or interactions, were observed for P_{ETCO_2} .

Cerebrovascular measures

Significant interaction effects for the impact of exercise between groups were apparent for ICA velocity, diameter, flow and shear rate, as well as MCAv and PCAv (Table 2, Figure 2 & 3; see Figures, Supplemental Digital Content 1 and 2, which also present compare between group velocity and flow data at %VO₂peak, %Wmax and at absolute watts, <http://links.lww.com/MSS/B506> and <http://links.lww.com/MSS/B507>). Post hoc analysis revealed that exercise increased ICA flow from BL at 20 ($\Delta+36.97\pm10.8$ ml.min⁻¹, CI=66.6 to 7.32, p=0.008), 40 ($\Delta51.26\pm10.8$ ml.min⁻¹, CI=.9 to 21.6, p=0.0001), and 60 ($\Delta63.62\pm10.8$ ml.min⁻¹, CI=93.2 to 34.0, p<0.0001) %WMax in CTRL participants, whereas no exercise-induced increases in ICA blood flow were apparent in either the HF or LVAD groups. Nonetheless, the enhanced ICA flow that was apparent in LVAD compared to the HF group at rest, remained during exercise at 20 (48.2 ± 10.8 ml.min⁻¹ CI=21.5 to 74.1, p=0.0001) and 40 (38.1 ± 10.8 ml.min⁻¹, CI=11.4 to 64.9, p=0.002), but not at 60 %Wmax.

There was no significant main effect of exercise (p=0.43) or group (p=0.32) on ICA diameter. Post hoc analysis of interaction effects revealed significantly lower ICA diameters (Table 2, Figure 2) in LVAD (4.81 ± 0.57 mm, 4.79 ± 0.59 mm, 4.77 ± 0.58 mm) participants compared to HF (5.26 ± 0.72 mm, 5.26 ± 0.72 mm, 5.19 ± 0.76 mm) and CTRL (5.28 ± 0.72 mm, 5.24 ± 0.67 mm, 5.28 ± 0.63 mm) participants at 20, 40 and 60 %WMax (p<0.0001), respectively.

Main effects of group (p=0.02) and exercise (p=0.0002) were identified for ICA velocity (Table 2, Figure 2). Post hoc analysis of the main effects revealed ICA velocities were, on average,

different when comparing LVADs ($+11.57 \pm 4.205 \text{ cm.s}^{-1}$, CI=0.37 to 22.78, $p=0.04$) and HF participants, whereas exercise-induced increases in ICA velocity from BL were only observed in the CTRL group (at 40% WMax $6.03 \pm 1.46 \text{ cm.s}^{-1}$, CI=2.02 to 10.05, $p=0.0009$ and 60% WMax $8.25 \pm 1.46 \text{ cm.s}^{-1}$, CI=4.23 to 12.26, $p<0.0001$). Analysis of interaction effects (Table 2, Figure 2) indicate significantly reduced ICA velocities in HF compared to CTRLS and LVADs throughout exercise.

Post hoc analysis of the main effect ($p=0.0001$) for exercise revealed an increase in MCAv from BL in both HF and CTRL participants, but not in LVAD subjects. CTRLs increased PCAv from BL (Table 2, Figure 3), but this effect was not apparent with exercise in the other groups. Significant MCAv and PCAv interactions (Table 2, Figure 3) were due to higher velocities throughout exercise in LVADs and CTRLS, compared to HF participants. Comparisons between CTRLs and LVADs revealed significant higher MCAv ($p=0.006$) and PCAv ($p<0.0001$) values at 60% WMax in CTRLS.

Discussion

It is well established that LVAD implantation, as a treatment for advanced HF, improves survival and enables rehabilitative approaches to be applied that can enhance functional capacity and quality of life (9). LVADs are increasingly used as a “destination therapy”, alongside their role in bridging to transplant and recovery. This is the first study, to our knowledge, to compare intracranial blood velocity and extra-cranial blood flow at rest and during exercise in LVAD, and

age- and sex-matched HF and healthy CTRL participants. Our principal finding was that LVAD implantation enhanced cerebral blood flow at rest compared to HF subjects and that this resting benefit was sustained during submaximal exercise. Furthermore, at rest, LVAD implantation normalized resting intracranial blood velocity and extracranial blood flows relative to CTRL. During exercise, however, intracranial and extracranial arterial flow responses were lower in LVAD subjects compared with healthy CTRLs, and did not increase as exercise intensified. As described below, these findings have implications for the prescription of effective exercise-based rehabilitation in LVAD patients.

Few previous studies have directly assessed cerebral blood flow responses during exercise in LVAD patients or compared them to HF and healthy CTRL groups. In healthy subjects, cerebral blood flow increases during exercise, until a plateau at approximately 60-70% of VO_2max (22). This did not occur in our LVAD group and, in contrast with CTRL and to a lesser extent HF subjects, responses did not increase as a function of exercise intensity. The disparity between the LVAD flow responses and those of healthy CTRLs increased as exercise intensified. Brassard *et al.* (3) recently demonstrated that cerebral blood velocity (i.e., MCAv) did not significantly increase during incremental exercise in LVAD subjects, but that perfusion increased modestly when pump speed was progressively increased. Our study compliments and adds to this observation in that we report that both anterior and posterior cerebrovascular responses are impaired, relative to well-matched CTRL subjects and that LVAD implantation does not adequately compensate for the demands of exercise. Our study also included novel volumetric flow measurements performed in the ICA which confirmed the intracranial velocity data, being lower during exercise in LVAD subjects than CTRL subjects. Taken together, our findings,

coupled with those of Brassard *et al.* (3) strongly suggest that the impaired cerebrovascular flow evident in HF subjects during incremental exercise, relative to healthy CTRL subjects, is not fully compensated for by the implantation of LVAD devices.

The cardiorespiratory mechanisms controlling cerebrovascular perfusion during exercise are complex, inter-dependent and exhibit multiple redundancy (2, 12). Exercise-induced changes occur as a result of the compound influence of metabolic and humoral factors and neuronal activation (1, 2, 23). Heart failure is a model of myriad systemic dysfunction, with abnormalities in each of the links in the Fick equation chain (2, 8). It is possible, for instance, that respiratory inefficiency contributes to the impairment we observed in brain blood flow response to exercise in the present study, but skeletal muscle abnormalities that induce metaboreflex activation likely also contribute, alongside activation of baroreflexes and chemoreflexes. A schema summarising the profound impact of mechanistic abnormalities in HF on cerebral perfusion was recently proposed (2). Interestingly, cardiac transplantation has beneficial impacts on cerebral blood flow in HF and increasing LVAD pump speed during exercise also enhances perfusion (2). Although our study was not designed to investigate the specific mechanisms responsible for impaired cerebral perfusion in HF and LVAD subjects, arterial blood pressure (24), $P_{ET}CO_2$ (19), cardiac output (25), shear stress (16), and cerebral metabolism (26) likely all play a role (2, 22). Further investigation into the regulation of brain blood flow in HF subjects including those instrumented with an LVAD, alongside measures of the integrated physiological responses to dynamic exercise, are needed, but it is likely that interventions, including exercise training (2, 27), that target the multiple dysfunctional pathways would improve cerebral blood flows during exercise.

In this context it is clear that one advantage of LVADs is that they enable HF subjects to participate more actively in exercise-based rehabilitation programs.

The impact that repeated episodes of low cerebral blood flow may have on brain function, cerebrovascular health and the risk of atherothrombotic events should be considered. Studies investigating cerebrovascular function in aging have indicated that enhanced brain blood flow is associated with greater fitness across the life span, alongside improved cognition and quality of life (28, 29). The long-term consequences of exposing patients to repeated conditions where cerebral perfusion is compromised in the face of increased cerebral metabolic demands induced by exercise, are currently unknown. Given that the matching of cerebral perfusion to metabolic demand (termed neurovascular coupling (30)) is a critical process regulating the supply oxygen and nutrients to the brain, any impairment in this response may be associated with poor cerebrovascular outcomes in the longer term (31). Moreover, since elevations in cerebral blood flow and related shear patterns are key mechanisms to improve cerebrovascular health (32), attenuated cerebral blood flow responses may hinder the potential cognitive benefits of exercise-based rehabilitation.

Limitations

A technical limitation of TCD ultrasound is that assessment of one ipsilateral artery is typically performed. To account for potential variation in contralateral blood flow distribution, we employed our standardized imaging practices (13, 19) to screen for any differences in contralateral flow in the extracranial arteries. No observable differences in contralateral flow

were observed in any of our LVAD, HF or CTRL subjects; therefore, resting intracranial (MCA and PCA) and extracranial (ICA and VA) cerebral arteries were assessed as valid surrogates for global brain vascular function. There is no evidence, to our knowledge, suggesting a disparate contralateral flow pattern in response to exercise in LVADs and healthy individuals. We used “volitional exhaustion” as a criterion for test cessation in our subjects and this may have resulted in some of the CTRLs achieving a criterion for maximal effort, whilst, as is typical, many of the HF subjects will not have attained this level of exertion. Indeed, it was recently observed that almost 50% of HF individuals fail to achieve a respiratory exchange ratio >1.10 during cardiopulmonary exercise testing (33). We therefore opted to present data at matched relative workloads (%Wmax) and %VO₂ peak (Table 2; see Figures, Supplemental Digital Content 1 and 2, which also present compare between group velocity and flow data at %VO₂peak, %Wmax and at absolute watts, <http://links.lww.com/MSS/B506> and <http://links.lww.com/MSS/B507>). Another limitation of this study was that intracranial diameters were not assessed. This is particularly relevant given the role of arterial PCO₂ on arterial calibre, which may impact the measurement of velocity. However, a novel aspect of our study was the assessment of ICA diameters as a surrogate for caliber changes that may contribute in cerebrovascular modulation. The similarity of our ICA flow and MCAv measures during exercise reassuringly supports the contention that the lack of diameter measures from the MCA may not have been a substantial limitation. It remains a limitation, however, that we were unable to collect VA measures during exercise to similarly support our PCA assessments. A further limitation is that our sample size did not allow for sub-group analysis of the impacts of sex, drugs or LVAD type on outcomes; this should be a focus in larger future studies. Finally, although we measured both intra- and extra-cranial blood flow and velocity, we did not assess cerebral oxygenation. We are therefore

not in a position to characterise Fick components related to oxygen delivery versus extraction (1-4). Such additional measures should be considered in future studies.

Conclusion

We have demonstrated that volumetric cerebral blood flow is attenuated during exercise in LVAD patients compared to healthy controls and that, in common with HF patients, there is limited compensatory increase in cerebrovascular perfusion to cope with the physiological demands of exercise. Caution is therefore warranted in the prescription of exercise in patients with LVAD and also advanced HF, with a suggestion that modality, intensity, frequency and progression all be adjusted conservatively in the first instance, and symptoms monitored closely during initial exercise bouts. Our findings should be taken into account when planning exercise interventions and in the consideration of the demands of acute exercise bouts on both the systemic and cerebral circulations in HF.

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List of Figures:

Figure 1. Individual (dots) and average (lines) resting flow in the internal carotid (ICA: panel A) and vertebral (VA: panel B) arteries, as well as intracranial velocity in the middle (MCAv: panel C) and posterior (PCAv: panel D) cerebral arteries in participants with left ventricular assist devices (LVAD), heart failure (HF) and healthy and sex-matched controls (CTRL). τ signifies statistical difference from CTRL; ϕ signifies statistical difference from HF.

Figure 2. Average hemodynamic responses (diameter [A]; velocity [B]; shear rate [C]; flow [D];) in the internal carotid artery (ICA) during BL and exercise at 20, 40 and 60% of the maximum achievable cycle ergometer workload (% Wmax) in participants with left ventricular assist devices (LVAD), heart failure (HF) and healthy and sex and age matched controls (CTRL). * signifies statistical difference from baseline; τ signifies statistical difference from CTRL; and ϕ signifies statistical difference from HF.

Figure 3. Average intracranial cerebral blood velocity at rest and during incremental exercise at 20, 40, and 60% of the maximum achievable workload (% Wmax) in the middle (MCAv; panel A) and posterior (PCAv; panel B) cerebral arteries in participants with left ventricular assist devices (LVAD), heart failure (HF) and healthy and sex and age matched controls (CTRL). * signifies statistical difference from baseline; τ signifies statistical difference from CTRL; and ϕ signifies statistical difference from HF.

Figure 1

Figure 2

Figure 3

Table 1 Frequency of medication use for LVAD and HF participants

Medical Therapy	LVAD (n=9)	HF (n=9)	P
ACE-I	9 (100%)	5 (56%)	0.04*
Angiotensin II receptor blockers	6 (67%)	4 (44%)	0.32
Beta blockers	8 (89%)	7 (78%)	0.50
Clopidogrel	7 (78%)	6 (67%)	0.50
Warfarin	9 (100%)	5 (56%)	0.04*
Diuretics	8 (89%)	7 (78%)	0.50
Digoxin	2 (22%)	4 (44%)	0.31
Aspirin	5 (56%)	5 (56%)	0.68
Sildenafil	3 (33%)	2 (22%)	0.50
Amiodarone	4 (44%)	5 (56%)	0.50
Fisher's Exact test performed on frequency of use.			

Table 2. Cardiorespiratory and cerebrovascular measures during incremental exercise in advanced heart failure subjects (HF), subjects instrumented with left ventricular assist devices (LVAD) and healthy age and sex matched controls (CTRL)

		%Wmax				Stats
		BL	20	40	60	
VO_2 (ml.kg ⁻¹ .min ⁻¹)	LVAD ^Φ	3.2 ± 0.3	6.2 ± 1.5* ^Φ	7.8 ± 2.0* ^Φ	9.5 ± 2.9* ^Φ	Exercise: <i>p</i> < 0.0001; Group: <i>p</i> = 0.0008; Interaction: <i>p</i> < 0.0001
	HF ^Φ	3.6 ± 0.6	8.1 ± 3.0* ^Φ	9.7 ± 3.4* ^Φ	11.4 ± 3.9 * ^Φ	
	CTRL	3.3 ± 0.5	13.2 ± 3.0*	15.6 ± 3.5*	19.0 ± 4.6*	
%VO ₂ peak	LVAD	27.0 ± 7.6	50.9 ± 13.6* ^Φ	62.8 ± 17.1* ^Φ	75.4 ± 18.3* ^Φ	Exercise: <i>p</i> < 0.0001; Group: <i>p</i> = 0.01; Interaction: <i>p</i> < 0.04
	HF	29.2 ± 5.7	64.1 ± 11.3*	76.1 ± 9.1*	89.4 ± 9.2*	
	CTRL ^Φ	14.8 ± 6.6 ⁺	51.1 ± 14.2* ⁺	62.0 ± 16.8* ⁺	72.2 ± 18.5* ⁺	
$P_{ET}CO_2$ (mmHg)	LVAD	30.5 ± 3.2	33.2 ± 4.4*	33.5 ± 4.6*	33.7 ± 5.8*	Exercise: <i>p</i> < 0.0001; Group: NS; Interaction: NS
	HF	28.6 ± 2.8	31.1 ± 4.0*	32.6 ± 4.4*	32.9 ± 4.9*	
	CTRL	33.3 ± 3.7	38.6 ± 3.5*	39.6 ± 3.3*	39.8 ± 3.0*	
MAP (mmHg)	LVAD	89 ± 12 ^{Φ+}	97 ± 11* ^{Φ+}	97 ± 9* ^{Φ+}	101 ± 8* ^{Φ+}	Exercise: <i>p</i> < 0.0001; Group: <i>p</i> = 0.001; Interaction: <i>p</i> = 0.002
	HF ^Φ	77 ± 13 ^Φ	81 ± 13* ^Φ	84 ± 15* ^Φ	87 ± 12* ^Φ	
	CTRL	100 ± 17	110 ± 18*	117 ± 21*	126 ± 18*	
ICA velocity (cm.s ⁻¹)	LVAD	37.1 ± 6.9 ^{Φ+}	40.6 ± 10.0 ⁺	39.7 ± 9.5 ⁺	39.4 ± 7.6 ^{Φ+}	Exercise: <i>p</i> = 0.0002; Group: <i>p</i> = 0.02; Interaction: <i>p</i> = 0.016
	HF	25.7 ± 6.1 ^Φ	27.4 ± 9.1 ^Φ	27.7 ± 10.2 ^Φ	29.3 ± 11.3 ^Φ	
	CTRL	33.9 ± 8.3	38.2 ± 8.4	40.0 ± 8.0*	42.2 ± 11.1*	
ICA diameter (mm)	LVAD	4.86 ± 0.58 ^{Φ+}	4.80 ± 0.57 ^{Φ+}	4.79 ± 0.59 ^{Φ+}	4.77 ± 0.58 ^{Φ+}	Exercise: NS; Group: NS; Interaction: <i>p</i> = 0.04
	HF	5.20 ± 0.69	5.26 ± 0.72	5.26 ± 0.72	5.19 ± 0.76	
	CTRL	5.14 ± 0.62	5.28 ± 0.72	5.24 ± 0.67	5.28 ± 0.63	
ICA flow (ml.min ⁻¹)	LVAD	212 ± 59.3 ⁺	225 ± 64 ^{Φ+}	222 ± 79 ^{Φ+}	206 ± 47 ^Φ	Exercise: <i>p</i> < 0.0001; Group: NS; Interaction: <i>p</i> = 0.004
	HF	162 ± 42 ^Φ	177 ± 60 ^Φ	184 ± 64 ^Φ	188 ± 63 ^Φ	
	CTRL	220 ± 106	257 ± 106*	271 ± 110*	284 ± 132*	
MCAv (cm.s ⁻¹)	LVAD	52.7 ± 14.6 ^{Φ+}	52.4 ± 14.4 ⁺	52.6 ± 14.8 ⁺	52.1 ± 14.6 ^{Φ+}	Exercise: <i>p</i> = 0.0001; Group: NS; Interaction: <i>p</i> = 0.0004
	HF	43.0 ± 15.8 ^Φ	45.3 ± 19.2 ^Φ	47.5 ± 20.9* ^Φ	47.9 ± 22.7* ^Φ	
	CTRL	47.2 ± 14.0	55.5 ± 13.1*	57.3 ± 13.8*	57.2 ± 13.0*	
PCAv (cm.s ⁻¹)	LVAD ^Φ	48.8 ± 14.6 ^{Φ+}	49.7 ± 15.0 ⁺	48.4 ± 13.6 ⁺	46.8 ± 12.3 ^{Φ+}	Exercise: <i>p</i> < 0.0001; Group: <i>p</i> = 0.04; Interaction: <i>p</i> < 0.0001
	HF	34.9 ± 7.6 ^Φ	37.8 ± 9.2 ^Φ	38.5 ± 9.2 ^Φ	37.9 ± 9.2 ^Φ	
	CTRL	43.6 ± 9.9	49.5 ± 10.3*	50.9 ± 11.2*	53.4 ± 12.4*	

* signifies statistical difference from baseline; ^Φ signifies statistical difference from CTRL; ⁺ signifies statistical difference from HF

Comparison of cerebral blood flow at similar absolute and relative workloads

Supplementary Figure 1: Hemodynamic intracranial (MCA & PCA velocity), and ICA responses (diameter, velocity, and flow) from BL in left ventricular assist device (LVAD) participants and age and gender matched heart failure (HF) and healthy controls (CTRL). Panels A-E represent the responses when relative exercise intensity is matched at 20% of the maximum achieved workload (%Wmax), Panels F-J when absolute workload is matched between LVADs and CTRLs (i.e., at 45 Watts).

Comparison of cerebral blood flow at similar relative Peak VO₂

Supplementary Figure 2: Intracranial velocity (MCAv & PCAv) and ICA blood flow at 60 and 75% VO₂ Peak in left ventricular assist device (LVAD) participants and age and gender matched heart failure (HF) and healthy controls (CTRL). τ indicates significant difference from LVAD (P<0.01); φ indicates significant differences from HF (p<0.01).