Relationship between cerebral blood flow and blood pressure in long-term heart transplant recipients

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ABSTRACT

Heart transplant recipients are at an increased risk for cerebral hemorrhage and ischemic stroke, yet the exact mechanism for this derangement remains unclear. We hypothesized that alterations in cerebrovascular regulation is principally involved. To test this hypothesis, we studied cerebral pressure-flow dynamics in 8 clinically stable male heart transplant recipients (62 ± 8 years of age and 9 ± 7 years post-transplant, mean ± SD), 9 male age-matched controls (63 ± 8 years) and 10 male donor controls (27 ± 5 years). To increase blood pressure variability and improve assessment of the pressure-flow dynamics, subjects performed squat-stand maneuvers at 0.05 and 0.10 Hz. Beat-to-beat blood pressure, middle cerebral artery velocity, and end-tidal carbon dioxide were continuously measured during five minutes of seated rest, and throughout the squat-stand maneuvers. Cardiac baroreceptor sensitivity gain and cerebral pressure-flow responses were assessed with linear transfer function analysis. Heart transplant recipients had reductions in R-R interval power and baroreceptor sensitivity low frequency gain ($P<0.01$) compared to both control groups; however, these changes were unrelated to transfer function metrics. Thus, in contrast to our hypothesis, the increased risk of cerebrovascular complication after heart transplantation does not appear to be related to alterations in cerebral pressure-flow dynamics. Future research is therefore warranted.

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Key Words: Cerebral Blood Flow; Cerebral Autoregulation; Heart Transplant Recipients; Baroreceptor Sensitivity; Cerebrovasculature

INTRODUCTION

The longevity of heart transplant recipients has increased from 18 days following the first heart transplantation surgery[1] to a current mean survival expectancy of over 10.5 years.[2] The improved survival has lead to alterations in the long-term functional outcomes post transplantation. For example, neurological impediments develop in approximately 60-80% of heart transplant recipients,[3-5] and have a 14-18% greater occurrence rate of cerebral hemorrhage or ischemic stroke.[3,5-7] The exact mechanism for these derangements however remains to be elucidated; however, adverse events may be the direct consequence of life-long immunosuppressant therapy,[8] or vascular remodeling secondary to chronic cerebral hypoperfusion associated with pre-transplant heart failure.[4,5,7]

We asked whether alterations in cerebral pressure-flow dynamics could also explain the increased risk. Indeed, because of cardiac allograft, there are marked reductions in heart rate variability[9,10] and baroreceptor sensitivity (BRS),[9] which could lead to unstable control of blood pressure in this clinical population. Evidence indicates that the responses of the cerebral vessels in some animals[11] and humans[12] are likely influenced by a coordinated reaction of the cardiovascular system as a whole especially when there are disturbances to the blood or oxygen supply to the brain.[13] Moreover, both animal[14,15] and human[12] studies have demonstrated the inverse relationship between cardiac BRS and dynamic cerebral autoregulation. In other words, at least in healthy young humans, dynamic cerebral autoregulation may compensate for reductions in cardiac BRS and vise-versa. These concepts have not been explored in a clinical model

(e.g., the heart transplant recipient) where cardiac baroreceptor function is markedly reduced or abolished. Thus, research is warranted in the long-term heart transplant recipient population to determine the impact of marked reductions in cardiac autonomic control on cerebral blood flow regulation.

Accordingly, we examined the dynamic relationship between beat-to-beat changes in blood pressure and cerebral blood flow in long-term heart transplant recipients under spontaneous conditions, as well as during frequency dependent squat-stand maneuvers. To control for the influence of heart transplantation *per se*, we compared patients with age-matched controls. To control for the influence of age, heart transplant recipients were also compared to a group of donor-controls. We hypothesized that heart transplant recipients would have reduced BRS, and impaired cerebral pressure-flow dynamics, independent of age.

METHODS

Ethical approval

The study was approved by the clinical ethical committees of the Universities of British Columbia and Alberta, and adhered to the principles of the Declaration of Helinski. All volunteers provided written informed consent.

Participants

Eight male clinically stable heart transplant recipients (62 ± 8 years of age, 9 ± 7 years post-transplant), 9 male age-matched controls (63 ± 8 years) and 10 male donor controls (27 ± 5 years), were recruited for this study (Table 1). Seven of the eight heart transplant recipients were ischemic pre-surgery etiology. All subjects were extensively

screened by the attending cardiologist for any clinical history of respiratory, cardiovascular or cerebrovascular diseases. Resting and exercise echocardiograms were performed by a cardiologist on all participants. In additional, we screened (via an transcranial Doppler examination) the anterior intra-cranial vessels for any signs intra-cranial stenosis; all subjects had normal examination results as indicated by normal intra-cranial velocity profiles.[16] All subjects were carefully screened for activity levels, withdrew from caffeine and alcoholic beverages for a period of 12 hours prior to the study and all medications were maintained for the study. Each subject underwent a familiarization of the laboratory and testing protocols.

Instrumentation

Three-lead electrocardiogram (ECG) was employed for the measurement of the R-R interval and heart rate. Blood pressure was measured in the finger by photoplethysmography (Finometer; Finapres Medical Systems, Amsterdam, The Netherlands). This method has been shown to reliably assess the dynamic changes in beat-to-beat blood pressure that correlate well with the intra-arterial recordings and can be used to quantify the dynamic pressure-flow relationship of cerebral circulation.[17] Intermittent blood pressure was also recorded in the arm by electrosphygmomanometry (SunTech Medical, Morrisville, NC, USA), with a microphone placed over the brachial artery and the Korotkoff sounds gated to the ECG. Throughout the experiment, the validity of the finger blood pressure recordings were intermittently confirmed at the brachial artery in the contralateral arm by sphygmomanometry.

Both right and left middle cerebral arteries (MCA) were insonated by placing a 2-MHz Doppler probe (Spencer Technologies, Seattle, WA, USA) to obtain bilateral

cerebral blood velocity. The MCA were identified according to their signal depth, wave form and velocities.[16] Once the MCA were identified the probes were secured and locked in place with a head-band (Spencer Technologies, Seattle, WA, USA). An index of cerebrovascular resistance (CVRi) was calculated from mean arterial pressure (MAP)/ mean MCA velocity (MCAv).

End-tidal CO_2 ($P_{ET}CO_2$) was measured using an online gas analyser (ML206; AD Instruments, Colorado Springs, CO, USA), calibrated with a known gas concentration prior to each subject. All data were recorded and stored for subsequent analysis using commercially available software (LabChart version 7.1; AD Instruments, Colorado Springs, CO, USA).

Procedure

At least 5 minutes of resting spontaneous baseline data were recorded in the seated position. These data were used for spectral analysis of spontaneous oscillations in blood pressure and cerebral blood flow velocity. Next the subjects performed repeated squat-stand maneuvers. The subjects mimicked the experimenter in performing these maneuvers. In random order, subjects then performed squat-stand maneuvers at 0.05 Hz (10 second squat–10 second stand) and then 0.10 Hz (5 second squat–5 second stand) for 5 minutes, with a 5-minute rest period to return to baseline levels in between trials. These data were used for the spectral analysis of the driven oscillations in blood pressure and MCAv and were performed to increase the blood pressure variability, resulting in increased coherence (allowing for a more robust mathematical assessment of the phase and gain metrics).[18] End tidal gases were monitored to ensure that normal breathing occurred and Valsalva-like maneuvers were avoided.

Data Processing

All data were simultaneously sampled at 1000 Hz via an analog-to-digital converter (Powerlab 16/30 ML880; AD Instruments, Colorado Springs, CO, USA). Real time beat-to-beat mean values of blood pressure and MCA velocity were determined from each R-R interval. All data were processed and analyzed with custom designed software in LabView 10 (National Instruments, Texas, USA).

Power spectrum and transfer function analysis

Beat-to-beat MAP and MCAv signals were spline interpolated and re-sampled at 4-Hz for spectral and transfer function analyses based on the Welch algorithm. Each 5-minute recording was first subdivided into 5 successive windows that overlapped by 50%. Data within each window were linearly detrended and passed through a Hanning window prior to fast Fourier transform analysis. For transfer function analysis, the cross-spectrum between MAP and MCAv was determined and divided by the MAP auto-spectrum to derive the transfer function coherence, gain, and phase.

Spontaneous MAP and MCAv power spectrum density (PSD), and the mean value of transfer function coherence, normalized gain and phase were calculated in the very low (VLF, 0.02-0.07 Hz) and low (LF, 0.07-0.20 Hz), frequency ranges as previously defined.[19] The transfer function coherence, gain and phase of the driven blood pressure oscillations were sampled at the driven frequency (0.05 or 0.10 Hz). Gain was normalized as % MCAv / absolute blood pressure, as MCAv varied between groups but blood pressure was not significantly different. The absolute gain values were not reported

in this study as the MCA diameter were not measured nor were repeated measures performed, thus making absolute gain comparisons across individuals unreliable. Individual phase and gain estimates were entered for subsequent analysis only where the corresponding coherence between blood pressure and MCA velocity$_{mean}$ was >0.5 indicating at least 50% shared variance.

R-R Interval and Cardiac Baroreceptor Sensitivity Gain

From the ECG and blood pressure waveform, we determined the time of each R wave, and beat-to-beat values of systolic blood pressure. The cardiac period (R-R interval) time series was checked for the presence of artifacts, and spuriously detected or missed R waves were corrected by linear interpolation. Power spectral analysis was performed on the R-R interval and systolic blood pressure. Both the R-R interval and beat-to-beat systolic blood pressure were high pass filtered to remove fluctuations of <0.015 Hz, low pass filtered to exclude components of >2 Hz (Nyquist frequency), and re-sampled at 4 Hz. These series were then passed through a Hanning window and subject to fast Fourier transform analysis. Spontaneous LF gain was assessed in the range of 0.04-0.15 Hz and driven BRS gain was assessed from the 0.10 Hz squat-stand maneuvers. This method has been previously validated against the modified Oxford method.[20]

Critical Closing Pressure and Pulsitility Index Calculations

Critical closing pressure was calculated by the linear extrapolation of the cerebral blood flow velocity and blood pressure relationship below the diastolic values to the

zero-flow pressure.[21] Pulsitility index was calculated as: (systolic MCAv – diastolic MCAv) / mean MCAv.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0. The effects of condition (spontaneous resting, 0.05 Hz, 0.10 Hz) or Group (heart transplant recipients, age-matched, donor-controls) on cerebral blood flow velocity, Heart Rate, blood pressure (mean and systolic), $P_{ET}CO_2$, CVRi, critical closing pressure, pulsitility index and transfer function coherence, normalized gain and phase were assessed using a one-way ANOVA with a post hoc Tukey comparison for group effects. Bivariate correlations between BRS gain and transfer function coherence, normalized gain and phase were performed using Pearson Product Moment. Data are presented as mean ± SD.

RESULTS

Demographics (Table 1 and 2)

There were no significant differences between groups for BMI (Table 1). By study design, donor-controls were significantly younger than heart transplant recipients and age-matched controls. During the seated baseline testing and both driven frequencies (0.05 Hz and 0.10 Hz) mean arterial pressure, systolic blood pressure, pulse pressure and $P_{ET}CO_2$ levels were comparable for all groups (Table 2). Critical closing pressures for all subjects were physiologically relevant values (all positive) and were comparable between all groups. Resting heart rate was reduced in the age-matched controls (68 ± 13 bpm) and donor-controls (63 ± 8 bpm) compared to heart transplant recipients (91 ± 8 bpm).

MCAv was reduced in both older populations (heart transplant recipients 41 ± 8; age-matched 42 ± 8 cm/s) compared to donor-controls (62 ± 7 cm/s). Puslitility index (arbitrary units) at rest was reduced in the heart transplant recipients (0.83 ± 0.12) compared to both the age-matched (1.01 ± 0.17) and donor (1.02 ± 0.11) controls. During the driven protocols, heart rate was similarly elevated in the heart transplant recipients compared to age-matched and donor-controls and the MCAv was reduced in compared to the donor-controls, pulsitility index was comparable for all groups (Table 2). The older populations (2.2-2.3 mmHg/cm/s) had an elevated CVRi compared to the younger group (1.4-1.5 mmHg/cm/s) across all testing protocols.

Representative data tracing – that was similar between groups – of blood pressure, MCAv and $P_{ET}CO_2$ for the seated baseline, 0.05 Hz and 0.10 Hz squat-stand manoeuvres from a heart transplant recipient are shown in Figure 1. As shown in Figure 1, the squat-stand maneuvers evoked clear oscillations in both blood pressure and MCAv, whereas $P_{ET}CO_2$ levels were well maintained in all groups (Table 2).

Cardiac Baroreceptor Sensitivity (Table 3)

The donor-controls had a significantly higher spontaneous BRS LF gain (10.8 ± 5.1 ms/mmHg) compared to both the heart transplant recipients (1.4 ± 1.2 ms/mmHg; *$p<0.01$)* and the age-matched controls (4.4 ± 1.8 ms/mmHg; *$p<0.01$*). The heart transplant recipients also had a significantly reduced BRS LF gain as compared to the age-matched controls (Table 3). During the 0.10 Hz squat-stand manoeuvres, all groups were significantly different (heart transplant recipients 0.2 ± 0.1 ms/mmHg; age-matched 2.0 ± 0.9 ms/mmHg; donor-controls 3.9 ± 1.0 ms/mmHg; *$p<0.03$,* Table 3). The donor-

controls showed a marked elevation in their R-R interval PSD when compared with both the heart transplant recipients ($p<0.01$) and age-matched controls ($p<0.05$) in the spontaneous and driven LF ranges (Table 3). The R-R interval PSD for the age-matched controls was also elevated when compared with the heart transplant recipients (Table 3).

Cerebral Pressure-Flow Dynamics (Table 4)

There were no differences between the groups (heart transplant recipients, age-matched and donor-controls) when comparing the power spectrums for MAP or MCAv in either the VLF or LF ranges, during spontaneous and driven conditions (Table 4). The MAP and MCAv PSD was significantly increased during the squat-stand manoeuvres for all groups.

Transfer function analysis phase and normalized gain was not significantly different between groups at either the 0.05 Hz or 0.10 Hz squat-stand frequencies (Figure 3). There was also no relationship to the increased CVRi in the heart transplant recipients and age-matched as compared to the donor-controls and any transfer functional analysis metrics (Table 4). The reductions in BRS in both the heart transplant recipients and age-matched controls under conditions of spontaneous rest, as well as both driven frequencies were unrelated to variability in the transfer function metrics.

DISCUSSION

To our knowledge, this is the first study to assess cerebral pressure-flow relationship in long-term heart transplant recipients. Our findings show that despite marked reductions in cardiac BRS in heart transplant recipients, cerebral pressure-flow

dynamics remain intact. Moreover, reductions in BRS were not correlated to inter-individual variability in transfer function analysis metrics in the heart transplant recipients.

Cardiac Baroreceptor Sensitivity in Heart Transplant Recipients

Following heart transplantation, the sympathetic and parasympathetic nerves that normally regulate heart rate are severed, leaving the heart denervated. Our findings are consistent with prior studies showing reduced cardiac BRS in short-term (< 24 months) heart transplant recipients.[22,23] In the longer-term (mean 5 years) heart transplant recipients, there is some evidence that partial sympathetic re-innervation may occur,[10] as reflected in an increase in the R-R interval power spectrum at 0.10 Hz. In this study, we observed a marked reduction in R-R interval power in the heart transplant recipients (reduced by >95% as compared to age-matched and >99% compared with donor-controls; Table 3), which was positively correlated with BRS gain under both spontaneous (R^2 = 0.38, $p<0.01$) and driven (R^2 = 0.60, $p<0.01$) conditions. There was also an increase in the R-R interval power spectrum at 0.10 Hz in the heart transplant recipients, indicating some re-innervation of the sympathetic nervous system.[10,23]

Cerebral Pressure-Flow Dynamics

Although the long-term heart transplant recipients had marked reductions in R-R interval and BRS gain (Table 3), these alterations did not impact their cerebral pressure flow dynamics (Table 4; Figure 3). We show that long-term heart transplant recipients have comparable reductions in MCAv and increases in CVRi compared to their age-

matched counterparts (Table 2). Moreover, the increase in CVRi with age does not appear to influence the transfer function analysis phase or normalized gain metrics studied in the present investigation – findings consistent with reports that cerebral pressure-flow dynamics are unaltered by age, at least up to the age of 75 [reviewed in:[24]]. We now extend these findings to include long-term heart transplant recipients (Table 4; Figure 3).

That long-term heart transplant recipients have comparable cerebral-pressure flow dynamics compared to both age-matched and donor-controls is clinically significant. We interpret these results to indicate that despite possible cerebrovascular remodeling during pre-transplant antecedent heart failure[4,5,7], and reductions in resting pulsitility index (Table 2) and cardiac BRS (Table 3), the cerebrovasculature is able to adapt to acute and marked (i.e., 40-45 mmHg) changes in arterial blood pressure (Fig 1; Table 2).

Relationship between cardiac baroreflex and transfer function metrics

The reduction in cardiac BRS in heart transplant recipients was not correlated with transfer function metrics during either spontaneous or driven conditions. These findings are consistent with a recent study[25] in healthy older adults, which showed that increases in BRS was not related to dynamic cerebral autoregulation metrics. The findings of these studies in older adults and in heart transplant recipients, contrast with those in young healthy adults which demonstrated that there was an inverse relationship between BRS and markers of dynamic cerebral autoregulation.[12] Thus, reductions in cardiac BRS in aging and heart transplantation seem to play a diminished role in the integrated regulation of CBF.

Limitations:

Transcranial Doppler ultrasonography:

The main assumption of transcranial Doppler is that the velocity recorded in the MCA is directly representative to changes in cerebral blood flow. Throughout situations where there are normal arterial blood gas levels and blood pressure ranges the majority of research provides evidence that transcranial Doppler provides a reliable index of cerebral blood flow [reviewed in:[16]].

Transfer Function Analysis:

Transfer function analysis applies a linear mathematical approach to interpret the relationship between the input blood pressure and the output cerebral blood flow. The work by Zhang et al.[19] has suggested that the cerebral autoregulatory system may be: linear, non-linear, have multiple inputs, or merely be two unrelated phenomena. Hence during this study we did not discuss cerebral autoregulation *per se*, but merely presented data regarding to the relationship that exists between blood pressure and cerebral blood flow. The coherence present within the analysis will affect the mathematical interpretability of the transfer function analysis (phase and gain)[26]. We employed the squat-stand maneuvers to non-pharmalogically increase blood pressure variability, enhancing the coherence (driven coherence was >0.98 a.u.) and allowing for more mathematically interpretable transfer function analysis and gain metrics.[18] In addition, we view the driven blood pressure challenges to be a realistic representation of natural oscillations that can occur to blood pressure activities of daily living (e.g., postural

changes, coughing, exercise, etc.) and thus makes our data set physiologically relevant. This methodology induced oscillations that were 40-45 mmHg (Table 2). Nevertheless, although the maximum myogenic regulatory control mechanism may not have been challenged enough to truly assess the risk factor for a cerebral haemorrhage or ischemic stroke, this would seem unlikely giving the physiological realistic changes in blood pressure.

Arteriosclerosis:

The long-term heart transplant recipient patients were not screened invasively in for arthrosclerosis in this study, as this is not a routine procedure for this population. The heart transplant recipients were more than five years post-transplant and did not have accompanying risk factors such as hypertension under resting conditions. Although the subjects within the current study did not undergo MRI, the normal intra-cranial velocities and dynamic pressure-flow relationships would indicate an absence of global cerebral arthrosclerosis. However, we cannot rule out the possibility of localized and regional arthrosclerosis.

Cross-Sectional Design:

As this study is drawing conclusions from a cross-section of the population it is not possible to make a causal inference in the relationship between BRS and cerebral blood flow regulation. It would be nearly impossible to perform a longitudinal study where the same population was followed from young healthy adults to older adults and had a subset of this population undergo heart transplant surgery. We would also like to acknowledge that the heart transplant recipients within this study were otherwise very

healthy individuals and our findings may not relate to heart transplant recipients with greater co-morbidities.

PERSPECTIVES

To our knowledge, this is the first study to date that has assessed the cerebral pressure-flow relationship in long-term heart transplant recipients. We have revealed 1) that in spite of reductions to BRS, long-term heart transplant recipients have comparable cerebral-pressure flow dynamics compared to both age-matched and donor-controls; and 2) the reductions in BRS in long-term heart transplant recipients were not related to any transfer function metrics. Together these data indicate that the cerebrovasculature in long-term heart transplant recipients is able to normally regulate the cerebral pressure-flow dynamics, and is unlikely to explain the increased occurrence of severe cerebrovascular complications documented in the population.

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DISCLOSURES

The authors have no conflicts of interest to declare.

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NOVELTY AND SIGNIFICANCE

1) This is the first study to have assessed the relationship between arterial blood pressure and cerebral blood flow in long-term heart transplant recipients
2) We have revealed 1) that in spite of reductions to BRS, long-term heart transplant recipients have comparable cerebral-pressure flow dynamics compared to both age-matched and donor controls; and 2) the reductions in BRS in long-term heart transplant recipients were not related to any transfer function metrics. Together these data suggest that the cerebrovasculature in long-term heart transplant recipients is able to normally regulate the cerebral pressure-flow dynamics, and is unlikely to explain the increased occurrence of severe cerebrovascular complications documented in the population.

FIGURE LEGENDS

Figure 1. Typical trace for blood pressure (BP), middle cerebral artery velocity (MCAv) and End Tidal CO_2 ($P_{ET}CO_2$) during spontaneous (top), 0.05 Hz (middle) and 0.10 Hz (bottom) trials from a long-term heart transplant recipient.

Figure 2. MCAv transfer function analysis of coherence, phase, and normalized gain in the very low frequency (VLF) and low frequency (LF) for the group means of the spontaneous data for the three group: AM: age-matched controls (solid), HTR: heart transplant recipients (long dash), DC: donor-controls (short dash).

Figure 3. MCAv transfer function analysis of coherence, phase, and normalized gain at the driven frequencies of 0.05 Hz (left) and 0.10 Hz (right) for the three group: AM: age-matched controls (black), HTR: heart transplant recipients (light grey), DC: donor-controls (dark grey).

TABLES

Table 1. Participant Characteristics

	HTR (n=8)	AM (n=9)	DC (n=10)
Age (years)	62 ± 8	63 ± 8	27 ± 5 *†
Body Mass Index (kg/m^2)	27 ± 4	26 ± 3	26 ± 5
Years after transplantation	9 ± 7		
Medications			
Corticosteroid	2		
Antiproliferative agent	4		
Calcinerurin inhibitor	4		
mTOR inhibitor	4		
Ca^{2+} channel blocker (diltiazem)	5	2	
ACE inhibitor	4	1	
Diuretic	3	1	
Aspirin	6	2	
Lipid –lowering agent	4		

Values are means ± SD. Seven HTR subjects were ischemic pre-surgery etiology, one was non-ischemic etiology. Heart transplant recipient (HTR); age-matched (AM); donor control (DC); target of rapamycin (TOR); angiotensin-converting enzyme (ACE). Statistical significance was set at $P < 0.05$, *denotes significance from HTR, †denotes significance from AM.

Table 2. Hemodynamic and Cerebrovascular Responses During Squat-Stand Maneuvers

	HTR	AM	DC
Baseline (Sitting)			
MAP (mmHg)	97 ± 8	99 ± 12	93 ± 5
Pulse Pressure (mmHg)	41 ± 16	55 ± 28	47 ± 17
Mean MCAv (cm/s)	41 ± 8	42 ± 8	62 ± 7*†
Pulsitility Index (a.u.)	0.83 ± 0.12	1.01 ± 0.17*	1.02 ± 0.11*
CVRi (mmHg/cm/s)	2.3 ± 0.5	2.3 ± 0.5	1.4 ± 0.2*†
CrCP (mmHg)	47 ± 19	46 ± 16	48 ± 17
Heart Rate (bpm)	91 ± 8	68 ± 13*	63 ± 8*
End Tidal CO_2 (mmHg)	36 ± 7	36 ± 4	38 ± 2
Squat Stand (0.05 Hz)			
MAP - Squat (mmHg)	122 ± 17	122 ± 15	111 ± 10
MAP - Stand (mmHg)	78 ± 18	78 ± 15	78 ± 12
Systolic BP – Squat (mmHg)	202 ± 38	193 ± 28	174 ± 19
Systolic BP – Stand (mmHg)	141 ± 51	134 ± 30	132 ± 17
Pulse Pressure - Squat (mmHg)	122 ± 33	107 ± 25	94 ± 15
Pulse Pressure - Stand (mmHg)	94 ± 51	83 ± 26	80 ± 12
Mean MCAv (cm/s)	43 ± 7	44 ± 8	62 ± 8*†
Pulsitility Index - Squat (a.u.)	0.93 ± 0.20	0.81 ± 0.17	0.87 ± 0.14
Pulsitility Index - Stand (a.u.)	1.56 ± 0.30	1.34 ± 0.35	1.53 ± 0.28
CVRi (mmHg/cm/s)	2.3 ± 0.4	2.2 ± 0.5	1.5 ± 0.2*†
Heart Rate (bpm)	105 ± 11	78 ± 14*	79 ± 8*
End Tidal CO_2 (mmHg)	37 ± 7	36 ± 3	40 ± 3
Squat-Stand (0.10 Hz)			
MAP - Squat (mmHg)	123 ± 20	128 ± 12	115 ± 10
MAP - Stand (mmHg)	78 ± 11	82 ± 10	75 ± 10
Systolic BP – Squat (mmHg)	204 ± 34	202 ± 26	181 ± 16
Systolic BP – Stand (mmHg)	150 ± 32	141 ± 20	132 ± 18
Pulse Pressure - Squat (mmHg)	120 ± 26	111 ± 26	98 ± 13
Pulse Pressure - Stand (mmHg)	107 ± 34	88 ± 19	84 ± 14
Mean MCAv (cm/s)	43 ± 9	44 ± 7	62 ± 8*†
Pulsitility Index - Squat (a.u.)	0.91 ± 0.21	0.81 ± 0.16	0.81 ± 0.13
Pulsitility Index - Stand (a.u.)	1.63 ± 0.27	1.43 ± 0.37	1.62 ± 0.25
CVRi (mmHg/cm/s)	2.3 ± 0.3	2.3 ± 0.5	1.5 ± 0.2*†
Heart Rate (bpm)	106 ± 10	82 ± 14*	80 ± 8*
End Tidal CO_2 (mmHg)	37 ± 6	38 ± 4	40 ± 4

Values are means ± SD. Heart transplant recipient (HTR); age-matched (AM); donor control (DC); mean arterial pressure (MAP); blood pressure (BP); arbitrary units (a.u.); mean middle cerebral artery velocity (MCAvmean); cerebrovascular resistance index (CVRi). Statistical significance was set at $P < 0.05$, *denotes significance from HTR, †denotes significance from AM.

Table 3. Transfer function analysis for cardiac baroreceptor sensitivity.

	HTR	AM	DC
Baseline (Sitting)			
LF RRI Power (ms^2)	23 ± 15	726 ± 665*	2842 ± 2920*†
BRS LF Gain (ms/mmHg)	1.4 ± 1.2	4.4 ± 1.8*	10.8 ± 5.1*†
Squat-Stand (0.10 Hz)			
RRI Power (ms^2)/Hz	1255 ± 1155	97773 ± 91881*	420052 ± 266339*†
BRS Gain (ms/mmHg)	0.2 ± 0.1	2.0 ± 0.9*	3.9 ± 1.0*†

Values are means ± SD. Age-Match Control (AM); Baroreceptor Sensitivity (BRS); Donor-Control (DC); Heart Transplant Recipient (HTR); R-R Interval (RRI); middle cerebral artery velocity (MCAv); low frequency (LF; 0.04-0.15 Hz). Statistical significance was set at $P < 0.05$, *denotes significance from HTR, †denotes significance from AM.

Table 4. Transfer function analysis between BP and MCAv.

	HTR	AM	DC
Baseline (Sitting)			
VLF MAP Power ($mmHg^2$)	8.261 ± 5.118	8.813 ± 7.619	8.554 ± 4.589
LF MAP Power ($mmHg^2$)	6.754 ± 4.705	5.093 ± 5.418	5.942 ± 3.164
VLF MCAv Power $(cm/s)^2$	3.071 ± 2.060	3.283 ± 3.814	5.316 ± 3.265
LF MCAv Power $(cm/s)^2$	2.784 ± 2.537	3.448 ± 6.187	6.069 ± 4.376
VLF Coherence (a.u.)	0.599 ± 0.240	0.661 ± 0.175	0.551 ± 0.155
LF Coherence (a.u.)	0.791 ± 0.093	0.713 ± 0.155	0.829 ± 0.045
VLF Phase (radians)	0.831 ± 0.420	0.883 ± 0.347	0.920 ± 0.432
LF Phase (radians)	0.416 ± 0.189	0.473 ± 0.155	0.570 ± 0.171
VLF Gain (%/mmHg)	1.110 ± 0.368	1.135 ± 0.344	1.242 ± 0.285
LF Gain (%/mmHg)	1.501 ± 0.256	1.635 ± 0.450	1.625 ± 0.239
Squat Stand (0.05 Hz)			
MAP Power ($mmHg^2$)/Hz	35423 ± 16637	32695 ± 15483	18639 ± 13019
MCAv Power $(cm/s)^2$/Hz	6410 ± 3582	6525 ± 2950	8305 ± 4839
Coherence (a.u.)	0.989 ± 0.010	0.984 ± 0.015	0.981 ± 0.013
Phase (radians)	0.650 ± 0.194	0.494 ± 0.189	0.727 ± 0.209
Gain (%/mmHg)	1.045 ± 0.321	1.025 ± 0.202	1.159 ± 0.208
Squat-Stand (0.10 Hz)			
MAP Power ($mmHg^2$)/Hz	21450 ± 7115	23389 ± 11799	14040 ± 7870
MCAv Power $(cm/s)^2$/Hz	6534 ± 3426	8893 ± 5863	11549 ± 5285
Coherence (a.u.)	0.993 ± 0.009	0.989 ± 0.021	0.988 ± 0.014
Phase (radians)	0.376 ± 0.102	0.310 ± 0.177	0.405 ± 0.119
Gain (%/mmHg)	1.285 ± 0.236	1.342 ± 0.478	1.527 ± 0.245

Values are means ± SD. Age-Match Control (AM); Donor-Control (DC); Heart Transplant Recipient (HTR); mean arterial pressure (MAP); arbitrary units (a.u.); middle cerebral artery velocity (MCAv); very low frequency (VLF; 0.02-0.07 Hz); low frequency (LF; 0.07-0.20 Hz). Statistical significance was set at $P < 0.05$, *denotes significance from HTR, †denotes significance from AM.