Cerebral Blood Flow

Relationship Between Cerebral Blood Flow and Blood Pressure in Long-Term Heart Transplant Recipients

Jonathan D. Smirl, Mark J. Haykowsky, Michael D. Nelson, Yu-Chieh Tzeng, Katelyn R. Marsden, Helen Jones, Philip N. Ainslie

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 5 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 with 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 seem to be related to alterations in cerebral pressure-flow dynamics. Future research is, therefore, warranted. (Hypertension. 2014;64:1314-1320.)

Key Words: autoregulation ■ blood pressure ■ cardiac transplantation ■ cerebrovascular circulation ■ transcranial Doppler ultrasonography

The longevity of heart transplant recipients has increased from 18 days after the first heart transplantation surgery1 to a current mean survival expectancy of for 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 ≈60% to 80% of heart transplant recipients3–5 and have a 14% to 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 therapy8 or vascular remodeling secondary to chronic cerebral hypoperfusion associated with pretransplant 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 variability8,9 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 animals11 and humans12 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 animal14,15 and human12 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 vice-versa. These concepts have not been explored in a clinical model (eg, 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 effect 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 with a group of donor controls. We hypothesized that heart transplant recipients would have

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reduced BRS, and impaired cerebral pressure-flow dynamics, independent of age.

Methods

Ethical Approval
The study was approved by the ethical committees of the Universities of British Columbia and Alberta and adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects. All volunteers provided written informed consent, and procedures were followed in accordance to institutional guidelines.

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 8 heart transplant recipients were ischemic presurgery 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 addition, we screened (via a transcranial Doppler examination) the anterior intracranial vessels for any signs of intracranial stenosis; in additional, we screened (via a transcranial Doppler examination) the anterior intracranial vessels for any signs of intracranial stenosis; all subjects had normal examination results as indicated by normal intracranial velocity profiles. All subjects were carefully screened for activity levels, withdrew from caffeine and alcoholic beverages for a period of 12 hours before the study, and all medications were maintained for the study. Each subject underwent a familiarization of the laboratory and testing protocols.

Instrumentation
Three-lead ECG was used 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.

Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>HTR (n=8)</th>
<th>AM (n=9)</th>
<th>DC (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±8</td>
<td>63±8</td>
<td>27±5*†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±4</td>
<td>26±3</td>
<td>26±5</td>
</tr>
<tr>
<td>Years after transplantation</td>
<td>9±7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiproliferative agent</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcinurin inhibitor</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca²⁺ channel blocker (diltiazem)</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means±SD. Seven HTR subjects were ischemic presurgery etiology, and 1 was nonischemic etiology. Statistical significance was set at P<0.05.

ACE indicates angiotensin-converting enzyme; AM, age-matched; DC, donor control; HTR, heart transplant recipient; and TOR, target of rapamycin.

*Significance from HTR.
†Significance from AM.

Interruption blood pressure was also recorded in the arm by electroplethysmomanometry (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 was intermittently confirmed at the brachial artery in the contralateral arm by sphygmomanometry.

Both right and left middle cerebral arteries (MCA) were insonated with a transcranial 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. 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 CO₂ (PₐCO₂) was measured using an online gas analyzer (ML206; AD Instruments, Colorado Springs, CO, USA) calibrated with a known gas concentration before 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 at 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). 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 MCAv 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 resampled 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 before 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 and the mean value of transfer function coherence, normalized gain, and phase were calculated in the very low (0.02–0.07 Hz) and low (LF; 0.07–0.20 Hz) frequency ranges as previously defined. 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 mean MCAv was >0.5, indicating ≥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 resampled 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 to 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, and 0.10 Hz) or group (heart transplant recipients, age-matched, and donor controls) on cerebral blood flow velocity, heart rate, blood pressure (mean and systolic), PrsCO2, CVRi, critical closing pressure, pulsitility index and transfer function coherence, normalized gain, and phase were assessed using a 1-way analysis of variance 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
There were no significant differences between groups for body mass index (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) MAP, systolic blood pressure, pulse pressure, and PrsCO2 levels were comparable for all groups (Table 2). Critical closing pressure 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 with 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 with donor controls (62±7 cm/s). Pulsitility index (arbitrary units) at rest was reduced in the heart transplant recipients compared with age-matched and donor controls, and the MCAv was reduced in comparison with 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 with 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 PrsCO2 for the seated baseline and 0.05 Hz and 0.10 Hz squat–stand maneuvers 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**

The donor controls had a significantly higher spontaneous BRS LF gain (10.8±5.1 ms/mm Hg) compared with both the heart transplant recipients (1.4±1.2 ms/mm Hg; P<0.01) and the age-matched controls (4.4±1.8 ms/mm Hg; P<0.01). The heart transplant recipients also had a significantly reduced BRS LF gain as compared with 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/mm Hg; age-matched, 2.0±0.9 ms/mm Hg; donor controls, 3.9±1.0 ms/mm Hg; P<0.03; Table 3). The donor controls showed a marked elevation in their R-R interval power spectrum density when compared with both the heart transplant recipients (P<0.01) and age-matched controls (4.4±1.8 ms/mm Hg; P<0.01; Table 3). The R-R interval power spectrum density for the age-matched controls was also elevated when compared with the heart transplant recipients (Table 3).

**Cerebral Pressure-Flow Dynamics**

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 very low frequency or LF ranges, during spontaneous and driven conditions (Table 4). The MAP and MCAv power spectrum density 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 CVR in the heart transplant recipients and age-matched as compared with 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 (Figure 2), as well as both driven frequencies (Figure 3), 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 interindividual variability in transfer function analysis metrics in the heart transplant recipients.

**Cardiac Baroreceptor Sensitivity in Heart Transplant Recipients**

After heart transplantation, the sympathetic and parasympathetic nerves that normally regulate heart rate are severed, leaving the heart denervated. Our findings are consistent with earlier 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 reinnervation 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

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**Figure 1.** Typical trace for blood pressure (BP), middle cerebral artery velocity (MCAv), and end-tidal CO₂ (P_{ET}CO_2) during spontaneous (top), 0.05 Hz (middle), and 0.10 Hz (bottom) trials from a long-term heart transplant recipient.
Table 3. Transfer Function Analysis for Cardiac Baroreceptor Sensitivity

<table>
<thead>
<tr>
<th>Baseline (Sitting)</th>
<th>HTR</th>
<th>AM</th>
<th>DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF RRI power, ms²</td>
<td>23±15</td>
<td>726±665*</td>
<td>2.842±2.920†</td>
</tr>
<tr>
<td>BRS LF gain, ms/mm Hg</td>
<td>1.4±1.2</td>
<td>4.4±1.8*</td>
<td>10.8±5.1†</td>
</tr>
<tr>
<td>Squat-stand (0.10 Hz)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRI power, ms/Hz</td>
<td>1255±1155</td>
<td>97773±91881*</td>
<td>420052±266339†</td>
</tr>
<tr>
<td>BRS gain, ms/mm Hg</td>
<td>0.2±0.1</td>
<td>2.0±0.9*</td>
<td>3.9±1.0†</td>
</tr>
</tbody>
</table>

Values are means±SD. Statistical significance was set at P<0.05. AM indicates age-matched control; BRS, baroreceptor sensitivity; DC, donor control; HTR, heart transplant recipient; LF, low frequency (0.04–0.15 Hz); MCAv, middle cerebral artery velocity; and RRI, R-R interval. *Significance from HTR. †Significance from AM.

by >95% as compared with age-matched and >99% compared with donor controls (Table 3), which was positively correlated with BRS gain under both spontaneous (R²=0.38, P<0.01) and driven (R²=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 reinnervation 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 affect their cerebral pressure flow dynamics (Table 4; Figures 2 and 3). We show that long-term heart transplant recipients have comparable reductions in MCAv and increases in CVRi compared with their age-matched counterparts (Table 2). Moreover, the increase in CVRi with age does not seem 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 Ref. 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 with both age-matched and donor-controls is clinically significant. We interpret these results to indicate that despite possible cerebrovascular remodeling during pretransplant antecedent heart failure24,25 and reductions in resting pulsatility index (Table 2) and cardiac BRS (Table 3), the cerebrovasculature is able to adapt to acute and marked (ie, 40–45 mm Hg) changes in arterial blood pressure (Figure 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 study25 in healthy older adults, which showed that increases in BRS were 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, 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.

Table 4. Transfer Function Analysis Between BP and MCAv

<table>
<thead>
<tr>
<th>Baseline (sitting)</th>
<th>HTR</th>
<th>AM</th>
<th>DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLF MAP power, mmHg²</td>
<td>8.261±5.118</td>
<td>8.813±7.619</td>
<td>8.554±4.589</td>
</tr>
<tr>
<td>LF MAP power, mmHg²</td>
<td>6.754±4.705</td>
<td>5.093±5.418</td>
<td>5.942±3.164</td>
</tr>
<tr>
<td>VLF MCAv power, cm/s²</td>
<td>3.071±2.060</td>
<td>3.283±3.814</td>
<td>5.316±3.265</td>
</tr>
<tr>
<td>LF MCAv power, cm/s²</td>
<td>2.784±2.537</td>
<td>3.448±6.187</td>
<td>6.069±4.376</td>
</tr>
<tr>
<td>LF coherence, a.u.</td>
<td>0.599±0.240</td>
<td>0.661±0.175</td>
<td>0.551±0.155</td>
</tr>
<tr>
<td>LF coherence, a.u.</td>
<td>0.791±0.093</td>
<td>0.713±0.155</td>
<td>0.829±0.045</td>
</tr>
<tr>
<td>VLF phase, radians</td>
<td>0.831±0.420</td>
<td>0.883±0.347</td>
<td>0.920±0.432</td>
</tr>
<tr>
<td>LF phase, radians</td>
<td>0.416±0.189</td>
<td>0.473±0.155</td>
<td>0.570±0.171</td>
</tr>
<tr>
<td>VLF gain, %/mm Hg</td>
<td>1.110±0.368</td>
<td>1.135±0.344</td>
<td>1.242±0.285</td>
</tr>
<tr>
<td>VLF gain, %/mm Hg</td>
<td>1.501±0.256</td>
<td>1.635±0.450</td>
<td>1.625±0.239</td>
</tr>
<tr>
<td>Squat-stand (0.05 Hz)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP power, mmHg²/Hg²</td>
<td>35423±16637</td>
<td>32695±15483</td>
<td>18639±13019</td>
</tr>
<tr>
<td>MCAv power, cm/s²/Hg²</td>
<td>6410±3582</td>
<td>6525±2950</td>
<td>8305±4839</td>
</tr>
<tr>
<td>Coherence, a.u.</td>
<td>0.989±0.010</td>
<td>0.984±0.015</td>
<td>0.981±0.013</td>
</tr>
<tr>
<td>Phase, radians</td>
<td>0.650±0.194</td>
<td>0.494±0.189</td>
<td>0.727±0.209</td>
</tr>
<tr>
<td>Gain, %/mm Hg</td>
<td>1.045±0.321</td>
<td>1.025±0.202</td>
<td>1.159±0.208</td>
</tr>
<tr>
<td>Squat-stand (0.10 Hz)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP power, mmHg²/Hg²</td>
<td>21450±7115</td>
<td>23389±11799</td>
<td>14040±7870</td>
</tr>
<tr>
<td>MCAv power, cm/s²/Hg²</td>
<td>6534±3426</td>
<td>8893±5863</td>
<td>11549±5285</td>
</tr>
<tr>
<td>Coherence, a.u.</td>
<td>0.993±0.009</td>
<td>0.989±0.021</td>
<td>0.988±0.014</td>
</tr>
<tr>
<td>Phase, radians</td>
<td>0.376±0.102</td>
<td>0.310±0.177</td>
<td>0.405±0.119</td>
</tr>
<tr>
<td>Gain, %/mm Hg</td>
<td>1.285±0.236</td>
<td>1.342±0.478</td>
<td>1.527±0.245</td>
</tr>
</tbody>
</table>

Values are means±SD. Statistical significance was set at P<0.05. AM indicates age-matched control; a.u., arbitrary units; DC, donor control; HTR, heart transplant recipient; LF, low frequency (0.07–0.20 Hz); MAP, mean arterial pressure; MCAv, middle cerebral artery velocity; and VLF, very low frequency (0.02–0.07 Hz). *Significance from HTR. †Significance from AM.

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, nonlinear, have multiple inputs, or merely be 2 unrelated phenomena. Hence during this
study, we did not discuss cerebral autoregulation per se, but merely presented data on 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 used the squat–stand maneuvers to nonpharmacologically 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 (eg, postural changes, coughing, exercise, etc.) and thus makes our data set physiologically relevant. This methodology induced oscillations that were 40 to 45 mm Hg (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 hemorrhage 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 for arteriosclerosis in this study, as this is not a routine procedure for this population. The heart transplant recipients were >5 years post transplant and did not have accompanying risk factors, such as hypertension, under resting conditions. Although the subjects within the present study did not undergo magnetic resonance imaging, the normal intracranial velocities and dynamic pressure-flow relationships would indicate an absence of global cerebral arteriosclerosis. However, we cannot rule out the possibility of localized and regional arteriosclerosis.

**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 healthy individuals, and our findings may not relate to heart transplant recipients with greater comorbidities.

**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 with 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
None.

References

Novelty and Significance

What Is New?
- This is the first study to assess the relationship between arterial blood pressure and cerebral blood flow in long-term heart transplant recipients.

What Is Relevant?
- In spite of reductions to baroreceptor sensitivity, long-term heart transplant recipients have comparable cerebral pressure-flow dynamics compared with both age-matched and donor controls.
- The reductions in baroreceptor sensitivity in long-term heart transplant recipients were not related to any transfer function metrics.

Summary
Together, these data suggest that the cerebrovasculature in long-term heart transplant recipients is able to normally regulate the cerebral blood flow dynamics and is unlikely to explain the increased occurrence of severe cerebrovascular complications documented in the population.
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