Complexity of middle cerebral artery blood flow velocity: effects of tilt and autonomic failure

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We examined spectral fractal characteristics of middle cerebral artery (MCA) mean blood flow velocity (MFV) and mean arterial blood pressure adjusted to the level of the brain (MAPbrain) during graded tilt (5 min supine, −10°, 10°, 30°, 60°, −10°, supine) in eight autonomic failure patients and age- and sex-matched controls. From supine to 60°, patients had a larger drop in MAPbrain (62 ± 4.7 vs. 23 ± 4.5 mmHg, P < 0.001; means ± SE) and MFV (16.4 ± 3.8 vs. 7.0 ± 2.5 cm/s, P < 0.001) than in controls. From supine to 60°, there was a trend toward a decrease in the slope of the fractal component (β) of MFV (MFV−β) in both the patients and the controls, but only the patients had a significant decrease in MFV−β (supine: patient = 2.21 ± 0.18, control = 1.99 ± 0.60; 60°: patient = 1.46 ± 0.24, control = 1.62 ± 0.19). The β value of MAPbrain (MAPbrain−β: 2.19 ± 0.05) was not significantly different between patients and controls and did not change with tilt. High and low degrees of regulatory complexity are indicated by values of β close to 1.0 and 2.0, respectively. The increase in fractal complexity of cerebral MFV in the patients with tilt suggests an increase in the degree of autoregulation in the patients. This may be related to the drop in MAPbrain. The different response of MFV−β compared with that of MAPbrain−β also indicates that MFV−β is related to the regulation of cerebral vascular resistance and not systemic blood pressure.

Spectral analysis; cerebral autoregulation; fractal

Syncope in patients with autonomic nervous system failure may be the result of insufficient regulation of mean arterial blood pressure (MAP), altered or impaired cerebral autoregulation, or some combination of the two. Autonomic failure is frequently associated with reduced beat-to-beat heart rate variability (HRV) (9, 10, 28). We have recently shown that beat-to-beat blood pressure variability (BPV), both systolic and diastolic, is also reduced in these patients (3). Specifically, low-frequency HRV and BPV power, associated with autonomic nervous system control, was affected. This is a consequence of neurological degeneration of the sympathetic and/or parasympathetic nervous systems.

Although some previous studies (27) of patients with autonomic failure have shown autoregulation to remain intact, with impaired blood pressure regulation, there may be changes in cerebral autoregulation. Examining the pattern of cerebral blood flow and MAP variability with tilt may provide useful information by allowing some insight into the behavior of the cerebral autoregulation mechanism in these patients.

Recent observations (7, 20) of both HRV and BPV have indicated that, underlying the harmonic components analyzed by spectral analysis, there is a pattern of fractal variability. The fractal property of a physiological system is identified by a characteristic 1/fβ function of spectral power. It has been speculated (20) that this pattern is important for the maintenance of cardiovascular homeostasis. Although not yet characterized as fractal, cerebral blood flow would not be expected to be different in this respect from other physiological signals.

Coarse graining spectral analysis (CGSA) has been used (29) to characterize the complexity of blood pressure and heart rate regulation. This is determined using the fractal spectral exponent β. High and low degrees of regulatory complexity are indicated by values of β close to 1.0 and 2.0, respectively. Complexity is thought to be related to the number of mechanisms interacting to produce the measured physiological signal. Recent investigation in our laboratory (3) of HRV and BPV in these patients showed reduced fractal power but similar complexity to age- and sex-matched controls. Furthermore, in these patients HRV complexity was reduced with tilt, whereas BPV complexity was unaffected by tilt. It was suggested that these results indicated reduced cardiovascular regulation but unaffected neural integration.

In this paper we examine complexity of MAP adjusted to the level of the brain (MAPbrain) and mean blood flow velocity (MFV) of the middle cerebral artery (MCA) of these autonomic failure patients and age-matched controls during graded tilt. CGSA of MAPbrain and MFV was used to explore the underlying physiological changes in the cardiovascular and cerebrovascular systems occurring with autonomic dysfunction. Our objective was to investigate the harmonic and fractal components of MAPbrain and MFV in these patients and to measure their response to tilt. On the basis of the results of the previous study (3), we expected reduced MAPbrain and cerebral MFV low-frequency power. We hypothesized that the beat-by-beat variability of cerebral blood flow velocity would be fractal and that this fractal variability would be related to the maintenance of cerebral blood flow (i.e., related to cerebral autoregu-
lation). We proposed that a decrease in $\beta$ (an increase in complexity) for MFV would indicate an increase in the number of mechanisms involved with cerebral autoregulation. With the increased orthostatic stress and decreased MAP (MAP\textsubscript{brain}) associated with tilt in the patients, we predicted an increase in the number of mechanisms involved with cerebral autoregulation and therefore an increase in MCA-MFV complexity.

**METHODS**

**Subjects.** Eleven patients (5 males and 6 females), previously described (3) (Table 1), with autonomic failure were observed during graded tilt in the autonomic function laboratory at Beth Israel Deaconess Medical Center (Boston, MA). Patients who were taking medication were asked to discontinue their medication at least 24 h before testing. Control subjects were selected to match the age and sex of each patient. Patients and control subjects gave informed consent to undergo the International Review Board-approved protocol. This protocol was presented in a previous paper (3) but will be briefly reported along with additional information pertaining to the measurement and analysis of cerebral blood flow.

**Experimental procedure.** A motorized tilt bed with a foot plate but no saddle support was used (Ratiotrol 3530-VS; Laberne, Columbia, SC). Subjects were instrumented in the supine position over a period of ~10 min. After this period, 5 min of baseline data were collected in the supine position. This was followed by 5 min in each of the following positions: −10° (head-down tilt, HDT), 10°, 30°, 60° (head-up tilt, HUT), −10°, and supine recovery. Subjects who became presyncopal during the HUT protocol were returned immediately to the −10° position for 5 min, followed by a 5-min supine recovery period.

**Data collection.** Hematocrit was determined for each subject at rest. R-R interval was obtained continuously from a standard four-lead electrocardiogram (ECG). Blood pressure was obtained by the noninvasive finger cuff method (Finapres 2300; Ohmeda, Englewood, CO) to provide beat-to-beat estimates of arterial blood pressure with the arm of the subject supported at the level of the left ventricle. Percent end-tidal CO\textsubscript{2} (PET\textsubscript{CO\textsubscript{2}}) and respiratory rate were measured by sampling exhaled CO\textsubscript{2} using a nasal adaptor (Datex Normocap 200, Helsinki, Finland). MFV of the MCA was measured noninvasively using transcranial Doppler (TCD) ultrasound (Transpect, Medasonics). The MCA was insonated through the temporal window using a 2-MHz probe. All TCD measurements were performed by the same operator.

**Data analysis.** Beat-to-beat analysis of these data was performed off line. MAP was adjusted to the level of the brain (MAP\textsubscript{brain}) by applying a hydrostatic correction. A single beat for both blood pressure and cerebral blood flow velocity was described by the pressure and velocity envelope tracings, respectively, between the initial increases in blood pressure or velocity after successive ECG R-waves. MAP and MFV were calculated as the arithmetic averages of the data points in each beat. The Doppler and blood pressure tracings were manually reviewed for anomalies and movement artifact. Any unusable blood flow velocity or blood pressure data were removed, and the time series was adjusted by interpolating new values from the two valid points surrounding the excluded segment. If more than 20% of any 256-beat segment was interpolated, the results were deemed invalid.

**Cerebral MFV and MAP\textsubscript{brain} complexity.** The beat-by-beat variability and fractal complexity of MFV and MAP\textsubscript{brain} were evaluated by CGSA (29). This method is a modification of the fast Fourier transform used by some investigators in studies of HRV. The advantage of this method over other techniques for spectral analysis is its ability to extract fractal components from the harmonic components (7, 29). Blood pressure signals have been shown (6, 7, 16, 29) to be fractal, that is, a broad-band, nonwhite signal underlies the (harmonic) variations that are normally taken to indicate parasympathetic and sympathetic regulatory activities.

The algorithm has been described in detail, along with a demonstration of its efficiency in extracting harmonic from fractal components (29). Briefly, the extraction of fractal and harmonic components is achieved by rescaling the data. The data are twice rescaled, once by sampling every second data point and once by sampling every data point twice before cross-correlation with the original data. Only the fractal components are retained after cross-correlation because of their self-similar properties, whereas the harmonic components are lost. A subtraction of the rescaled cross-correlation from an autocorrelation of the original therefore yields the harmonic spectral power.

The total power (P\textsubscript{tot}) can therefore be divided into fractal (P\textsubscript{frac}) and harmonic (P\textsubscript{harm}) components. The harmonic component can be divided into two frequency regions: high frequency (H1; ≥0.15 Hz) and low frequency (L0; 0–0.15 Hz). The high-frequency region is respiratory related, whereas the low-frequency region is a consequence of several factors. From the harmonic component, or the total harmonic power (P\textsubscript{harm}), the integrated power at 0.0–0.15 Hz (P\textsubscript{int}) and 0.15–0.50 Hz (P\textsubscript{int}) can be calculated.

The fractal component has linear scaling across a wide range of frequencies when the data are plotted as log spectral power versus log frequency in what is commonly called the $1/f^\beta$ relationship (20, 24, 26, 29). The $\beta$ value is the slope of the linear regression applied to these data. When the value of $\beta$ is close to 1, there is a high level of complexity because the data frequently change direction toward or away from the mean. In contrast, $\beta$ close to 2 represents a low level of complexity with less complex changes of the measured data (6, 20, 29). In a less complex system, feedback control is probably dominated by a reduced number of inputs (17).

Yamamoto and Hughson (30) investigated the effects of data length on the interpretation of data from CGSA. Less of the fractal signal was extracted at small data lengths (256 compared with 8,500 beats), and as a consequence the magnitude of the harmonic powers was found to also be dependent on data length. On the other hand, the parameter

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Diagnosis</th>
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</thead>
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<tr>
<td>1</td>
<td>M</td>
<td>59</td>
<td>SDS</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>51</td>
<td>PAF</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>57</td>
<td>PAF</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>54</td>
<td>PAF</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>68</td>
<td>PAF</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
<td>61</td>
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<tr>
<td>8</td>
<td>F</td>
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<td>9</td>
<td>F</td>
<td>42</td>
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</tr>
<tr>
<td>10</td>
<td>F</td>
<td>61</td>
<td>PAF</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>82</td>
<td>PAF</td>
</tr>
</tbody>
</table>

M, male; F, female; SDS, Shy-Drager syndrome; PAF, pure autonomic failure; IDDM, insulin-dependent diabetes mellitus.
Table 2. Mean arterial blood pressure and spectral power for autonomic failure patients and controls

<table>
<thead>
<tr>
<th></th>
<th>MAPbrain, mmHg</th>
<th>PTOT, mmHg^2</th>
<th>PHarm, mmHg^2</th>
<th>PLO, mmHg^2</th>
<th>PH, mmHg^2</th>
<th>PFrac, mmHg^2</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>93.6 ± 2.9</td>
<td>6.65 ± 2.6</td>
<td>0.73 ± 0.15</td>
<td>0.50 ± 0.13</td>
<td>0.25 ± 0.08</td>
<td>5.70 ± 2.24</td>
<td>2.16 ± 0.13</td>
</tr>
<tr>
<td>Controls</td>
<td>80.9 ± 2.7</td>
<td>7.48 ± 2.6</td>
<td>0.96 ± 0.15</td>
<td>0.84 ± 0.13</td>
<td>0.12 ± 0.08</td>
<td>6.80 ± 2.24</td>
<td>2.46 ± 0.13</td>
</tr>
<tr>
<td>P (group)</td>
<td>0.008</td>
<td>0.800</td>
<td>0.309</td>
<td>0.084</td>
<td>0.271</td>
<td>0.733</td>
<td>0.126</td>
</tr>
<tr>
<td>P (tilt)</td>
<td>&lt;0.001</td>
<td>0.325</td>
<td>0.043</td>
<td>0.455</td>
<td>0.001</td>
<td>0.333</td>
<td>0.150</td>
</tr>
</tbody>
</table>

Values for patients and controls are means ± SE. MAPbrain, mean arterial blood pressure adjusted to brain level; PTOT, total spectral power; PHarm, harmonic spectral power; PLO, harmonic low-frequency spectral power; PH, harmonic high-frequency spectral power; PFrac, fractal spectral power; and β, slope of fractal component of MAP. P < 0.05 indicates statistical significance. P (group), comparison of main effects between patients and control; P (tilt), comparison of main effects over tilt. *If P (tilt) < 0.05, then post hoc analyses (Student-Newman-Keuls test) between tilt conditions were conducted. MAPbrain and PH had significant post hoc differences, shown in Figs. 1 and 3, respectively.

Table 3. Middle cerebral artery blood flow velocity spectral power for autonomic failure patients and controls

<table>
<thead>
<tr>
<th></th>
<th>MFV, cm/s</th>
<th>PTOT, cm/s^2</th>
<th>PHarm, cm/s^2</th>
<th>PLO, cm/s^2</th>
<th>PH, cm/s^2</th>
<th>PFrac, cm/s^2</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>57.2 ± 2.6</td>
<td>6.53 ± 1.44</td>
<td>0.65 ± 0.12</td>
<td>0.41 ± 0.07</td>
<td>0.25 ± 0.08</td>
<td>5.83 ± 1.43</td>
<td>1.82 ± 0.09</td>
</tr>
<tr>
<td>Control</td>
<td>47.5 ± 2.6</td>
<td>3.23 ± 0.29</td>
<td>0.44 ± 0.12</td>
<td>0.37 ± 0.07</td>
<td>0.07 ± 0.08</td>
<td>2.80 ± 0.27</td>
<td>1.88 ± 0.06</td>
</tr>
<tr>
<td>P (group)</td>
<td>0.021</td>
<td>0.111</td>
<td>0.221</td>
<td>0.698</td>
<td>0.151</td>
<td>0.155</td>
<td>0.894</td>
</tr>
<tr>
<td>P (tilt)</td>
<td>&lt;0.001</td>
<td>0.451</td>
<td>0.432</td>
<td>0.716</td>
<td>0.002</td>
<td>0.398</td>
<td>0.032</td>
</tr>
</tbody>
</table>

MFV, mean blood flow velocity. *If P (tilt) < 0.05, then post hoc analyses (Student-Newman-Keuls test) between tilt conditions were conducted. MFV, PH, and β had significant post hoc differences, shown in Figs. 1, 3, and 4, respectively.

for describing the fractal component, β, and the ratio of low to high power were less susceptible to changes in data length. We wanted to compare the harmonic and the fractal components and chose a constant data length. Because of the time spent at each condition, we used a data length of 256 beats.

Statistical analysis. Statistical analysis of variables across the tilt levels (baseline, –10°, 10°, 30°, 60°, –10°, and recovery), comparing patients with age-matched healthy controls, was performed using a nested (subjects within tilt) two-way repeated-measures analysis of variance. All data were analyzed with SigmaStat (Jandel Scientific, San Rafael, CA) using the Kolmogorov-Smirnov test for normality and the Levene median test for equal variance. If main effects or interactions (P < 0.05) were detected, subsequent post hoc analysis using a Student-Newman-Keuls test was performed (P < 0.05). All data are expressed as means ± SE.

RESULTS

Because of technical difficulties and noise, only eight of the patients had sufficient TCD data for spectral analysis (subjects 1–8). None of these patients presented presyncopal symptoms during the tilt test. For statistical purposes, only the eight matched control subjects were used in the final analysis.

End-tidal CO2 responses were similar in both patients and controls, with patients dropping from 6.13 ± 0.5% while supine to 5.77 ± 0.4% at 60° HUT and controls dropping from 6.06 ± 0.6% while supine to 5.80 ± 0.6% at 60° HUT. Resting hematocrit levels also were not significantly different between the patients (39.7 ± 4%) and controls (40.7 ± 3%).

There were significant differences in the mean values, averaged over the 256 beats, of MAPbrain (Table 2) and MCA MFV (Table 3) between patients and controls and with tilt. From supine to 60° (Fig. 1), patients had a significant decrease in MAPbrain (105 ± 4.7 to 43 ± 4.5 mmHg, P < 0.01) and MFV (61 ± 3.6 to 44 ± 5.2 cm/s, P < 0.001) and controls had a significant decrease in MAPbrain (88 ± 4.5 to 65 ± 4.7 mmHg, P < 0.001) and a nonsignificant decrease in MFV (51 ± 2.8 to 44 ± 3.1 cm/s).

Furthermore, MAPbrain was significantly higher in patients in the supine position and significantly lower in patients in the 60° HUT position. Overall, the patients had a significantly higher MFV, but post hoc analysis revealed no differences between patients and controls over the levels of tilt. In both groups the smaller change in MFV with tilt compared with MAPbrain indicates a decrease in cerebral vascular resistance when estimated as MAPbrain/MFV (1).

Plots of MAPbrain and MFV harmonic power spectra with tilt for a patient and age-matched control are shown in Fig. 2. The low- and high-frequency components are observable in all the power spectra. As expected, there are marked differences between the patient and control power spectra. Most notable is the increased MAPbrain and MFV high-frequency power in the patients.

Spectral power. Both MAPbrain and MFV PTOT and PFrac were not different between patients and controls and were unaffected by tilt (Tables 2 and 3). Percent fractal for MAPbrain (controls = 82 ± 2.5%, patients = 86 ± 2.2%) and MFV (controls = 86 ± 1.8%, patients = 85 ± 1.7%) was not significantly different between patients and controls. Although MAPbrain PHarm showed a significant main effect change with tilt (P = 0.043; Table 2), subsequent post hoc analysis did not indicate differences between the levels of tilt. MFV PHarm was not different between patients and controls or over the different levels of tilt (Table 3). There was a trend (P = 0.084; Table 2) toward reduced MAPbrain, but not MFV (P = 0.698; Table 3). PLO. Both MAPbrain (P = 0.001; Table 2) and MFV (P = 0.002; Table 3) PH were significantly affected by tilt. Subsequent analysis revealed that only the patients had a significant increase in PH between the supine and the 60° HUT positions.
The patients also had a significantly greater PHI at 60° HUT compared with controls (Fig. 3).

The spectral exponent for blood pressure (MAP brain-β) was determined for both the controls and patients but was found not to be different between patients and controls and did not change with tilt. Heart rate complexity was also not different between patients and controls but decreased with increased tilt.

In this paper we have shown that cerebral blood flow velocity has a variability signal that in appearance is similar to that of blood pressure. We have also shown that the response of MFV complexity to tilt is not the same as that of heart rate or blood pressure; however, the response is predictable based on the autoregulatory model presented in the introduction. In the baseline (supine) position, both the signal complexity of MAP brain and the signal complexity of MFV are not different; however, with tilt the MFV signal complexity increases. Although this increase was only significant in the patients, the controls also showed the same trend. We hypothesize that this increase in complexity is due to an increased number of mechanisms involved with cerebral blood flow regulation in the face of reduced MAP brain. This is supported by the significant correlation between MFV-β and MAP brain in the patients. This change in complexity was greater in the patients due to a larger change in MAP brain related to their autonomic dysfunction. Furthermore, we have shown a larger increase in autoregulation from supine to 60° HUT in these patients (4). We predict that, in a healthy population, this increase in complexity would be significant given a sufficient drop in MAP brain.

The fall in CO₂ from supine to 60° HUT was similar in both patients and controls and was not large enough to make a significant difference in MFV. Even in patients who experienced a slightly larger change in CO₂, the drop in CO₂ from supine to 60° HUT was only 0.36% (2.7 mmHg). Furthermore, this drop occurred at a time when MAP brain was very low, at which point the effect of CO₂ on MFV is known to be diminished (12).

**DISCUSSION**

With autonomic failure both sympathetic and parasympathetic nervous system control of circulation can be affected (2, 8, 21–23). Our laboratory (3) recently reported that low-frequency HRV and BPV are both reduced in these patients. We also reported that systolic (SAP) and diastolic arterial blood pressure (DAP) signal complexities were not different between patients and controls and did not change with tilt. Heart rate complexity was also not different between patients and controls but decreased with increased tilt.

In this paper we have shown that cerebral blood flow velocity has a variability signal that in appearance is similar to that of blood pressure. We have also shown that the response of MFV complexity to tilt is not the same as that of heart rate or blood pressure; however, the response is predictable based on the autoregulatory model presented in the introduction. In the baseline (supine) position, both the signal complexity of MAP brain and the signal complexity of MFV are not different; however, with tilt the MFV signal complexity increases. Although this increase was only significant in the patients, the controls also showed the same trend. We hypothesize that this increase in complexity is due to an increased number of mechanisms involved with cerebral blood flow regulation in the face of reduced MAP brain. This is supported by the significant correlation between MFV-β and MAP brain in the patients. This change in complexity was greater in the patients due to a larger change in MAP brain related to their autonomic dysfunction. Furthermore, we have shown a larger increase in autoregulation from supine to 60° HUT in these patients (4). We predict that, in a healthy population, this increase in complexity would be significant given a sufficient drop in MAP brain.

The fall in CO₂ from supine to 60° HUT was similar in both patients and controls and was not large enough to make a significant difference in MFV. Even in patients who experienced a slightly larger change in CO₂, the drop in CO₂ from supine to 60° HUT was only 0.36% (2.7 mmHg). Furthermore, this drop occurred at a time when MAP brain was very low, at which point the effect of CO₂ on MFV is known to be diminished (12).

**Methodological considerations.** The use of continuous noninvasive blood pressure monitoring has extended our ability to observe beat-to-beat BPV. The finger monitor can be used for spectral analysis of BPV, but caution is needed when interpreting the low-frequency region. Omboni et al. (19) found increased low-frequency power with the finger monitor compared with intra-arterial measurements, although they were unable to determine whether this was due to measurement error or amplification with the blood pressure monitor. In the present study, the same blood pressure monitor was used for all subjects, with comparisons made between the patient and control groups. Interpretations were only made on the basis of these intergroup comparisons and not from absolute values, and therefore there should be no reason to doubt the validity of these comparisons.

The present study required continuous, beat-to-beat measurements of cerebral blood flow dynamics. TCD, a noninvasive ultrasound method of estimating changes in cerebral blood flow in the territory of the insonated vessel, is the only technique that could provide us with
these data. This method, however, does not measure flow directly but instead measures flow velocity. The relationship between the velocity changes measured and the changes in actual cerebral blood flow depends on the diameter of the insonated vessel. Peripheral resistance vessels downstream from the insonated vessel change diameter with autoregulation, which affects flow, and hence flow velocity, in the insonated vessel. Previous studies (11, 18) have validated the use of TCD under a variety of conditions known to affect cerebral perfusion. This study presents a situation similar to a previous study (5) in our laboratory based on lower body negative pressure; because a decrease in MFV was observed with HUT, this could only be explained two ways: either blood flow in the territory of the MCA decreased or the diameter of the MCA increased. Previous studies (15) have found an increase in sympathetic activity with HUT, which if anything may cause some vasoconstriction, not dilatation, of the MCA. Although this increase in sympathetic activity may have been reduced or even absent in patients, they would most likely have also experienced a drop in MCA blood flow, given the severe drop in arterial blood pressure observed during HUT. The presyncopal episodes experienced by two of the patients (3) (not included in this paper due to insufficient TCD data) further supports the concept of a reduced MCA flow. We therefore believe that changes in MCA caliber are likely to be minimal but that, even if such changes did take place, they would not have adversely affected our interpretation of the fall in MFV as a fall in actual MCA blood flow during HUT.

The other methodological consideration deals with the use of changes in MAP brain to represent changes in cerebral perfusion pressure (CPP). Because CPP = MAP brain – intracranial pressure (ICP), this assump-
tion is valid only if changes in ICP are minimal. The validity of assuming minimal ICP changes during HUT has been demonstrated by Rosner et al. (25), who showed a drop in ICP of only 1 mmHg for every 10° of HUT. This drop is much lower than the MAP\textsubscript{brain} changes we observed and would not affect the outcome of the present study. Furthermore, ICP is expected to remain nearly constant within a given tilt segment, so it would not be a factor in our analysis of the dynamics within each segment. Most importantly, because ICP changes during HUT are thought not to be mediated by the autonomic nervous system (25), any changes in ICP should have had the same effect on both the patient and control groups, and hence our comparison of the two groups is valid.

Cerebral blood flow variation. Any changes in cerebrovascular blood flow should reflect changes in blood pressure entering the cerebral vasculature. However, because of the autoregulatory ability of the cerebrovascular system, signal transduction from pressure to flow may be modified through changes in the diameter of cerebrovascular arterioles. Our data clearly show that the harmonic variations in MAP\textsubscript{brain} and MFV are similar. Low-frequency power was not affected by tilt. High-frequency power was affected, but only in the patients. The effect of BPV on MFV variation in the high-frequency region can be clearly observed in Figs. 2 and 3. The change in high-frequency power in blood pressure is due to the effects of autonomic failure on baroreflex activity. In another paper (3), data from our laboratory were presented showing a significant increase in SAP and DAP P\textsubscript{HI} power in patients but not in control subjects. Our observation of increased MAP\textsubscript{brain} P\textsubscript{HI} is consistent with these findings. The MAP\textsubscript{brain} harmonic variation is directly reflected in the MFV signal.

Fractal nature of MFV and MAP\textsubscript{brain}. Previous research supports the concept that heart rate and systolic blood pressure have fractal variability and that the fractal component in humans is a large percentage (70–90%) of both HRV (7, 13, 30) and systolic BPV (6, 13). We have now shown that cerebral blood flow is fractal and that its complexity changes with blood pressure. A fractal signal is one that is self similar (29), that is, when viewed over different time scales, the pattern would be similar. It has been previously speculated that this fractal information is important in the maintenance of cardiovascular homeostasis (6, 7, 20). The complexity of the overall blood pressure and blood flow velocity variability can be estimated by the slope of the linear regression of log fractal spectral power versus log frequency (14). The changes in the slope can be seen in Fig. 4.

In previous studies (3, 6) in which the fractal components of HRV and BPV were investigated, it was concluded that the overall central control mechanisms for HRV and BPV must be independent, because the slope of the fractal component of BPV remained constant, whereas that for HRV increased as the level of orthostatic stress was increased. A similar conclusion can now be made between blood pressure and cerebral...
blood flow, because the slope of the fractal component for MFV decreased with increasing HUT, whereas the slope for MAP\textsubscript{brain} remained constant. Furthermore, we can also conclude that overall central control mechanisms for cerebral blood flow must be different from heart rate because in these patients the slope of the HRV fractal component increased as the level of tilt increased.

It is also significant that, although MFV-\(\beta\) in the control group did not change significantly with tilt, it did show a trend in the same direction as in the patients. If, as previously suggested, the fractal component represented by \(\beta\) is related to the complexity of the overall MFV signal, then both patients and controls were not different in this respect. In other words, the increase in the number of mechanisms involved with cerebral blood flow regulation increases. The different response of cerebral blood flow regulation increases with increased complexity with tilt. The different response of cerebral blood flow regulation increases with decreased blood pressure and increased cerebral vascular stress, the number of mechanisms involved with decreased blood pressure and increased cerebrovascular resistance and not systemic blood pressure regulatory controls, although only MAP\textsubscript{brain} had a trend toward increased complexity.

In conclusion, CGSA of cerebral blood flow velocity provided information with respect to cerebral blood flow regulation not present in the standard analyses of cerebral autoregulation. We have demonstrated important differences between blood pressure and blood flow regulation with orthostatic stress. The harmonic components of blood pressure and blood flow responded similarly to the tilt protocol. Both had increased high-frequency power in the patients compared with the controls, although only MAP\textsubscript{brain} had a trend toward increased low-frequency power in the patient group. The increase in the high-frequency variation in patient, but not control, MAP\textsubscript{brain} may be linked to a reduced vagal baroreflex in the patients.

The decrease in MFV-\(\beta\) in the patients was related to the decrease in MAP\textsubscript{brain} with tilt. This response appeared to be normal, because the control group, with a smaller decrease in MAP\textsubscript{brain}, also had a trend toward increased complexity with tilt. The different response of MFV-\(\beta\) compared with that of MAP\textsubscript{brain}-\(\beta\) indicates that MFV-\(\beta\) is related to the regulation of cerebral vascular resistance and not systemic blood pressure regulatory mechanisms. The increase in complexity suggests that, with decreased blood pressure and increased cerebrovascular stress, the number of mechanisms involved with cerebral blood flow regulation increases.

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