Cerebral pressure-flow relations in hypertensive elderly humans: transfer gain in different frequency domains

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Serrador, Jorge M, Farzaneh A. Sorond, Mitul Vyas, Margaret Gagnon, Ikechukwu D. Iloputaife, and Lewis A. Lipsitz. Cerebral pressure-flow relations in hypertensive elderly humans: transfer gain in different frequency domains. J Appl Physiol 98: 151–159, 2005. First published September 10, 2004; doi:10.1152/japplphysiol.00471.2004.—The dynamics of the cerebral vascular response to blood pressure changes in hypertensive humans is poorly understood. Because cerebral blood flow is dependent on adequate perfusion pressure, it is important to understand the effect of hypertension on the transfer of pressure to flow in the cerebrovascular system of elderly people. Therefore, we examined the effect of spontaneous and induced blood pressure changes on beat-to-beat and within-beat cerebral blood flow in three groups of elderly people: normotensive, controlled hypertensive, and uncontrolled hypertensive subjects. Cerebral blood flow velocity (transcranial Doppler), blood pressure (Finapres), heart rate, and end-tidal CO2 were measured during the transition from a sit to stand position. Transfer function gains relating blood pressure to cerebral blood flow velocity were assessed during steady-state sitting and standing. Cerebral blood flow regulation was preserved in all three groups by using changes in cerebrovascular resistance, transfer function gains, and the autoregulatory index as indexes of cerebral autoregulation. Hypertensive subjects demonstrated better attenuation of cerebral blood flow fluctuations in response to blood pressure changes both within the beat (i.e., lower gain at the cardiac frequency) and in the low-frequency range (autoregulatory, 0.03–0.07 Hz). Despite a better pressure autoregulatory response, hypertensive subjects demonstrated reduced reactivity to CO2. Thus, otherwise healthy hypertensive elderly subjects, whether controlled or uncontrolled with antihypertensive medication, retain the ability to maintain cerebral blood flow in the face of acute changes in perfusion pressure. Pressure regulation of cerebral blood flow is unrelated to cerebrovascular reactivity to CO2.

THE DYNAMICS OF THE CEREBRAL VASCULAR RESPONSE TO BLOOD PRESSURE CHANGES IN HYPERTENSIVE HUMANS IS POORLY UNDERSTOOD. ONE WOULD EXPECT THAT HYPERTENSION RESULTS IN GREATER PERIPHERAL VASCULAR STIFFNESS, PRESUMABLY INCLUDING THE CEREBRAL VESSELS, WHICH IN TURN WOULD INCREASE THE PULSATILITY OF THE FLOW THROUGH CEREBRAL ARTERIES.

Transcranial Doppler ultrasonography (TCD) provides the unique opportunity to examine changes in cerebral blood flow velocity (CBFV) both on a beat-by-beat basis and within a beat. By using this methodology, in combination with beat-by-beat noninvasive blood pressure measures, it is possible to examine the transfer of pressure to cerebral flow as a measure of autoregulation (1). Because autoregulation can take several seconds to engage, previous work has examined transfer of pressure to flow velocity in the low-frequency range (<0.5 Hz) and found that autoregulation remains intact in aging (5, 17, 23), controlled hypertension (7, 17, 30), and uncontrolled hypertension (7).

Our laboratory recently extended this work by examining how transfer of pressure into flow velocity is affected within the cardiac cycle (i.e., ~1 Hz), finding that it was similar between healthy elderly and young subjects (20). In hypertensive subjects, we would expect that increased stiffness in cerebral vessels would result in greater passive transmission of pressure to flow (i.e., before autoregulation has time to engage), and thus cardiac-frequency gain would be increased. In a system that is normally autoregulating, as hypertensive subjects have been shown to do, higher perfusion pressure would be associated with greater cerebrovascular resistance (CVR), which would reduce transfer function gain in the low-frequency region where autoregulation is active. Thus one would expect, in hypertensive subjects, that gains in the low-frequency regions would be normally low but in cardiac-frequency regions would be abnormally elevated.

To better understand the cerebrovascular autoregulatory dynamics in hypertensive subjects, we studied pressure-flow relations during posture change, computed transfer function gains over low- and cardiac-frequency regions, and examined the relations of these gains to vascular resistance. We hypothesized that autoregulation would be intact but that there would be greater transmission of pressure to flow within the cardiac cycle (before autoregulation is engaged) due to increased vascular stiffness.

METHODS

Subjects

Sixty subjects (age 72 ± 4 yr) were recruited from the local community through newspaper advertisements and the Harvard Cooperative Program on Aging subject registry. Subjects were classified into three groups on the basis of screening: 1) “normotensive” (blood pressure <140/90 mmHg) (n = 22) and on no blood pressure-lowering medications, 2) “controlled hypertensive” (n = 20) and well controlled (blood pressure <140/90 mmHg) on blood pressure-lowering medications, and 3) “uncontrolled hypertensive” (n = 18) (systolic blood pressure >160 mmHg) with or without blood pressure-lowering medications.

All subjects were carefully screened with a medical history, physical examination, ECG, and echocardiogram to exclude acute medical conditions or cardiovascular diseases other than hypertension. A
carotid Doppler study was performed on hypertensive subjects to exclude carotid artery stenosis. Subjects were also evaluated to ensure an adequate TCD insonation window for the middle cerebral artery (MCA). The hospital institutional review board approved the study, and all subjects provided written, informed consent.

Of the controlled hypertensive subject group, no subjects were treated with more than two antihypertensives for blood pressure control, and 14 subjects were treated with a single antihypertensive agent; 8 subjects were treated with an angiotensin-converting enzyme inhibitor, 4 subjects were treated with a diuretic, 1 subject was treated with a calcium channel blocker, and 1 subject was treated with an angiotensin II receptor antagonist. Two subjects were treated with an angiotensin-converting enzyme inhibitor and a diuretic, three with calcium channel blockers and diuretics, and one with a calcium channel blocker and angiotensin II receptor antagonist. All medications were taken the morning of the study.

Of the uncontrolled hypertensive subject group, four subjects were not taking antihypertensives before study enrollment, seven were treated with angiotensin-converting enzyme inhibitors, two were treated with a diuretic, one was treated with a calcium channel blocker, and one was treated with an angiotensin II antagonist. Three subjects were on combined medications of diuretic and α-adrenergic receptor inhibitor; calcium channel blocker and α-adrenergic receptor inhibitor; and calcium channel blocker and angiotensin II antagonist. Subjects were tapered off of their ineffective prestudy medications over a period of 1–2 wk depending on medication and dosage. Studies were conducted after these subjects were off of all cardiovascular medications for 7–10 days.

Experimental Protocol

Instrumentation. Subjects reported to the cardiovascular laboratory in the postabsorptive state, ≥2 h after their last meal. Each subject was instrumented with a three-lead ECG (Collins, TX) to obtain heart rate and a photoplethysmographic cuff on the middle finger of the right hand slung at the level of the right atrium to obtain noninvasive beat-by-beat blood pressure (Finapres, Ohmeda, CO). The MCA was insonated by placing a 2-MHz Doppler probe (Nicolet Companion, WI) over the temporal window to measure blood flow velocity as described by Aaslid et al. (2). The envelope of the velocity waveform was derived from the fast Fourier transformation of the Doppler signal. All physiological signals were digitized at 500 Hz by using a commercially available digitizer (Windaq, Dataq Instruments, Columbus, OH) and stored on a computer for offline analysis.

Sit-stand protocol. Orthostatic hypotension was induced to assess cerebral autoregulation by asking subjects to perform an active sit-stand protocol, described previously by Lipsitz et al. (17). Subjects sat in a straight-backed chair with their legs elevated at 90° in front of them. They were then asked to stand. Standing was defined as the moment both feet touched the floor. Subjects performed two trials of a 5-min sit followed by standing for 1 min, and one trial of a 5-min sit followed by a 6-min stand. The longer standing period was used to compute the pressure-flow transfer function as described below. Respiration was paced by aural entrainment at 0.25 Hz during all data-collection periods to control end-tidal CO2 and to permit spectral analysis at low frequencies without the influence of respiratory cycles.

CO2 reactivity protocol. Cerebrovascular reactivity to CO2 was measured to determine whether any changes in cerebral blood flow regulation were due to a general abnormality in cerebrovascular reactivity or selectively in response to a change in perfusion pressure. Two trials were performed, where subjects breathed a mixture of 5% CO2 and 95% air from a 5-liter rebreathing bag at 15 breaths/min (0.25 Hz) for 1 min each trial. Continuous end-tidal CO2 levels were measured during the trials by a gas analyzer through a sampling tube attached to the expiration pathway. Previous work has found that changes in cerebral blood flow in response to increasing arterial CO2 are unaffected by hypoxia (10).

Data Processing and Analysis

Postprocessing was done using custom-written MATLAB scripts. Beat-to-beat R-R intervals were determined from the R wave of the ECG. Systolic, diastolic, and mean values for blood pressure and CBFV were determined from the associated waveforms. To ensure quality of data, the same experienced research nurse performed all TCD evaluations using standard evaluation techniques. Finapres blood pressures were compared with arm cuff pressures during baseline to ensure values were consistent.

To evaluate the beat-to-beat dynamics of arterial blood pressure (ABP) and CBFV responses to acute posture changes, we calculated the differences between the sitting value (averaged over a period of 50 s) and the value at the nadir of blood pressure (average of 5 values surrounding the nadir) for both mean pressure and velocity for each trial. We also expressed these changes as a percentage of the baseline value. The average of two trials for a group was then computed.

We assessed the autoregulatory response to transient orthostatic hypotension by determining the absolute and percent change in CVR (= ABP/CBFV) from sitting (average of 50 s) to the nadir of blood pressure during stand (average of 5 points). Furthermore, we determined the dynamic autoregulatory index (ARI) by using the method described by Tiecks et al. (29) to quantify the CBFV response to dynamic changes in ABP. The actual CBFV response was compared with a family of theoretical responses calculated for the given ABP drop, and the closest fit was selected as that trial’s dynamic ARI. An ARI of zero suggests no regulation, and nine suggests maximum regulation (29).

Coherence and transfer function analyses using the ABP and CBFV signals’ autospectra during the 5-min sit and stand periods were also performed. The time series data were interpolated at 5 Hz to provide equidistant samples. The power spectrum density, based on Welch’s algorithm of averaging periodograms was calculated for the filtered signals using a sliding window with a width of 500 points and an overlap of 250 points after detrending and application of a Hanning filter. Coherence (C) of the frequency content (f) between the ABP and CBFV time series was calculated from the power spectra (P) for both the sitting and standing positions using the following formula:

\[
C_x(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}
\]

where \(x\) is the input signal (mean ABP) and \(y\) is the output (CBFV). The transfer function gain (H) was also computed for the sitting and standing positions using the following formula:

\[
H_x(f) = \frac{P_{xy}(f)}{P_{xx}(f)}
\]

This method assesses autoregulation by examining the relative change in beat-by-beat CBFV with each beat-by-beat change in ABP. Cerebral autoregulation maintains CBFV relatively constant by using changes in CVR to buffer changes in ABP that would otherwise cause large fluctuations in CBFV. If autoregulation is functioning properly, changes in ABP cause minimal changes in CBFV, and thus transfer function gains should be low. When autoregulation is impaired, changes in ABP cause large changes in flow and thus gains should be high.

We calculated cerebrovascular reactivity by using three methods. To calculate standard CO2 reactivity, we plotted the CBFV of each beat during the rebreathe with the corresponding end-tidal CO2 value. The slope of this relationship was used as an index of CO2 reactivity (cm−1 s−1 · %CO2−1).

We also calculated cerebrovascular conductance (CVC; mean CBFV/mean ABP) for each beat and plotted this against the associated end-tidal CO2 value. The slope of this relationship was used as an index of CVC reactivity to CO2 (CVC reactivity; cm·s−1·mmHg−1 · %CO2−1).
Because cerebrovascular reactivity is a measure of how much the cerebral arteries dilate for a given CO2 stimulus, it is important that any constriction due to a rise in systemic blood pressure be accounted for. We developed the following technique to analyze cerebral blood flow changes due to CO2, independent of those due to changes in blood pressure during hypercapnia. First, we calculated the CVC (= CBVF/ABP) for each beat. Then we calculated a “pressure-related” CVC, assuming that pressure autoregulation would keep CBVF constant at the baseline level (before giving the CO2 stimulus). The pressure-related CVC was then subtracted from the total CVC, leaving us with the CVC contribution that was purely due to the CO2 stimulus. The “CO2-specific” CVC at each beat was then plotted against end-tidal CO2 for the coinciding breath, and the slope of this relation was used as an index of CO2-specific reactivity (cm$^3$·s$^{-1}$·mmHg$^{-1}$·%CO2$^{-1}$).

### Statistical Analysis

The effects of posture (sitting vs. standing) or group (normotensive vs. controlled hypertensive vs. uncontrolled hypertensive) on CBVF, heart rate, ABP, end-tidal CO2, CVC, and transfer function gains were assessed by using a repeated-measures two-way ANOVA, respectively, with a post hoc Bonferroni test for multiple comparisons. Data are presented as means ± SE, and levels of $P < 0.05$ are considered statistically significant.

### RESULTS

#### Subject Characteristics

Descriptive statistics for the three groups of subjects are provided in Table 1. All three groups had similar ages and gender distributions. The uncontrolled hypertensive subjects had significantly higher systolic blood pressure, diastolic blood pressure, and mean ABP.

#### Cerebrovascular Reactivity

There was a trend toward lower total CO2 reactivity in the seated position in controlled and uncontrolled hypertensive subjects, but this difference was not statistically significant (Table 2). To examine the cerebrovascular response that was due specifically to changes in arterial CO2, we examined changes in CVC that were corrected for changes in ABP (as detailed in METHODS). Using this method, we found that CO2 reactivity was in fact significantly lower in hypertensive subjects (both controlled and uncontrolled) compared with normotensive subjects. Interestingly, the increase in ABP and end-tidal CO2 during the rebreathing procedure was similar between groups, suggesting that the difference in conductance was not due to pressure effects.

### Response to Postural Change

As expected, initial sitting blood pressures were higher in the uncontrolled hypertensive subjects than in the normotensive subjects (Table 3). In addition, the controlled hypertensive subjects demonstrated a slightly higher ABP than normotensive subjects but significantly lower than uncontrolled hypertensive subjects. In contrast, there was no difference in CBVF between normotensive subjects and either controlled or uncontrolled hypertensive subjects. However, controlled hypertensive subjects had lower sitting flow velocities than uncontrolled hypertensive subjects. CVR was similar between all groups.

On moving from the sitting to standing position, all subjects demonstrated a similar drop in ABP that was associated with a decrease in cerebral flow velocity. The decline in ABP had a similar temporal pattern in all three groups. Interestingly, the normotensive subjects had the largest decrease in CBVF, whereas both controlled and uncontrolled hypertensive subjects had smaller declines (Fig. 1). Consistent with intact cerebral autoregulation, all subjects had a reduction in CVR during the postural decrease in ABP. Although normotensive subjects demonstrated a slightly higher ABP than normotensive subjects but significantly lower than uncontrolled hypertensive subjects. CVR was similar between all groups.

### Table 1. Baseline subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>NT</th>
<th>CHT</th>
<th>UHT</th>
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<tbody>
<tr>
<td>$n$</td>
<td>21</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Age, yr</td>
<td>70±4</td>
<td>72±5</td>
<td>74±4</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>13:8</td>
<td>10:10</td>
<td>9:9</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>125±11</td>
<td>135±8</td>
<td>162±7‡</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>72±6</td>
<td>78±5</td>
<td>84±7‡</td>
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<tr>
<td>Mean BP, mmHg</td>
<td>90±7</td>
<td>97±5</td>
<td>110±5*‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>59±6</td>
<td>64±7</td>
<td>64±8</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n$, no. of subjects. Baseline characteristics were determined from sphygmomanometry while seated. NT, normotensive subjects; CHT, controlled hypertensive subjects; UHT, uncontrolled hypertensive subjects; BP, blood pressure. *Significant difference from NT, $P < 0.05$. ‡Significant difference between CHT and UHT, $P < 0.05$.

### Table 2. Cerebrovascular reactivity

<table>
<thead>
<tr>
<th></th>
<th>NT</th>
<th>CHT</th>
<th>UHT</th>
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<tbody>
<tr>
<td>CO2 reactivity, (cm$^3$·s$^{-1}$·%CO2$^{-1}$)</td>
<td>18.7±1.5</td>
<td>14.0±2.0</td>
<td>15.5±1.7</td>
</tr>
<tr>
<td>CVC reactivity, (cm$^3$·s$^{-1}$·mmHg$^{-1}$·%CO2$^{-1}$)</td>
<td>0.15±0.02</td>
<td>0.10±0.02</td>
<td>0.11±0.02</td>
</tr>
<tr>
<td>CO2 specific reactivity, (cm$^3$·s$^{-1}$·mmHg$^{-1}$·%CO2$^{-1}$)</td>
<td>0.33±0.03</td>
<td>0.21±0.03*</td>
<td>0.22±0.03*</td>
</tr>
<tr>
<td>ΔABP, mmHg</td>
<td>9.0±1.4</td>
<td>9.3±1.4</td>
<td>9.8±2.3</td>
</tr>
<tr>
<td>ΔCBVF, cm/s</td>
<td>16.4±1.2</td>
<td>15.1±1.3</td>
<td>14.7±1.4</td>
</tr>
<tr>
<td>ΔEnd-tidal CO2, %</td>
<td>1.1±0.1</td>
<td>0.9±0.1</td>
<td>1.0±0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Reactivity to CO2 during 1-min rebreath of 5% CO2 based on 3 different calculations outlined in METHODS. CVC, cutaneous vascular conductance; ABP, arterial BP; CBVF, cerebral blood flow velocity; Δ, change. *Significant difference from NT, $P < 0.05$.

### Table 3. Response to postural change

<table>
<thead>
<tr>
<th></th>
<th>NT</th>
<th>CHT</th>
<th>UHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (sitting)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABP, mmHg</td>
<td>89±11</td>
<td>93±16*</td>
<td>107±15†</td>
</tr>
<tr>
<td>CBVF, cm/s</td>
<td>35±11</td>
<td>32±9</td>
<td>37±9†</td>
</tr>
<tr>
<td>CVR, mmHg·s·cm$^{-1}$</td>
<td>2.81±0.91</td>
<td>3.21±1.1</td>
<td>3.04±0.8</td>
</tr>
<tr>
<td>End-tidal CO2, Torr</td>
<td>30±3</td>
<td>30±4</td>
<td>30±5</td>
</tr>
</tbody>
</table>

Changes from sitting to nadir of standing ABP

<table>
<thead>
<tr>
<th></th>
<th>NT</th>
<th>CHT</th>
<th>UHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔABP, mmHg</td>
<td>-25±8</td>
<td>-22±7</td>
<td>-21±8</td>
</tr>
<tr>
<td>ΔCBVF, cm/s</td>
<td>-6±7</td>
<td>-3±4*</td>
<td>-3±4*</td>
</tr>
<tr>
<td>ΔCBVF, %</td>
<td>-15±16</td>
<td>-10±14</td>
<td>-9±12*</td>
</tr>
<tr>
<td>ΔCVR, mmHg·s·cm$^{-1}$</td>
<td>-0.37±0.59</td>
<td>-0.42±0.56</td>
<td>-0.34±0.62</td>
</tr>
<tr>
<td>ΔCVR, %</td>
<td>-13±19</td>
<td>-13±14</td>
<td>-12±17</td>
</tr>
<tr>
<td>ΔCO2, Torr</td>
<td>-2.4±0.8</td>
<td>-4.5±0.7</td>
<td>-3.9±0.9</td>
</tr>
<tr>
<td>Time to nadir of CBVF, s</td>
<td>4.69±2.92</td>
<td>5.6±3.09</td>
<td>5.19±4.36</td>
</tr>
<tr>
<td>Time to nadir of BP, s</td>
<td>8.72±2.34</td>
<td>9.2±3.01</td>
<td>9.75±3.88</td>
</tr>
<tr>
<td>Autoregulatory index</td>
<td>5.8±0.5</td>
<td>5.7±0.5</td>
<td>6.5±0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. Response of subjects to standing is shown. Baseline sitting was calculated from 50 before initiation of stand procedure. BP was determined from photoplethysmography (Finapres). CVR, cerebrovascular resistance. *Significant difference from NT, $P < 0.05$. †Significant difference between CHT and UHT, $P < 0.05$.
subjects demonstrated the greatest decrease in CBFV, they had the smallest change in end-tidal CO₂, suggesting the greater cerebral hypoperfusion was not the result of hyperventilation.

Cerebral Autoregulatory Characteristics

To examine the cerebral blood flow response to spontaneous changes in blood pressure, transfer function gains were calculated during steady-state periods, both sitting and standing in three frequency bands: low frequency (0.03–0.07 Hz); high frequency (0.07–0.15 Hz), and cardiac frequency surrounding the heart rate (~1 Hz).

Hemodynamic response. All three groups had similar heart rates sitting (normotensive, 60 ± 8; controlled hypertensive, 62 ± 8; uncontrolled hypertensive, 62 ± 9 beats/min) that increased when standing (normotensive, 69 ± 10; controlled hypertensive, 71 ± 9; uncontrolled hypertensive, 69 ± 2 beats/min).

Low-frequency (autoregulatory) band. Gain in the low-frequency band was not significantly different between sitting and standing within any of the groups (Fig. 2). However, normotensive and controlled hypertensive subjects had significantly higher gains than uncontrolled hypertensive subjects in both positions. Although transfer function gains were different between groups, there was no difference in coherence or phase, indicating that the uncontrolled hypertensive subjects were demonstrating better attenuation of low-frequency cerebral flow fluctuations in response to blood pressure changes, as would be expected with better autoregulation. This was not due to differences in blood pressure fluctuations because ABP power in the low-frequency range was not significantly different between groups (P = 0.394). 

High-frequency band. In the high-frequency power band, there was also no difference between sitting and standing. However, in this frequency band, controlled and uncontrolled hypertensive subjects had similar gains, both of which were lower than in normotensive subjects. The lower gains in the uncontrolled hypertensive subjects were also associated with lower coherence values than the normotensive or controlled hypertensive subjects. Phase lags were not different between groups (Fig. 2). Again, these differences in gains were not due to differences in blood pressure fluctuations because ABP power was not significantly different between groups.

Cardiac-frequency band. To determine pressure-flow relations within the cardiac cycle, we examined the transfer function gains in the cardiac frequency. Cardiac frequency gain was lower in both controlled and uncontrolled hypertensive subjects compared with normotensive subjects, with no differences in coherence or phase between groups. In this frequency band, ABP power was significantly different between all three groups in both the sitting (normotensive, 37 ± 13; controlled hypertensive, 81 ± 14; uncontrolled hypertensive, 124 ± 15 mmHg²/Hz; P < 0.05) and standing positions (normotensive, 34 ± 11; controlled hypertensive, 48 ± 12; uncontrolled hypertensive, 111 ± 13 mmHg²/Hz; P < 0.05). Interestingly, whereas gain was not different between controlled and uncontrolled hypertensive subjects, ABP power was significantly

Fig. 1. Mean response during sit to stand maneuver in normotensive (NT; n = 22), controlled hypertensive (CHT; n = 20), and uncontrolled hypertensive (UHT; n = 18) subjects. Time 0 represents point at which subject’s feet touched the floor and stand was initiated. Note scales for each graph have the same range but have been adjusted to align baseline values for each group to compare relative changes during standing. Values are means ± SE.
higher in the uncontrolled hypertensive subjects ($P < 0.05$). This suggests that differences in cardiac-frequency gain were not solely due to differences in blood pressure fluctuations between the groups.

**CVR and Transfer Function Gains**

Because the resistance of the cerebral vasculature could affect the transfer of pressure into flow, we examined the relationship between transfer function gain and CVR in the sitting position (Fig. 3).

In the cardiac-frequency range, there was a significant inverse correlation between CVR and gain for all groups ($P < 0.001$). Interestingly, the normotensive subjects demonstrated a stronger inverse relationship (slope $= -0.20$, $R^2 = 0.65$) than the controlled and uncontrolled hypertensive subjects (slope $= -0.08$, $R^2 = 0.29$). These data suggest that vascular resistance has a stronger effect on gain in normotensive than hypertensive subjects. As can be seen in Fig. 3, hypertensive subjects had lower cardiac-frequency gains, which remained similar as CVR increased. In contrast, normotensive subjects with low CVR had much larger gains than normotensive subjects with high CVR.

In the low-frequency range, we found similar results with the normotensive subjects again demonstrating an inverse re-
relation between CVR and gain (slope = -0.10, $R^2 = 0.33$, $P = 0.007$). In contrast, there was no significant correlation for the hypertensive subjects ($R^2 = 0.01$, $P = 0.667$). In the high-frequency range, normotensive and controlled hypertensive subjects had significant correlations ($R^2 = 0.23$, $P < 0.03$), with the normotensive subjects again showing a steeper inverse relationship (slope $-0.12$ vs $-0.07$). In contrast, uncontrolled hypertensive subjects had no significant correlation ($P = 0.35$).

**Relationship Between Transfer Function Gain and CBFV Response to Standing**

To study the relationship between beat-to-beat cerebral blood flow regulation in the steady state and the ability to regulate cerebral blood flow during an orthostatic blood pressure change, we examined the correlation between the sitting transfer function gain and the change in CBFV during the sit to stand maneuver (Fig. 4). In the cardiac-frequency band, subjects demonstrated a significant inverse relationship between sitting cardiac gain and the change in CBFV during the sit to stand maneuver (slope $-11.2$, $R^2 = 0.25$, $P < 0.001$), such that higher gains were associated with greater flow velocity declines. A significant but weaker relationship was also seen when comparing sitting high-frequency gain with the change in CBFV during standing (slope $-7.5$, $R^2 = 0.16$, $P = 0.002$). In contrast, there was no significant correlation between sitting low-frequency gain and CBFV change (slope $-7.9$, $R^2 = 0.06$, $P = 0.06$). Although this relationship was almost significant, it was only able to account for 6% of the variance in the drop in CBFV, suggesting that sitting low-frequency gain is not a good predictor of cerebral flow changes with standing. Interestingly, standing low-frequency gain was a much better predictor (slope $-18.7$, $R^2 = 0.23$, $P < 0.001$) being able to account for 23% of the variance in the orthostatic drop in CBFV (data not shown).

**DISCUSSION**

This study provides three main findings. First, cerebral blood flow regulation appears to be well maintained in both controlled and uncontrolled elderly hypertensive subjects in response to a postural challenge. Second, reactivity to CO2 pressure was engaged. CBFV takes 1–2 s to respond after a sudden blood pressure decline (1). Because the time to nadir of blood pressure was 8 s in all groups (Table 3), this explanation seems unlikely.

Another possibility is that reductions in pressure resulted in spontaneous blood pressure changes, both aspects need to be examined.

Changes in posture are known to cause transient decreases in blood pressure (17, 30). Because previous work suggests that the lower limit of autoregulation is higher in uncontrolled hypertensive patients compared with well-controlled hypertensive or normotensive subjects (28), it is possible that orthostatic decreases in pressure, especially if greater in uncontrolled hypertensive subjects due to baroreflex impairment, could result in more severe decreases in cerebral blood flow if pressure falls below the lower limit of autoregulation. However, both our controlled and uncontrolled hypertensive subjects were better able to maintain CBFV than normotensive subjects, despite similar decreases in blood pressure with standing (Fig. 1). Previous work has found similar improved autoregulatory responses in younger hypertensive subjects (age $-49$ ± $14$ yr), both when moving from a squatting to standing position (30) and during head-up tilt (21).

One possible explanation for better maintenance of cerebral blood flow in hypertensive subjects is that decreases in blood pressure occurred more rapidly in the normotensive subjects, and thus autoregulatory mechanisms did not have time to engage. CBFV takes 1–2 s to respond after a sudden blood pressure decline (1). Because the time to nadir of blood pressure was $>8$ s in all groups (Table 3), this explanation seems unlikely.

Another possibility is that reductions in pressure resulted in normotensive subjects moving below the lower limit of autoregulation. Once below the lower limit of autoregulation, cerebral autoregulatory mechanisms are no longer able to engage, and thus flow falls linearly with pressure. Waldemar et
al. (31) found that in five of seven hypertensive patients (age 27–57 yr) the lower limit of autoregulation was within 14 mmHg of baseline blood pressures. In contrast, Strandgaard (28) found that in uncontrolled hypertensive subjects (age 44–64 yr) with baseline blood pressures of 145 ± 17 mmHg, the lower limit of autoregulation was 113 ± 17 mmHg, an ∼32-mmHg difference. On the basis of our previous work (17), we know that blood pressure decreases with standing in hypertensive elderly subjects are ∼26 mmHg. Thus it is possible that postural reductions in blood pressure could result in some subjects falling below the lower limit of autoregulation. However, if this were true, we would expect the recovery of CBFV to follow that of blood pressure (i.e., flow would passively increase with pressure). Comparison of time to nadir of flow (∼5 s) demonstrates that CBFV is increasing well before blood pressure begins to return to baseline levels. Similarly, the ARI was not different between groups, suggesting that autoregulation was intact during orthostasis (Table 3).

The better maintenance of cerebral blood flow could be the result of less severe postural hypocapnia because it is well known that postural hypocapnia results in reductions in cerebral blood flow (22). However, our hypertensive subjects tended to have a greater reduction in end-tidal CO₂ during standing than the normotensive subjects (Table 3). This greater hypocapnia should have resulted in greater cerebral hypoperfusion. Thus hypertensive subjects were maintaining cerebral blood flow despite greater postural hypocapnia. The reduced cerebrovascular reactivity may be partially responsible for this observation. Taken in totality, our data suggest that hypertensive subjects may in fact have better cerebral autoregulation than normotensive subjects.

To further study autoregulation, we examined the steady-state transfer function gain between blood pressure and CBFV velocity. In contrast to previous findings of similar transfer function gains between normotensive subjects and untreated hypertensive patients (7), we found that gains were reduced in the hypertensive patients. Previous research has suggested that gains in the low-frequency range (0.03–0.07 Hz) represent autoregulatory processes (20, 33). This is consistent with the idea that autoregulation requires several seconds to engage, and thus slow fluctuations in pressure should be attenuated in cerebral blood flow if autoregulation is intact. Our data demonstrate that uncontrolled hypertensive subjects had significantly lower gains that either controlled hypertensive subjects or normotensive subjects (Fig. 2). Similarly, gains in the high frequency range (0.07–0.15 Hz) were lower than normotensive subjects. These findings are also consistent with improved autoregulation in the uncontrolled hypertensive subjects compared with normotensive subjects.

Because transfer function gains at the cardiac frequency represent the transfer of blood pressure fluctuations to CBFV within the beat, we would expect gains in this frequency range to represent the passive transmission of pressure to flow because autoregulatory processes likely do not have sufficient time to respond. Surprisingly, both controlled and uncontrolled hypertensive subjects demonstrated significantly lower gains in this frequency range than normotensive subjects. Assuming hypertensive subjects had decreased compliance of their cerebrovascular bed, we would have expected increased gain reflecting greater passive transmission of pressure to flow. It is possible that this difference was due to differing vascular states in the three groups. Increases in cerebrovascular resistance could change the transduction characteristics of the vascular bed. However, if this were true, we would expect that all three groups would demonstrate similar correlations between cardiac frequency gain and CVR (i.e., changes in CVR would be correlated to changes in gain). This was only true for normotensive subjects who demonstrated a significantly increased cardiac gain with lower cerebrovascular resistance (Fig. 3). In contrast, both controlled and uncontrolled hypertensive subjects had reduced gains, regardless of associated CVR. These data suggest that, in normotensive subjects, transfer of pressure to flow within the beat is partially determined by cerebrovascular state, with dilated beds resulting in attenuated transmission (i.e., lower cardiac frequency gains) and constricted beds having greater transmission. In contrast, hypertensive subjects had similar cardiac frequency gains regardless of cerebrovascular state.

Another possible mechanism for these reduced gains could be reductions in stroke volume or cardiac output limiting cerebral blood flow. However, gains were reduced in the controlled and uncontrolled hypertensive subjects, even though controlled hypertensive subjects had similar heart rates and blood pressure to normotensive subjects during steady-state sitting and standing, suggesting similar cardiac outputs and stroke volumes. Thus these data suggest that changes in stroke volume and cardiac output are not likely the cause of reduced transfer function gains.

Taken together these data suggest that, in normotensive elderly, cerebrovascular tone had a direct effect not only on the passive transmission of pressure to flow but also on the attenuation of transmission of blood pressure fluctuations into cerebral blood flow (i.e., low-frequency gain). In contrast, both controlled and uncontrolled hypertensive subjects have reduced passive transmission of pressure to flow as well as better attenuation of blood pressure fluctuations transmission. Although it is unexpected that hypertensive subjects would have better attenuation of pressure fluctuations, one possible explanation is that hypertension has resulted in permanent remodelling of the cerebrovasculature.

Our laboratory’s previous work using a windkessel model to simulate this blood flow response to standing found that increased pulsatility in CBFV was associated with increased CVR and decreased compliance of the cerebrovascular bed (24). Conversely, one would expect that increases in compliance or distensibility would result in decreased CBFV pulsatility and attenuation of transmission of pressure to flow in the high-frequency range. However, it seems counterintuitive that hypertensive subjects would have increased compliance (i.e., less stiff cerebral vessels). Interestingly, previous work in animals has shown that cerebral arterioles hypertrophy and become more distensible with chronic hypertension (4). This increase in distensibility could result in greater attenuation of pulse pressure within the beat. Because we were unable to directly measure cerebral vessel distensibility in our subjects, it is unclear whether this mechanism can explain the differences in cardiac frequency gain.

Studies of cerebrovascular reactivity to CO₂ in elderly humans have produced conflicting results. Aging has been shown...
to either have no effect on cerebrovascular reactivity (11, 12) or to be associated with reduced reactivity (15, 17, 19, 23). One potential difficulty associated with assessing reactivity to CO2 is the inherent response of the cerebrovasculature to blood pressure changes. Increases in arterial CO2 may be associated with corresponding increases in blood pressure (Table 2). Because cerebral autoregulation operates to maintain cerebral blood flow relatively constant, as pressure increases, CVR will increase. In contrast, increasing arterial CO2 will cause cerebrovascular resistance to decrease. Thus, if the pressure increase during hypercapnia is not accounted for, the dilation associated with increased arterial CO2 will appear blunted. In fact, Edwards et al. (8, 9) recently reported that CO2 reactivity obtained from rapid two-breath increases in end-tidal CO2 without associated increases in pressure were more accurate than steady-state increases in CO2 with associated blood pressure increases.

By calculating the theoretical CVR necessary to maintain flow constant in the face of increasing pressure, we can determine the component of resistance change that was likely due solely to CO2 changes. Using this methodology we found that hypertensive subjects had reduced CO2 reactivity compared with normotensive subjects, despite normal pressure regulation. Reduced reactivity may have been adaptive in the hypertensive group, because they had greater postural hypocapnia. Thus reduced arterial CO2 during upright posture will produce less of a reduction in cerebral blood flow in these subjects.

Our data suggest that use of CO2 reactivity as an indicator of cerebral autoregulation may be inappropriate. Our findings are supported by several studies reporting that CO2 reactivity is maintained when pressure autoregulation is impaired (3, 6, 16, 18, 25, 27, 32).

One limitation of the TCD methodology used in our study is that CBFV rather than flow is measured. For velocity changes to be equivalent to flow changes, arterial diameter at the point of insonation must remain constant. Our laboratory has previously measured MCA diameter by magnetic resonance imaging combined with TCD assessment and found no change in artery diameter during stimuli such as lower body negative pressure or changes in end-tidal CO2 (26). Similarly, other work has found that changes in velocity significantly correlate with cerebral blood flow changes (13, 14).

Another inherent limitation with using both noninvasive blood pressure and ultrasound measures are inherent differences in the measured vs. actual values of ABP or cerebral blood flow, respectively. Whereas previous work has found that direct measures of a pressure waveform via arterial line in the brachial artery corresponded well with the finapres waveform in one subject (33), it is possible that Finapres-derived waveforms do not accurately reflect the pressure waveform in the MCA. Similarly, whereas mean arterial diameter within the beat does not appear to change, it is possible that pulsatile changes in diameter were different between groups. If diameter were to increase more in the uncontrolled hypertensive subjects, velocity increases would be attenuated even if cerebral blood flow were actually increasing significantly. Further work is required to determine whether differences in cardiac gain may be due to these issues.

**Perspective**

Our data demonstrate that cerebral autoregulation remains intact in elderly hypertensive subjects. In fact, transfer function gains were lower in hypertensive subjects, whether blood pressure was well controlled or uncontrolled with antihypertensive medication. Thus hypertensive subjects demonstrated better attenuation of blood pressure fluctuations into cerebral blood flow both within the beat (i.e., at the cardiac frequency) and in the low-frequency range (0.03–0.07 Hz). Despite a better pressure autoregulatory response, hypertensive subjects demonstrated reduced reactivity to CO2. Further work is required to determine the role of antihypertensive treatment in these cerebrovascular changes. However, it appears as though otherwise healthy hypertensive elderly patients can safely undergo blood pressure reduction, without concern for cerebral hypoperfusion.

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