Predicting cerebral blood flow response to orthostatic stress from resting dynamics: effects of healthy aging

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Am J Physiol Regulatory Integrative Comp Physiol 281: R716–R722, 2001.—The transfer function relating arterial pressure (AP) to cerebral blood flow velocity (CBFV) during resting conditions has been used to predict the CBFV response to hypotension. We hypothesized that this approach could predict the CBFV response to posture change in elderly individuals if impaired autoregulation allowed changes in AP to be passively transferred to CBFV. AP (Finapres) and CBFV (middle cerebral artery transcranial Doppler) were measured in 10 healthy young (age 24 ± 1 yr) and 10 healthy elderly (age 72 ± 3 yr) subjects during 5 min of quiet sitting and 1 min of active standing while breathing was paced at 0.25 Hz. Transfer functions between AP and CBFV changes during sitting were estimated from each full waveform in both low-frequency (LF; 0.05–0.2 Hz) and heartbeat-frequency (HBF; 0.7–1.4 Hz) ranges. The impulse-response function was used to compute changes in CBFV during posture change. The LF transfer function did not predict orthostatic changes in CBFV in either group, suggesting normal cerebral autoregulation. In the HBF range, the prediction was high in elderly (R = 0.65 ± 0.23) but not young subjects (R = 0.19 ± 0.35; P < 0.003, young vs. elderly). Thus rapidly acting regulatory mechanisms that reduce the transmission of beat-to-beat changes in AP to CBFV may be engaged during posture change in young but not elderly subjects. autoregulation; transfer function; hypotension; pulsatility; vascular stiffness

RECENT STUDIES USING TRANSFER function analyses have shown that the relationship between arterial pressure (AP) and transcranial Doppler-derived cerebral blood flow velocity (CBFV) oscillations during resting conditions can be used to predict the CBFV response to a sudden blood pressure reduction during leg-cuff deflation (14, 20). This analytic approach may be particularly useful in elderly patients if it can identify those at risk of cerebral hypoperfusion during orthostatic hypotension. If elderly people have impairments in cerebral autoregulation that allow changes in AP to be passively transferred to CBFV, then the resting transfer function relating these signals may be a particularly good predictor of the CBFV response to orthostasis in these individuals.

Normal cerebral autoregulation acts like a high-pass filter (6) and blunts the transfer of low-frequency (LF) AP oscillations (<0.2 Hz) onto CBFV. Therefore, we hypothesized that the transfer function describing the dynamic relationship between AP and CBFV would yield poor predictions of the LF CBFV response to posture change in healthy young subjects. Moreover, in the higher frequency range of the cardiac cycle (0.7–1.4 Hz), where cerebral autoregulatory mechanisms are presumably not operative, we postulated that the transfer function would provide a good prediction of the CBFV response to orthostasis. Accordingly, in this study, we computed the transfer function between resting AP and CBFV, used the corresponding impulse-response function to predict the CBFV response to sudden pressure changes during standing, and compared the predicted and observed responses between groups of healthy young and healthy elderly subjects.

METHODS

This study evaluated data obtained from 10 healthy young subjects (age 24 ± 1 yr) and 10 healthy elderly subjects (age 72 ± 3 yr), who have been described elsewhere (9). Subjects were recruited from among laboratory personnel, volunteers responding to newspaper advertisements, and members of the Harvard Cooperative Program on Aging subject registry. The subjects were carefully screened with a medical history, physical examination, and electrocardiogram (ECG) to exclude acute and chronic medical conditions and focal neurologic abnormalities or carotid bruits. The presence of carotid and/or cerebral vascular disease was excluded by the absence of stroke or transient ischemic attack (TIA) by previous history. No subjects took medications or smoked cigarettes. Subjects were also evaluated for an adequate temporal window for insonation of the middle cerebral artery (MCA). The study was approved by the Hebrew Rehabilitation Center for

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Aged (HRCA) hospital institutional review board, and all subjects provided informed consent.

Experimental Protocol

Instrumentation. Subjects reported to the Cardiovascular Laboratory at the HRCA in the postabsorptive state, at least 2 h after their last meal. Three ECG leads were attached to the chest for measurement of the R-R interval, and the finger cuff of a photoplethysmographic noninvasive AP monitor (Finapres, Ohmeda, CO) was placed on the middle finger of the right hand to measure beat-to-beat AP. The hand was supported by a sling at the level of the right atrium to eliminate hydrostatic pressure effects. Finapres measurements were initially corroborated by standard measurements of AP with an oscillometric cuff on the upper arm (Dinamap, Critikon, FL). To assess breathing frequency and tidal volume during the protocol, respiration was measured continuously with an inductive plethysmograph (Respirtrac, Ambulatory Monitoring, NY) attached to two elastic respiratory transducer bands, one around the midchest and the other around the abdomen.

Transcranial Doppler (TCD) ultrasonography was used to measure the changes in MCA blood flow velocity in response to beat-to-beat AP changes during sitting and standing. On the basis of previous studies showing no changes in MCA diameter during moderate changes in AP induced by orthostatic stress (16) and other stimuli (11), we assumed that changes in CBFV reflected relative changes in cerebral blood flow.

The 2-MHz probe of a Nicolet Companion portable Doppler system was placed over the temporal bone just above the zygomatic arch between the frontal process and the front of the ear to insonate the MCA. The MCA-CBFV signal was identified according to the criteria of Aaslid et al. (1) and recorded at a depth of 50–65 mm. Once an optimal signal was obtained, the probe was strapped to the subject’s head and locked in position with a Mueller-Moll probe fixation device. The envelope of the velocity waveform, derived from a fast-Fourier analysis of the Doppler frequency signal, was digitized at 500 Hz; displayed simultaneously with the blood pressure, ECG, and respiration signals; and stored with these signals in the computer for off-line analysis.

Standing Protocol

After subjects were instrumented, they sat in a straight-backed chair with their legs elevated at 90 degrees on a stool in front of them. Subjects rested in the sitting position for 5 min, then stood in an upright position for 1 min. The initiation of standing was timed from the moment both feet touched the floor. Respiration was paced at 0.25 Hz during data collection to isolate the respiratory frequency cycle and maintain a constant minute ventilation. Although it is possible that cerebral perfusion during standing can be influenced by changes in intracranial pressure, our sit-to-stand procedure was designed to keep the head in the same position to avoid different gravitational effects on intracranial pressure.

Data Processing and Analysis

Data were displayed and digitized in real time at 500 Hz with commercially available data-acquisition software (Windaq, Dataq Instruments) on a personal computer (NEC Pentium 90 MHz). The transfer function analysis was performed on the AP and CBFV time series (full waveform) (8).

To compute power spectra for the sitting AP and CBFV time series, the Welch algorithm for averaging periodograms was used (2, 17). The time series were low-pass filtered with a cut-off frequency of 4 Hz (Fig. 1) and then divided into six equal overlapping segments. Each segment was detrended, Hanning-windowed, and fast-Fourier transformed. The periodograms were averaged to produce the spectrum estimate. The calculations were carried out using MATLAB software.

Transfer function analysis quantifies the extent to which the input signal, AP, is reflected in the output signal, CBFV. Knowledge about the transfer function also enables one to predict the output for any given input. The transfer function $H(f)$ is computed as follows (15)

$$H(f) = \frac{S_{pv}(f)}{S_{pp}(f)}$$

where $S_{pv}$ is the autospectrum of changes in AP, $S_{pp}$ is the cross-spectrum between AP and CBFV, and $f$ is frequency.

The transfer function magnitude $|H(f)|$ and phase spectrum $\phi(f)$ were expressed as the real $[H_R(f)]$ and imaginary parts $[H_I(f)]$ of the complex transfer function as

$$|H(f)| = (H_R(f)^2 + H_I(f)^2)^{1/2}$$

$$\phi(f) = \arctan[H_I(f)/H_R(f)]$$

The magnitude reflects the degree to which AP oscillations at a discrete frequency become manifest in CBFV oscillations, i.e., it provides a measure of the gain between AP and CBFV.

For each subject, the coherence $MSC(f)$ between AP and CBFV signals was calculated across all frequencies from 0 to 1.5 Hz using the following formula

$$MSC(f) = \frac{|S_{pv}(f)|^2}{S_{pp}(f)S_{pv}(f)}$$

where $S_{pv}$ is the autospectrum of changes in CBFV. The coherence is a statistical measure of the linearity of the input/output relationship and thus the reliability of the transfer function.

All but 1 of the 20 subjects had >10% variability in the mean AP signal, and all but two subjects had coherence values above 0.5 in the frequency ranges of interest, which were considered necessary criteria for applying the transfer function analysis (13). Because exclusion of the two subjects not meeting these criteria did not alter the results, their data are included in the analysis.

To predict the changes in CBFV during posture change, the AP during posture change was convolved with the impulse-response function obtained as the inverse Fourier transform of the transfer function estimated under sitting steady-state conditions. The predicted changes in CBFV were then compared with the measured changes in CBFV using Pearson correlation coefficients ($R$), which give the degree of prediction (7).

We tested the reliability of the impulse-response analysis by deriving the transfer function from the first 150 s of sitting steady-state data, then we used it to predict the next 45 s of sitting steady-state CBFV. The average correlations between predicted and actual data were 0.87 for elderly and 0.80 for young subjects.

To study the effect of different rates of change of AP on our ability to predict change of CBFV, we computed impulse responses over different physiologic frequency ranges. From previous studies using transfer-function approaches (8, 9, 14, 15, 20, 21), it appears that cerebral autoregulation operates most effectively (i.e., the transfer gain between AP and CBFV is lowest) from 0 to 0.05 Hz, then gradually becomes ineffective (i.e., the gain gradually increases) from 0.05 to 0.3 Hz. Cerebral autoregulation is not known to operate over higher frequency ranges. Separate analyses were carried out over the following frequency ranges: 1) LF from 0.05 to 0.2 Hz (corresponding to cerebral autoregulation), 2) heartbeat frequency (HBF) from 0.7 to 1.4 Hz (corresponding to the heart rate), and 3) both LF and HBF.

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above frequency regions were selected because only these frequency ranges (except 0.2–0.3 Hz) satisfied the conditions of sufficient power in AP and CBFV signals and an average coherence >0.5. The frequency range between 0.2 and 0.3 Hz was excluded to avoid the effects of paced respiration. To obtain the impulse responses, the transfer function was filtered to isolate the LF, HBF, or both LF and HBF ranges, then the inverse Fourier transform was applied. The results from the young and elderly subjects were compared using t-tests. \( P < 0.05 \) was considered statistically significant. All data are reported as means ± SE. To account for the possibility of nonnormal distributions for some of the data, a nonparametric Wilcoxon rank-sum test was also performed (10). The \( P \) values obtained from the t-test and Wilcoxon rank-sum test did not differ significantly; therefore, the t-test results are presented.

RESULTS

Subject Hemodynamic Characteristics

Basal sitting conditions. There was no significant difference in systolic blood pressure (116 ± 4 vs. 123 ± 5 mmHg), diastolic blood pressure (69 ± 3 vs. 68 ± 4 mmHg), or heart rate (69 ± 3 vs. 62 ± 1 beats/min), respectively, between young and elderly groups. There was no significant difference in mean AP (MAP) between young (94.1 ± 2.2 mmHg) and elderly (87.2 ± 2.9 mmHg) subjects, but the mean CBF velocity (MBCFV) was significantly higher in the young subjects (52.2 ± 2.2 cm/s) compared with elderly subjects (35.5 ± 2.3 cm/s; \( P < 0.05 \)).

The AP and CBFV power spectra during the 5-min sitting period are shown for a young subject in Fig. 1 and summarized for the two groups of subjects in Table 1. The most significant fluctuation in the AP and CBFV signals is contributed by the heartbeat (HBF region), which is represented by a power band located from 0.7 to 1.4 Hz for young subjects and from 1.05 to 1.26 Hz for elderly subjects. However, some concentrated power in the LF range 0.05–0.2 Hz also could be identified (Fig. 1). The average AP and CBFV power tended to be greater for young subjects in the LF range

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Fig. 1. Time series of arterial pressure (AP) and cerebral blood flow velocity (CBFV) before and after posture change (the beginning of posture change is indicated by an arrow) for a single young subject. AP and CBFV frequency spectra and the coherence, gain, and phase relating these signals are shown for the 5-min period of sitting for the same subject. Both AP and CBFV have significant power in low-frequency (0.05–0.2 Hz) and heartbeat-frequency (0.7–1.4 Hz) ranges. The power near 0.25 Hz is due to paced respiration. Inset: power spectrum for the low-frequency range for clarity.
but greater for elderly subjects in the HBF range (Table 1). There were no differences in coherence or gain in either frequency range for the two groups of subjects.

Response to standing. At the onset of standing, MAP fell by 24.3 ± 2.1 mmHg in the young subjects and by 21.0 ± 2.2 mmHg in the elderly subjects; this decline was more rapid in the young (6.8 ± 1.9 s) compared with the elderly (10.4 ± 3.0 s; Table 2). The rate of decline was significantly different between groups (P < 0.004). The MAP recovery time (time taken to reach steady state from nadir) was also significantly less in the young subjects compared with the elderly subjects (P < 0.004). The fall in MCBFV was greater in the young (−10.1 ± 1.1 cm/s) than in elderly (−5.3 ± 1.2 cm/s) subjects (P < 0.05), but the rate of fall was not significantly different between the groups (Table 2). The MCBFV recovery time was greater in the elderly (11.1 ± 2.1 s) than in the young subjects (6.0 ± 1.3 s; P < 0.00001).

For the young subjects (e.g., see Fig. 1), MCBFV fell immediately after posture change, then overshoot before returning to baseline. In addition, pulsatility widened; that is, systolic CBFV increased (by 14.1 ± 1.8 cm/s) and diastolic CBFV decreased (by −23.3 ± 1.3 cm/s). These high-frequency changes in beat-to-beat pulsatility were less pronounced in the elderly, where systolic CBFV increased by only 7.4 ± 1.1 cm/s and diastolic CBFV decreased by −16.9 ± 1.2 cm/s (Fig. 2). The widening of pulsatility during standing was also accompanied by a greater increase in heart rate in the young (26 ± 1) compared with the elderly (11 ± 1; P < 0.000001). Because the LF and HBF responses differed between groups, we examined these frequency ranges separately.

Predicting the CBFV Response to Posture Change

LF response (0.05–0.2 Hz). The coherence and gain in the LF range during steady-state sitting conditions for both young and elderly subjects are shown in Table 3. Average coherence and transfer gain, respectively, were similar for both groups (Table 3). The LF impulse-response function was convolved with the observed AP during posture change to obtain the predicted CBFV during posture change. In this frequency range, the mean observed and predicted CBFVs were used in the calculation of the Pearson correlation coefficients. For both young and elderly groups, the correlations between the observed and predicted CBFV were poor and not statistically significant (Table 3).

HBF response (0.7–1.4 Hz). All subjects demonstrated higher coherence and similar gain between AP and CBFV in the HBF range (Table 3) compared with the LF range (Table 3). The coherence and gain in the HBF range were significantly greater in the young (P < 0.000001). The coherence and gain were higher in the young group compared with the elderly group (Table 3).

Table 1. Average AP power, CBFV power, coherence, and gain in LF and HBF regions for young and elderly groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>0.05–0.2 Hz (LF)</th>
<th>0.7–1.4 Hz (HBF)</th>
<th>P value (&lt;)</th>
<th>P value (&lt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP power</td>
<td>1.05 ± 0.59</td>
<td>0.59 ± 0.52</td>
<td>0.08</td>
<td>5.49 ± 1.46</td>
</tr>
<tr>
<td>CBFV power</td>
<td>0.59 ± 0.32</td>
<td>0.34 ± 0.33</td>
<td>0.11</td>
<td>3.72 ± 1.41</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.65 ± 0.14</td>
<td>0.64 ± 0.17</td>
<td>0.92</td>
<td>0.92 ± 0.07</td>
</tr>
<tr>
<td>Gain</td>
<td>0.73 ± 0.23</td>
<td>0.73 ± 0.24</td>
<td>0.99</td>
<td>0.79 ± 0.20</td>
</tr>
</tbody>
</table>

Table 2. ∆ in heart rate, MAP, and MCBFV and average time taken (in s) for MAP and MCBFV to reach their nadir and to recover to steady state from the nadir during standing for young and elderly subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Young</th>
<th>Elderly</th>
<th>P Value (&lt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ Heart rate</td>
<td>26 ± 1</td>
<td>11 ± 1</td>
<td>0.000001</td>
</tr>
<tr>
<td>∆ MAP</td>
<td>−24.3 ± 2.1</td>
<td>−21.0 ± 2.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Time to MAP nadir</td>
<td>6.8 ± 1.9</td>
<td>10.4 ± 3.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Time to MAP recovery</td>
<td>8.2 ± 1.6</td>
<td>10.6 ± 3.0</td>
<td>0.004</td>
</tr>
<tr>
<td>MCBFV</td>
<td>−10.1 ± 1.1</td>
<td>−5.3 ± 1.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Time to MCBFV nadir</td>
<td>5.9 ± 1.8</td>
<td>8.5 ± 4.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Time to MCBFV recovery</td>
<td>6.0 ± 1.3</td>
<td>11.1 ± 2.1</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

Values are means ± SE. P values were obtained by t-test comparing young and elderly subjects. ∆, Average change; MAP, mean AP; MCBFV, mean CBFV.
there was no significant difference in coherence or gain, respectively, between the two groups. The 0.7- to 1.4-Hz impulse-response function successfully predicted the high-frequency response to posture change in elderly subjects ($R = 0.65 \pm 0.23$) but not in the young ($R = 0.19 \pm 0.35$). There was a significant difference in the degree of prediction ($R^2$) between the groups ($P < 0.003$, Table 3).

**Frequency range 0.05–0.2 and 0.7–1.4 Hz.** The impulse-response function containing frequency ranges 0.05–0.2 and 0.7–1.4 Hz was also used to predict CBFV during posture change. In this frequency range, the prediction was higher for the elderly subjects ($R = 0.49 \pm 0.26$) than for the young subjects ($R = 0.18 \pm 0.29$), and the difference between the groups was statistically significant ($P < 0.03$). An example of the predicted and measured CBFV response for an elderly subject is shown in Fig. 3.

**DISCUSSION**

The results of this study elucidate several important aspects of pressure-flow relationships in the MCA circulation and their alterations in healthy elderly subjects. First, with the use of transfer-function analyses, it is evident in young subjects that the linear relationship between AP and MCA blood flow velocity during sitting steady-state conditions is altered during orthostatic stress across a wide range of physiological frequencies. This finding suggests that various regulatory responses to transient hypotension during standing blunt the transmission of AP changes onto cerebral blood flow. Moreover, it suggests that the mechanisms governing pressure-flow relationships during basal conditions are different from those engaged during a
perturbation such as standing. The mechanisms called into play during active standing include LF (<0.2 Hz) vascular responses (18) in the peripheral cerebral circulation (e.g., autoregulatory myogenic vasodilatation) and systemic circulation (vasoconstriction) as well as HBF (0.7–1.4 Hz) systemic hemodynamic responses [e.g., cardiovagal baroreflexes that increase heart rate (5)].

Second, our analysis suggests that in healthy elderly subjects, LF cerebral autoregulation remains intact, but higher frequency regulatory mechanisms affecting cerebral blood flow velocity are altered. Thus HBF-AP oscillations are passively transmitted to cerebral blood flow in supine and upright positions without intervening adaptive responses. This finding may reflect vascular stiffening in the older subjects, leading to more passive transmission of pressure onto CBFV. Furthermore, the increase in cerebral blood flow pulsatility (4) seen in young subjects during posture change (Fig. 1) may reflect rapid circulatory adjustments in the cerebral vasculature, which loses compliance with advancing age. The increased systolic pulse-wave amplification observed in the young group may be due to greater cardioacceleration (3, 12). Elderly subjects have impaired cardioacceleration during orthostatic stress that may be responsible for diminished pulse amplification (5).

Third, our study suggests that a linear model may not be appropriate to predict changes in cerebral blood flow during orthostatic stress. The simple linear relationship between pressure and flow that describes the resting state may not be adequate to describe the multiple interacting control mechanisms that maintain blood pressure and cerebral blood flow during posture change.

The results of our transfer-function analysis in the LF range may appear to conflict with the work of Zhang et al. (20) and Panerai et al. (14), who reported good correlations between measured and predicted CBFV after thigh-cuff deflation in healthy subjects. This discrepancy may be due to a different stimulus used in our study to induce transient changes in AP. In our study, posture change was used, rather than thigh-cuff deflation, to reproduce a hypotensive stress encountered in everyday life. An important difference lies in the time taken for AP to reach its nadir during these two hypotensive stresses. With the thigh-cuff method, AP appeared to reach its nadir in <5 s (20), whereas after posture change, AP reaches its nadir in 7–10 s (Table 2). Because AP reached its nadir over a longer time interval in our protocol, there was ample time for autoregulation to blunt the transmission of AP changes onto CBFV. Previous studies using the thigh-cuff method may have achieved such rapid blood pressure changes that autoregulatory mechanisms were not engaged. Furthermore, in our study, impulse-response functions were computed only in physiological frequency ranges where there was adequate power and coherence between the AP and CBFV signals. These ranges are readily apparent in the time-series data for these signals (Figs. 1–3), where LF trends and beat-to-beat oscillations are visible.

In conclusion, the present study suggests that although both young and elderly subjects have intact cerebral autoregulatory mechanisms that reduce the transmission of LF AP changes onto CBFV during posture change, there is a deterioration of HBF regulatory mechanisms in the elderly. This loss of rapid adaptive responses to posture change may make elderly individuals vulnerable to transient cerebral hypoperfusion during beat-to-beat fluctuations in AP. A clinical study of elderly patients with cerebrovascular disease and healthy controls showed a relationship between increased short-term blood pressure variability determined by 24-h monitoring and vascular dementia (19). This lends support to the notion that short-term fluctuations in blood pressure may predispose elderly individuals to cerebral ischemia.

**Perspectives**

With the recent development of transcranial Doppler technology that can record beat-to-beat CBFV, cerebral autoregulation has been viewed as a dynamic process acting like a high-pass filter (6). This dynamic model of autoregulation predicts that slow LF fluctuations in blood pressure (<0.2 Hz) would be buffered by the dilation or constriction of cerebral arterioles in response to reductions or elevations, respectively, in perfusion pressure. Consistent with this model, the transfer function relating LF blood pressure and CBF signals during supine rest cannot predict the CBF response to mild orthostatic hypotension during 6–10 s of standing. In contrast, rapid changes in blood pressure occurring over the period of one heartbeat would produce similar changes in cerebral perfusion, unless other regulatory processes intervened. Our results provide new evidence that rapidly acting regulatory processes do, in fact, alter the transmission of beat-to-beat blood pressure changes to CBF in healthy young but not elderly subjects. This high-frequency regulation is evident in the widening of CBF pulsatility, but not pulse pressure, after standing in young subjects. Because an increase in pulsatility may represent increased pulse-wave reflection due to downstream vasoconstriction (12), it is possible that young subjects experience an initial increase in cerebral vascular resistance followed by autoregulatory vasodilation in response to orthostatic hypotension. Elderly subjects with greater cerebral vascular resistance at the outset (9) may lack vasoconstrictor reserve but retain their ability to vasodilate during autoregulation. This possibility requires further study.

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