Increases in cerebrovascular impedance in older adults

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Zhu Y, Tseng BY, Shibata S, Levine BD, Zhang R. Increases in cerebrovascular impedance in older adults. J Appl Physiol 111: 376–381, 2011. First published May 26, 2011; doi:10.1152/japplphysiol.01418.2010.—This study explored a novel method for measuring cerebrovascular impedance to quantify the relationship between pulsatile changes in cerebral blood flow (CBF) and arterial pressure. Arterial pressure in the internal or common carotid artery (applanation tonometry), CBF velocity in the middle cerebral artery (transcranial Doppler), and end-tidal CO2 (capnography) were measured in six young (28 ± 4 yr) and nine elderly subjects (70 ± 6 yr). Transfer function method was used to estimate cerebrovascular impedance. Under supine resting conditions, CBF velocity was reduced in the elderly despite the fact that they had higher arterial pressure than young subjects. As expected, cerebrovascular resistance index was increased in the elderly. In both young and elderly subjects, impedance modulus was reduced gradually in the frequency range of 0.78–8 Hz. Phase was negative in the range of 0.78–4.3 Hz and fluctuated at high frequencies. Compared with the young, impedance modulus increased by 38% in the elderly in the range of 0.78–2 Hz and by 39% in the range of 2–4 Hz (P < 0.05). Moreover, increases in impedance were correlated with reductions in CBF velocity. Collectively, these findings demonstrate the feasibility of assessing cerebrovascular impedance using the noninvasive method developed in this study. The estimated impedance modulus and phase are similar to those observed in the systemic circulation and other vascular beds. Moreover, increases in impedance in the elderly suggest that arterial stiffening, besides changes in cerebrovascular resistance, contributes to reduction in CBF with age.

cerebral blood flow; aging; vascular impedance; transcranial Doppler; Fourier analysis

HUMAN CIRCULATION IS DYNAMIC IN NATURE because of the intermittent injection of blood from the heart into the circulation, which results in pulsatile changes in arterial pressure and blood flow. However, so far, most studies of cerebral blood flow (CBF) have been conducted under “steady-state” conditions due to limitations in methods for measuring CBF with high temporal resolution (25).

The recent development of transcranial Doppler (TCD) can be used to measure pulsatile changes in CBF velocity (CBFV) in the basal cerebral arteries with a high temporal resolution (~10 ms) (1). Assuming that the radius of insonated cerebral arteries remains constant, changes in CBFV are equal to changes in blood flow. Furthermore, advances in arterial applanation tonometry can now be used to measure pulsatile changes in arterial pressure noninvasively in the carotid artery as a surrogate for cerebral arterial pressure (17). Collectively, these developments in technology have provided the needed tools to study the dynamic nature of the cerebral circulation at time scales of less than a cardiac cycle.

The relationship between pulsatile changes in blood flow and arterial pressure is determined mainly by vascular impedance (22, 27). Notably, in differences from vascular resistance, which is determined by mean blood flow and pressure, vascular impedance is defined in the frequency domain and is influenced not only by vascular resistance but also by arterial stiffness, inertia of blood flow, and pressure wave reflections (22, 27). Assessment of vascular impedance is essential (22) for our understanding of cardiovascular hemodynamics under normal and diseased conditions (21).

Most studies observed that brain perfusion was reduced in the elderly (4, 14). However, the underlying mechanisms are not completely understood. Reduction in cerebral blood flow with aging has been related to a decreased brain metabolic rate or cerebrovascular dysfunction manifested by arterial stiffening and/or endothelial dysfunction (12, 18).

The purpose of this study was to develop a noninvasive method to measure cerebrovascular impedance to quantify the relationship between pulsatile changes in CBF and arterial pressure. We hypothesized that the estimated cerebrovascular impedance modulus and phase would be similar to those observed in the systemic circulation and other peripheral vascular beds. Furthermore, we hypothesized that cerebrovascular impedance would be increased in older adults, and these changes would be correlated with a reduction in CBFV.

METHODS

Subjects. Six healthy young subjects (3 women) and nine elderly subjects (7 women) participated in this study. All subjects were carefully screened for cardiovascular and cerebrovascular diseases, diabetes, and hypertension with a detailed medical history and a physical examination, including a 12-lead electrocardiogram (ECG). High resolution carotid ultrasonography was performed to exclude moderate to severe stenosis (>50%). All subjects signed an informed consent form approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and the Presbyterian Hospital of Dallas.

Instrumentation. The ECG was recorded using a three-lead system (Hewlett-Packard). Intermittent arterial pressure was measured in the arm using electrophysmographonanography (Suntech). End-tidal CO2 (ETCO2) and breathing frequency were monitored with a nasal cannula using capnography (Cappogard; Novametrix). The carotid and brachial pressure waveforms were obtained from the right internal (ICA) or common carotid (CCA) and the brachial artery, respectively, using applanation tonometry (SphygmoCor 8.0; ATCor Medical). During these measurements, the pressure sensor was placed directly and pressed slightly on the arteries at a location where a strong pulse was felt, and the site was well supported by a bone structure (28). CBF velocity was measured ipsilaterally in the middle cerebral artery (MCA) using TCD ultrasonography (Multi-Dop X2; DWL). A 2-MHz Doppler probe was placed over the temporal window and fixed at a constant angle with a probe holder (Spencer Technologies). Doppler
signal sampling depth was between 42 and 55 cm, and the angle of insonation was adjusted to optimize the signal quality according to standard procedures (1). All signals were stored on a computer using a commercial software package for data acquisition, with a sampling frequency of 200 Hz (Biopac Systems).

**Experimental procedures.** Experiments were performed in an environmentally controlled laboratory with an ambient temperature of 22°C. Subjects refrained from caffeinated beverages or alcohol ≥24 h before the study. After the subject had rested in the supine position for ≥10 min, intermittent cuff arterial pressure was measured repeatedly three times, and these measurements were averaged to obtain systolic, diastolic, and mean arterial pressure. Then, stable carotid artery and three times, and these measurements were averaged to obtain systolic, diastolic, and mean arterial pressure. Then, stable carotid artery and brachial artery pressure waveforms were recorded continuously, using applanation tonometry each for ≥10 s, with simultaneous measurement of CBF velocity, ECG, and ETCO₂. During these measurements, subjects were instructed to breathe normally and to avoid body movement and swallow maneuvers that may have affected signal acquisition. The pressure and CBF velocity waveforms were inspected visually to obtain stable and high-quality data and to exclude those with artifacts.

**Data analysis.** The pressure waveforms measured with applanation tonometry in the carotid artery were calibrated to the brachial arterial pressure according the recommended procedures (13). Briefly, the systolic and diastolic pressures measured with an electrosphygmonanometer in the upper arm were assigned to the peaks and troughs of the pressure waveforms measured with the tonometry in the brachial artery. The calibrated brachial pressure waveforms were integrated to obtain mean blood pressure. The carotid arterial pressure waveforms were calibrated by assuming that the mean and diastolic pressures of the carotid artery were equal to those of brachial arterial pressure (13, 17).

Steady-state heart rate, brachial and carotid arterial pressure, and CBF velocity were obtained as the average of beat-by-beat values. ETCO₂ was obtained as the average of breath-by-breath values. Cerebrovascular resistance index was calculated as a ratio of mean carotid arterial pressure (CABP) to mean CBFV [cerebrovascular resistance index (CVRI) = CABP/CBFV].

Fourier analysis was used to obtain harmonic components of the CABP and CBFV (Fig. 1). A transfer function method was used to estimate cerebrovascular impedance from pulsatile changes in CBFV and CABP (2). For impedance calculation, changes in CBFV were used as an “input,” whereas changes in arterial pressure were used as an “output” signal. Thus, the estimated impedance reflects mainly the vascular load distal to the site of pressure and flow measurement and may also account for the inertia of blood flow and/or pressure wave reflections (24). Auto-spectra and cross-spectra of CBF velocity and CABP were estimated using the Welch algorithm (29). Briefly, time series of CBFV and CABP waveforms were resampled at 100 Hz, and the mean values of time series were removed. Then, these data were subdivided into 256 point segments (2.56 s), with 50% overlap for spectral estimation. To reduce potential effects of including fractional cardiac cycles in these data segments on spectral estimation, each data segment was multiplied by a Hamming window prior to the periodogram estimation and average (19). This process resulted in a spectral resolution of ~0.39 Hz for impedance estimation.

The modulus of cerebrovascular impedance was obtained to quantify the magnitude of the relationship between pulsatile changes in CBFV and arterial pressure. The estimated phase was used to quantify the temporal relationship between these two variables. Of note, the estimated phase was corrected for a potential influence of pressure wave propagations from the internal or common carotid artery to the middle cerebral artery where CBFV was obtained, and the correction was based on a measured pulse wave velocity (~12 m/s) and an estimated distance of ~10 cm in a previous study (9). Furthermore, coherence function was estimated to assess the linear relationship between changes in CBFV and arterial pressure.

For statistical analysis, the impedance modulus, phase, and coherence were averaged for each of 2-Hz intervals from 0.78 to 8 Hz, where most of the energy of signals was contained (Fig. 1). Of note, the first frequency interval used was from 0.78 to 2 Hz to highlight the changes associated with the fundamental harmonics related to the resting heart rate (Fig. 1).

Statistics analysis. Unpaired t-tests were performed for comparisons of steady-state hemodynamic data between the young and elderly.

![Fig. 1. Left: time series of cerebral blood flow velocity (CBFV) and carotid arterial pressure (CABP) from a young subject. Right: spectra of CBFV and CABP. Note that the first harmonic of CBFV and CABP corresponding to the resting heart rate has the highest value and that most energy of harmonic oscillations is contained in the first 5–8 harmonics. Similar results were observed in all subjects.]()
RESULTS

All subjects were healthy except for one elderly subject who had mild hypertension (148/75 mmHg). The data from this individual were included because all values obtained were within one standard deviation of those obtained from other subjects. The ranges of systolic and diastolic pressure for the elderly were 95–148 and 59–80 mmHg, respectively. Demographic characteristics of participants are shown in Table 1. Compared with young subjects, systolic, diastolic, mean, and pulse CBF velocities were all reduced in the elderly despite the fact that they had higher diastolic and mean arterial pressure (Table 1). As expected, the cerebrovascular resistance index was increased. No changes in ETCO2 were observed between the groups.

Fourier analysis of pulsatile changes in CBFV and CABP showed that most of energy of these variables was contained in the first five to eight harmonics <10 Hz (Fig. 1). These were observed consistently in all subjects.

In both young and elderly subjects, the impedance modulus was reduced gradually from 0.78 to 8 Hz. Phase was negative in the range from 0.78 to 4.3 Hz (zero-crossing at 4.3 Hz) and fluctuated at high frequencies (Fig. 2). When comparisons were made between the groups, impedance modulus in the elderly was greater by 38% in the frequency range of 0.78–2 Hz and by 39% in the range of 2–4 Hz relative to young subjects ($P < 0.05$). Of note, with frequency extending to zero, the impedance modulus approaches CVRI, which was also greater in the elderly (Fig. 2 and Table 2). A trend toward increases in impedance modulus at high frequencies >4 Hz also was observed in the elderly (Fig. 2 and Table 2). Phase did not change between the two groups.

Coherence function was close to 1 in young subjects in the frequency range of 0.78–6 Hz (Fig. 2). Coherence was reduced to $\approx$4 and 7 Hz in the elderly (Fig. 2 and Table 2). Finally, reductions in systolic and diastolic CBFV were correlated with increases in cerebrovascular impedance in the elderly in the frequency range of 0.78–6 Hz (Fig. 3).

DISCUSSION

This is the first study of cerebrovascular impedance based on transfer function analysis of pulsatile changes in CBF velocity and carotid arterial pressure in young and older adults. The primary findings are threefold. First, we demonstrated the feasibility of assessing cerebrovascular impedance using the method developed in this study. Second, we found that the estimated
impedance modulus and phase were similar to those observed in the systemic circulation and other peripheral vascular beds. Finally, cerebrovascular impedance was increased in the elderly, which was correlated with reductions in CBF velocity. In the following, we will discuss the methodological issues for measuring vascular impedance and the potential mechanisms for increases in cerebrovascular impedance in older adults as well as the clinical perspective of this study.

Measurement of cerebrovascular impedance. Different types of vascular impedance have been defined according to the model used to describe the pressure-flow relationship of a given vascular bed (22). However, the term “vascular impedance” usually refers to vascular input impedance, which quantifies the pressure-flow relationship at the input site of a given vascular bed. Ideally, changes in pressure and blood flow should be measured simultaneously and at the same site to assess input impedance.

In this study, TCD was used to measure pulsatile changes in CBF velocity in the MCA. The potential limitations are that CBF velocity rather than volumetric blood flow was measured for the assessment of cerebrovascular impedance. Changes in CBF velocity are equal to changes in blood flow only if the MCA diameter remains unchanged. In this regard, if the diameter of MCA in the elderly was smaller than that in the young, as suggested in a previous study (7), increases in cerebrovascular impedance in the elderly may be underestimated if volumetric blood flow was used for impedance calculation. However, this possibility would strengthen rather than weaken the observation of this study.

Furthermore, applanation tonometry was used to measure pulsatile changes in arterial pressure in the carotid artery as a surrogate for cerebral arterial pressure. It must be highlighted that measurement of carotid arterial pressure using tonometry is not likely to be a trivial task (23). The operator must be well

Table 2. Cerebrovascular impedance modulus, phase, and coherence in young and elderly subjects

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Modulus, mmHg·cm⁻¹·s⁻¹</th>
<th>Phase, rads</th>
<th>Coherence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Elderly</td>
<td>Young</td>
</tr>
<tr>
<td>0.78–2 Hz</td>
<td>0.82 ± 0.19</td>
<td>1.13 ± 0.30*</td>
<td>−0.08 ± 0.10</td>
</tr>
<tr>
<td>2–4</td>
<td>0.62 ± 0.087</td>
<td>0.86 ± 0.16†</td>
<td>−0.11 ± 0.19</td>
</tr>
<tr>
<td>4–6</td>
<td>0.47 ± 0.062†</td>
<td>0.58 ± 0.10†</td>
<td>0.09 ± 0.22†</td>
</tr>
<tr>
<td>6–8</td>
<td>0.37 ± 0.048†</td>
<td>0.46 ± 0.11†</td>
<td>0.08 ± 0.31†</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 for differences between the young and elderly in the same frequency range; †P < 0.05 for differences between 0.78 and 2 Hz and high-frequency harmonics.

Fig. 3. Correlation between changes in CBFV and cerebrovascular impedance modulus. Reductions in systolic and diastolic CBFV in older adults were correlated with increases in cerebrovascular impedance in the frequency ranges of 0.78–2, 2–4, and 4–6 Hz. Data from young subjects; ◦data from the elderly. Of note, removal of the highest impedance data from 1 elderly subject reduced the statistical significance of the correlations between systolic CBFV and impedance modulus in the frequency range of 2–6 Hz.

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Furthermore, applanation tonometry was used to measure pulsatile changes in arterial pressure in the carotid artery as a surrogate for cerebral arterial pressure. It must be highlighted that measurement of carotid arterial pressure using tonometry is not likely to be a trivial task (23). The operator must be well
trained to be able to measure tonometric signal correctly. In addition, calibration of the carotid arterial pressure with brachial pressure may be influenced by vascular aging. However, this influence will most likely be on systolic rather than diastolic or mean pressure (21, 24).

It is also possible that pressure waveforms measured in the ICA or CCA may not be the same as that in the MCA because of pressure wave reflections and the presence of large cerebral artery resistance (6, 22, 27). This uncertainty is likely to be particularly relevant if pressure was measured in the CCA since pressure wave reflections from both the internal and external carotid vasculature may influence these measurements.

In this regard, our preliminary observations suggest that pressure waveforms measured in the CCA were similar to those in the ICA (data did not show). Whether measurement of pressure exclusively in the ICA using an ultrasound-guided technique improves the accuracy of impedance estimation needs to be determined. Furthermore, considering the fact that the MCA is a direct extension of the ICA, the distance between the ICA and MCA is relatively short (~10 cm), and the diameters of these arteries are relatively large (ICA, 4–7 mm; MCA, 2–3 mm), we speculate that the influences of aforementioned confounding factors on the amplitude of pressure waveforms, thus the estimation of impedance modulus, are likely to be small (9).

However, a potential influence of a delayed time of pressure wave propagation from the carotid artery to the MCA on the phase estimation may not be negligible. A previous study showed that pressure wave velocity from the internal carotid artery to the MCA is about 12 m/s (9). Assuming that the distance between the two measurement sites is about 10 cm, the time delay for pressure wave propagation would be about 8 ms. This time delay can lead to a phase difference in pressures of about 0.2 rads at 4 Hz. For these considerations, the phase estimates were corrected accordingly for each of the frequencies in this study. Notably, phase correction for the elderly may be overestimated if their pulse wave velocity was higher than in young subjects (15).

Transfer function analysis was used to estimate cerebrovascular impedance based on pulsatile changes in CBF velocity and arterial pressure. The transfer function method is valid only if the system to be identified is linear regardless of the specific properties of the input signal to the system (either periodic or random) (2). The estimated impedance modulus and phase were similar to those observed in the systemic circulation and other peripheral vascular beds (21, 22, 24, 27). That is, impedance modulus was reduced gradually from the fundamental harmonics to a nonzero asymptote, and phase was negative at low frequencies and fluctuated at high frequencies (22). These observations suggest that the cerebrovascular bed shares similar mechanical properties as those of other vascular beds in accommodating pulsatile changes in blood flow and pressure. Interestingly, cerebrovascular resistance index (equivalent to the impedance modulus at zero frequency) was about three- to sixfold lower than those observed in the other vascular beds (except for the renal circulation), consistent with high flow and low resistance of the cerebral circulation (20).

Finally, coherence function between pulsatile changes in CBF velocity and arterial pressure was close to 1 in the frequency range from 0.78 to 6 Hz, where most of the energy of the harmonic oscillations was contained (31). These data support the validity of using the transfer function method in this study and extended previous studies by demonstrating a linear relationship between pulsatile changes in CBF velocity and arterial pressure in the cerebral circulation. However, coherence was reduced at the frequencies of around 4 and 7 Hz in the elderly. It is possible that either age-related vascular changes and/or a low signal/noise ratio may reduce the coherence at these frequencies.

Cerebrovascular impedance in older adults. Aging is a strong risk factor for cerebrovascular disease (5, 16). Decline in CBF is one of the most observed changes of cerebral hemodynamics in older adults (4, 14). Consistent with previous studies, we found that systolic, diastolic, mean, and pulse CBF velocity were all deceased in the elderly. Notably, cerebrovascular impedance was increased in the elderly, and increases in cerebrovascular impedance were correlated with reductions in CBF velocity. These data are consistent with the hypothesis that, besides changes in brain metabolic rate with aging, cerebrovascular dysfunction may lead to reduction in brain perfusion in older adults.

Age-related changes in mechanical properties of the cerebral blood vessels may account for increases in cerebrovascular impedance. With age, the presence of arteriosclerosis, thickening of the blood vessel wall, and increases in the ratio of collagen to elastin content as well as cross-linking of the collagen by advanced glycation end products can all lead to increases in arterial stiffness (7, 12). In addition, endothelial dysfunction and vessel wall smooth muscle cell degeneration may result in impaired vasodilatory responses and sustained cerebral vasoconstriction with age (11). Similar to other vascular beds, both arterial stiffening and vasoconstriction may lead to increases in cerebrovascular impedance in older adults (22).

However, inferring mechanical properties of cerebral blood vessels from the measured impedance can be a challenging, if not a daunting, task (26). In practice, an average of impedance moduli at high frequencies has been used to estimate vascular “characteristic impedance,” an index used mainly to reflect arterial stiffness (22). In the present study, not only cerebrovascular resistance index but also impedance modulus in the frequency range of 0.78–4 Hz was increased in the elderly. Thus, it is likely that both arterial stiffening and increases in vascular resistance contribute to the observed changes in cerebrovascular impedance in the elderly.

Clinical perspective. Assessment of cerebrovascular impedance provides a new method for studying cerebral hemodynamics at the time scales of equal to or less than a cardiac cycle (10). Specifically, assessment of cerebrovascular impedance can provide novel insights into cerebrovascular function that determines to what extent each of the harmonic oscillations in pulsatile arterial pressure is related to changes in cerebral blood flow. Based on extensive studies in other vascular beds, this information most likely reveals changes in cerebrovascular resistance and/or vascular stiffness under specific experimental conditions (27). In this regard, increases in cerebral arterial stiffness are likely to be an important risk factor for brain diseases such as stroke, white mater lesions, and dementia (8). Further studies are warranted to understand the underlying mechanisms and to elucidate the clinical importance of assessment of cerebrovascular impedance under physiological and
pathophysiological conditions. Finally, employment of arterial Windkessel or other modeling methods in combination with direct measurement of regional arterial stiffness may provide insights into the relative contributions of changes in vascular resistance and/or vascular stiffness to increases in cerebrovascular impedance with aging (30).

Study limitations. The sample size of this study is small, and the potential influence of sex on the study outcome cannot be excluded. However, significant increases in cerebrovascular impedance were observed in the elderly, indicating high sensitivity of this index to assess changes in cerebrovascular function with age. In addition, the reproducibility of the method needs to be established, although previous studies have documented the high reproducibility of both TCD for measuring CBF velocity and arterial applanation tonometry for measuring carotid arterial pressure if these measurements were performed carefully under well-controlled experimental conditions (3, 17). Finally, as discussed above, the specific mechanisms for increases in cerebrovascular impedance in older adults cannot be determined in this study.

In summary, this study developed a noninvasive method for assessment of cerebrovascular impedance from pulsatile changes in CBF velocity and arterial pressure. The findings of an increase in cerebrovascular impedance in older adults and its correlation with reduction in CBF velocity suggest that reduction in cerebral blood flow with aging is likely to be induced by both arterial stiffening and increases in vascular resistance.

GRANTS
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DISCLOSURES
The authors declare that they have no conflict of interest.

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