Age-Related Changes in Carotid Artery Flow and Pressure Pulses
Possible Implications for Cerebral Microvascular Disease

Kozo Hirata, MD; Toshio Yaginuma, MD; Michael F. O'Rourke, MD, DSc; Masanobu Kawakami, MD

Background and Purpose—We sought to establish the relation between the pulsatile components of pressure and flow waveforms in the carotid artery and their change with age.

Methods—Distention (pressure) and axial flow velocity waveforms were recorded noninvasively and simultaneously from the common carotid artery of 56 healthy subjects aged 20 to 72 years.

Results—There was a close relation between the time intervals of pressure and flow waves: from foot to first shoulder or peak, to second shoulder or peak, and to incisura (r=0.97, P<0.0001 for each), which approximated the line of identity. The peak and nadir of flow velocity decreased with age, but late systolic flow augmentation increased substantially (1.6 times in the older group); this can be attributed to earlier wave reflection from the lower body. Pressure augmentation index (PAI) and flow augmentation index (FAI) increased similarly with age (PAI (%)=0.84×age−26.6; FAI (%)=0.75×age+11.9; both P<0.0001).

Conclusions—Arterial stiffening with aging increases carotid flow augmentation and can explain the increasing flow fluctuations in cerebral blood vessels. Measurement of carotid FAI may provide a gauge for risk of cerebral microvascular damage, just as PAI provides a gauge for risk of left ventricular hypertrophy and failure. (Stroke. 2006; 37:2552-2556.)

Key Words: carotid flow waveforms ■ flow augmentation ■ pulse wave encephalopathy ■ wave reflection

More often than not, noninvasive measures of arterial stiffness in humans entail analysis of carotid artery pulsations. “Aortic” pulse wave velocity is determined from the delay of the wave foot between carotid and femoral sites.1,2 The carotid pressure wave has been used as a surrogate of the ascending aortic pressure wave in studies of ascending aortic impedance, with change in age, in normal populations, and in the presence of disease.3–6 The carotid pressure wave is also interpreted independently under different pathological conditions from change in its late systolic augmentation.7,8

In contrast to the carotid pressure waveform, the clinical significance of the pulsatile component of the carotid flow wave is not fully understood, even though it is frequently recorded as a part of population studies or for clinical investigation of possible carotid disease. Although it is accepted that upper-body flow waveforms are completely different from wave patterns in the ascending aorta and in lower-body arteries, such waves are known to show considerable variability in normal human subjects2,9; their relation with the carotid pressure wave and with subsequent disease has not been considered.

The present study was undertaken to establish the relation between pulsatile components of the pressure/diameter wave in the carotid artery and the accompanying flow wave in normal subjects at different ages.

Methods

Patient Population

Seventy healthy, unmedicated volunteers were recruited during a 3-month period at a health awareness center at Omiya Medical Center, Saitama, Japan. Fourteen subjects were excluded after interview and examination on the basis of a history of hypertension, diabetes mellitus, hypercholesterolemia, or any cardiovascular disease or from finding of a seated blood pressure after rest of ≥140/90 mm Hg, a fasting glucose value ≥110 mg/dL, a cholesterol value ≥240 mg/dL, or some combination thereof. Fifty-six subjects (mean±SD age, 48.2±14.3 years) were entered into the study (Table 1). Informed consent was obtained from all subjects according to institutional guidelines.

Blood Pressure Measurement

Brachial blood pressure was measured on the left arm in the supine position, before carotid distention (pressure) and flow velocity waveforms were recorded. Brachial mean blood pressure was calculated as diastolic blood pressure (DBP)+[(0.33×pulse pressure)].
Measurements of Carotid Pressure and Flow Velocity Waveforms

The distention and flow velocity waves of the right common carotid artery were measured simultaneously with an ultrasound QFM1100 system (Hayashi Electric Co, Kawasaki, Japan), after the subjects had rested in a supine position for 10 minutes. As previously reported, this device determines the flow velocity waveform by the continuous-wave Doppler method (frequency of probe, 5 MHz) and the arterial internal diameter by the phase-locked echo-tracking method (frequency of probe, 7.5 MHz), with good accuracy and reproducibility. Measurements of carotid pressure can be inaccurate, so that the distension waveform is preferred as a noninvasive surrogate of carotid pressure. At least 5 carotid distention (pressure) and flow velocity waveforms obtained from a stable area of the record were analyzed to determine the following parameters (Figure 1): peak systolic flow velocity (V_s); end-diastolic flow velocity (V_e); peak flow velocity of the secondary rise in the common carotid flow velocity waveform (Vsr); and mean flow velocity (Vm). Pressure augmentation index (PAI) of the distention (pressure) waveform was defined by the following formula as reported by Laurent et al: (P^2 / H^2 P_0) / (P^2 / H^2 P_0), in which P_2 is peak lumen diameter, P_0 is minimal (end diastolic) lumen diameter, and P_1 is the lumen diameter at the inflection point of the carotid distention (pressure) waveform. Flow augmentation index (FAI) was defined similarly as (Vsr − V_e)/(V_s − V_e). Like PAI, it is an index related to the amplitude and timing of wave reflection. \( \Delta \rho \) and \( \Delta f \) were defined respectively as the time between the wave foot and the peak of the initial rise in the carotid distention (pressure) waveform (P1) and the flow velocity waveform (Vs); \( \Delta TP \) and \( \Delta TF \) were defined as the time between the wave foot and the peak of the secondary rise in the common carotid distention (pressure) waveform (P2) and in the common carotid flow velocity waveform (Vsr), respectively. EDp and EDf were defined as the time between the wave foot and the incisura of the carotid distention (pressure) and flow waveforms, respectively. Flow volume was calculated from the flow velocity and the corresponding internal diameter of the vessel wall.

Statistical Analysis

Statistical analysis was performed with StatView (version 5.0, Abacus Concepts, Inc, Berkeley, Calif). The relation between 2 variables was determined by Pearson’s correlation coefficient. A difference was considered significant at \( P < 0.05 \). All data are expressed as mean ± SD.

Results

Apart from age, which ranged from 20 to 72 years, and sex, the population was homogeneous (Table 1). There was no

---

**Table 1. Basic Characteristics and Linear Regression Data for Basic Characteristics vs Age**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.5 ± 14.3</td>
<td>0.073</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>38/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.72 ± 11.1</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>Brachial systolic BP, mm Hg</td>
<td>121.4 ± 14.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>72.6 ± 9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial pulse pressure, mm Hg</td>
<td>48.7 ± 10.8</td>
<td>0.328</td>
<td>0.0139</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>88.9 ± 10.0</td>
<td>0.095</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66.7 ± 10.5</td>
<td>0.319</td>
<td>0.0161</td>
</tr>
</tbody>
</table>

NS indicates not significant.

---

**Figure 1. Definitions of measurements obtained from pressure (top) and flow (bottom) waveforms in the common carotid artery.**

**Figure 2.** Representative pressure (top) and flow velocity (bottom) in a healthy 23-year-old subject (A) and in a healthy 65-year-old subject (B).
change in brachial systolic blood pressure or DBP with age, but there was a small change in brachial pulse pressure and heart rate.

The carotid pressure waveform was completely different from the carotid flow waveform, and there were substantial changes in both with age (Figure 2). The pressure waveform was similar to that previously described2–7,17,18 for the carotid artery and proximal aorta, whereas the carotid flow wave was different from that seen in other arteries with respect to 3 features: a sharp early systolic peak, a second late systolic peak, and maintained high flow velocity at the end of diastole (Figures 1 and 2). Despite such differences between pressure and flow waveforms, there were close associations between components of the waves and consistent patterns of change in both with aging.

**Associations**

Associations between features of the pressure and flow waves were so close and consistent as to indicate a functional relation (Figure 3A). The time from wave foot to peak flow (Δtf) was the same as the time from wave foot to first pressure inflection or peak (Δtp), and the time to second systolic flow peak (ΔTF) was the same as that to late systolic pressure inflection or peak (ΔTP). The time to end systole was likewise the same in pressure and flow waves, as gauged from the wave foot to the sharp dip in pressure or flow wave, which marked aortic valve closure (EDp and EDd).

There was also a close association (Figure 3B) between carotid PAI as measured conventionally2,7,17 and FAI, expressed as the amplitude of the difference between Vsr and Ved, divided by the amplitude of the flow velocity pulse (FAI; see Figure 1). PAI is accepted as a measure of wave reflection from peripheral sites.2–8,17 Similarities of FAI to PAI indicate that the fluctuations in flow are likewise a consequence of wave reflection from peripheral sites.

**Aging Change**

In this healthy cohort (Table 2), carotid systolic and pulse pressure increased with age. The Δtp, Δtf, ΔTP, and ΔTF were decreased, but EDp and EDd did not change with age. There was a progressive decrease in peak and end-diastolic flow velocity and a trend to a decrease Vm. These decreases disappeared when expressed as flow volume (Table 2). In contrast to the falls in peak and diastolic velocity with age, there was no change in Vsr but an increase in Vsr–Ved. This was greater still when expressed as volume flow (Table 2). Changes in the pressure and flow waveforms with age were accompanied by increase in both PAI and FAI (Table 2 and Figure 4).

**Discussion**

Data presented here provide a firm basis for explaining the shape of both flow and pressure waveforms in the carotid artery of normal human subjects. Explanations support those already provided for the innominate and brachial arteries.2–9,19

### TABLE 2. Flow and Pressure Waveform Indices of the Common Carotid Artery of the 56 Healthy Subjects

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>Carotid Systolic BP, mm Hg*</th>
<th>Carotid Pulse Pressure, mm Hg†</th>
<th>Diastolic Diameter, mm‡</th>
<th>Vs, cm/s‡</th>
<th>Vs Flow, mL/min</th>
<th>Ved, cm/s‡</th>
<th>Ved Flow, mL/min</th>
<th>Vm, cm/s</th>
<th>Vm Flow, mL/min</th>
<th>Vsr, cm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>14</td>
<td>101.8 ± 9.8</td>
<td>29.3 ± 6.4</td>
<td>5.87 ± 0.57</td>
<td>68.6 ± 7.7</td>
<td>1194.8 ± 230.4</td>
<td>18.5 ± 2.4</td>
<td>305.8 ± 83.1</td>
<td>26.0 ± 2.9</td>
<td>440.6 ± 95.6</td>
<td>33.3 ± 5.1</td>
</tr>
<tr>
<td>40–59</td>
<td>30</td>
<td>110.5 ± 12.3</td>
<td>35.9 ± 8.0</td>
<td>6.84 ± 0.77</td>
<td>50.7 ± 7.2</td>
<td>1043.2 ± 262.6</td>
<td>15.4 ± 6.4</td>
<td>313.1 ± 60.2</td>
<td>24.2 ± 4.2</td>
<td>493.9 ± 91.0</td>
<td>32.2 ± 4.9</td>
</tr>
<tr>
<td>&gt;60</td>
<td>12</td>
<td>109.3 ± 14.2</td>
<td>41.1 ± 5.7</td>
<td>6.71 ± 0.76</td>
<td>47.2 ± 8.9</td>
<td>1010.8 ± 257.4</td>
<td>13.5 ± 2.7</td>
<td>289.8 ± 84.4</td>
<td>23.7 ± 4.4</td>
<td>504.7 ± 151.3</td>
<td>33.1 ± 6.5</td>
</tr>
<tr>
<td>All</td>
<td>56</td>
<td>108.1 ± 12.5</td>
<td>35.4 ± 8.2</td>
<td>6.46 ± 0.79</td>
<td>53.7 ± 11.7</td>
<td>1074.2 ± 259.3</td>
<td>15.7 ± 3.1</td>
<td>306.3 ± 71.1</td>
<td>24.4 ± 3.9</td>
<td>482.9 ± 108.3</td>
<td>32.7 ± 5.3</td>
</tr>
</tbody>
</table>

Abbreviations are defined in the text and expressed as mean ± SD. n, No. of subjects investigated.

Symbols express significance of correlation between age and each parameter: *P<0.05; †P<0.01; ‡P<0.0001.
The complex patterns of flow in upper-body arteries belie the simple impedance patterns that result from a comparison of frequency components of pressure and flow waves (supplemental Figure I, available online at http://stroke.ahajournals.org), which imply the influence of a functionally discrete reflecting site in the vascular bed beyond. The unusual patterns of flow in upper-body arteries can be explained on the basis of an early return of wave reflection from local upper-body sites and their interaction with later wave reflection coming in the opposite direction from sites in the lower part of the body (supplemental Figure II, available online at http://stroke.ahajournals.org). The effects of aging are readily explained on the basis of an earlier return of wave reflection from the lower body, as a consequence of aortic degeneration and increased aortic pulse wave velocity. The only difference in carotid compared with innominate and brachial flow is that the peak of the flow wave is unmistakable, whereas the shoulder of the flow wave is often indistinct, especially as measured by carotid tonometry.

Carotid tonometry is widely used to assess the effects of wave reflection through measurement of PAI. The major problem in this measurement is detection of an inflection point on the wave that corresponds to the peak of carotid flow. Use of the method reported here simplifies and increases the accuracy of measuring pressure augmentation, because the peak of the flow wave is unmistakable, whereas the shoulder of the pressure wave is often indistinct, especially as measured by carotid tonometry.

The effects of carotid (and aortic) PAI with age are well known and include increased left ventricular load, left ventricular hypertrophy, left ventricular failure, and increased severity and extent of coronary atherosclerosis. Data presented here show that this increased pressure augmentation with age is accompanied by increased late systolic flow augmentation in the carotid artery as well (Figure 4 and Table 2). This is not immediately apparent on inspection of the augmentation in the carotid artery and in a peripheral artery during local vasodilation of its vascular bed.

In the presence of microvascular rarefaction with age, velocity fluctuations would be expected to increase in the microvasculature, even if volume carotid flow pulsations were unchanged. This has been confirmed. However, there is another factor as well. The early systolic flow peak, a high-frequency component of the wave, attenuates in arteries leading down to the cerebral microvasculature.

In fact, fluctuations of flow in cerebral veins and capillaries are of low frequency and, though delayed, appear to correspond to late systolic flow augmentation in the carotid or cerebral arteries rather than to an early systolic flow peak with respect to timing and amplitude (ie, to $V_{sr}$–$V_{ed}$, not to $V_{ed}$–$V_{ed}$). An increased amplitude of such cerebral venous flow pulsations has been noted in older persons and in those with vascular dementia and has been related to “pulse wave encephalopathy.”

It has been shown that cerebral microvascular disease is increased in the presence of aortic stiffening and it has been hypothesized that such microvascular disease is caused by increased pulsatile shear forces in these vessels from increased pulsatile flow velocity. Such a view is based on the similarity of cerebral vascular lesions in humans and experimental animals with aging and hypertension and with lesions in human lungs when pulsatile blood flow is increased over many years as a consequence of congenital heart disease with left-to-right shunt. It is also based on the calculated yield stress of endothelial cells, which approaches values for disruption in the presence of high pulsatile flow, together with an increase in permeability in the endothelial cells.

<table>
<thead>
<tr>
<th>Var Flow, mL/min</th>
<th>Var–Ved, cm/s</th>
<th>Vsr–Ved Flow, mL/min</th>
<th>$\Delta p$, ms</th>
<th>$\Delta f$, ms</th>
<th>$\Delta T_{p}$, ms</th>
<th>$\Delta T_{f}$, ms</th>
<th>$\Delta T_{p}$, ms</th>
<th>$\Delta T_{f}$, ms</th>
<th>$\Delta E_{p}$, ms</th>
<th>$\Delta E_{f}$, ms</th>
<th>PAI, %</th>
<th>FAI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>639.0 ± 178.1</td>
<td>14.7 ± 5.0</td>
<td>333.3 ± 121.7</td>
<td>133.2 ± 21.1</td>
<td>132.0 ± 18.7</td>
<td>256.1 ± 36.6</td>
<td>260.6 ± 39.2</td>
<td>322.3 ± 26.6</td>
<td>321.4 ± 23.9</td>
<td>-6.0 ± 13.0</td>
<td>30.5 ± 13.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>751.5 ± 136.8</td>
<td>17.0 ± 3.5</td>
<td>438.5 ± 97.5</td>
<td>103.2 ± 22.9</td>
<td>103.8 ± 22.0</td>
<td>223.2 ± 30.2</td>
<td>223.1 ± 29.1</td>
<td>308.7 ± 27.8</td>
<td>310.7 ± 29.2</td>
<td>18.5 ± 9.3</td>
<td>51.6 ± 13.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>813.6 ± 270.7</td>
<td>19.6 ± 4.6</td>
<td>523.8 ± 193.9</td>
<td>97.7 ± 11.7</td>
<td>97.3 ± 12.0</td>
<td>215.8 ± 37.5</td>
<td>215.9 ± 35.8</td>
<td>316.0 ± 28.0</td>
<td>316.0 ± 25.3</td>
<td>25.5 ± 8.0</td>
<td>59.1 ± 11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>736.7 ± 189.3</td>
<td>17.0 ± 4.4</td>
<td>430.5 ± 142.7</td>
<td>109.5 ± 22.6</td>
<td>109.4 ± 21.7</td>
<td>229.8 ± 36.3</td>
<td>231.0 ± 37.1</td>
<td>313.6 ± 27.6</td>
<td>314.5 ± 27.0</td>
<td>13.8 ± 15.5</td>
<td>47.9 ± 16.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
attributable to the high shear stress across them. The enhanced permeability in small vessels has been reported as a manifestation of damage to small vessels in the brain and has been proposed as an important pathogenesis of cerebral microvascular disease.

Our analysis of components of the carotid artery flow waveform only supports the aforementioned view. The hypothesis needs to be confirmed by further study, which would investigate the relation of cerebral microvascular flow pulsations and carotid augmented flow. However, our study results and the views presented here have the potential to explain classic and recent studies of vascular microscopy in humans and experimental animals, transient or persistent white matter hypertensities, lacunar infarcts in older subjects, and the results of antihypertensive therapy, which reduces wave reflection.

Disclosures
Michael O’Rourke is a founding director of ArCor Medical, manufacturer of systems for analyzing arterial pulse. The remaining authors have no relationships to disclose.

References
Age-Related Changes in Carotid Artery Flow and Pressure Pulses: Possible Implications for Cerebral Microvascular Disease
Kozo Hirata, Toshio Yaginuma, Michael F. O'Rourke and Masanobu Kawakami

Stroke. 2006;37:2552-2556; originally published online August 31, 2006;
doi: 10.1161/01.STR.0000242289.20381.f4
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/37/10/2552

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/