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
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.10,11 Carotid distention waveforms were calibrated by brachial mean blood pressure and DBP to obtain carotid pressure values and were regarded as the carotid pressure waveform.5,12,13 Measured invasively, carotid distension and pressure waveforms are virtually identical14; tonometric measures of carotid pressure can be inaccurate15, so that the distension waveform is preferred as a noninvasive surrogate of carotid pressure.12,13

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 (Vs); end-diastolic flow velocity (Ved); 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 al13: 

\[ \frac{P_2 - P_0}{P_1} \]

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 

\[ \frac{V_{sr} - Ved}{Vs - Ved} \]

Like PAI, it is an index related to the amplitude and timing of wave reflection.16 \( \Delta P_1 \) and \( \Delta T_f \) 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). \( \Delta T_P \) and \( \Delta T_F \) 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

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**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>-0.024</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.72±11.1</td>
<td>0.328</td>
<td>0.0139</td>
</tr>
<tr>
<td>Brachial systolic BP, mm Hg</td>
<td>121.4±14.3</td>
<td>0.024</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>72.6±9.3</td>
<td>0.338</td>
<td>0.0139</td>
</tr>
<tr>
<td>Brachial pulse pressure, mm Hg</td>
<td>48.7±10.8</td>
<td>0.005</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>88.9±10.0</td>
<td>0.031</td>
<td>0.0161</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66.7±10.5</td>
<td>0.031</td>
<td>0.0161</td>
</tr>
</tbody>
</table>

NS indicates not significant.
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 described 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 ($\tau_{fp}$) was the same as the time from wave foot to first pressure inflection or peak ($\tau_{tp}$), and the time to second systolic flow peak ($\Delta T_{FP}$) was the same as that to late systolic pressure inflection or peak ($\Delta T_{PF}$). 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 ($E_D$ and $E_D$).

There was also a close association (Figure 3B) between carotid PAI as measured conventionally and FAI, expressed as the amplitude of the difference between $V_{sr}$ and $V_d$, 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. 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 $\Delta p$, $\Delta t$, $\Delta T_{FP}$ and $\Delta T_{PF}$ were decreased, but $E_D$ and $E_D$ did not change with age. There was a progressive decrease in peak and end-diastolic flow velocity and a trend to a decrease $V_{sr}$. 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 $V_{sr}$ but an increase in $V_{sr}$--$V_d$. 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.

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Group, y</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>Var, 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>66.8 ± 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>
<td></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>
<td></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>
<td></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>
<td></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 (Figures 1 and 2) is the continued high velocity in end diastole, which is attributable to the vasodilated brain being the major organ supplied by this artery. Similar high-velocity flow at end diastole is seen in the renal artery and in a peripheral artery during local vasodilation of its vascular bed.

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 carotid flow velocity waveforms (Figure 2), nor through consideration of difference between peak and nadir of the flow velocity waveforms (Vs − Ved significantly decreased with aging (P < 0.0001); data not shown). Carotid dilation with normal aging has already been reported, and the magnitude was similar with our study result. This and heart rate increases are attributable to a velocity decrease in this study.

**Figure 4.** Relation between FAI (solid circles, top) and carotid PAI (open diamonds, bottom) with age. Regression line for FAI: y = 0.75x + 11.9. Regression line for PAI: y = 0.84x − 26.6.

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 Vs − Ved, not to Vs − Ved). 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 2.** Continued

<table>
<thead>
<tr>
<th>Var Flow, ml/min†</th>
<th>Var − Ved, cm/s†</th>
<th>Var − Ved Flow, ml/min‡</th>
<th>Δtp, ms‡</th>
<th>Δtf, ms‡</th>
<th>ΔTP, ms‡</th>
<th>ΔTF, ms‡</th>
<th>EDp, ms</th>
<th>EDf, 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>132.3 ± 21.3</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>
</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>223.7 ± 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>
</tr>
<tr>
<td>813.6 ± 270.7</td>
<td>19.6 ± 4.6</td>
<td>523.8 ± 193.9</td>
<td>97.5 ± 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>
</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>
</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 hyperintensities, lacunar infarcts in older subjects, and the results of antihypertensive therapy, which reduces wave reflection.

Disclosures

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

References

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