Evaluation of Common Carotid Hemodynamic Forces
Relations With Wall Thickening

Claudio Carallo, Concetta Irace, Arturo Pujia, Maria Serena De Franceschi, Anna Crescenzo, Corradino Motti, Claudio Cortese, Pier Luigi Mattioli, Agostino Gnasso

Abstract—The localization of atherosclerotic lesions is influenced by hemodynamic factors, namely, shear stress and tensile forces. The present study investigated the relationships between shear stress and circumferential wall tension and between these hemodynamic factors and the intima-media thickness (IMT) of the common carotid artery in healthy men. Fifty-eight subjects were studied. Shear stress was calculated as blood viscosity × blood velocity/internal diameter. Circumferential wall tension was calculated as blood pressure × internal radius. Blood velocity, internal diameter, and IMT were measured by high-resolution echo-Doppler. Mean shear stress was 12.6 ± 3.3 dynes/cm² (mean ± SD; range, 4.8 to 20.4) and was inversely related with age, blood pressure, and body mass index (BMI). Mean circumferential wall tension was 3.4 ± 0.6 × 10⁴ dynes/cm (range 2.4 to 5.6) and was directly associated with age and BMI. IMT was inversely associated with shear stress (r = 0.55, P < 0.0001) and directly associated with circumferential wall tension (r = 0.43, P < 0.0001). In multiple regression analysis, shear stress and (marginally) cholesterol were independently associated with IMT, whereas circumferential wall tension, age, and BMI were not. These findings confirm that common carotid shear stress varies among healthy individuals and decreases as age, blood pressure, and BMI increase. Our findings also demonstrate that circumferential wall tension is directly associated with wall thickness, age, and BMI and that shear stress is associated with common carotid IMT independent of other hemodynamic, clinical, or biochemical factors. (Hypertension. 1999;34:217-221.)

Key Words: carotid arteries ■ atherosclerosis ■ stress, mechanical ■ tensile stress ■ tunica media

Atherosclerosis is a systemic disease, caused or favored by systemic risk factors, that localizes in particular regions of the arterial tree, probably through interaction with local predisposing factors.¹–² Among the predisposing factors, the hemodynamic forces (shear stress and tensile stress) generated by flowing blood are of utmost importance.³–⁶ Shear stress is the frictional force that acts tangentially to the endothelial surface. Tensile stress is the circumferential wall tension divided by wall thickness, and it acts perpendicularly to the arterial wall and results from the extensional (dilating) effect of blood pressure on the vessel. These hemodynamic forces also influence the vessel wall structure and development and contribute to the regulation of vascular tone.⁵,⁷–¹¹ In vitro and in vivo experiments have demonstrated that vessels tend to maintain constant shear stress in response to flow changes.¹²–¹⁴ We have previously demonstrated that common carotid artery shear stress in healthy men in vivo decreases with increasing age, blood pressure, and body mass index (BMI) and that low shear stress values are associated with intima-media thickening, an echographic index of early atherosclerosis.¹⁵ Furthermore, in subjects with asymmetrical carotid atherosclerosis, we have found lower shear stress values in the carotid artery with lesions versus the plaque-free contralateral carotid artery.¹⁶

Our previous works focused exclusively on shear stress. In the present study, we investigated the relationships between shear stress and circumferential wall tension and between these hemodynamic factors and the common carotid wall thickness in healthy men in vivo.

Methods

Fifty-eight healthy men participated in a regional cardiovascular disease prevention campaign. Nonsmokers, nonob diabetics, and non-hypertensives (blood glucose ≤ 6.11 mmol/L; blood pressure ≤ 140/90 mm Hg), with total cholesterol and triglycerides that did not exceed 6.46 mmol/L and 2.26 mmol/L, respectively, and who did not use any drugs were enrolled.

Systolic (SBP) and diastolic (DBP) blood pressure were measured with a standardized Hawksley random-zero sphygmomanometer on the right arm after the participant had rested for ≥ 5 minutes. The average of the second and third of 3 readings was computed. Mean blood pressure (MBP) was computed as DBP + one third of differential pressure. Height and weight were measured by routine methods. BMI was computed as weight (kg) divided by height (m²) squared. Blood lipids and glucose were measured with commercially available kits.

© 1999 American Heart Association, Inc.

Hypertension is available at http://www.hypertensionaha.org
Echo-Doppler examination for atherosclerotic lesion detection and for arterial diameter, intima-media thickness (IMT), and blood flow velocity measurements was performed with an ECG-triggered high-resolution ATL Ultrasound 9 HDI instrument (Advanced Technology Laboratories, Inc) that was equipped with a 5-MHz to 10-MHz multifrequency linear probe. The common carotid artery, carotid bulb, internal carotid artery, and external carotid artery were studied in longitudinal and transverse planes with anterior, lateral, and posterior approaches. Each segment was classified as normal, with plaque, or with stenosis. A segment classified as normal showed an absence of plaque and stenosis. A segment with plaque showed localized lesion that encroached the lumen of thickness \(>1.3\) mm, no spectral broadening or only in the deceleration phase of systole, and systolic peak flow velocity \(<120\) cm/s. Segments with stenosis showed spectral broadening throughout systole or systolic peak flow velocity \(>120\) cm/s. Eleven subjects had plaque in one of the examined segments (2 subjects had plaque in the common carotid artery), but no stenoses were found. For arterial diameter, IMT, and blood flow velocity measurement, the examination was then continued as previously described.15 Briefly, all measurements were performed in the common carotid arteries, 1 to 2 cm proximal to the bulb. Internal diameter (ID) was defined as the distance between the leading edge of the echo produced by the intima-lumen interface of the bulb. Internal diameter (ID) was measured from the near wall and the leading edge of the echo produced by the intima-lumen interface of the bulb. Internal diameter (ID) was measured in vitro at 37°C on the same day as the echo-Doppler examination with a cone/plate viscometer (Wells-Brookfield DV III).

Peak \(T_p\) and mean \(T_m\) circumferential wall tension were calculated by Laplace law according to the following formulas:

\[
T_p (\text{dynes/cm}) = \text{SBP} \times (\text{ID}^2/2)
\]

\[
T_m (\text{dynes/cm}) = \text{MBP} \times (\text{ID}^2/2),
\]

where SBP and MBP are expressed in dynes/cm² and ID in cm.

Peak \(T_p\) and mean \(T_m\) tensile stress were computed as:

\[
\tau_p (\text{dynes/cm}^2) = \frac{T_p}{\text{IMT}}
\]

\[
\tau_m (\text{dynes/cm}^2) = \frac{T_m}{\text{IMT}},
\]

where IMT is expressed in cm.

Peak \(\tau_p\) and mean \(\tau_m\) wall shear stress were calculated according to the following formulas:

\[
\tau_p (\text{dynes/cm}^2) = \frac{4 \eta V_s/\text{ID}_t}{2}
\]

\[
\tau_m (\text{dynes/cm}^2) = \frac{4 \eta V_s/\text{ID}_h}{2},
\]

where \(V\) is expressed in cm/s, ID in cm, and \(\eta\) in poise.

Young’s modulus (\(E\)), a measure of the stiffness of the arteries, was computed as follows:

\[
E (\text{dynes/cm}^2) = \frac{\left(\text{SBP} - \text{DBP}\right) \times \text{ID}_h/[(\text{ID}_t - \text{ID}_h) \times \text{IMT}]}\]

where \(\text{ID}_h = \text{ID}_t - \text{ID}_a/3\). SBP and DBP are expressed in dynes/cm² and ID and IMT in cm.

To test the reproducibility of shear stress and circumferential wall tension calculations, 5 healthy male volunteers >18 years of age were studied 3 to 5 times in a period of 6 to 8 weeks. For each subject, the average of several examinations was calculated and the ratio between each individual value and the average value was determined. The coefficient of variation for \(\text{ID}_t\) was 1.09 ± 0.42%; \(V_s\), 5.39 ± 1.41%; \(\tau_p\), 5.00 ± 2.41%; and \(\tau_m\), 1.84 ± 0.96%.

All variables considered had normal distribution. Unpaired \(t\) test was used to compare shear stress values between arteries with IMT > or <780 \(\mu\)m. Because the right and left sides were analyzed separately, regression analyses were based on 116 samples. Simple regression analysis was used to test the association between variables. To allow for the independent contribution of hemodynamic forces, age, BMI, and total cholesterol to IMT, a multiple regression analysis was performed. In regression analyses, peak and mean values yielded similar results. Because of the amplification of brachial pulse pressure and because mean arterial pressure (MAP) values are virtually identical in brachial and carotid artery,15 only the latter are presented.

### Results
Table 1 shows clinical and biochemical characteristics of the 58 participants. Table 2 shows the vascular wall and hemodynamic characteristics of the 116 common carotid arteries examined. \(\tau_p\) and \(\tau_m\) showed a considerable scattering of values within a wide range. Sixteen arteries had IMT that exceeded the mean +1 SD (780 \(\mu\)m), a value usually considered to be pathological thickening of the arterial wall. In these arteries, \(\tau_m\) was significantly lower than arteries with IMT \(>780\) \(\mu\)m.

### Table 1. Clinical and Biochemical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.0</td>
<td>14.3</td>
<td>21–74</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>118.0</td>
<td>13.2</td>
<td>96–140</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77.2</td>
<td>7.4</td>
<td>60–90</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>90.8</td>
<td>8.6</td>
<td>77–106</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.0</td>
<td>8.6</td>
<td>44–85</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.8</td>
<td>2.7</td>
<td>19.9–29.9</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.97</td>
<td>0.80</td>
<td>3.36–6.46</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.19</td>
<td>0.30</td>
<td>0.62–2.27</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.28</td>
<td>0.61</td>
<td>0.32–2.26</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.12</td>
<td>0.74</td>
<td>3.77–6.11</td>
</tr>
<tr>
<td>Blood viscosity, cP</td>
<td>4.6</td>
<td>0.4</td>
<td>3.5–5.3</td>
</tr>
</tbody>
</table>

### Table 2. Vascular Wall and Hemodynamic Characteristics of the Common Carotid in the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT, (\mu)m</td>
<td>666</td>
<td>115</td>
<td>390–1020</td>
</tr>
<tr>
<td>Internal diameter, T wave, mm</td>
<td>5.6</td>
<td>0.7</td>
<td>4.3–8.2</td>
</tr>
<tr>
<td>Internal diameter, R wave, mm</td>
<td>6.1</td>
<td>0.7</td>
<td>4.8–8.9</td>
</tr>
<tr>
<td>Peak blood flow velocity, cm/s</td>
<td>84.1</td>
<td>21.8</td>
<td>43.1–155.7</td>
</tr>
<tr>
<td>Mean blood flow velocity, cm/s</td>
<td>37.5</td>
<td>6.8</td>
<td>20.3–52.5</td>
</tr>
<tr>
<td>Peak shear stress, dynes/cm²</td>
<td>25.6</td>
<td>7.8</td>
<td>9.3–47.1</td>
</tr>
<tr>
<td>Mean shear stress, dynes/cm²</td>
<td>12.6</td>
<td>3.3</td>
<td>4.8–20.4</td>
</tr>
<tr>
<td>Peak circumferential wall tension, (10^9) dynes/cm</td>
<td>4.8</td>
<td>0.9</td>
<td>3.3–8.3</td>
</tr>
<tr>
<td>Mean circumferential wall tension, (10^9) dynes/cm</td>
<td>3.4</td>
<td>0.6</td>
<td>2.4–5.6</td>
</tr>
<tr>
<td>Peak tensile stress, (10^9) dynes/cm²</td>
<td>73.5</td>
<td>14.4</td>
<td>46.3–109.0</td>
</tr>
<tr>
<td>Mean tensile stress, (10^9) dynes/cm²</td>
<td>51.4</td>
<td>9.3</td>
<td>32.7–75.9</td>
</tr>
<tr>
<td>Young’s modulus, (10^9) dynes/cm³</td>
<td>98.3</td>
<td>45.6</td>
<td>38.1–238.7</td>
</tr>
</tbody>
</table>
Figure 1. Scatterplot showing IMT by mean wall shear stress ($\tau_w$).

<780 $\mu$m (9.1 ± 2.7 versus 13.2 ± 3.0 dynes/cm², $t=5.14$, $P<0.0001$).

$\tau_w$ was inversely related with IMT ($r=0.55$, $P<0.0001$; Figure 1), age ($r=0.63$, $P<0.0001$), SBP ($r=0.35$, $P<0.0001$), and BMI ($r=0.38$, $P<0.0001$). The association between $\tau_w$ and IMT was accounted for mainly by a direct correlation between wall thickness and ID$_a$ and an inverse correlation with $V_{ca}$. $\tau_w$ was not associated with IMT. $T_m$ was directly associated with IMT ($r=0.43$, $P<0.0001$; Figure 2). It was also directly associated with age ($r=0.34$, $P<0.0001$) and BMI ($r=0.34$, $P=0.0001$), whereas $\tau_m$ was not.

There was an inverse association between $\tau_m$ and $T_m$ ($r=0.66, P<0.0001$). This result could be expected because the diameter is in the numerator in circumferential wall tension and in the denominator for shear stress calculation.

IMT was directly associated with age ($r=0.43$, $P<0.0001$), BMI ($r=0.22$, $P<0.05$), and total cholesterol ($r=0.20$, $P<0.05$), but not with SBP. Young’s modulus was directly associated with age ($r=0.49$, $P<0.0001$), thus indicating an increasing arterial stiffness with age.

A multiple regression analysis that included $\tau_m$, $T_m$, total cholesterol, age, and BMI as independent variables and IMT as a dependent variable showed that $\tau_m$ was strongly and independently associated with IMT (Table 3). $T_m$ and total cholesterol were weakly correlated with IMT, whereas age and BMI were not.

**Discussion**

The results of the present study confirm, in a larger group of subjects, that wall shear stress of the common carotid artery greatly varies among healthy individuals and decreases with aging and with increasing values of SBP and BMI. In addition, we demonstrate that circumferential wall tension increases with aging and increasing BMI. Both hemodynamic forces are associated with common carotid IMT, but only shear stress acts as an independent factor.

It is necessary to clarify some methodological points before discussing the results. Echography, which was used to measure IMT, does not allow the differentiation of the 3 components of the arterial wall (ie, intima, media, and externa). Therefore, it is not possible to discriminate between wall thickening caused by tunica media hypertrophy and a properly defined atherosclerotic process, and this is important when we examine the associations reported in the present study. However, the presence of plaque in the carotid tree or a common carotid IMT >750 $\mu$m or >mean+1 SD of the sample (780 $\mu$m in the present study) is usually considered indicative of the presence of atherosclerosis. It is necessary to clarify some methodological points before discussing the results. Echography, which was used to measure IMT, does not allow the differentiation of the 3 components of the arterial wall (ie, intima, media, and externa). Therefore, it is not possible to discriminate between wall thickening caused by tunica media hypertrophy and a properly defined atherosclerotic process, and this is important when we examine the associations reported in the present study. However, the presence of plaque in the carotid tree or a common carotid IMT >750 $\mu$m or >mean+1 SD of the sample (780 $\mu$m in the present study) is usually considered indicative of the presence of atherosclerosis.

**Table 3. Results of the Stepwise Regression Analysis**

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>Multiple $R^2$</th>
<th>F Ratio</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mean shear stress</td>
<td>0.31</td>
<td>49.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>Total cholesterol</td>
<td>0.33</td>
<td>4.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Mean circumferential wall tension, age, and BMI did not significantly improve the regression model.

A given IMT might have a different impact on the tensile support as a consequence of a different composition of the arterial wall. Blood pressure values used to calculate circumferential wall tension, tensile stress, and Young’s modulus have been recorded at the brachial artery. It is known that the brachial/carotid SBP ratio is not constant over the life span: it is $>1$ in the young and $\approx 1$ in older individuals. However, although a slight difference in the absolute values cannot be excluded, a strong correlation between brachial and common carotid blood pressure exists. Indeed, brachial blood pressure has been widely used in studies of carotid compliance. In addition, the absolute value of MAP is considered identical in brachial and carotid arteries, and we have found similar results with MAP instead of SBP when calculating tensive forces. In addition, heart rate might influence the calculation of tensive forces, by exaggerating the pulse pressure difference between central and peripheral sites. However, heart...
rate–adjusted circumferential wall tension, tensile stress, and Young’s modulus yielded results similar to those reported.

The present results confirm, in a larger group of subjects, the described inverse association between shear stress and IMT in the common carotid artery. The association is strong and independent of circumferential wall tension and of clinical and biochemical risk factors for atherosclerosis. This finding is further strengthened by the observation that shear stress is markedly lower in common carotids with an IMT >mean +1 SD versus arteries with a thinner arterial wall. Several in vitro studies have focused on the molecular basis of the relation between shear stress and atherosclerosis. Shear stress modulates the local production of vasoactive and mitogenic substances. The end result of low or oscillating shear stress values is the development of conditions that favor atherosclerosis and, consequently, intimal thickening.

IMT increases with increasing values of \( T_p \), but this relationship is weaker than that observed between shear stress and IMT. Furthermore, in multiple regression analysis, shear stress was the only hemodynamic factor independently associated with common carotid wall thickness. Arterial districts involved by the atherosclerotic process are usually sites of both elevated tensile forces and low shear stress. This association is also based on arterial diameter, which enters into the calculation of both hemodynamic forces and makes it difficult to distinguish the respective role of these factors on atherosclerosis development. The present findings support the possibility that the relation between high circumferential wall tension and early atherosclerotic lesions identified as common carotid wall thickening is mediated by low shear stress conditions. However, it has been demonstrated that \( T_p \) is a main determinant of the tunica media of the arteries and influences its thickness to warrant an appropriate tensile stress. This association between \( T_p \) and IMT described in the present study could also be based on this mechanism. This is indirectly confirmed by the finding that tensile stress, which is the circumferential wall tension adjusted for arterial wall thickness, is constant for increasing age and BMI.

Another finding of the present study is that the values of shear stress vary among healthy individuals at the common carotid level. This result was already reported in a previous study based on a smaller group of subjects and seems to be in contrast with previous experiments that show that blood flow variations are usually compensated by lumen diameter adjustments to restore basal shear stress value. This apparent discrepancy is probably because the cited studies are based on acute or short-term observations of vessel size variations after blood flow increases (fistula model) or decreases (stenosis model), whereas our study points at evaluating hemodynamic forces in different subjects. Indeed, the shear stress variability is related to clinical features, such as age, blood pressure, and BMI. This is not surprising because other studies have also demonstrated an increase of common carotid diameter with increasing age, blood pressure, and BMI: lumen diameter is used to calculate shear stress.

The causes of vascular lumen variation are unclear and probably complex. Normally, the artery responds to the dilating effect of blood pressure by the main structures present in the tunica media: elastic fibers, which operate when vessel dilation is low, and muscular fibers, which work at higher dilations. In humans, aging is accompanied by a subversion of arterial wall, which involves splitting and fractures of elastic fibers and increased collagen fibers and intercellular matrix. The vessel becomes larger and stiffer, probably because the retentive function of elastic laminae is lost and the wall tension is ensured mainly by the less distensible muscular fibers. Our results also confirm that common carotid stiffness significantly increases with age. These histological and functional changes might be explained by the “stress fatigue” theory: the cyclic stress acting over many years on the arterial wall might cause a fatigue failure in a portion of the elastic component of the arteries. Interestingly, the arteries of hypertensive patients, which are subject to high cyclic stress, generally show these histological alterations early in the course of life.

Another proposed mechanism to explain the larger lumen diameter in arterial hypertension is a higher circumferential wall tension caused by the elevated distending pressure. This might be partly true also for the elderly, because blood pressure increases with aging. In addition, the endothelial dysfunction recently demonstrated in aging and in hypertensive patients might play a role in the disturbance of vessel lumen.

Vessel dilation might also be a consequence of atherosclerotic lesions. It has been postulated, for coronary arteries, that atherosclerotic plaques that occupy ≤40% of the potential lumen area induce an increase in blood flow velocity and a consequent vessel dilation, probably to restore wall shear stress. An overcompensation could be responsible for the enlarged diameters observed in these situations. At the present, the mechanisms that underlie overcompensation have not been demonstrated. Furthermore, this would be in opposition to the finding that hypercholesterolemia is associated with smaller versus larger vessel diameter in the common carotid, whereas hypertension shows an opposite association, although both are risk factors for atherosclerosis.

On the basis of the results of this study and on the above observations, it can be hypothesized that the alterations of elastic tissue in the tunica media make the large and elastic conductance arteries unable to tightly set stress force values thus creating local wall shear stress reductions that predispose individuals to atherosclerosis. Even in the presence of systemic risk factors, small vessels are usually devoid of atherosclerosis, because they are mainly muscular and therefore probably able to keep shear forces constant. It will be important to perform follow-up investigations to verify the causal relationships between hemodynamic forces and atherosclerosis development.

References


Evaluation of Common Carotid Hemodynamic Forces: Relations With Wall Thickening
Claudio Carallo, Concetta Irace, Arturo Pujia, Maria Serena De Franceschi, Anna Crescenzo, Corradino Motti, Claudio Cortese, Pier Luigi Mattioli and Agostino Gnasso

Hypertension. 1999;34:217-221
doi: 10.1161/01.HYP.34.2.217

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/34/2/217

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/