Wall Shear Stress Is Associated With Intima-Media Thickness and Carotid Atherosclerosis in Subjects at Low Coronary Heart Disease Risk

Concetta Irace, MD; Claudio Cortese, MD; Elio Fiaschi, MD; Claudio Carallo, MD; Eduardo Farinaro, MD; Agostino Gnasso, MD

**Background and Purpose**—Systemic and local coronary heart disease (CHD) risk factors participate in atherogenesis. The role of wall shear stress, a major local risk factor, remains to be elucidated.

**Methods**—Two hundred thirty-four subjects were carefully characterized for the presence of hypertension, hyperlipidemia, diabetes mellitus, obesity, and cigarette smoking and were divided into low- and high-risk groups. They underwent echo-Doppler examination of the carotid arteries. Atherosclerotic plaques and stenoses were detected, intima-media thickness (IMT) was measured, and wall shear stress was calculated.

**Results**—One hundred eight subjects were classified as low-risk individuals. The prevalence of carotid atherosclerosis in this group was 18.5%. Wall shear stress was 24.23 ± 7.21 dyne/cm² in individuals without atherosclerosis and 16.89 ± 5.48 in those with atherosclerosis (P < 0.000). In multiple regression analyses, wall shear stress, body mass index, and HDL cholesterol were inversely associated and total cholesterol was directly associated with the presence of atherosclerosis; only wall shear stress was associated with IMT. In the high-risk group the prevalence of atherosclerosis was 45.2%. Wall shear stress was 20.44 ± 6.82 dyne/cm² in subjects without atherosclerosis and 17.84 ± 6.88 dyne/cm² in those with atherosclerosis (P = 0.037). Age was the only variable associated with both carotid atherosclerosis and IMT.

**Conclusions**—In subjects traditionally considered at low CHD risk, intima-media thickening and carotid atherosclerosis are significantly associated with low wall shear stress. In contrast, in subjects at high CHD risk, the contribution of wall shear stress seems to be masked, and age becomes the only factor significantly associated with both carotid atherosclerosis and IMT. *(Stroke. 2004;35:464-468.)*

Key Words: atherosclerosis ■ blood flow ■ carotid arteries ■ risk factors ■ ultrasonography

Atherosclerosis is a systemic, multifactorial disease. In addition to systemic coronary heart disease (CHD) risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, and cigarette smoking, local hemodynamic factors participate in the physiopathology of atherogenesis, accounting for the focal nature of the process.1,2 Wall shear stress and tensile stress are the 2 principal local factors involved in arterial remodeling and atherogenesis.3,4 Wall shear stress represents the frictional force that blood flow exerts at the endothelial surface of the vessel wall. It is now accepted that chronic exposure of endothelial cells to high levels of shear stress causes them to exhibit an atheroprotective phenotype.5,6 In accord with this, an association has been demonstrated between low wall shear stress and intima-media thickness (IMT) and plaques of the common carotid arteries.7,8 Although evidence that shear stress influences the atherosclerotic process is consistent, its exact role is not yet defined. Increased CHD risk and a low level of wall shear stress probably interact to cause damage to the arterial wall. We have therefore hypothesized that, in subjects at low systemic CHD risk, atherogenesis is influenced by low wall shear stress. We investigated wall shear stress in the common carotid artery and systemic CHD risk factors in relation to carotid atherosclerosis and IMT in subjects deemed to be at low or high CHD risk.

**Subjects and Methods**
Enrolled subjects were participants in a regional cardiovascular disease prevention campaign examined between January and October 2002. Details of this campaign have been given previously.9 All participants were informed about the aim of the campaign and the aims of the present study, and written informed consent was obtained before examination. For the present study the analyses were restricted to subjects whose data regarding CHD risk factors and echo-Doppler examination were complete (n = 234).
All subjects were examined in the morning in a room at 22°C, after overnight fasting. Subjects who drank coffee or smoked were not included in the study. Blood pressure, height, and weight were measured by routine methods. Body mass index (BMI) was computed as weight (in kilograms) divided by height (in meters squared). Smoking habit and drug use were evaluated by questionnaire.

Echo-Doppler examination was performed by use of an ECG-triggered instrument, equipped with a 5- to 10-MHz multifrequency high-resolution linear probe, as previously described. The subjects were kept in the supine position with their heads slightly extended. A preliminary scan of internal, external, and common carotid arteries was done to evaluate the presence of plaques and/or stenoses. Plaque was defined as a localized lesion encroaching the lumen of thickness ≥1.3 mm, with no spectral broadening or only in the deceleration phase of systole, and systolic peak velocity <120 cm/s. Stenosis was defined as spectral broadening throughout systole and/or peak flow velocity ≥120 cm/s. Arterial diameter, IMT, and blood flow velocity were measured in the common carotid arteries 1 to 2 cm proximal to the bulb. The common carotids were studied in longitudinal and transverse planes with anterior, lateral, and posterior approaches. The sonographer, who was the same throughout the study, recorded the examination on videotape. A reader, who was the same throughout the study and who was blinded with regard to the subject investigated, performed the measurement of internal diameter (ID) and IMT. ID was defined as the distance between the leading edge of the echo produced by the intima-lumen interface of the near wall and the leading edge of the echo produced by the lumen-intima interface of the far wall. For shear stress calculation, ID was measured at the T wave of the cardiac cycle. Diameters used in the analysis represent the mean of diameters measured in the lateral and posterior projections.

IMT was measured offline, as previously described. Images were selected from video recordings, displayed on a computer screen, and analyzed by software that allows quantitative evaluation of the IMT. For each participant, 3 measurements pertaining to the anterior, lateral, and posterior projections of the far wall were performed on each side. The average of the 3 measurements was used to calculate IMT.

Systolic blood flow velocity was detected with the sample volume reduced to the smallest possible size (1 mm) and placed in the center of the vessel. The angle between the ultrasound beam and the longitudinal vessel axis was kept between 44° and 56°. After 1 minute for stabilization, peak systolic velocity (V) was recorded as the mean of the last 3 cardiac cycles.

Blood was withdrawn from an antecubital vein after echo-Doppler examination. Blood lipids and glucose were measured by commercial kits. Blood viscosity (η) was measured, at a shear rate of 225/s, in vitro at 37°C, by use of a cone/plate viscometer.

Peak wall shear stress (τ) was calculated according to the following formula, as previously described: τ = 4 · V · η/ID, where η is expressed in centimeters per second, η in poise, and ID in centimeters.

Peak wall shear stress was also calculated. Results were similar to those obtained with peak wall shear stress and have not been reported. The coefficient of variation for wall shear stress calculation was 4.00 ± 2.20% (mean ± SD; range, 1.91% to 7.63%).

CHD risk factors were defined as follows: hypertension as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive drugs; hyperlipidemia as total cholesterol >5.17 mmol/L and/or triglycerides >2.26 mmol/L and/or use of lipid-lowering drugs; diabetes as fasting blood glucose >7.0 mmol/L and/or use of antidiabetic drugs; obesity as BMI ≥30.0 kg/m²; and smoking as current smoking.

Mean wall shear stress was also calculated. Results were similar to those obtained with peak wall shear stress and have not been reported.

### Table 1. Clinical and Biochemical Characteristics of Subjects, According to CHD Risk Profile

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>108</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>72/36</td>
<td>74/52</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>49.6±13.9</td>
<td>57.3±9.2</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122.4±16.1</td>
<td>132.0±20.7</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.8±8.4</td>
<td>80.7±10.7</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.10±3.34</td>
<td>29.21±4.75</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Total chol, mmol/L</td>
<td>5.30±0.95</td>
<td>7.70±1.32</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>HDL chol, mmol/L</td>
<td>1.37±0.45</td>
<td>1.28±0.39</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.30±0.67</td>
<td>1.86±1.16</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.23±0.83</td>
<td>7.94±3.12</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>21.3</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>IMT, μm</td>
<td>672±120</td>
<td>729±167</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>τ (dynes/cm²)</td>
<td>22.93±7.46</td>
<td>19.19±6.91</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; chol, cholesterol.

### Statistical Analyses

Data are presented as mean±SD unless otherwise stated. Student’s 2-tailed unpaired t test was used for comparison of means between subjects at low and high CHD risk. Simple linear regression analysis was used to test the association between wall shear stress and IMT in low- and high-risk groups and to adjust wall shear stress for age. Multiple stepwise logistic and linear regression analyses were used to test the association between systemic and local risk factors and presence of atherosclerosis and IMT. The results of the aforementioned analyses were similar when data of either left or right common carotid were used. In text and tables, only data of the right side are presented.

### Results

Two hundred thirty-four subjects were enrolled, of whom 146 were men and 88 women. Fifty subjects had no CHD risk factor, 65 had only 1, 55 had 2, 41 had 3, 18 had 4, and 5 had all 5 risk factors. One hundred eight subjects (72 men and 36 women) were classified at low risk and 126 (74 men and 52 women) at high risk (Table 1). As expected, high-risk subjects were older and had higher levels of blood pressure, lipids, glucose, and BMI and a higher prevalence of smoking. They also had increased IMT and lower wall shear stress values.

In the low-risk group, 20 subjects (18.5%) had carotid atherosclerosis. Table 2 shows the characteristics of low-risk subjects according to the presence or absence of carotid atherosclerosis. Subjects with atherosclerosis were older and had higher concentrations of total cholesterol. They also had markedly increased IMT and lower wall shear stress values. The latter difference was also highly significant after adjustment for age.

Fifty-seven subjects (45.2%) in the high-risk group had carotid atherosclerosis. As shown in Table 3, they were older and had higher IMT and lower wall shear stress values. After adjustment for age, the difference in wall shear stress disappeared.

IMT and wall shear stress were inversely correlated (Figure 1). In the low-risk group, the correlation was strong and
significantly \((r=0.551, P<0.0001)\), whereas in the high-risk group it was weak and did not reach statistical significance \((r=0.165, P>0.1)\).

To evaluate the independent association of systemic and local risk factors with IMT, a marker of early atherosclerosis, or with plaques and stenosis, which represent signs of a more advanced process, multiple stepwise linear and logistic regression analyses were performed separately in low- and high-risk groups. In low-risk subjects, wall shear stress, BMI, and HDL cholesterol were inversely related and total cholesterol was directly related to carotid atherosclerosis (Table 4). Wall shear stress was the only variable significantly associated with IMT in linear regression analysis (Table 5).

In the high-risk group, only age was significantly associated with both carotid atherosclerosis and IMT (Tables 4 and 5).

To further define the role of wall shear stress, participants were then divided into 3 groups according to wall shear stress distribution: low \((\tau <17.31 \text{ dyne/cm}^2)\), intermediate \((17.31 \text{ to } 23.22 \text{ dyne/cm}^2)\), or high \((\tau >23.22 \text{ dyne/cm}^2)\). As shown in Figure 2, the prevalence of carotid atherosclerosis was 50% in the low wall shear stress group, 29.5% in the intermediate wall shear stress group, and 19.2% in the high wall shear stress group \((P<0.000)\). After we accounted for age, the prevalence of carotid atherosclerosis was 44.9% in the low wall shear stress group \((\tau <18.00 \text{ dyne/cm}^2)\) and 26.9% in both the intermediate \((\tau 18.00 \text{ to } 22.85 \text{ dyne/cm}^2)\) and high \((\tau >22.85 \text{ dyne/cm}^2)\) wall shear stress groups \((P<0.001)\).

**Discussion**

The results of the present study demonstrate that, in subjects considered at low CHD risk, the presence of carotid atherosclerosis is significantly associated with low wall shear stress. This finding is further strengthened by the association between IMT of the carotid arteries and wall shear stress. In subjects at high CHD risk, in contrast, the contribution of wall shear stress seems to be masked, and age becomes the only factor associated with both carotid atherosclerosis and IMT.
Wall shear stress is probably the most important local factor able to influence atherogenesis. We have previously demonstrated that IMT, a marker of early atherosclerosis, is inversely related to wall shear stress values in the common carotid artery in healthy subjects. Furthermore, in highly selected subjects with asymmetrical carotid atherosclerosis, we found that the plaques were localized in the carotid arteries with lower values of shear stress. These and many other observations in the literature supported the hypothesis of an interaction between systemic and local risk factors able to influence atherogenesis and lesion localization. The importance of local factors, however, remained unexplored. We therefore designed the present study to investigate the contribution of shear stress to the atherosclerotic process in different clinical settings. The finding that wall shear stress plays a major role in subjects at low CHD risk is not surprising and is potentially important to identify individuals who are prone to atherosclerosis but otherwise considered healthy. The prevalence of plaque and/or stenosis of the carotid tree is 18.9% in this group in the present study. It is likely that, of the low systemic CHD risk, these subjects will not receive enough “therapeutic” attention and atherosclerosis will progress to clinical manifestation.

The lack of any association between wall shear stress and IMT or carotid atherosclerosis in high-risk individuals is also an interesting finding. It is likely that the burden of the systemic CHD risk profile overcomes the effect of a single risk factor. Indeed, none of the 5 classic systemic risk factors associated with carotid atherosclerosis. Age probably integrates presence and time of exposure to all CHD risk factors and was therefore the only variable associated with carotid atherosclerosis. Furthermore, it is possible that low wall shear stress is only relevant for the development of atherosclerosis and loses importance when lesions are established.

It may be expected that, in the high-risk group, subjects without atherosclerosis would exhibit very high values of shear stress, but this was not the case. The reasons why subjects with a heavy CHD risk profile do not develop atherosclerosis are numerous. Genetic factors may be important, but some known risk factors, such as fibrinogen level, alcohol use, low physical activity, homocysteine level, and others not investigated in the present study, may also play a role. In addition, the manner in which risk factors are classified and defined may be inaccurate. Low-level, long-lasting risk factors may be more deleterious than high-level but short-lasting ones. Wall shear stress was not extremely high in individuals without atherosclerosis in the high-risk group, but it was markedly higher than in subjects with atherosclerosis in the low-risk group (20.44±6.82 versus 16.89±5.48 dyne/cm², respectively). We also hypothesized regarding a threshold level of wall shear stress. The atheroprotective effect may be maximal above a given value; in this case an elevated burden of risk is required to cause arterial damage. For decreasing levels of shear stress, in which there is decreasing protection of the arteries, a low burden of risk can also cause damage. Since shear stress decreases with age, it will eventually cross the threshold, exposing the arterial wall to the impact of risk factors. This hypothesis needs to be tested, and our data do not currently allow us to define such a threshold value. However, for age-adjusted wall shear stress levels <18 dyne/cm², the prevalence of carotid atherosclerosis markedly increases in the present population. Therefore, although the cutoff level has not yet been defined, a wall shear stress value of approximately 18 dyne/cm² merits attention.

The mechanisms by which low wall shear stress can cause arterial damage are known: increased fluid residence time and transport of atherogenic particles, increased platelet and macrophage adhesion to the arterial wall, modulation of the...
transcription of genes for nitric oxide,19–21 platelet-derived growth factor and transforming growth factor-β1,22,23 and increased local production of mitogenic substances. Recently, the influence of shear stress on endothelial function and nitric oxide production and breakdown has also been reported.24–26 Independently of the prominent mechanisms, high wall shear stress is atheroprotective, and low wall shear stress is probably atherogenic; the boundary between high and low needs to be defined.

The measurement of wall shear stress is a possible limitation of the present study. Intraoperator variability is acceptable.7 However, interoperator variability is a potential problem when the vessel is insonated and centerline velocity is obtained, and this may make results from different research laboratories difficult to compare.

Furthermore, the binary description of atherosclerosis as either present or absent is arbitrary and does not take into consideration the disease state, which of course has varying degrees. However, it is simple and convenient and allows the definition of consistent groups of subjects. Studies enrolling a larger number of participants could use a more accurate score to define the degree of atherosclerosis.

**Perspectives**

We believe that our study data disclose interesting new perspectives. The finding that low wall shear stress is a major factor in the development of carotid atherosclerosis, in subjects otherwise at low risk, may be of help in clinical practice, suggesting the need for more or less intensive treatment of these subjects. The search for factors (genetic, environmental, therapeutic) able to influence the level of wall shear stress can provide a more comprehensive approach to understanding the atherosclerotic process. We have many efficacious treatment opportunities to combat traditional risk factors, eg, antihypertensive, lipid-lowering, and antidiabetic agents. However, it is not known whether these treatments also influence wall shear stress. It cannot be excluded that part of the protective effect of these drugs, beyond their risk factor reduction, is due to an increase in wall shear stress. This field is completely open and needs to be explored. Other medications, existing or new, may prove to be efficacious in increasing shear stress levels, thus becoming part of the armamentarium against atherosclerosis.

**Acknowledgment**

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**References**


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