Low Wall Shear Stress in Carotid Arteries in Subjects with Left Ventricular Hypertrophy
Yinong Jiang, Katsuhiko Kohara, and Kunio Hiwada

Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular complications including atherosclerosis. The close linkage between LVH and carotid atherosclerosis has been the focus of much research. However, the underlying mechanism linking the two conditions is not fully understood. Low wall shear stress contributes to intimal thickening and atherosclerosis development as a local mechanism. In the present study, we investigated the relationship between wall shear stress and LVH in subjects with risk factors for atherosclerosis.

Eighty subjects with at least one risk factor for atherosclerosis; ie, hypertension, diabetes mellitus, hyperlipidemia, or smoking, were enrolled. Intimal-medial thickness (IMT), number of plaques, internal dimensions, and blood flow velocity in the common carotid artery were evaluated. Wall shear stress was calculated using a Poiseuillean parabolic model of velocity distribution: shear stress \( \frac{55}{4} \times \frac{33}{33} \times \frac{22}{22} \) blood viscosity \( \times \) central flow velocity/internal dimension. Subjects were divided into two groups; LVH(−) (n = 36) and LVH(+) (n = 44), according to their left ventricular mass index (LVMI).

Mean shear stress and systolic peak shear stress were significantly lower in subjects with LVH compared with subjects without LVH. Furthermore, mean shear stress \( r = -0.42, P < .0001 \) and peak shear stress \( r = -0.31, P < 0.01 \) were significantly inversely related to LVMI. Stepwise regression analysis revealed that wall shear stress independently correlated with LVMI as well as IMT. These results indicate that low shear stress could function as a local factor in the development of atherosclerosis in subjects with LVH.


KEY WORDS: Wall shear stress, carotid artery, intimal-medial thickness, left ventricular hypertrophy.
However, the underlying mechanisms linking LVH and carotid atherosclerosis are not fully understood. Wall shear stress, the frictional force produced by the circulating blood column on the intimal surface of the vessel, has been shown to play an important role in the progression of atherosclerosis.\textsuperscript{9–14} Atherosclerotic lesions had been shown to develop in regions of high shear stress,\textsuperscript{10} but recent experiments suggest that the occurrence of low shear stress correlates with lesion development.\textsuperscript{11,12} In vitro experiments also indicate that shear stress protects against the development of atherosclerosis.\textsuperscript{13–18} In a human study, IMT of the common carotid artery showed a significant negative correlation with shear stress in normal subjects,\textsuperscript{19} as well as in hypertensive patients.\textsuperscript{20} It was also shown that wall shear stress was significantly lower in carotid arteries with plaque.\textsuperscript{21}

Because arterial dilatation and blood flow velocity relate directly to wall shear stress,\textsuperscript{19–21} the morphologic as well as functional alterations in the carotid artery associated with LVH could result in the change of wall shear stress. Low shear stress induced by those alterations could act as a local factor in the progression of atherosclerosis. However, there has been no study investigating the relationship between wall shear stress and LVH. In the present study we evaluated wall shear stress by a noninvasive technique in subjects with risk factors for atherosclerosis.

**MATERIALS AND METHODS**

**Study Population** Eighty subjects with at least one risk factor for atherosclerosis, ie, hypertension, diabetes mellitus, hyperlipidemia, or smoking, participated in this study. They were recruited from consecutive patients who underwent evaluation of hypertension or atherosclerosis at Ehime University Hospital from December 1997 to December 1998. All subjects were untreated or had discontinued their therapy at least 1 week before the investigation. Hypertension was diagnosed as systolic blood pressure $\geq 140$ mm Hg or diastolic blood pressure $\geq 90$ mm Hg on more than three separate measurements in the outpatient clinic. Patients with valvular heart disease, heart failure, or a history of previous myocardial infarction or stroke were excluded from the study. Subjects were divided into two groups based on the presence of LVH. All procedures were approved by the ethical committee of Ehime University Hospital. Informed consent for the procedures was obtained from each patient.

**Echo-Doppler Examination of Carotid Artery** Carotid arteries were evaluated with an SSD-2000 (Aloka Co., Ltd. Tokyo, Japan) using a 7.5-MHz probe equipped with a Doppler system as previously described.\textsuperscript{6,20} After having the subject rest for at least 10 min in the supine position with the neck in slight hyperextension, we evaluated an optimal visualization of the common carotid artery, carotid bulb, and extracranial internal and external carotid arteries on both sides. From multiple approaches, we detected the presence of plaque as the presence of wall thickening at least 50% greater than the thickness of the surrounding wall. From anterior, lateral, and posterior approaches, IMT of the far wall was measured in both common carotid arteries 1 and 2 cm proximal to the bulb and averaged to obtain mean IMT. Measurements were never taken at the level of a discrete plaque. Hemodynamically significant luminal stenosis ($\geq 50\%$) was not detected in any subject.

Two-dimensionally guided M-mode tracings of the right common carotid artery at 1 cm proximal to the bulb were recorded with simultaneous electrocardiogram and phonocardiogram. M-mode images were obtained in real time using a frame grabber. The axial resolution of the M-mode system was 0.1 mm. End-diastolic and peak-systolic internal diameters were obtained from a continuous tracing of the intimal-luminal interface of the near and far walls of the common carotid artery in three cycles and averaged.

Doppler evaluation was performed on the right common carotid artery at the same site. The carotid artery was scanned in the anterior projection. Under guidance with color flow mapping, the sample volume was located at the center of the vessel. Peak systolic and diastolic velocities were measured from the blood flow wave in three cardiac cycles and averaged. Mean velocity was obtained by integration of the flow velocity curves. All measurements were performed in the upstream of the presence of the plaque. The variation coefficient for IMT was 1.6%.

**Wall Shear Stress** On the day of echo-Doppler examination, blood was withdrawn for the determination of blood viscosity. The blood was anticoagulated with heparin (35 IU/mL). The viscosity was measured with a cone/plate viscometer (Biorheolizer Tokimec, Osaka, Japan). The viscosity at shear rates of 375/s and 150/s was obtained, and the regression between shear rate and viscosity was determined for each patient. Between the shear rate of 1000/s and 100/s, blood viscosity is linearly related to shear rate.\textsuperscript{22}

In vivo wall shear rates were calculated using a Poiseuillean parabolic model of velocity distribution across the arterial lumen based on the assumption of laminar blood flow, according to the following formulae:\textsuperscript{19–21}

\[
\text{Peak-systolic shear rate} = \frac{4 \times \text{peak-systolic velocity}}{\text{peak-systolic internal diameter}}
\]
Mean shear rate = 4 × mean velocity/end-diastolic internal diameter.

The viscosity in situ, at both peak systolic shear rate and mean shear rate, were calculated from the regression line between shear rate and viscosity for each subject. Peak and mean wall shear stress were obtained by multiplying shear rate and viscosity.19–21

The reproducibility of shear stress was evaluated in five subjects. Echo-Doppler evaluation and blood viscosity measurements were repeated every week for 4 weeks. The variation coefficients averaged 2% and 3% for systolic and diastolic internal diameters, 6% for blood viscosity, and 12% and 9% for systolic and mean blood flow velocity. The variation coefficients were 8% and 6% for peak and mean shear stress, respectively.

**Determination of Left Ventricular Mass Index**

Echocardiographic studies were carried out using an SSD-9000 echocardiograph with a 3.5-MHz transducer (Aloka Inc.) according to the recommendations of the American Society of Echocardiography.23,24 Recordings were made at a paper speed of 100 mm/s. Left ventricular mass was estimated using the formula of Devereux and Reichek24,25 (Penn convention): LVM (g) = 1.04[(LVDd + IVST + PWT)³ – (LVDd)³] – 13.6, and was divided by the body surface area to obtain LVMI. Relative wall thickness (RWT) was measured at end-diastole as the ratio of 2 times PWT/LVDd. LVH was defined as LVMI > 108 g/m² in women and 118 g/m² in men.5,26 The variation coefficient for LVM determination was 4%.

**Statistical Analysis**

Data are expressed as mean ± SD. Differences between groups were assessed by ANOVA. Difference in prevalence was analyzed by $\chi^2$ test. Pearson’s correlation coefficient was used to test association. Stepwise regression analysis was applied to evaluate the determinant factors of IMT and LVMI. A $P < .05$ was defined as statistically significant.

**RESULTS**

**Study Subjects and Common Carotid Arteries**

Table 1 summarizes the clinical profiles of subjects with and without LVH. There were no differences in age, gender, and other risk factors except for hypertension between the two groups. The prevalence of hypertension was significantly higher in subjects with LVH, whereas the prevalences of smoking, hyperlipidemia, and diabetes mellitus were not significantly different between the two groups. The structural and functional parameters related to shear stress are summarized in Table 2. Subjects with LVH had significantly increased IMT, greater carotid arterial dimension, and slower blood velocity than those without LVH. There was no significant difference in blood viscosity between the two groups. Both peak systolic and mean shear stress were significantly lower in subjects with LVH.

**Left Ventricular Mass Index and Wall Shear Stress**

Left ventricular mass index showed a significant positive correlation with systolic carotid internal diameter ($r = 0.46$) and diastolic carotid internal diameter ($r =
TABLE 2. STRUCTURE, FUNCTIONAL PARAMETERS, AND SHEAR STRESS IN COMMON CAROTID ARTERY IN SUBJECTS WITH AND WITHOUT LEFT VENTRICULAR HYPERTROPHY

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Left Ventricular Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(-)</td>
</tr>
<tr>
<td>Intimal-medial thickness (mm)</td>
<td>0.79 ± 0.16</td>
</tr>
<tr>
<td>Number of plaques</td>
<td>0.2 ± 0.6</td>
</tr>
<tr>
<td>Systolic carotid internal diameter (mm)</td>
<td>7.0 ± 0.9</td>
</tr>
<tr>
<td>Diastolic carotid internal diameter (mm)</td>
<td>6.7 ± 0.8</td>
</tr>
<tr>
<td>Viscosity at 150 s(^{-1}) (centipoise)</td>
<td>4.8 ± 0.7</td>
</tr>
<tr>
<td>Viscosity at 375 s(^{-1}) (centipoise)</td>
<td>4.2 ± 0.7</td>
</tr>
<tr>
<td>Peak-systolic velocity (cm/s)</td>
<td>81.5 ± 17.7</td>
</tr>
<tr>
<td>Mean velocity (cm/s)</td>
<td>41.3 ± 10.9</td>
</tr>
<tr>
<td>Mean shear rate (s(^{-1}))</td>
<td>252 ± 72</td>
</tr>
<tr>
<td>Viscosity at mean shear rate (centipoise)</td>
<td>5.1 ± 8.0</td>
</tr>
<tr>
<td>Mean wall shear stress (dyne/cm(^2))</td>
<td>12.8 ± 4.0</td>
</tr>
<tr>
<td>Peak shear rate (s(^{-1}))</td>
<td>475 ± 120</td>
</tr>
<tr>
<td>Viscosity at peak shear rate (centipoise)</td>
<td>4.0 ± 7.9</td>
</tr>
<tr>
<td>Peak wall shear stress (dyne/cm(^2))</td>
<td>18.0 ± 4.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Presence of Plaque and Wall Shear Stress

Plaque(s) were observed in 31 subjects. In 23 subjects, plaque(s) were located in the right carotid artery. And in 14 patients, plaque(s) were located in either the internal carotid or bulb. Nine plaques were observed in the right common carotid arteries; however, all of them were located downstream of the place we measured blood flow velocity. When analysis was restricted to the arteries without plaque, there was still a significant negative correlation between LVMI and mean wall shear stress (r = -0.35, P = .015), as well as peak shear stress (r = -0.37, P = .008).

DISCUSSION

Left ventricular hypertrophy is a well-documented independent risk factor for cardiovascular complications. LVMI also showed a significant negative correlation with peak systolic velocity (r = -0.26) and mean velocity (r = -0.36). There was a significant negative correlation between mean wall shear stress and LVMI (Fig. 1). Peak shear stress also showed a significant negative correlation with LVMI (r = -0.31, P < .01).

Intimal-medial thickness also showed a significant negative correlation with peak systolic wall shear stress (r = -0.41, P < .001) as well as mean wall shear stress (r = -0.39, P < .001).

To further determine which parameters were directly related to LVH and carotid atherosclerosis, stepwise regression analyses were performed for IMT and LVMI with age, gender, pulse pressure, body mass index, and mean wall shear stress. They revealed that wall shear stress independently correlated with LVMI as well as IMT (Table 3).
as well as other pathologic conditions. A close linkage between LVH and atherosclerosis has also been well demonstrated. It has been shown that LVMI is significantly related to IMT, prevalence of plaques, and dilatation of the common carotid artery. Furthermore, LVH has been shown to be associated with the alteration of carotid arterial functional properties including reduced distensibility. Although the prevalences of carotid hypertension and of functional abnormalities are high in hypertensive patients with LVH, carotid hypertrophy and LVH do not share the same predisposing factors. The underlying mechanism linking LVH and carotid atherosclerosis is not fully understood.

The present study provided evidence that morphologic as well as functional alterations of the common carotid artery observed in subjects with LVH were associated with low shear stress in the common carotid artery. Furthermore, we also showed that low shear stress was independently associated with LVMI as well as IMT.

The Poiseuillean parabolic model of velocity distribution is based on the assumption that the blood flow is laminar. The presence of plaque induces an asymmetrical shape of the velocity profile, and thus the parabolic model would no longer be adequate to calculate shear rate. In the present study, none of the plaque(s) were present upstream of the Doppler sampling position. We further analyzed arteries free from plaque to eliminate the possible influence of the plaque on the velocity distribution. This also revealed that there was a significant negative correlation between LVMI and wall shear stress in the carotid artery free from the plaque.

Although the mechanism of how the shear stress influences atherosclerosis has not been fully understood, nitric oxide (NO) produced from the endothelial cells may underlay this mechanism. Stimulation of mRNA levels of NO synthase (NOS) and the production of NO have been shown to be induced by shear stress. Other possible mechanisms have been extensively investigated in vitro studies. Shear stress has been shown to downregulate the expression of VCAM-1, upregulate cyclooxygenase-2, induce tissue plasminogen activator, stimulate superoxide dismutase and activate transforming growth factor-1. All these changes produced by shear stress could result in protection against the atherogenic process.

However, whether low shear stress is a causal factor for atherosclerosis in vivo in subjects with LVH or whether low shear stress is the result of morphologic change in the artery remains to be determined. Lower shear stress has also been shown in hypertensive patients than in normotensive subjects. A high prevalence of hypertension in LVH subjects may in part explain the finding in the present study of lower shear stress in subjects with LVH. Because shear stress is a direct function of blood viscosity, blood flow velocity, and lumen diameter, both carotid arterial dilatation and the concomitant decrease in blood flow velocity observed in patients with LVH are responsible for the low shear stress in subjects with LVH. Recently, demonstrated an age-dependent decline of shear stress in normal subjects. An increase in vessel diameter concomitant with reduced distension with increasing age was shown to maintain storage capacity. Because it has been demonstrated that subjects with LVH have reduced distensibility of the common carotid artery, the same mechanism may serve to explain the dilatation of the common carotid artery resulting in reduction of shear stress.

In the present study, we evaluated the reproducibility of the method every week for 4 weeks. Although there was no difference in wall shear stress obtained at 1 week and 4 weeks after the termination of the treatment, there is a possibility that 1 week’s discontinuation of the treatment was not long enough to eliminate the effect of drugs on carotid arterial dimension, carotid arterial blood flow velocity, and blood viscosity. The effects of antihypertensive treatment on wall shear stress, especially its relevance to the regression of LVH, should be investigated.

In conclusion, our study demonstrated that local wall shear stress is low in subjects with LVH. Low shear stress may be one of the underlying mechanisms of the development of atherosclerosis in subjects with LVH.

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