Mechanical stresses on the arterial wall have been shown to participate in the pathogenesis of atherosclerosis as local factors. Wall shear stress and stretch are the most important hemodynamic forces involved, in addition to the radial compressive pressure. In recent studies, an association between mechanical stresses and atherosclerosis in the carotid artery has been reported. Shear stress has been shown to be negatively related to carotid intima-media thickness (IMT) in healthy individuals and patients with diabetes mellitus, hypertension, and left ventricular hypertrophy. Carallo et al reported that in healthy individuals, circumferential wall tension was positively correlated with carotid IMT. Since atherosclerosis is a complex trait closely associated with multiple risk factors, including hypertension, dyslipidemia, and diabetes mellitus, mechanical forces could change in response to these risk factors.

Shear stress is a tangential force on the endothelial surface produced by the friction of blood flow. As the stretch stimulus, mechanical strain produced by the stretch apparatus has been used in vitro, while as the circumferential wall tension, the normal mechanical force due to transmural pressure has been investigated in vivo. In vivo, mechanical strain depends on the property of the artery; circumferential wall tension may result in a larger mechanical strain in an elastic vessel than in a more rigid artery. It has also been shown that circumferential deformation and wall tension may act differently. Accordingly, the stretch stimulus can be evaluated as 2 factors in vivo: circumferential strain and mechanical wall tension. However, no study has evaluated circumferential strain and wall tension simultaneously as mechanical stress in vivo.

The objective of the present study was to elucidate the relationship between local mechanical forces and risk factors for atherosclerosis. Furthermore, circumferential strain was also evaluated as mechanical stretch in vivo in addition to wall tension.

Subjects and Methods

Study Population
Participants in the study were 117 subjects with at least 1 of the following risk factors for atherosclerosis: hypertension, dyslipidemia, diabetes mellitus, and/or current smoking. Hypertension was
defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg without medication in the outpatient clinic on at least 2 separate measurements. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL (7 mmol/L), 2-hour blood glucose after oral glucose tolerance test ≥200 mg/dL (11.1 mmol/L), or use of medication for diabetes. Dyslipidemia was defined as total cholesterol ≥220 mg/dL (5.69 mmol/L), and/or HDL cholesterol ≤35 mg/dL (0.90 mmol/L), and/or triglyceride ≥150 mg/dL (1.71 mmol/L). All current smokers smoked ≥10 cigarettes per day, while nonsmokers did not smoke cigarettes at all. Subjects were recruited from consecutive patients who underwent evaluation of hypertension or atherosclerosis at Ehime University Hospital from December 1997 to June 1999. All subjects were untreated or had discontinued their therapy at least 1 week before the investigation. Twenty subjects matched for age and sex and free from any risk factors were recruited as normal controls. All procedures were approved by the ethical committee of Ehime University Hospital. Informed consent to the procedures was obtained from each subject.

Echo-Doppler Examination of Carotid Artery
Carotid arteries were evaluated with SSD-2000 apparatus (Aloka Co, Ltd) with a 7.5-MHz probe equipped with a Doppler system, as previously described.6 In brief, with the neck in slight hyperextension, we evaluated an optimal visualization of the common carotid arteries (CCAs) after the subjects rested for at least 10 minutes. From multiple approaches, we detected the presence of discrete segments of atherosclerosis (plaque). Plaque was defined as the presence of wall thickening at least 50% greater than the thickness of the surrounding wall. IMT of the far wall was measured in the right CCA 1 cm proximal to the bulb from anterior, lateral, and posterior surrounding wall. IMT of the far wall was measured in the right CCA wall thickening at least 50% greater than the thickness of atherosclerosis (plaque). Plaque was defined as the presence of wall thickening at least 50% greater than the thickness of the surrounding wall. IMT of the far wall was measured in the right CCA 1 cm proximal to the bulb from anterior, lateral, and posterior approaches and averaged to obtain mean IMT. Measurements were never taken at the level of a discrete plaque.

Two-dimensionally guided M-mode tracings of the right CCA at 1 cm proximal to the bulb were recorded with simultaneous ECG and phonocardiogram. M-mode images were obtained in real time. End-diastolic (IDd) and peak-systolic (IDs) internal diameters were obtained by continuous tracing of the intimal-luminal interface of the near and far walls of the CCA in 3 cycles and averaged. The axial resolution of the M-mode system was 0.1 mm.

Doppler evaluation was performed on the right CCA at the same site and, if a plaque was present, upstream of the plaque. The carotid artery was scanned in the anterior projection. Under guidance with color flow mapping, 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 45° and 55°. 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 45° and 55°. Systolic peak velocity and mean velocity were obtained as the mean of 3 cardiac cycles.

SBP and DBP were measured by the same investigator (Y.J.) in the patient’s right arm with a mercury sphygmomanometer with the patient lying in the supine position for >10 minutes. Mean blood pressure (MBP) was obtained as (SBP+2×DBP)/3. Smoking was not permitted on the day of the examination. Total cholesterol, HDL cholesterol, triglyceride, and fasting glucose were measured with commercially available kits.

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 (Biorheoeizer TOKIMEC). 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 a shear rate of 1000/s and 100/s, blood viscosity has been shown to be linearly related to shear rate.25

In vivo wall shear rates were calculated with the use of a poiseuillean parabolic model of velocity distribution across the arterial lumen based on the assumption of laminar blood flow, according to the following formulas4-6-7:

\[
\text{Wall Shear Stress} = \frac{\text{Peak-systolic velocity}}{\text{ID}_d} \times \frac{8}{3} \times \frac{\text{Diameter}}{\text{Length}}
\]

Peak-systolic shear rate = 4×peak-systolic velocity/IDd
Mean shear rate = 4×mean velocity/IDd

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 values were obtained by multiplying shear rate and viscosity, with the assumption that blood is a newtonian fluid.4,5,7

Circumferential Wall Tension and Strain
Peak and mean circumferential wall tension values were obtained by Laplace’s law according to the report of Carallo et al:6

Peak circumferential wall tension (dyne/cm) = SBP×(IDd/2)
Mean circumferential wall tension (dyne/cm) = MBP×(IDd/2)

Arterial strain in the circumferential direction of the carotid artery was obtained as (IDc−IDd)/IDd (%).17

Reproducibility of Measurements
Echo-Doppler evaluation and blood viscosity measurement were repeated every week for 4 weeks in 5 subjects. 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 averaged 8% for both SBP and DBP. The variation coefficients were 6% and 4% for mean shear stress and circumferential wall tension, respectively. There were no differences in these parameters between 1 week and 4 weeks after the cessation of treatment.

Statistical Analysis
All values are expressed as mean±SD. Pearson’s correlation coefficient was used to test the association. ANOVA was used to compare the difference among groups. Stepwise regression analysis was used to evaluate the independent parameters for mechanical stresses. P<0.05 was considered statistically significant.

Results
Table 1 summarizes the demographic profiles of control subjects and subjects with risk factors. Atherosclerotic and...
hemodynamic characteristics are summarized in Table 2. All parameters of mechanical forces were significantly different between the 2 groups. Mechanical forces in subjects with risk factors were characterized by low wall shear stress, high circumferential wall tension, and reduced strain.

The relationships between mechanical forces and IMT are illustrated in Figure 1. There was a significant negative correlation between shear stress and IMT and a significant positive correlation between wall tension and IMT. However, there was no significant relationship between strain and IMT. The relationships between risk factors for atherosclerosis and mechanical forces and their relating parameters viscosity, arterial dimension, and blood velocity are summarized in Table 3. Blood pressure, HDL cholesterol, triglyceride, fasting blood glucose, and smoking were risk factors with a specific association with mechanical forces.

The cumulative effect of risk factors on mechanical forces is illustrated in Figure 2. Shear stress showed a significant negative relationship and circumferential wall tension showed a significant positive relationship with the number of risk factors. However, this dependency was not observed for strain. Stepwise regression analysis further revealed that the number of risk factors was significantly associated with mechanical forces independently of IMT (Table 4).

Discussion

Shear stress participates in the modulation of endothelial function.1–2 Recent studies both in vitro and in vivo indicate that low shear stress is related to atherosclerosis.1,13–16 Stretch also plays a pivotal role in the progression of atherosclerosis.1–3 The molecular mechanisms as well as clinical observations suggest that a high stretch stimulus is related to atherosclerosis.1–3 In the present study the relationship between mechanical forces and carotid atherosclerosis was evaluated in patients with risk factors, including hypertension, dyslipidemia, and/or diabetes. In this population, we confirmed previous findings that shear stress showed a significant negative correlation and circumferential wall stress showed a significant positive correlation with IMT.

The association between several risk factors and carotid atherosclerosis has been extensively studied.10–13 The relationship between risk factors and mechanical forces has also been investigated in a few studies. Shear stress has shown no change18 or was decreased6 in non–insulin-dependent diabetes mellitus. In previous studies we observed reduced shear stress in hypertensive patients8 as well as in subjects with left ventricular hypertrophy.9 In the present study we further observed that the associations with mechanical forces were different among risk factors. SBP showed a significant negative correlation with shear stress and strain. HDL cholesterol showed a significant positive correlation with shear stress and a negative correlation with wall tension. Fasting blood glucose was negatively associated with shear stress, while smoking showed a significant negative association with shear stress and a positive association with wall tension. Furthermore, the findings in the present study that the accumulation of risk factors precipitated alteration of mechanical stresses and that the number of risk factors was independently associated with mechanical forces indicate the additive effect of risk factors on mechanical forces.

As underling mechanisms, the association between risk factors and components of the mechanical forces viscosity,
dimension, and blood velocity was also investigated. The association between structural and functional parameters of the CCA with risk factors for atherosclerosis has been reported. CCA diameter has been shown to be related to risk factors for atherosclerosis, including hypertension and smoking.10,19,20 We also observed reduced blood flow velocity in hypertensive patients.21 The reduced shear stress in non–insulin-dependent diabetes mellitus patients has been shown to be a consequence of both decreased flow velocity and larger carotid diameter, by the same method as that used in the present study.6 It was also shown that carotid diameter increases in compensation for increased wall thickness.22 In the present study we further observed that the association between risk factors and the components of mechanical forces was significantly different among risk factors. Since shear stress is the direct consequence of carotid diameter, blood viscosity, and flow velocity, and wall tension is the product of blood pressure and carotid diameter, the alteration of these components associated with risk factors influences the mechanical forces. These findings indicate that alteration of the mechanical forces coincides with morphological and functional changes observed in response to the risk factors for atherosclerosis.

As the stretch stimulus, in vitro studies have investigated the effect of expansion of endothelium and vascular smooth muscle cells cultured on an elastic membrane mounted in a stretch device.1,2,14,15 Clinically, circumferential wall tension obtained by Laplace’s law was used as the stretch stimulus in vivo.7 Although circumferential wall stress dilates arteries, mechanical force evaluated in an in vivo study is actually different from stretch. Furthermore, Dobrin2 showed that medial thickening occurred in response to circumferential deformation but not to circumferential wall tension in a vein-graft model, in which he discriminated tension and deformation by using a band to narrow the carotid artery proximal to the vein graft. This finding suggests that the effect of circumferential wall tension and strain may be different in vivo. In the present study we did not find any association between strain and carotid atherosclerosis, suggesting that wall tension was more closely related to atherosclerosis than circumferential deformation in vivo.

Although we evaluated the hemodynamic forces in the carotid artery, the findings in the present study may be expanded to other arteries. The parallel alteration of the vessel diameters has been reported in carotid arteries, iliac arteries, femoral arteries, and popliteal arteries as a common pathological response in early atherosclerosis.23 Brachial arterial diameter has also been reported to be larger in diabetic patients24 and hypertensive patients25 than in control subjects. These findings indicate that risk factor–dependent alteration of hemodynamic forces may be a generalized phenomenon in systemic arteries.

Pulse pressure has been shown to be the major determinant of cardiovascular risk in elderly hypertensive subjects.26 In the present study pulse pressure showed significant association between strain and carotid atherosclerosis, suggesting that wall tension was more closely related to atherosclerosis than circumferential deformation in vivo.

Although we evaluated the hemodynamic forces in the carotid artery, the findings in the present study may be expanded to other arteries. The parallel alteration of the vessel diameters has been reported in carotid arteries, iliac arteries, femoral arteries, and popliteal arteries as a common pathological response in early atherosclerosis.23 Brachial arterial diameter has also been reported to be larger in diabetic patients24 and hypertensive patients25 than in control subjects. These findings indicate that risk factor–dependent alteration of hemodynamic forces may be a generalized phenomenon in systemic arteries.

Gnasso et al5 investigated wall shear stress in the carotid artery with plaque. They found that wall shear stress is lower in the carotid arteries where plaques are present than in plaque-free arteries. They concluded that shear stress in the CCA would influence downstream parameters. In the present study 13 plaques were observed in the right CCAs. Although all of those measured for determination of blood flow velocity were located downstream, it is also conceivable that the presence of plaque downstream could influence hemodynamic parameters upstream. It has also been reported that blood velocity and blood flow in the CCA were reduced in the presence of stenosis of the internal carotid artery.28 These

<table>
<thead>
<tr>
<th>TABLE 3. Correlation Coefficients Between Risk Factors and Mechanical Forces and Related Parameters in Total Population</th>
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<tr>
<td></td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Body mass index</td>
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<tr>
<td>SBP</td>
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<td>DBP</td>
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<td>Pulse pressure</td>
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<td>Total cholesterol</td>
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<td>Triglyceride</td>
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<td>Fasting blood glucose</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>No. of risks</td>
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</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001.
findings suggest that the presence of plaque may influence hemodynamic parameters in addition to the risk factors discussed in this study.

Although the methods used in the present study have been reported in previous studies, there are several limitations of an indirect estimation of hemodynamic parameter. The rationale for the poiseuillean parabolic model of blood flow velocity distribution is based on the assumption of laminar blood flow in the CCA. We could not eliminate the possibility that the presence of plaque, even downstream, may interfere with laminar blood flow. Pulse pressure and SBP significantly increase from the central to the peripheral arteries. Since we calculated systolic wall tension using brachial SBP, it is possible that we overestimated systolic wall tension, especially in those of younger age with tall stature.

In summary, risk factors for atherosclerosis were significantly associated with alteration of mechanical forces. The accumulation of risk factors caused further deteriora-

### Table 4. Stepwise Regression Analysis for Mechanical Forces and Risk Factors for Atherosclerosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>F</th>
<th>Partial Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of risks</td>
<td>10.4</td>
<td>0.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IMT</td>
<td>6.7</td>
<td>-0.29</td>
<td>0.0016</td>
</tr>
<tr>
<td>Age</td>
<td>6.1</td>
<td>-0.20</td>
<td>0.015</td>
</tr>
<tr>
<td>No. of risks</td>
<td>51.0</td>
<td>0.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>11.9</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Stepwise regression analyses for mean shear stress and mean circumferential wall tension were performed with the following parameters: age, sex, body mass index, IMT, number of risk factors. The parameters entered into the equations are listed in the table.

### Acknowledgments

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### References


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