Multiaxial Mechanical Characteristics of Carotid Plaque
Analysis by Multiarray Echotracking System

Anna Paini, MD; Pierre Boutouyrie, MD, PhD; David Calvet, MD; Mustapha Zidi, PhD; Enrico Agabiti-Rosei, MD; Stéphane Laurent, MD, PhD

Background and Purpose—Carotid plaque rupture depends on the various types of mechanical stresses. Our objective was to determine the multiaxial mechanical characteristics of atherosclerotic plaque and adjacent segment of the common carotid artery.

Methods—A novel noninvasive echotracking system was used to measure intima-media thickness, diameter, pulsatile strain, and distensibility at 128 sites on a 4-cm long common carotid artery segment. The study included 62 patients with recent cerebrovascular ischemic event and either a plaque on the far wall of common carotid artery (n=25) or no plaque (n=37).

Results—The mechanical characteristics of the carotid segment devoid of plaque did not differ between the two groups. Among patients with plaque, 16 had a larger radial strain at the level of plaque than at the level of adjacent common carotid artery (pattern A: outward-bending strain). The eight patients who had an opposite pattern (inward-bending strain) were more often dyslipidemic (100% versus 56% P=0.03) and type 2 diabetic (63% versus 12%, P=0.04) than pattern A patients. Strain gradient significantly decreased in parallel with the presence of dyslipidemia and/or type 2 diabetes. Longitudinal gradients of distensibility and Young’s elastic modulus were consistent with strain gradients.

Conclusions—Type 2 diabetes and dyslipidemia were associated with a stiffer carotid at the level of the plaque than in the adjacent common carotid artery leading to an inward-bending stress. The analysis of plaque mechanics along the longitudinal axis may afford useful information, because repetitive bending strain of an atherosclerotic plaque may fatigue the wall material and result in plaque rupture. (Stroke. 2007;38:117-123.)

Key Words: atherosclerotic plaque ■ carotid artery ■ mechanics ■ stiffness ■ ultrasound
50% of the surrounding intima to media wall thickness value or structure that encroaches into the arterial lumen of at least 0.5 mm or plaques on the far wall of the CCA. Plaque was defined as a focal

Dyslipidemia was defined as abnormal fasting plasma cholesterol levels or the current use of lipid-lowering agents. Smoking status was defined as current or past use versus never.

Training was defined as probable or possible according to National Institute of Health’s Physicians or the emergency ambulance service.

Subjects and Study Design
The study cohort included 62 consecutive patients hospitalized in the stroke unit of Hôpital Sainte-Anne in Paris from April 28 to September 22, 2005, with a final diagnosis of ischemic stroke or transient ischemic attack. Transient ischemic attacks were classified as probable or possible according to National Institute of Neurological Disorders and Stroke criteria. Patients were referred to our stroke unit by emergency departments of local hospitals we are accustomed to working with or referred directly by general practitioners or the emergency ambulance service.

Our standard workup included brain magnetic resonance imaging, a 12-lead electrocardiogram or a three-lead monitoring, standard blood tests, cervical arteries (Doppler ultrasound and/or cervical gadolinium-enhanced magnetic resonance angiography), and echocardiography. Magnetic resonance imaging was performed on a 1.5-T magnetic resonance unit equipped with echoplanar capability (Signa; General Electric Medical Systems). Vascular risk factors known before stroke or transient ischemic attack, coexisting comorbidities and treatment before stroke, or transient ischemic attack were systematically recorded. Causes of stroke were classified according to TOAST criteria.10

Essential hypertension was defined as those individuals who had systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg or treated with blood-pressure-lowering drugs. Diabetes was indicated by abnormal fasting plasma glucose levels or the current use of insulin or an oral hypoglycemic agent. Dyslipidemia was defined as abnormal fasting plasma cholesterol (low-density lipoprotein cholesterol) levels or the current use of lipid-lowering agents. Smoking status was defined as current or past use versus never.

Patients were divided into two groups according to the presence of plaques on the far wall of the CCA. Plaque was defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima to media wall thickness value or demonstrates a thickness of 1.5 mm as measured from the media–adventitia interface to the intima–lumen interface.11 All patients signed an informed consent.

Methods
The noninvasive investigation was performed in a room dedicated to echography after 15 minutes of recumbent rest. Two physicians (A.P., P.B.), trained and certified in vascular echography, performed blood pressure and arterial measurements.

Before the ultrasound examination, three brachial blood pressure measurements were taken (Omron 705 CP; Ohmeda) and the average of the last two brachial blood pressure and arterial measurements.

All patients underwent CCA measurements with a novel system (ArtLab, ESAOTE, Italy) based on high-resolution echotrack technology (WallTrack system), including the use of a 128 RF line multiarray.12 Rough RF data are analyzed online and 6-second cineclips are stored without compression (120 Mbytes) for offline analysis. This novel technology gives access to all major mechanical parameters for 4-cm arterial segments: intima-media thickness (IMT), internal diameter (D₀), and radial wall strain (ie, the pulsatile strain in the radial direction [(D₀−D₂)/(D₀)]) in the artery as a hollow structure were assessed through cross-sectional distensibility and compliance. The elastic properties of the arterial wall material were estimated with the incremental elastic modulus (Einc, also named Young’s elastic modulus). Cross-sectional distensibility and compliance. The elastic properties of the arterial wall material were estimated with the incremental elastic modulus (Einc, also named Young’s elastic modulus).

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Each carotid plaque was insonated in different axes to determine the position in which the major body of plaque was imaged. Transverse sections were performed to check that the lateral extension of the plaque was small and less than 45° of angle. Then, longitudinal measurements were performed upstream of the carotid plaque and at the site of the plaque (Figure 2). For simplification, eight adjacent zones (5 mm, ie, 16 RF lines) were defined starting from zone 1 immediately close to the bulb to zone 8 further upstream. Data (IMT, diameter, strain, distensibility, and so on) were averaged within each zone. For each individual, the zones corresponding to the localization of the plaque were determined and contrasted against the upstream zones where IMT appeared normal.

Data Analysis
Data were expressed as mean±SD. Quantitative variables were compared by means of an unpaired or a paired (upstream and at the site of plaque) Wilcoxon nonparametric test. Categorical variables were compared by means of a χ² test. Associations between arterial parameters and quantitative factors were analyzed with general linear model–analysis of variance. A value of P<0.05 was considered significant. Statistical analysis was performed using NCSS 2004 package software (Hintze JL).

Results
Patients With and Without Plaque
Patients were divided into two groups according to the presence or absence of plaque at the site of the CCA: 37 subjects had no plaque and 25 subjects had plaque. Demographic and hemodynamic characteristics of the two groups are shown in Table 2. Among 62 patients, 89% had an ischemic stroke and 11% a transient ischemic attack. The territory of stroke was the carotid artery in 50 patients (81%), the vertebrobasilar territory in five patients (8%), and remained undetermined in seven patients (11%). Patients with plaque were significantly older and had a higher SBP and PP than patients without plaque (P<0.05). Both groups were comparable for gender, weight, height, diastolic and mean blood pressure. The prevalence of hypercholesterolemia was higher in patients with plaque (72% versus 35%, P<0.005).

However, no significant difference was observed between groups concerning the prevalence of hypertension, diabetes, smoking, and cardiovascular treatments before ischemic events (antihypertensive drugs, use of statins or fibrates, use of antiplatelet drugs). Etiologies of strokes did not differ significantly between patients with or without plaque.

Mechanical characteristics of the CCA were compared in both groups. Arterial parameters of all CCA zones did not significantly differ in patients without plaque (data not shown) and were thus averaged. They were compared with arterial parameters in zones upstream of the plaque in patients with plaque. Carotid IMT at the site of the normal arc and at the site of the carotid plaque is represented proportionally to the values of Tables 3 and 4.

Each carotid plaque was insonated in different axes to determine the position in which the major body of plaque was imaged. Transverse sections were performed to check that the lateral extension of the plaque was small and less than 45° of angle. Then, longitudinal measurements were performed upstream of the carotid plaque and at the site of the plaque (Figure 2). For simplification, eight adjacent zones (5 mm, ie, 16 RF lines) were defined starting from zone 1 immediately close to the bulb to zone 8 further upstream. Data (IMT, diameter, strain, distensibility, and so on) were averaged within each zone. For each individual, the zones corresponding to the localization of the plaque were determined and contrasted against the upstream zones where IMT appeared normal. Longitudinal strain gradient was defined as the carotid strain at the level of the plaque minus carotid strain in adjacent “normal” CCA strain independently of the distance between plaque and normal CCA. It was used to determine the extent of longitudinal bending strain.14

Data Analysis
Data were expressed as mean±SD. Quantitative variables were compared by means of an unpaired or a paired (upstream and at the site of plaque) Wilcoxon nonparametric test. Categorical variables were compared by means of a χ² test. Associations between arterial parameters and quantitative factors were analyzed with general linear model–analysis of variance. A value of P<0.05 was considered significant. Statistical analysis was performed using NCSS 2004 package software (Hintze JL).
(P=0.01) after adjustment for age and SBP, two factors that differed between the groups (Table 3). No significant difference between groups was observed for the other parameters (Table 3).

### TABLE 3. Arterial and Mechanical Parameters of the CCA in Patients With or Without Plaque (measurements performed on the proximal CCA)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without Plaque (n=37 subjects)</th>
<th>With Plaque (n=25 subjects)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter, external, mm·10⁻³</td>
<td>8198±988</td>
<td>8443±975</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter, internal, mm·10⁻³</td>
<td>6623±985</td>
<td>6689±983</td>
<td>NS</td>
</tr>
<tr>
<td>IMT, mm·10⁻³</td>
<td>791±121</td>
<td>877±130</td>
<td>0.01</td>
</tr>
<tr>
<td>Ds−Dn, mm·10⁻³</td>
<td>423±176</td>
<td>457±207</td>
<td>NS</td>
</tr>
<tr>
<td>Radial strain, Dn−D−D/Dn, %</td>
<td>5.36±2.38</td>
<td>5.56±2.42</td>
<td>NS</td>
</tr>
<tr>
<td>Distensibility, kPa−1·10⁻³</td>
<td>19.6±15.4</td>
<td>17.1±10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Compliance, m²·kPa−1·10⁻⁷</td>
<td>6.02±4.40</td>
<td>5.55±3.33</td>
<td>NS</td>
</tr>
<tr>
<td>Young elastic modulus, kPa</td>
<td>677±427</td>
<td>751±560</td>
<td>NS</td>
</tr>
<tr>
<td>Circumferential wall stress, kPa</td>
<td>71.2±16.7</td>
<td>70.9±17.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Adjusted to age and SBP.

NS indicates nonsignificant.

**Patients With Plaque**

The maximum IMT value on the plaque was 1495±106 mm·10⁻³. When we considered the mean IMT value along a 0.5-cm plaque length, it was lower (1143±134 mm·10⁻³) by definition. In the group of 25 patients with plaque, we analyzed the difference between arterial parameters at the site of the plaque (ie, on the distal CCA) and upstream (ie, on the proximal CCA). Only one patient was excluded from this analysis because of the proximal extension of the plaque with no apparently “normal” CCA. In the 24 patients as a whole, IMT and external diameter at the site of plaque were higher than in adjacent CCA (P<0.05) (data not shown).

We analyzed the strain characteristics along the longitudinal axis of the CCA segment. Strain gradient was calculated as the carotid strain at the level of the plaque minus carotid strain in adjacent CCA and was used to determine the extent of longitudinal bending strain. We observed that 16 patients had a larger radial strain at the level of plaque than at the level of adjacent CCA (further defined as pattern A, ie, strain gradient was >1) and that eight patients had a smaller radial strain at the level of plaque than at the level of adjacent CCA (further defined as pattern B, ie, strain gradient was <1) (Figure 2).

Pattern B patients were more often dyslipidemic (9 of 16 versus 8 of 8, P=0.03) and type 2 diabetic (2 of 16% versus
TABLE 4. Arterial Parameters at the Level of the CCA and at the Level of Plaque in Patients With a Strain Pattern Type A or B

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pattern A (n=16 subjects)</th>
<th>P (plaque versus CCA)</th>
<th>Pattern B (n=8 subjects)</th>
<th>P (plaque versus CCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CCA</td>
<td>Plaque</td>
<td>CCA</td>
<td>Plaque</td>
</tr>
<tr>
<td>Diameter, external, mm · 10^-3</td>
<td>8093±1043</td>
<td>8251±895</td>
<td>NS</td>
<td>8498±768</td>
</tr>
<tr>
<td>Diameter, internal, mm · 10^-3</td>
<td>6258±953</td>
<td>5934±923</td>
<td>0.04</td>
<td>6908±875</td>
</tr>
<tr>
<td>IMT, mm · 10^-3</td>
<td>917±113</td>
<td>1158±125</td>
<td>&lt;0.001</td>
<td>794±129</td>
</tr>
<tr>
<td>D5−D6, mm · 10^-3</td>
<td>397±207</td>
<td>560±259</td>
<td>&lt;0.01</td>
<td>575±156</td>
</tr>
<tr>
<td>Radial strain, %</td>
<td>4.96±2.56</td>
<td>6.5±2.53</td>
<td>&lt;0.01</td>
<td>6.74±1.66</td>
</tr>
<tr>
<td>Distensibility, kPa^−1 · 10^-3</td>
<td>16.6±12.4</td>
<td>22.3±11.2</td>
<td>&lt;0.001</td>
<td>18.2±3.9</td>
</tr>
<tr>
<td>Compliance, m² · kPa^−1 · 10^-7</td>
<td>4.84±3.60</td>
<td>6.20±2.92</td>
<td>&lt;0.01</td>
<td>6.96±2.30</td>
</tr>
<tr>
<td>Young elastic modulus, kPa</td>
<td>802±669</td>
<td>374±173</td>
<td>&lt;0.01</td>
<td>543±146</td>
</tr>
<tr>
<td>Circumferential wall stress, kPa</td>
<td>65.0±15.5</td>
<td>53.1±13.5</td>
<td>&lt;0.001</td>
<td>82.8±16.4</td>
</tr>
<tr>
<td>Longitudinal strain gradient, %</td>
<td>1.7±2.5</td>
<td></td>
<td></td>
<td>-2.2±1.3</td>
</tr>
</tbody>
</table>

NS indicates nonsignificant.
incremental elastic modulus to estimate the elastic properties of the arterial wall material, like in our previous studies.13 We used a well-known method derived from mechanical engineering, which allows calculating the parameters of interest for shells of revolution and thick-walled tubes16,18 and evaluating the properties of an equivalent material (equivalent in volume to the arterial wall with homogeneous and linear deformation under physiological pressures). We used this method for three reasons. First, heterogeneity was limited with a mean maximum IMT of 1.49 mm at the site of the plaque (Table 4) compared with a mean IMT of normal CCA between 0.79 and 0.92 mm (Table 4). Second, the thickness of the plaque was moderate in the present study with a mean maximum of 1.49 mm for a mean lumen diameter of 6.19 mm. Thus, the geometry of these early atherosclerotic plaques was different from severe plaques reported in the literature.4,6 Third, a detailed analysis of a heterogeneous material, using a finite element method, was not in the scope of the present study.

In all patients, the internal carotid artery was stenotic, often calcified, and the algorithm of the ArtLab system was not adapted to the interface recognition in such plaque. Indeed, the algorithm of the ArtLab system was developed to assess thickened walls or small plaques, like those observed at the site of the CCA.

We included patients with a recent ischemic stroke and with a lesion of the internal carotid artery to increase the probability to detect an abnormal pattern of arterial deformation along the ipsilateral CCA. Plaque was either continuous with the culprit plaque on the internal carotid (n=11) or not (n=13). Stroke was not attributed to the studied CCA plaque.

Interpretation of Findings
The main findings of our study are the following: (1) the mechanical characteristics of the proximal carotid segment did not differ between patients with carotid plaque and patient without; (2) the elasticity of plaque was either higher or lower than in the adjacent CCA; and (3) patients who had a lower elasticity at the site of the plaque than in adjacent CCA (pattern B) were more often dyslipidemic and type 2 diabetic than patients who had an opposite strain gradient (pattern A).

Strain gradient along the CCA can be considered as an indicator of the disturbed integrity of the vessel wall and hence a possible predictor of vessel wall fragility leading to plaque rupture. We determined two different patterns of longitudinal strain gradient: in pattern A, carotid was outwardly strained in the zone affected by plaque; in pattern B, carotid was inwardly strained in the zone affected by plaque. In pattern A, arterial wall material was more elastic at the site of the plaque than upstream, whereas it was the converse in pattern B. Pattern B patients were more often dyslipidemic and type 2 diabetic than pattern A patients. In the whole group of patients with carotid plaque, strain gradient significantly decreased in parallel with the presence of dyslipidemia and/or type 2 diabetes (none, one of those, both) (Figure 3).

These results suggest that the changes in plaque composition and geometry associated with type 2 diabetes and dyslipidemia increase the stiffness of the wall material and limit the strain of the whole carotid wall induced by pulsatile pressure. Arterial stiffness can be increased by advanced glycation end products, which cause crossbridges between macromolecules of the extracellular matrix.19 Initial atheroma formation in response to high glycemia19 is associated with reduced wall elastic modulus.8

The relationship between longitudinal strain gradient and plaque rupture is not unequivocal. Rupture is associated with stress concentrations, which are affected by plaque lipid composition, fibrous cap thickness, plaque area, plaque shoulder, histology, and inflammation.2,4 Plaque mechanics are generally analyzed in a cross-section, and circumferential stress concentrations were found to be maximum at the shoulder of the fibrous cap of an asymmetric plaque with increased lumen convexity.2-4 However, heterogeneity of arterial mechanics should also be analyzed along the longitudinal axis, because it may generate stress concentrations at the junction of distensible and stiff areas. In addition, fatigue, which refers to a chronic failure process induced by repetitive loading, may lead to plaque rupture through stress levels that are much lower than the critical stress.4 Repetitive bending strain of an atherosclerotic plaque in the longitudinal axis may fatigue the wall material and result in plaque rupture.

Type 2 diabetes and dyslipidemia have been reported as risk factors for plaque rupture.20 These observations and the present study suggest that pattern B patients, having more often type 2 diabetes and dyslipidemia, would be more exposed to plaque rupture than pattern A patients in response to a specific bending strain. Whether stress concentrations and fatigue, generated by an inward-bending stress; expose the plaque to a greater risk of rupture than stress concentrations21 and fatigue generated by an outward-bending stress (pattern A) remains to be determined.

In conclusion, type 2 diabetes and dyslipidemia were associated with a stiffer carotid at the level of the plaque than in adjacent CCA, leading to an inward bending stress. The analysis of plaque mechanics along the longitudinal axis may afford useful information, because repetitive bending strain of an atherosclerotic plaque may fatigue the wall material and result in plaque rupture.

Disclosures
None.

References
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