Local Effects of Atherosclerotic Plaque on Arterial Distensibility

Cristina Giannattasio, Monica Failla, Guglielmo Emanuelli, Alessandra Grappiolo, Lucia Boffi, Davide Corsi, Giuseppe Mancia

Abstract—Hypertension, diabetes, and hypercholesterolemia are characterized by a reduction in arterial distensibility and by accelerated atherosclerosis. Whether arterial stiffening is an inherent feature of these conditions or just the consequence of the atherosclerotic clinical or subclinical lesions is not known, however. Our aim was to obtain information on this issue by directly measuring, in humans, arterial distensibility both at the site of an atherosclerotic lesion and at the proximal normal site. In 10 patients (8 men; mean±SEM age, 65.2±3.4 years) affected by monolateral hemodynamic significant internal carotid artery stenosis, we measured arterial distensibility (Wall Track System; PIE Medical) bilaterally, both at the internal carotid artery and at the common carotid artery level. In the common carotid artery, measurements were made 3 cm below the bifurcation. In the affected internal carotid artery, measurements were made at the plaque shoulder (wall thickness of 2 mm). Measurements were made in the contralateral internal carotid artery at a symmetrical level. Arterial wall thickness was measured in the same site of arterial distensibility. Arterial distensibility was less in the internal than in the common carotid artery, with a marked reduction at the plaque internal carotid artery level compared with the corresponding contralateral site (−45%, P<0.01). It was also less, however, in the common carotid artery branching into the atherosclerotic internal carotid artery than in the contralateral common carotid artery (−25%, P<0.05). Wall thickness was similar in the 2 common carotid arteries and obviously greater in the affected internal carotid artery than in the contralateral artery. Arterial distensibility was markedly less in the internal carotid artery where there was a plaque compared with the intact contralateral internal carotid artery; it was also less, however, in the common carotid artery of the affected side in comparison with the contralateral common carotid artery. This provides evidence that the effect of a plaque on arterial mechanical properties is not limited to the actual plaque site but rather extends to a considerable degree in a proximal direction. (Hypertension. 2001;38:1177-1180.)

Key Words: arteries ■ atherosclerosis ■ plaque

Several studies have shown that conditions such as hypertension, diabetes, and, to a lesser extent, hypercholesterolemia are characterized by a reduction in arterial distensibility.1-4 This has clinical implications because studies in animals have reported a reduction in arterial distensibility to be accompanied by accelerated atherosclerosis, possibly because arterial stiffening increases the traumatic effect of intravascular pressure on the vessel wall.5 In hypertension, diabetes, and hypercholesterolemia, atherosclerosis starts before the appearance of the clinical complications of these conditions. This poses the question of whether arterial stiffening is an inherent feature of these conditions or just the consequence of the atherosclerotic lesions. In the present study, our aim was to obtain information on this issue by directly measuring in humans arterial distensibility both at the site of an atherosclerotic lesion and at the proximal normal site.

Methods

Subjects

We investigated 10 patients (8 men; mean±SEM age, 65.2±3.4 years) selected on a consecutive basis if they (1) were <75 years old and had (2) hemodynamically significant stenosis of an internal carotid artery (>75%) on color Doppler echocardiography and angiography, (3) no atherosclerotic lesions in the ipsilateral common carotid artery, and (4) no atherosclerotic lesions in the contralateral common and internal carotid arteries. All patients had to be in sinus rhythm and devoid of major systemic diseases. Four of 10 patients were hypertensive on long-term treatment with conventional drugs (a diuretic plus an ACE inhibitor or an angiotensin II receptor antagonist). Two patients had type 2 diabetes mellitus and were receiving oral drug therapy. Six patients were ex-smokers, and the remaining 4 had never smoked. All subjects agreed to participate in the study after being informed of its nature and purpose. The protocol of the study was approved by the ethics committee of our hospital.

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Diastolic Diameters and Systolic-Diastolic Diameter Changes in 4 Arterial Sites Examined

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Contralateral Side</th>
<th>Stenotic Side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common Carotid Artery</td>
<td>Internal Carotid Artery</td>
</tr>
<tr>
<td>Diastolic diameter, mm</td>
<td>8.5±0.2</td>
<td>6.5±0.1</td>
</tr>
<tr>
<td>Systolic–diastolic diameter change, μm</td>
<td>450.8±39.8</td>
<td>274.8±43.1</td>
</tr>
</tbody>
</table>

Data are mean±SEM.
*P<0.05, †P<0.01 vs corresponding values of contralateral side.

Arterial Distensibility

Arterial distensibility was assessed with an echo-tracking device (Wall Track System; PIE Medical). The device made use of a highly focalized transducer operating at a frequency of 7.5 MHz that was manually positioned over the vessel to be examined, with gel used as the medium. With the subject supine and the neck in partial extension, the transducer was oriented perpendicularly to the longitudinal axis of the vessel based on the acoustic Doppler signal and on the B-mode echo image, so that its focal zone was located in the center of the artery and the backscatter echoes from both the anterior and the posterior walls could be clearly visualized and electronically digitized (via an analogue-digital fast transducer) to allow internal diameter variations to be derived at a 50 Hz with a spatial resolution of 300 μm.

The arterial diameter at diastole and the systolic-diastolic diameter changes were measured bilaterally at both the internal carotid artery and the common carotid artery levels. In the common carotid artery, measurements were made 3 cm below the bifurcation. In the affected internal carotid artery, measurements were made at the plaque shoulder where the wall had a thickness of 2 mm. Measurements were made in the contralateral internal carotid artery at a symmetrical level. Wall thickness also was measured at the site of the arterial distensibility measurements. Measurements were obtained through an ultrasonographic device (SONOS 5500; Agilent Technologies) by first scanning the artery in B mode, then freezing the digitized image in M mode, and finally tracking the inner hypoechoic and the middle anechogenic wall layers.

In each subject, heart rate was measured with ECG. Blood pressure was measured from a brachial artery with a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. It was further measured with a semiautomatic device (Dinamap), and carotid artery distensibility was derived according to the equation:

\[
\text{Distensibility} = \frac{2(D_d - D_s)}{D_s} \times P,
\]

where \(D_d\) is the diastolic diameter of the vessel, \(D_s\) is the systolic-diastolic diameter change, and \(P\) is the corresponding brachial pulse pressure.

Integrated Backscatter Measurements

On both the common and internal carotid arteries of the affected side, at the same sites in which arterial distensibility and wall thickness were measured, we also made use of an ultrasound color Doppler echocardiography device (SONOS 5500) to obtain a signal to analyze with a special software package (ie, acoustic densitometry) as described by Takisue et al using a 7.5-MHz linear-array transducer (axial resolution, 0.1 mm). This system provides envelope-detected integrated backscatter (IBS) images in which the gray level is displayed proportional to the IBS power. A maximum of 60 frames displayed at a real-time frame rate of 30 Hz (30 frames/s) are captured in cine-loop memory and subsequently stored on an optical disk in digital format with the same resolution of the scan converted memory (512×512, 8 bits). The return echoes that impinge on the individual elements of the phased-array transducer are amplified, mixed to the intermediate frequency, and summed with appropriate time delays to obtain a focused beam. This intermediate-frequency signal, which is uniquely related to the radiofrequency signal, is sent to either a standard ultrasound video processing chain or a special IBS processor before scan conversion. Then the processor computes the IBS power along each scan line before scan conversion and real-time display on the ultrasound monitor. The resulting image is relatively free of random acoustic noise because of the local averaging or integration of the backscatter signal power along each scan line. The IBS image is internally calibrated in decibels and has a dynamic range of 64 dB in the SONOS 5500 system. In the present study, we used 21×21 pixel rectangular regions of interest (ROIs). The average power of the IBS signal contained within the ROI was measured and displayed in decibels for a total of 60 time frames. The system automatically calculated the average value of the IBS signal, which was also displayed in decibels. As previously described, we adopted adventitia as the reference object. Absolute IBS values of the adventitia were between 52 and 54 dB.

Protocol and Data Analysis

Each subject was asked to come to the outpatient clinic of the San Gerardo University Hospital in the afternoon after a 12-hour abstinence from alcohol and caffeine consumption. The study (which began 3 hours after a light meal) had the following protocol: (1) blood pressure was measured 3 times with a mercury sphygmomanometer with the subject in the sitting position, (2) the subject was placed supine in a quiet room kept at constant temperature (21°C) with the Dinamap device in place, and (3) after a 15-minute interval, blood pressure was measured 3 times with the Dinamap device and carotid artery examination was carried out with the Wall Track System (each vessel site was examined 5 times for 6 seconds each) at 2-minute intervals. (4) The internal and common carotid arteries of the affected side were subjected to IBS measurements. Arterial distensibility and IBS measurements were each obtained by a single investigator (C.G. and M.F., respectively). Data were calculated by investigators unaware of ultrasound characteristics of the patients. In each patient, the sphygmomanometric values and the Dinamap values, as well as the diastolic arterial diameter, the systolic-diastolic diameter change, the intima-media thickness, and the calculated distensibility values for each investigated vessel, were averaged. In our laboratory, the intrasession and intraobserver coefficients of variation for common and internal carotid diameter values are 1.7% and 2.0%, respectively. The corresponding coefficient of variation for wall intima-media thickness and IBS values are 3% and 2.5%, respectively. Results from individual subjects were averaged and are shown as mean±SEM values separately for each arterial site examined. The statistical significance of the differences in mean values was assessed by 2-way ANOVA. The 2-tailed t-test for paired and unpaired observations was used to locate the statistical significance of between-group differences using the Bonferroni correction for multiple comparisons. \(P<0.05\) was taken as the level of statistical significance.

Results

In the 10 patients, sphygmomanometric systolic blood pressure was 152.3±2.7 mm Hg and diastolic blood pressure was 84.2±2.3 mm Hg. The corresponding values for Dinamap blood pressure measurements were 149.1±3.2 and 76.8±3.0 mm Hg, with a pulse pressure of 72.3±3.0 mm Hg.

As shown in the Table, diastolic diameter and systolic-diastolic diameter changes were less in (1) the internal than the common carotid artery and (2) the internal carotid artery.
of the affected than that of the unaffected side. Wall thickness was similar in the 2 common carotid arteries but, as expected, much greater in the internal carotid artery of the affected side than in that of the unaffected side. Arterial distensibility was less in the internal than in the common carotid artery with a marked reduction at the plaque internal carotid artery level compared with the corresponding contralateral site. It was also less, however, in the common carotid artery branching into the atherosclerotic internal carotid artery than in the contralateral common carotid artery (Figure).

The IBS values were markedly different at the plaque level compared with the ipsilateral common carotid artery. In the former, the value was 23.08 ± 3.1, whereas in the latter, it was 16.6 ± 1.6. The difference was statistically significant (P < 0.05).

Discussion

In our patients, arterial distensibility was markedly less in the internal carotid artery where there was plaque compared with the intact contralateral internal carotid artery. This confirms the observations that arterial segments that show atherosclerotic lesions are characterized by marked stiffening.10–13 This may have adverse consequences because reduction in vessel expansion and arterial stiffening may further reduce blood flow already curtailed by the stenosis. It may also increase the traumatic effect of intravascular pressure on the vessel wall, favoring plaque destabilization and rupture. Our study provides a major novel finding; that although entirely devoid of any atherosclerotic lesion, the common carotid artery at the side on which the internal carotid artery had a plaque also showed a reduced distensibility compared with the contralateral common carotid artery. This provides evidence that the effect of a plaque on arterial mechanical properties is not limited to the actual plaque site but rather extends to a considerable degree in a proximal direction. We can speculate that 3 factors are involved. First, the physiological displacement of a large artery wall during the cardiac cycle may be made more difficult if a plaque creates an immobile site more distally. Second, a distal plaque may disturb proximal blood flow (ie, it may slow flow velocity and/or favor a turbulent flow regimen). This may in turn alter endothelial factor bioactivity in a way that increases smooth muscle contraction within the arterial wall, making the vessel stiffer. Third, the alterations in vascular wall structure typical of an atherosclerotic plaque (loss of elastic tissue, increase in collagen, increase in lipids, etc) may extend well above the actual plaque site. In this context, it is important to emphasize that whatever are the mechanisms, this proximal reduction in arterial distensibility occurred in the absence of any increase in wall thickness. This provides a further example that changes in arterial distensibility and wall thickness are not invariably related, probably because the composition is more important than the amount of wall tissue.14,15 The proximal extension of the arterial stiffening among at a plaque site may have 2 implications. First, the plaque extends its stiffening influence to relatively large segments of the arterial tree, suggesting that its direct stiffening role is not a minor one. Second, the common carotid artery stiffening in the presence of a distal plaque may favor atherosclerosis after plaque removal by endarterectomy, thereby playing an adverse pathophysiological role. In the present study, the arterial pressure measurements used to quantify arterial distensibility were obtained from the brachial artery (ie, where pulse pressure magnitude and waveform are different from those within the carotid artery). However, (1) the possible error inherent to this procedure was identical for the left and right carotid arteries (whose comparison was the goal of the study) and (2) the difference between carotid and brachial pulse pressure was likely to be modest in consideration of the age of the enrolled patients.
References
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