Compressibility of the Carotid Artery in Patients With Pseudoxanthoma Elasticum

Pierre Boutouyrie, Dominique P. Germain, Anne-Isabelle Tropeano, Brigitte Laloux, Franck Carenzi, Mustapha Zidi, Xavier Jeunemaitre, Stéphane Laurent

Abstract—The arterial wall has generally been considered as noncompressible in in vitro studies. However, compressibility of the arterial wall (CAW) has never been studied in vivo in humans. Large interstitial proteoglycans play a major role in sustaining the compression generated by pulsatile forces. The aims of the present study were to develop an experimental methodology for the assessment of CAW in vivo in humans and to study CAW in patients with pseudoxanthoma elasticum (PXE), a genetic disease characterized by proteoglycan accumulation and fragmented, swollen, and calcified elastic fibers in connective tissues. We studied 19 female patients with PXE and 15 normal female control subjects matched for age and blood pressure. A high-resolution echo-tracking system was used for the continuous determination of internal diameter and wall thickness at the site of the common carotid artery. Matrices of the radiofrequency signal were analyzed with a dedicated software to measure carotid wall cross-sectional area every 4 milliseconds during 4 to 6 cardiac cycles. CAW was calculated as the stroke change in cross-sectional area. CAW was 44% higher in patients with PXE than in control subjects (6.8±2.6% versus 4.7±2.7%, respectively; P<0.05). In control subjects, CAW decreased with age in a linear manner (r=−0.75, P<0.01). In PXE patients, the relationship with age was not homogeneous: CAW tended to increase with age before 40 years (P=0.07) and significantly decreased with age in older patients (P<0.01). Carotid geometry and elastic properties did not differ between PXE patients and control subjects. In conclusion, CAW was measurable in vivo and noninvasively in humans. The higher CAW of PXE patients compared with that of control subjects suggests that proteoglycans are important determinants of compressibility. (Hypertension. 2001;38:1181-1184.)

Key Words: proteoglycans ■ biomechanics ■ arteries

P
cince studies, showing that excised arterial tissues were isovolumic under varying degrees of strain, have led to the assumption that the arterial wall was incompressible.1–3 However, to our knowledge, the compressibility of the arterial wall (CAW) has never been studied in vivo in humans. In the present study, we took advantage of the high spatial resolution of an echo-tracking system4 to determine the time changes in wall cross-sectional area during the cardiac cycle. It is possible to calculate the stroke change in wall cross-sectional area to approach the volumetric strain, an index of compressibility.1–3,5 The CAW expresses fluid exchanges between arterial wall and blood or surrounding tissues. Thus, an increase in compressibility may favor the development of atherosclerotic lesions, through an increase in the transmural transport of atherogenic lipoproteins, and their retention within the arterial wall.6

Because proteoglycans are considered to be key components for maintaining shape and sustaining compression generated by pulsatile forces,7,8 we studied, in addition to normal subjects, patients with pseudoxanthoma elasticum (PXE). PXE is a genetic disease, recently related to mutations in the ABCC6 gene9–12 and characterized by proteoglycan accumulation13 and numerous systemic manifestations, including skin abnormalities and large artery calcifications and stenosis. The diagnosis relies on clinical features and the histological demonstration of abnormal, calcified elastic fibers in the dermis through the use of special stains (orcein and von Kossa). Despite identification of the genetic defect, little is known about the pathogenesis of vascular lesions in PXE and the means for preventing arterial complications in young adults, such as peripheral occlusive disease, transient ischemic attacks, and occasionally myocardial infarction and gastrointestinal bleeding. Because the CAW expresses fluid exchanges between blood and the arterial wall, and leakage from the wall to the environment, and because proteoglycans favor fluid storage and release,7,8 we hypothesized that the accumulation of proteoglycans in PXE tissues would be associated with abnormally compressible arterial tissue.

Thus, the aims of the present study were to develop an experimental methodology for assessment of CAW in vivo in normal subjects and to compare it with that of PXE patients.
Methods

We included 19 female patients who had PXE. The diagnosis of PXE was made by the conjunction of typical skin lesions, angioid streaks on funduscopic examination, and the presence of calcified elastic fibers in the dermis in all the patients at histology. Fifteen female control subjects were matched for age and blood pressure.

Arterial Parameters

All patients and subjects were studied in a quiet room with a controlled temperature of 22±1°C as previously described.14 Blood pressure was monitored with an oscillometric method (Dinamap model 845; Critikon). Carotid external diameter (Di) and intima-media thickness (IMT) were measured on the distal wall of the right common carotid artery, 1 to 2 cm beneath the bifurcation, with a high-precision echo-tracking device (Wall Track System; PIE Medical), as previously described, validated, and used in clinical studies.14

We developed a novel methodology to determine the stroke changes in carotid wall cross-sectional area (WCSA). To assess the change in WCSA as function of time, both the Di and IMT as function of time were needed, assuming a circular shape of the carotid artery cross section. Briefly, the recorded radiofrequency (RF) matrix, corresponding to 4- to 6-second acquisitions, were analyzed using the inboard software of the Wall Track System. A first analysis was performed by positioning the volume samples on the adventitia-media (proximal wall) and media-adventitia (distal wall) interfaces. A second analysis of the same RF matrix was performed after the proximal volume sample was moved on the blood–intima interface of the distal wall. Then, 2 time series were generated, corresponding to the stroke changes in Di and IMT (Figure 1). These time series were carefully synchronized with the ECG R wave and used to calculate stroke changes in WCSA, expressed as a percent of the WCSA value (Figure 1) through the use of a dedicated software. This value was obtained on a beat-to-beat basis and retained as a compressibility index. It was averaged over studies.14

Cross-sectional distensibility coefficient was calculated as DC=ΔA/A · ΔP, where A is the diastolic lumen area, ΔA is the stroke change in lumen area, and ΔP is local pulse pressure (PP). Local carotid PP, directly measured with applanation tonometry,14 was used in these calculations. The elastic properties of the arterial wall material were estimated with the incremental elastic modulus (Einc), calculated, as previously described,15 as Einc=[3(1+1/A/ WCSA)]/DC, where A is the diastolic lumen area and DC is the cross-sectional distensibility.

Statistical Analysis

PXE patients were compared with control subjects by nonparametric Mann-Whitney U test for difference in median values. Data are expressed as mean±SD. Associations between arterial parameters and quantitative factors were analyzed with GLM-ANOVA and robust multiple linear regression procedure performed either in the whole population (including diagnosis as dummy variable) or in separate populations.16 All tests were performed using NCSS2000 software (J. Hintze, Nashville, Tenn). P<0.05 was considered significant, and tests were 2-sided.

Results

Patients with PXE and control subjects were comparable in terms of age and brachial blood pressure (Table 1). Patients with PXE were significantly smaller and had smaller body surface areas (BSAs) than control subjects. Thus, BSA was used as an adjustment variable.

TABLE 1. Descriptive Parameters of 19 PXE Patients and 15 Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>PXE Patients</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41±14</td>
<td>43±16</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159±5</td>
<td>166±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>56±6</td>
<td>59±9</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.57±0.09</td>
<td>2±0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>68.70±2.74</td>
<td>22±3</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>122±22</td>
<td>115±14</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>68±9</td>
<td>70±9</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial MBP, mm Hg</td>
<td>86±13</td>
<td>85±10</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±11</td>
<td>68±9</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid PP, mm Hg</td>
<td>51±17</td>
<td>47±16</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure. Values are mean±SD.
TABLE 2. Carotid Artery Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>PXE Patients</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal diameter, mm</td>
<td>5.15±0.78</td>
<td>5.21±0.81</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke change in diameter, mm/10^3</td>
<td>486±177</td>
<td>404±153</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IMT, mm/10^3</td>
<td>600±101</td>
<td>568±144</td>
<td>NS</td>
</tr>
<tr>
<td>Wall cross-sectional area, mm/10^3</td>
<td>10.89±2.78</td>
<td>10.35±3.24</td>
<td>NS</td>
</tr>
<tr>
<td>Wall-to-lumen ratio</td>
<td>0.24±0.05</td>
<td>0.22±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>CS distensibility, kPa/10^3</td>
<td>36.08±24.51</td>
<td>31.14±18.86</td>
<td>NS</td>
</tr>
<tr>
<td>Young’s elastic modulus, kPa</td>
<td>373±244</td>
<td>431±243</td>
<td>NS</td>
</tr>
<tr>
<td>Circumferential wall stress, kPa</td>
<td>51±17</td>
<td>54±16</td>
<td>NS</td>
</tr>
</tbody>
</table>

The short-term within-observer within-patient repeatability between 2 determinations of carotid internal diameter and wall thickness, performed at 15 minutes, was assessed in control subjects. The absolute difference between measurements 1 and 2 did not exceed 6% of the mean value for each parameter.

Common carotid artery parameters were only marginally different between PXE and control subjects. Only absolute stroke change in diameter was increased in PXE patients compared with control subjects (486±177 versus 403±153 μm, respectively; P<0.001). This difference persisted after adjustment for age, BSA, and mean blood pressure. Carotid IMT, internal diameter, distensibility, elastic modulus, and circumferential wall stress did not differ between the 2 groups.

CAW was 44% higher in patients with PXE than in control subjects (6.8±2.6% versus 4.7±2.7%, respectively; P<0.05). In control subjects, compressibility decreased with age in a linear fashion (r = -0.75, P<0.01) (Figure 2). In PXE patients, the relationship with age was not homogeneous (Figure 2): compressibility tended to increase with age before 40 years (P=0.07) and significantly decreased with age in older patients (P<0.01). The scatter of the CAW data according to age, which is apparent in Figure 2, may be explained by the influence of carotid IMT on CAW. Indeed, CAW decreased significantly (P<0.05) with IMT in both groups.

Discussion

In the present study, we were able to noninvasively detect small changes in the WCSA during the cardiac cycle at the site of the carotid artery in control subjects and to show that the changes were significantly larger in age- and blood pressure-matched PXE patients.

Methodological Issues

The CAW expresses fluid exchanges between blood and the arterial wall, and leakage from the wall to the environment, accompanying compressive stress. To our knowledge, in vivo assessment of arterial compressibility has never been performed. In the present study, we took advantage of the high spatial resolution of an echo-tracking system to determine the time changes in WCSA during the cardiac cycle. It was possible to calculate the stroke change in WCSA to approach the volumetric strain, an index of compressibility. One hypothesis underlining such an assessment is that the length of a given arterial segment does not change during the cardiac cycle. Although it was not possible to check it in the present study, it is generally accepted that longitudinal stretch of arteries is minimal during the cardiac cycle, because of the tethering by collateral branches and attachments with surrounding structures. The choice of the common carotid artery was dictated by practical considerations. The carotid artery is the superficial elastic artery with the largest stroke change in diameter, for which the largest changes in WCSA were expected.

Calculations of CAW were performed from the measurements of carotid internal diameter and wall thickness. In normal subjects, the short-term within-observer within-patient repeatability of these measurements was excellent, with an absolute difference between 2 measurements of <6% of the mean value, as in previous studies. Indeed, this methodology was sensitive enough to detect a significant difference in CAW between PXE patients and control subjects.

We found substantially higher values of CAW than those reported in vitro, which were in the range of 0.50% to 1.26% of the nondeformed tissue volume per 10-kPa compressive stress loading in the radial direction. This difference may be explained by the fact that in the present study, CAW was determined under pulsatile conditions in vivo in humans. In addition, our objective was not to determine absolute values but rather to demonstrate the feasibility of such measurements, applicable to the comparison of normal and pathological arteries.

Compressibility in PXE Patients

Despite the recent identification of the molecular basis of PXE (ie, mutations in the ABCC6 gene), the pathogenesis of vascular lesions is still unknown. One hallmark of PXE is the coexistence in the affected and nonaffected skin of huge amounts of microfibrillar matter, corresponding to the accumulation of fragmented, swollen, and incomplete elastin fibers, together with low sulfated proteoglycans. We can conclude that at a given age, common carotid arteries from PXE patients were more compressible than those from control subjects, because the stroke change in WCSA was higher in PXE patients than in control subjects, with no difference in local PP. Thus, we confirmed our hypothesis that the accumulation of proteoglycans in PXE tissues is
associated with an increase in CAW. A likely possibility is that the increased compressibility occurred through an increased storage into and release of fluids, toward either the lumen or surrounding tissues, from a larger amount of proteoglycans in the arterial wall.

In PXE patients, compressibility tended to increase with age in young patients and to decrease in older ones. This observation is consistent with the pathogenesis of arterial lesions in PXE patients: PXE is characterized by an early accumulation of proteoglycans in large arteries, followed by calcifications at an older age, which may attenuate fluid exchanges between blood, the arterial wall, and surrounding tissues. However, these results should be viewed with caution, because of the uneven distribution of CAW according to age. To what extent an increase in CAW may favor the occurrence of calcifications in PXE arterial tissues remains to be determined, although some mechanisms may be suggested, including the potentiation, by proteoglycans, of the uptake of oxidized LDL by macrophages.

The negative relationships between CAW and IMT, observed in control subjects and PXE patients, are consistent with an influence of the changes in extracellular matrix and smooth muscle cells that accompany arterial wall thickening on fluid exchanges. Despite the higher CAW in PXE patients, there was no difference in geometrical (internal diameter, IMT) and functional parameters (distensibility, elastic modulus) between PXE patients and control subjects. The relationships between CAW and these parameters are unclear, and further evaluation of geometrical and functional properties of the arterial tree is required to better understand the pathogenesis of PXE.

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References
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