Arterial Remodeling and Stiffness in Patients With Pseudoxanthoma Elasticum

Dominique P. Germain,* Pierre Boutouyrie,* Brigitte Laloux, Stéphane Laurent

Objective—Proteoglycans organize the extracellular matrix, act as signaling molecules, and are involved in cell migration and proliferation. They may play an important role in arterial geometric and elastic properties. The aim of the present study was to determine large artery phenotype in patients with pseudoxanthoma elasticum (PXE), a genetic disease characterized by proteoglycan accumulation and fragmented elastic fibers in connective tissues.

Methods and Results—In 27 patients with PXE (25 females and 2 male) and 27 control subjects matched by age, sex, and blood pressure, we noninvasively determined the common carotid and radial artery diameter, intima-media thickness (IMT), and distensibility with high-definition echo-tracking systems and applanation tonometry. Patients with PXE had a significantly higher carotid IMT (611 ± 106 versus 520 ± 76 μm, P < 0.001) independently of body surface area, age, and mean blood pressure. The increase in carotid IMT predominated in older patients with PXE at the time of examination. No significant difference in carotid elastic properties was observed between patients with PXE and control subjects. At the site of the radial artery, distensibility was significantly higher in patients with PXE than in control subjects (11.6 ± 1.4 versus 5.9 ± 3.4 kPa·1·0.10−2; P = 0.02) and internal diameter was lower (1.66 ± 0.51 versus 2.07 ± 0.36 mm; P < 0.01) without change in intima-media thickness and Young’s elastic modulus.

Conclusions—Phenotypic changes of superficial arteries in patients with PXE were represented by a thickening of the carotid artery and a reduced stiffness of the radial artery and predominated in older female patients. (Arterioscler Thromb Vasc Biol. 2003;23:836-841.)

Key Words: arterial stiffness ■ intima-media thickness ■ biomechanics ■ large arteries

Pseudoxanthoma elasticum (PXE) is an inherited systemic disorder of connective tissue, affecting the skin, the eyes, and the vascular system, with highly variable phenotypic expression.1 The most apparent clinical feature of PXE is the skin manifestation, which consists of yellow-orange papular lesions with initial predilection in the flexural areas of the body. Ocular findings include angioid streaks, diffuse mottling of the retina, optic nerve drusen, peripheral retinal scars, as well as macular degeneration attributable to leaking subretinal neovascularization. Vascular involvement is common, and patients with PXE typically present with arteriosclerosis, hypertension, transient ischemic attacks, and occlusive vascular changes at young ages.2 Cardiovascular complications, mainly coronary artery disease, are rare but can be life threatening.2 The estimated prevalence of PXE is 1 in 70 000 to 100 000.3 Although autosomal recessive inheritance (OMIM 264800) is most frequently found in PXE, autosomal dominant segregation (OMIM 177850) has also been proposed.4

The PXE locus has been mapped to chromosome 16p13.1, and mutations in the ABCC6 gene (previously known as MRP6 or eMOAT), encoding a 1503-amino acid putative membrane transporter of unknown function, have recently been simultaneously disclosed by 5 research groups as the genetic defect responsible for PXE.5–9 The existence of pseudogenes has been subsequently documented.10–13 The R1141X mutation in the ABCC6 gene is associated with a sharply increased risk of premature coronary artery disease.14 Histopathology of biopsies from clinically affected skin shows morphologically altered elastic fibers, which are fragmented and swollen and appear calcified when examined by special stains (eg, von Kossa), whereas PXE has also been characterized by proteoglycans accumulation, including heparan-sulfate and chondroitin-6-sulfate proteoglycans, glycosaminoglycan hyaluronic acid, decorin, and biglycan.15–17 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.

Large proteoglycans are generally considered a key component for maintaining shape and sustaining compression generated by pulsatile forces.18,19 In a previous study,20 we showed that the compressibility of the arterial wall, calculated

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as the stroke change in cross-sectional area during the cardiac cycle, was 44% higher in patients with PXE than in controls, a finding that is consistent with the accumulation of heparan-sulfate proteoglycans in PXE tissues.\textsuperscript{15}

Proteoglycans may also influence the geometric and elastic properties of the arterial wall through other mechanisms. Indeed, the small leucine-rich proteoglycans, like decorin and biglycan, organize the extracellular matrix, particularly the collagenous network, act as signaling molecules, and are involved in cell migration and proliferation.\textsuperscript{15,21} They also interact with macromolecules that enter the vascular wall, such as oxidized LDL, and thus may favor lipoprotein retention and atherosclerosis.\textsuperscript{22} Experimental data indicate that changes in the arterial content of specific proteoglycans are associated with changes in arterial stiffness. Indeed, in spontaneously hypertensive rats, the increase in arterial stiffness in response to a high-sodium diet or a diuretic was related to the decrease in hyaluronan content.\textsuperscript{23} In rat mesenteric arteries, partial removal of chondroitin-dermatan sulfate-containing glycosaminoglycans from the arterial wall increased vascular stiffness.\textsuperscript{24}

Thus, we hypothesized that the changes in the composition and content of proteoglycans occurring in the arterial wall of PXE patients would modify wall thickness and distensibility. In the present study, we determined the phenotype at 2 arterial sites, a proximal predominantly elastic one, the common carotid artery, and a distal muscular medium-sized artery, the radial artery, in a large cohort of patients with PXE. Because age, sex, and blood pressure (BP) are 2 major determinants of arterial geometric and elastic properties, we compared patients with PXE with age-, sex-, and BP-matched healthy controls.

Methods

We included 27 patients (25 female and 2 male) affected with PXE. The diagnosis of PXE was made by one of the investigators (D.P.G.) from the conjunction of typical skin lesions, angioid streaks on funduscopic examination, and the presence of fragmented and calcified elastic fibers on skin biopsies. All patients had positive von Kossa staining.

Partial genotyping of the \textit{ABCC6} gene was performed for most patients. Various mutations were identified, among which the nonsense \textit{R1141X} was the most prevalent. This is in line with the high frequency of this mutation in patients with PXE originating from Europe.\textsuperscript{13,14} The existence of 2 pseudogenes highly homologous to \textit{ABCC6} related to the decrease in hyaluronan content.\textsuperscript{23} In rat mesenteric arteries, partial removal of chondroitin-dermatan sulfate-containing glycosaminoglycans from the arterial wall increased vascular stiffness.\textsuperscript{24}

### Table 1. Demographics in Patients With PXE and in Control Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PXE (n=27)</th>
<th>Controls (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42±14</td>
<td>42±14</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ratio, M/F</td>
<td>2/25</td>
<td>2/25</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160±7</td>
<td>164±7</td>
<td>0.012</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60±15</td>
<td>67±14</td>
<td>0.045</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.62±0.20</td>
<td>1.72±0.17</td>
<td>0.012</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>122±20</td>
<td>122±21</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>68±9</td>
<td>72±11</td>
<td>0.035</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>86±13</td>
<td>89±14</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking,* yes/no</td>
<td>7/20</td>
<td>8/19</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension,† yes/no</td>
<td>5/22</td>
<td>4/23</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±9</td>
<td>68±9</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma total cholesterol, mmol/L</td>
<td>5.45±0.79</td>
<td>5.62±1.04</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma LDL cholesterol, mmol/L</td>
<td>3.43±0.88</td>
<td>3.66±0.95</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma triglycerides, mmol/L</td>
<td>1.03±0.47</td>
<td>1.22±0.54</td>
<td>NS</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Current smokers vs never or past; †current hypertension (SBP>140 mm Hg or DBP>90 mm Hg), treated or not.

Results

Patients with PXE and controls were comparable in term of sex ratio, age, systolic and mean brachial BP, heart rate, hypertension, smoking, and lipid profile (Table 1). Diastolic BP was significantly lower in patients with PXE. Despite the matching procedure, height, weight, and body surface area (BSA) remained significantly lower in patients with PXE than in control subjects. Thus, BSA was used as an adjustment variable in some analyses.

Carotid IMT was significantly higher (+18%) in patients with PXE than in controls (611±106 versus 520±76 \( \mu \text{m} \), \( P<0.001 \); median and 25th to 75th percentiles: 609 \( \mu \text{m} \) [550 to 680] in PXE versus 527 \( \mu \text{m} \) [473 to 590], respectively) (Table 2). This difference persisted (\( P<0.001 \)) after adjustment on age, BSA, and mean BP. When carotid IMT was analyzed according to age as a categorical variable (younger or older than 40 years), it was significantly higher in older patients with PXE than in controls (656±71 versus 510±90 \( \mu \text{m} \), \( P<0.001 \); median and 25th to 75th percentiles: 657 \( \mu \text{m} \) [595 to 746] in PXE versus 483 \( \mu \text{m} \) [442 to 601], respectively) but not in younger patients. There was a significant interaction between age and diagnosis (two-way ANOVA, \( P<0.001 \)) (Figure 1). No significant difference in lumen diameter was observed between patients with PXE and controls. Wall cross-sectional area was significantly higher in patients with PXE (+19%, \( P<0.01 \)). A significant relationship between the wall cross-sectional area and age was observed in patients with PXE (\( r=0.727; P<0.01 \)) but not in controls (Figure 2). When carotid WCSSA was analyzed according to age as a categorical variable (younger or older than 40 years), it was significantly higher in older patients with PXE than in controls but not in younger patients.
TABLE 2. Carotid Artery Parameters in Patients With PXE and in Control Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PXE (n=27)</th>
<th>Controls (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal diastolic diameter, mm</td>
<td>5.14±0.72</td>
<td>5.26±0.69</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke change in diameter, μm</td>
<td>480±169</td>
<td>476±183</td>
<td>NS</td>
</tr>
<tr>
<td>Relative stroke change in diameter, %</td>
<td>7.7±3.2</td>
<td>7.6±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Intima-media thickness, μm</td>
<td>611±106</td>
<td>520±76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wall cross-sectional area, mm²</td>
<td>11.1±2.8</td>
<td>9.4±1.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CS distensibility, kPa⁻¹·0.10⁻³</td>
<td>34.5±23.3</td>
<td>36.3±24.3</td>
<td>NS</td>
</tr>
<tr>
<td>CS compliance, m²·kPa⁻¹·0.10⁻²</td>
<td>6.65±3.61</td>
<td>7.54±4.54</td>
<td>NS</td>
</tr>
<tr>
<td>Young’s elastic modulus, kPa</td>
<td>370±224</td>
<td>436±328</td>
<td>NS</td>
</tr>
<tr>
<td>Circumferential wall stress, kPa</td>
<td>49±15</td>
<td>61±20</td>
<td>0.015</td>
</tr>
<tr>
<td>Local PP, mm Hg</td>
<td>53±18</td>
<td>48±19</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid PP/brachial PP</td>
<td>0.94±0.31</td>
<td>0.95±0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid PP/radial PP</td>
<td>1.20±0.38</td>
<td>1.49±0.76</td>
<td>NS</td>
</tr>
<tr>
<td>PWV_C, m/s</td>
<td>12.8±5.0</td>
<td>11.8±3.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean±SD. CS indicates cross-sectional; PP, pulse pressure; PWV_C, carotid-femoral pulse wave velocity. No adjustment was made.

Carotid circumferential wall stress was significantly lower in patients with PXE than in controls. Carotid stroke change in diameter, distensibility, compliance, Young’s elastic modulus, and carotid-femoral pulse wave velocity did not differ between the 2 groups, although a significant relationship between each of these parameters and age (P<0.01 for all) was observed in the whole population (negative correlation for stroke change in diameter, distensibility, and compliance and positive correlation for Young’s elastic modulus and pulse wave velocity). The ratio between carotid pulse pressure and radial pulse pressure was significantly higher in patients with PXE than in controls.

Radial artery distensibility was significantly higher in patients with PXE than in control subjects (11.6±11.4 versus 5.9±3.4 kPa⁻¹·0.10⁻³; P=0.02) (Table 3). This difference persisted (P<0.001) after adjustment on age, BSA, and mean BP. A tendency (P=0.057) for a higher relative stroke change in diameter was observed in patients with PXE. No significant difference in compliance and elastic modulus was observed between groups. Internal and external diameters and wall cross-sectional area were significantly lower in patients with PXE than in controls (P<0.01, P<0.01, and P=0.02, respectively), whereas IMT and circumferential wall stress did not differ between groups.

Discussion

Despite the recent identification of the molecular basis of PXE (ie, mutations in the ABCC6 gene),5–9 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 various types of proteoglycans.15–17

Interpretation of Findings

Cardiovascular involvement is common, and patients with PXE typically present at young age with hypertension,

TABLE 3. Radial Artery Parameters in Patients With PXE and in Control Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PXE (n=27)</th>
<th>Controls (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal diastolic diameter, mm</td>
<td>1.66±0.51</td>
<td>2.07±0.36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>External diastolic diameter, mm</td>
<td>2.07±0.55</td>
<td>2.51±0.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke change in diameter, μm</td>
<td>34±24</td>
<td>32±20</td>
<td>NS</td>
</tr>
<tr>
<td>Relative stroke change in diameter, %</td>
<td>2.3±1.8</td>
<td>1.5±0.8</td>
<td>0.057</td>
</tr>
<tr>
<td>Intima-media thickness, μm</td>
<td>212±52</td>
<td>221±71</td>
<td>NS</td>
</tr>
<tr>
<td>Wall cross-sectional area, mm²</td>
<td>1.28±0.58</td>
<td>1.61±0.64</td>
<td>0.02</td>
</tr>
<tr>
<td>CS distensibility, kPa⁻¹·0.10⁻³</td>
<td>11.6±11.4</td>
<td>5.9±3.4</td>
<td>0.02</td>
</tr>
<tr>
<td>CS compliance, m²·kPa⁻¹·0.10⁻²</td>
<td>0.22±0.28</td>
<td>0.21±0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Young’s elastic modulus, kPa</td>
<td>18±18</td>
<td>20±8</td>
<td>NS</td>
</tr>
<tr>
<td>Circumferential wall stress, kPa</td>
<td>47±17</td>
<td>59±17</td>
<td>NS</td>
</tr>
<tr>
<td>Local pulse pressure, mm Hg</td>
<td>39±15</td>
<td>41±11</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean±SD. No adjustment was made.
calcifications at the site of large arteries, and occlusive vascular changes indiscernible from atherosclerosis.¹² To our knowledge, the present cohort is the largest one studied for cardiovascular changes. We observed that patients with PXE had a higher carotid IMT together with an unchanged internal diameter, which indicates an outward hypertrophic remodeling.²⁵ That it was observed only in older patients with PXE suggests a slowly occurring process. Various mechanisms may be suggested to explain the progressive wall thickening. They include proteoglycan accumulation, a growth-promoting effect of some proteoglycans,¹⁸,²¹ and an accelerated atherosclerosis. Indeed, proteoglycans interact with macromolecules that enter the vascular wall, such as oxidized LDL, potentiating their uptake by macrophages, and thus favor lipoprotein retention.²² We previously showed a higher compressibility of the carotid artery wall in patients with PXE, consistent with a key role of large proteoglycans in maintaining shape and sustaining compression generated by pulsatile forces.¹⁸–¹⁹ We suggested that the increased compressibility could reflect an increased storage into and release of fluids, either toward the lumen or surrounding tissues, from a larger amount of proteoglycans in the arterial wall.¹⁹ This process could potentiate the development of atherosclerotic lesions through an increased retention of atherogenic lipoproteins.²² It should be noted that several patients with PXE and control subjects had borderline high total and LDL cholesterol and that some of them had high total and LDL cholesterol.²⁶ This is not surprising in the French population. However, a major point is that plasma total and LDL cholesterol values did not differ between patients with PXE and control subjects. Interestingly, we did not observe a significant wall thickening at the site of the radial artery, which is generally considered protection against atherosclerosis.²⁷,²⁸ However, our argumentation for an accelerated atherosclerosis at the site of the carotid artery is limited, because ultrasound imaging cannot discriminate between the intima layer and the media layer of the vessel wall to distinguish true arteriosclerosis, ie, the adaptive response of the media layer to changes in tensile stress, from atherosclerosis, viewed as a disorder restricted to the intima layer.²⁹

In patients with PXE, elastic fibers in large arteries are abnormal and display fragmentations and calcifications.¹⁵–¹⁷ These changes, similar to those occurring with aging, are expected to increase arterial stiffness. However, we observed no significant change in carotid distensibility in patients with PXE, suggesting that other mechanisms were involved. Indeed, recent studies showed that an abnormal structure of elastin fibers can lead to proliferation of smooth muscle cells and changes in wall stiffness.³⁰ We previously reported, like others, an increase in carotid distensibility in patients with Williams syndrome, who are hemizygotes for the elastin gene.³¹,³² In addition, studies in elastin knockout mice showed that disruption of elastin was enough to induce subendothelial proliferation of smooth muscle and contribute to obstructive arterial disease. These authors³⁰ suggested that elastin has not a purely structural role but also a regulatory function during arterial development, controlling proliferation of smooth muscle and stabilizing arterial structure. Thus, we suggest that in patients with PXE, the abnormalities of the elastin network at the site of large arteries could lead to proliferation of smooth muscle cells and wall hypertrophy without increase in wall stiffness.

Because fragmentations and calcifications of elastic fibers, which are characteristic of aging, should theoretically lead to a reduction in arterial distensibility, other mechanisms should compensate for these alterations to explain the unchanged distensibility at the site of the carotid artery and the increased distensibility observed at the site of the radial artery in patients with PXE. We suggest that the tridimensional reorganization of the arterial wall components, which accompanies arterial wall hypertrophy at the site of the carotid artery, may shift the mechanical load from stiff to distensible components, thus maintaining normal elastic properties despite the abnormalities in elastic fibers. We previously raised a similar hypothesis in patients with sustained essential hypertension³³,³⁴ to explain why arterial compliance remained unchanged despite an increased distending pressure. Because radial artery wall thickness was not increased in patients with PXE, other mechanisms should be evoked to explain the hyperdistensibility of the radial artery. We suggest that this may be attributable to the inward remodeling, unloading the stiff components of the arterial wall. Changes in the elasticity of the arterial wall material are less likely, because Young’s elastic modulus, which gives information on the elastic properties of the arterial wall material, did not differ between PXE and controls for a given circumferential wall stress.

The influence of radial artery hyperdistensibility on systemic hemodynamics is limited, because medium-sized arteries contribute only to a small extent to systemic distensibility. By contrast, carotid-femoral pulse wave velocity, which is measured along the aortic and aortiliac pathway, has a higher clinical relevance. We observed no significant difference between patients with PXE and controls in carotid-femoral pulse wave velocity, which is consistent with the unchanged distensibility at the site of the carotid artery. At that site, in the absence of inward remodeling, there may be no unloading of stiff material and thus no change in distensibility.

The clinical manifestations of PXE, which include peripheral occlusive disease, transient ischemic attacks, and myocardial infarction, suggest an arterial remodeling at the site of medium-sized and small arteries, leading to obstructive disease. The lower radial artery internal diameter of patients with PXE observed in this study may be representative of an inward remodeling of medium-sized and smaller arteries, leading to the progression reduction of the lumen and subsequent ischemia of target organs. The mechanism through which the reduction in lumen diameter was associated with a reduced wall cross-sectional area remains to be elucidated. Indeed, wall cross-sectional area was expected to be not significantly different between patients with PXE and controls, because the maintenance of arterial mass was unchanged, or even increased, similar to what occurred at the site of the carotid artery.

Limitations of the Study
The difference in carotid IMT and radial distensibility between patients with PXE and controls might have been
exaggerated by selecting control subjects of shorter stature and lower weight than the usual control groups in our previous studies and thus with small carotid IMT and low radial distensibility. However, this was not the case, because patients with PXE in the present study had still significantly higher carotid IMT and radial artery distensibility than control patients with higher height and BSA (data not shown). 35

Most patients of our cohort were women. This may have been attributable to a recruitment bias, because women consulted, mainly for esthetic reasons, with the dermatologist. Although our patients seemed more healthy and with less vascular complications than previously published populations, 1, 2 several patients had mediocalciosis and stenoses of large arteries. No patient had suffered a transient ischemic attack. As discussed above, although several patients with PXE and control subjects had borderline high or high total and LDL cholesterol, patients with PXE did not differ in lipid profile from control subjects (Table 1).

To rule out any gender effect, we analyzed the cohort after exclusion of male patients with PXE and control subjects and found similar findings as observed in the mixed population, i.e., a higher carotid IMT (609±110 versus 521±79 μm; P<0.01) and a higher radial artery distensibility (12.3±11.5 versus 5.9±3.5 kPa−1·0.10−3; P<0.02) in female patients with PXE than in female controls.

The menopausal status and the use of a hormone replacement therapy, which are known to affect large artery elastic properties, 36 were not available in the present PXE cohort and control group. Because menopause occurs between 45 and 55 years of age and because IMT was higher in older patients with PXE than in older controls, we performed a first comparison in women older than 45 years and a second one in women older than 55 years. In women older than 45 years, carotid IMT was significantly higher in patients with PXE than in controls (669±118 μm in PXE [n=13] versus 499±93 μm in controls [n=12], P<0.01; medians and 25th to 75th percentiles: 680 μm [602 to 757] in PXE versus 480 μm [421 to 601] in controls, respectively). In addition, in women older than 55 years, carotid IMT was higher in patients with PXE than in controls (687±197 μm in PXE [n=4] versus 505±79 μm in controls [n=4]). As discussed above, that it was observed only in older patients with PXE suggests a slowly occurring process, consistent with an accelerated atherosclerosis. Thus, because sex and hormonal status influence arterial properties and because most patients and controls were female, it can be considered that the present findings apply to female patients with PXE.

In conclusion, we showed that, in female patients with PXE, phenotypic changes of superficial arteries were represented by thickening of the carotid artery and reduced stiffness of the radial artery. These data suggest that proteoglycans may influence arterial geometric and elastic properties through their interactions with extracellular matrix components and growth factors.

Acknowledgments
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