Mechanical properties of the common carotid artery in Williams syndrome

Y Aggoun, D Sidi, B I Levy, S Lyonnet, J Kachaner, D Bonnet

Abstract

Objective—To determine whether arterial wall hypertrophy in elastic arteries was associated with alteration in their mechanical properties in young patients with Williams syndrome.

Methods—Arterial pressure and intima–media thickness, cross-sectional compliance, distensibility, circumferential wall stress, and incremental elastic modulus of the common carotid artery were measured non-invasively in 21 Williams patients (mean (SD) age 8.5 (4) years) and 21 children of similar age.

Results—Systolic and diastolic blood pressures were higher in Williams patients (125/66 v 113/60 mm Hg, p < 0.05). The mean (SD) intima–media thickness was increased in Williams patients, at 0.6 (0.07) v 0.5 (0.03) mm (p < 0.001). Normotensive Williams patients had a lower circumferential wall stress (2.1 (0.5) v 3.0 (0.7) mm Hg, p < 0.01), a higher distensibility (1.1 (0.3) v 0.8 (0.3) mm Hg⁻¹.mm Hg⁻¹, p < 0.01), similar cross-sectional compliance (0.14 (0.04) v 0.15 (0.05) mm².mm Hg⁻¹, p > 0.05), and lower incremental elastic modulus (7.4 (2.0) v 14.0 (5.0) mm Hg⁻¹; p < 0.001).

Conclusions—The compliance of the large elastic arteries is not modified in Williams syndrome, even though increased intima–media thickness and lower arterial stiffness are consistent features. Therefore systemic hypertension cannot be attributed to impaired compliance of the arterial tree in this condition.

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Keywords: elastin; Williams syndrome; hypertension; compliance

Microdeletion of chromosome 7q, encompassing the elastin locus, has been identified by fluorescent in situ hybridisation in patients with Williams syndrome. The pathophysiological mechanism is not yet clear but elastin hemizygosity is certainly implicated in the pathogenesis of the arteriopathy of Williams syndrome. Systemic hypertension is a common feature in this condition, and may be caused by renal artery stenosis. However, hypertension often remains unexplained in these patients. It has been attributed to reduced compliance of the entire arterial tree associated with diffuse hypertrophy of the media. In vitro and in vivo studies have shown that increased arterial wall thickness is a common phenotypic trait of the Williams syndrome. However, arterial wall hypertrophy in hypertensive subjects is not necessarily associated with reduced distensibility. In adult Williams syndrome patients, hypertension can cause remodelling of the conductance arteries, overriding primitive alterations of their mechanical properties related to elastin hemizygosity. In this study, we sought to determine whether arterial wall hypertrophy of the common carotid artery, a large proximal and conductance artery, was associated with alterations in its mechanical properties in young patients with Williams syndrome.

Methods

PATIENTS AND CONTROLS

Twenty-one patients with Williams syndrome aged 3.5–19 years (mean (SD) age 8.5 (4) years) and 21 control children (9 (2) years) were included in the study. The diagnosis of Williams syndrome relied on typical facial appearance and hemizygosity at the elastin locus in all patients. Williams patients with either renal artery stenosis or receiving antihypertensive drugs were excluded from the study. Fifteen of the 21 Williams patients had a mild supravalvar aortic stenosis (range 12–20 mm Hg). The remaining six patients had no left heart obstruction. None of the Williams patients in this series had coarctation of the aorta and none underwent coarctation repair. Informed consent of the parents was obtained for all subjects. The investigation was performed in a controlled environment kept at 22 (2)°C. Blood pressure was measured with a mercury sphygmomanometer with a cuff adapted to the arm circumference of the child, who was recumbent for at least 15 minutes before the measurement.

ARTERIAL MEASUREMENTS

Non-invasive arterial measurements were performed with a real-time B-mode ultrasound imager (Acuson XP128, Acuson, Mountain View, California, USA). The right common carotid artery was examined with a 7 MHz vascular probe following a procedure described previously. The intima–media thickness and lumen diameter measurements were performed in the same arterial segment in all subjects. This segment was located 1–2 cm above the bifurcation of the right common carotid artery. Echographic imaging of the common carotid artery was obtained in the anteroposterior projection with the patient lying supine and the head in the axis. The same physician...
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OV-line image analysis was performed using R triggering) was transferred to a computer. When two series of paired measurements were compared, the results were analysed in two steps according to Bland and Altman.3 The correlation between the measured values (the linear relation equation, correlation coefficient, and p value) was calculated. The first step was used to gauge the degree of agreement between the two series of measures. Second, the relative differences within each pair of measures (Di) were plotted against the mean of the pair to make sure that no obvious relation appeared between estimated value (mean) and Di. The lack of agreement between the two measures was estimated by the mean difference Di and the standard deviation of the differences.

Repeatability of intima–media thickness and diastolic and systolic diameter measurements was investigated in 10 subjects by calculating the repeatability coefficient (RC), as defined by the British Standard Institution according to the formula $RC^2 = \frac{\sum Di^2/n}{n}$, where $n$ is the sample size and $Di$ the relative difference within each pair of measures. This coefficient is the standard deviation of the estimated difference between two repeated measurements. RC values for intraobserver repeatability (comparison of two determinations obtained two hours apart by the same observer) for intima–media thickness and diastolic and systolic diameter were 43 µm, 212 µm, and 153 µm, respectively. These values were small when compared with the actual values of common carotid intima–media thickness and the diastolic and systolic diameters—565 (21) µm, 5143 (68) µm, and 5847 (603) µm, respectively—and compared with the difference between Williams patients and controls.

Statistical analysis
Summary statistics are presented as mean (SD) and range. Univariate comparisons of data in the two groups was made using the unpaired Student’s t test or the Mann–Whitney test as appropriate for interval variables. Fisher’s exact test was used for categorical variables.
Table 1 Demographic data and pressure values of Williams patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Williams patients (n=21)</th>
<th>Controls (n=21)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.5 (4.0)</td>
<td>9.0 (2.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>31 (20)</td>
<td>29 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.05 (0.5)</td>
<td>0.97 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>125 (18)</td>
<td>113 (10)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>66 (8)</td>
<td>60 (9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>59 (14)</td>
<td>54 (7.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean (SD). BSA, body surface area.

Table 2 Morphometric and haemodynamic variables in normotensive Williams patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive Williams patients (n=12)</th>
<th>Controls (n=21)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima–media thickness (mm)</td>
<td>0.61 (0.08)</td>
<td>0.51 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic diameter (mm)</td>
<td>4.1 (0.4)</td>
<td>5.1 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMT/diastolic diameter</td>
<td>0.15 (0.02)</td>
<td>0.10 (0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distensibility (mm Hg⁻¹)</td>
<td>1.1 (0.3)</td>
<td>0.8 (0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cross sectional compliance (mm²/mm Hg⁻¹)</td>
<td>0.14 (0.04)</td>
<td>0.15 (0.05)</td>
<td>NS</td>
</tr>
<tr>
<td>Circumferential wall stress (mm Hg⁻¹)</td>
<td>2.1 (0.5)</td>
<td>3.0 (0.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Young’s elastic modulus (Einc) (mm Hg⁻¹)</td>
<td>7.4 (2.0)</td>
<td>14.0 (5.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD). IMT, intima–media thickness.

Table 3 Comparison of morphometric and haemodynamic variables in Williams patients with and without hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive Williams patients (n=9)</th>
<th>Normotensive Williams patients (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima–media thickness (mm)</td>
<td>0.68 (0.07)</td>
<td>0.61 (0.04)</td>
</tr>
<tr>
<td>Distensibility (mm Hg⁻¹)</td>
<td>1.0 (0.4)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Cross sectional compliance (mm²/mm Hg⁻¹)</td>
<td>0.18 (0.06)</td>
<td>0.14 (0.04)</td>
</tr>
<tr>
<td>Circumferential wall stress (mm Hg⁻¹)</td>
<td>2.5 (0.6)</td>
<td>2.1 (0.5)</td>
</tr>
<tr>
<td>Young’s elastic modulus (Einc) (mm Hg⁻¹)</td>
<td>9.5 (7.0)</td>
<td>7.4 (2.0)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
different components of the extracellular matrix to aortic tensile strength and stiffness are not well known. Loss of medial elastin increases pressure dependent circumferential wall stress and it has been suggested that this promotes endothelial damage and aneurysm formation. Anomalies of medial elastic function in Williams syndrome might not be directly related to quantitative loss of elastin in the arterial wall. Bruel and colleagues recently showed that inhibition of the formation of the cross links between collagen by the lysosomale degradation results in destabilisation of the arterial wall, with increased diameter and reduced stiffness. Such improvement in arterial wall stiffness has also been reported when the accumulation of advanced glycosylation end products on collagen is prevented by aminoguanidine treatment in diabetic rats as well as in normotensive aged WAG/Rij rats. In these studies, no changes in elastin and collagen concentrations were found. Another recent study showed that removal of the microfibrils from elastin reduced the modulus of the pig aortic elastic tissue, even though no evidence of elastin hydrolysis could be observed. A quantitative change in biosynthesis appears to alter the organisation of the various medial elements during development, and this is supported by knock out of the elastin locus in a developmental disorder, Williams syndrome. Nature Genet 1993;5:11–16. 

Acknowledgments

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CONCLUSIONS

We have shown that the functional compliance of the common carotid artery is not significantly modified in Williams syndrome, although increased intima-media thickness and lower arterial stiffness are consistent features. Thus systemic hypertension in patients cannot be attributed to impaired compliance of the arterial tree in this condition. Other pathogenic mechanisms for systemic hypertension need to be evaluated, such as resetting of the baroreceptors in response to alterations in the sensing of wall stress.

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References


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