Central Pulse Pressure Is a Major Determinant of Ascending Aorta Dilation in Marfan Syndrome

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Background—In patients with Marfan syndrome (MFS), brachial pulse pressure (PP) has been recognized as a risk factor for aortic dilatation, leading to aortic dissection, the main cause of premature death. However, the relationships between aortic PP, aortic stiffness, and aortic root dilation have not been investigated. Our main objective was to determine whether central PP, which takes into account wave reflections and aortic stiffness, is a better determinant of ascending aorta diameter than brachial PP in MFS patients.

Methods and Results—Twenty patients with confirmed MFS and 20 age- and sex-matched control subjects were included in this cross-sectional, noninvasive study. Elastic properties of the abdominal aorta and common carotid, common femoral, and radial arteries were calculated from the pulsatile changes in arterial diameter and pressure. The ascending aorta diameter, measured with conventional echocardiography, was 37% larger in MFS than in control subjects ($P<0.001$). Arterial distensibility was 38% lower in MFS than in control subjects at the site of the abdominal aorta ($P<0.01$) but not at other sites (common carotid, common femoral, and radial arteries). Independently of age and body surface area, ascending aorta diameter was positively correlated with carotid PP in MFS ($P<0.01$) and negatively in control subjects ($P<0.01$) but was not correlated with brachial PP and mean blood pressure.

Conclusions—In patients with MFS, local PP, estimated from carotid PP, was a major determinant of ascending aorta diameter, whereas brachial PP was not. Increased arterial stiffness was confined to the aorta. (Circulation. 1999;99:2677-2681.)

Key Words: blood pressure ■ arteries ■ aorta ■ Marfan syndrome

The Marfan syndrome (MFS) is a connective tissue disorder inherited as an autosomal dominant trait, characterized by abnormalities involving the skeletal, ocular, and cardiovascular systems. MFS results from mutations in the gene encoding fibrillin-1 and subsequent abnormalities in elastic fibers. A clinical hallmark and the major cause of morbidity and premature death in MFS is aortic root dilatation and associated aortic regurgitation, dissection, and rupture. The exact mechanisms leading to dilatation are not fully understood, but steady and pulsatile stresses probably play an important role. Abnormal elastic fibers and decreased cross-linking of elastin may alter load-bearing by the aorta and predispose to fragmentation of elastic fibers, microdissection, degeneration, and fibrosis of the media.

In MFS patients, the initial aortic size is an independent predictor of aortic dilatation, whereas brachial systolic and pulse pressures (PPs) are not. However, brachial PP may not accurately reflect local PP acting on the ascending aorta (AsAo), because increased wave reflections affect peripheral PP to a lesser extent than central PP. Thus, taking brachial PP instead of local PP into account may underestimate the role of pulsatile stress on aortic dilatation. We hypothesized that central PP, which takes wave reflections and aortic stiffness into account, is a better determinant of AsAo diameter than brachial PP in MFS patients. In the present study, carotid PP, measured with applanation tonometry and calibrated with brachial blood pressure (BP), was used as a surrogate for aortic PP.

An increased wall stiffness of the thoracic aorta has been reported from invasive and noninvasive studies, in adults and children, and has been attributed to abnormalities of elastic fibers. Despite these studies, there is little information concerning the elastic properties of the various arterial segments downstream of the aortic root and the resulting PP at the site of the AsAo in patients with MFS. Therefore, the objectives of the present noninvasive study were to determine, in MFS patients, (1) whether central PP, which takes into account wave reflections and aortic stiffness, was a better determinant of AsAo diameter than brachial PP and (2) whether arterial stiffness was increased at arterial sites...
downstream of the AsAo accessible to noninvasive investigation: the abdominal aorta (AbAo) and the common carotid (CCA), common femoral (CFA), and radial (RA) arteries.

Methods

Patients and Subjects
Twenty patients (17 to 61 years old) were included in this noninvasive cross-sectional study. All patients were examined in the outpatient clinic devoted to MFS in the Hôpital Ambroise Paré. Patients with a history of aortic dissection or aortic surgery were excluded. Only patients who fulfilled the strict criteria for MFS were included in the study. Six patients had mild aortic regurgitation (4 with 1+ and 2 with 2+) and 8 had minimal mitral regurgitation (7 with 1+, 1 with 2+) as defined by Doppler echocardiography. Six patients were receiving long-term treatment with a β-blocker, which was stopped the day before the study. The 14 other patients were not taking any drug.

Twenty age- and sex-matched normal subjects constituted the normal control group. The study was approved by the institutional review committee of Broussais Hospital, and the subjects gave informed consent.

Cardiac Measurements

Echocardiographic examination was performed with commercially available equipment (Apogée CX 200, Advanced Technology Laboratory) according to the recommendations of the American Society of Echocardiography. Aortic root diameter was measured according to Roman et al. at end diastole, in the parasternal long-axis view, at 3 levels: annulus (aortic valve insertion), sinuses of Valsalva, and supra-aortic ridge. The largest diameter, always at the level of the sinuses of Valsalva, was taken as the AsAo diameter for this study. Aortic arch diameter was measured with the transducer placed on the suprasternal notch. Left ventricular mean wall thickness, mass index, and shortening fraction were calculated according to Devereux et al.

Arterial Measurements

CCA and RA pressure waveforms were recorded noninvasively with a pencil-type probe incorporating a high-fidelity Millar strain-gauge transducer (SPT-301, Millar Instruments). The CCA pressure wave was calibrated assuming that brachial and carotid mean and diastolic BPs were equal, as previously described. No calibration was required for RA PP because of the very good agreement between radial and brachial diastolic BP after adjustment to mean BP.

End-diastolic ID and pulsatile changes in diameter were measured on the right CCA and CFA and on the AbAo with a 7.5-MHz pulsed ultrasound echotesting system (Wall Track System, Neurodata) through the analysis of the radiofrequency signal obtained after B-mode echocardiographic localization (Sigma 44 Kontron), as previously described. Wall thickness was measured at the site of the CCA but not at the CFA and AbAo because of insufficient repeatability. Measurements of RA ID and wall thickness were obtained on the right arm with a 10-MHz ultrasound system analyzing the radiofrequency signal (NIUS 02, SMH), as previously described.

Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MFS (n=20)</th>
<th>Control Subjects (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>37±12</td>
<td>36±9</td>
<td></td>
</tr>
<tr>
<td>Sex ratio, M/F</td>
<td>9/11</td>
<td>11/9</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>178±10</td>
<td>176±9</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66±10</td>
<td>69±13</td>
<td></td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.82±0.18</td>
<td>1.84±0.20</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>110±10</td>
<td>114±9</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>64±9</td>
<td>68±6</td>
<td></td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>79±9</td>
<td>84±4</td>
<td></td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>46±8</td>
<td>46±7</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67±10</td>
<td>64±9</td>
<td></td>
</tr>
</tbody>
</table>

BP was measured at the brachial artery level with a mercury sphygmomanometer. No significant difference was observed for all parameters between patients with MFS and control subjects. Values are mean±SD.

Statistics

Data are expressed as mean±SD. Quantitative variables were compared by means of an unpaired Student’s t test and categorical variables by means of a χ² test. Multivariate regression models were constructed in each group (control subjects and MFS) and included mean BP and other variables (age, sex, body surface area [BSA], carotid PP, and brachial PP). A robust multiple stepwise regression analysis was performed. A value of P<0.05 was considered significant. The statistical analysis was performed by means of an NCSS 6.0 package software (J.L. Hintze, Kaysville, Utah).

Results

The baseline characteristics were not significantly different between patients with MFS and control subjects (Table 1).

Aortic Geometry and Cardiac Function

The diameter of the AsAo was significantly larger in MFS than in control subjects at the site of the sinuses of Valsalva only (Table 2). Left ventricular diameter in systole or dias-

Table 2. Echocardiographic Measurements of Aortic Size and Cardiac Function in Patients With MFS and Control Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MFS (n=20)</th>
<th>Control Subjects (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annulus, mm</td>
<td>24.5±5.0</td>
<td>22.1±3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sinuses of valsalva (AsAo), mm</td>
<td>43.4±7.4</td>
<td>31.7±3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supra-aortic ridge, mm</td>
<td>32.7±4.7</td>
<td>28.5±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic arch, mm</td>
<td>22.9±4.5</td>
<td>20.8±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>51.0±4.8</td>
<td>50±4</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>31.2±5.6</td>
<td>30±6</td>
<td>NS</td>
</tr>
<tr>
<td>LV mean wall thickness, cm</td>
<td>8.5±2.2</td>
<td>8.2±3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Shortening fraction, %</td>
<td>61±6</td>
<td>60±9</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>98±29</td>
<td>89±34</td>
<td>NS</td>
</tr>
</tbody>
</table>

The largest diameter, always at the level of the sinuses of Valsalva, was considered to be AsAo diameter for this study. Values are mean±SD.
Introduction

The present study was designed to determine whether the level of left ventricular wall thickness, shortening fraction, and left ventricular mass index were not significantly different between the 2 groups.

Arterial Geometry and Function

The diameters of the AbAo, CCA, CFA, and RA were not statistically different between the 2 groups (Tables 3 and 4). Absolute and relative stroke changes in AbAo diameter were lower in patients with MFS than in control subjects, whereas those of the CCA, CFA, and RA were not significantly different between the 2 groups. CCA and RA intima-media thicknesses were not significantly different between the 2 groups. Cross-sectional distensibility of the AbAo was lower in MFS than in control subjects, whereas distensibility and compliance of the CCA, CFA, and RA were not significantly different between the 2 groups.

Carotid and RA PPs

Carotid PP, radial PP, carotid/brachial PP ratio, and carotid/radial PP ratio were not significantly different between the 2 groups (Table 4). Carotid PP was significantly correlated with radial PP in MFS ($r=0.74$; $P<0.01$) and in control subjects ($r=0.52$; $P<0.05$).

Influence of Local PP on AsAo Diameter

In patients with MFS, AsAo diameter was positively associated with carotid PP, independently of aging and BSA, whereas in control subjects, AsAo diameter was negatively associated with carotid PP (Table 5). Carotid PP alone explained 7% of aortic diameter variance in MFS patients ($R^2$ increment, Table 5). Brachial PP, systolic BP, and mean BP were not significantly related to AsAo diameter when introduced into the model instead of carotid PP. Thus, in addition to age and BSA, carotid PP was a good predictor of dilation of the AsAo in these patients, whereas brachial BPs were not.

Discussion

The new findings of the present study are that in patients with MFS, (1) carotid PP, used as a surrogate for central PP, is a major determinant of AsAo diameter, independently of age and BSA and (2) increased arterial stiffness is confined to the aorta.

AsAo Diameter and PP

Patients with MFS have a larger diameter of the AsAo than age- and sex-matched control subjects, as previously report-
In MFS patients in the present study, carotid PP was a significant determinant of AsAo diameter, independently of aging and BSA, whereas brachial PP and radial PP were not. This is consistent with the hemodynamic feature that increased wave reflections affect brachial PP to a lesser extent than central PP.5 The ratio of carotid/brachial PP, an index of pulse-wave amplification, was also significantly and positively associated with AsAo diameter, independently of age and BSA.

An explanation for the positive relationship between AsAo diameter and carotid PP may be suggested from biomechanical principles.19 Although to the best of our knowledge there is no direct evidence that the degree of dilation in MFS patients relates to the degree of elastin abnormality (ie, the extent of the primary disease), aortic dilation is most likely due to the failure by elastic fibers to sustain physiological hemodynamic stress, by analogy with aging. It is well accepted that the enlargement of elastic arteries of normal subjects with aging is associated with a progressive disorganization of elastic fibers, which show thinning and fragmentation.20 These changes are generally considered signs of mechanical failure and fatigue of biomaterials.19 That AsAo diameter was related to carotid PP but not mean BP suggests that cyclic stress (PP) plays a more important role than steady stress (mean BP). According to engineering principles, the fatiguing effect of cyclic stress is dependent on both the number of cycles and the amplitude of stress. Interestingly, in the present study, AsAo diameter of MFS was significantly and positively associated with aging and PP, which may be considered practical estimates of the number of cycles and the amplitude of stress, respectively.

A potential limitation of the study is that carotid PP was calibrated with brachial mean and diastolic BPs.15 The conditions for applying this method of calibration may not be fully reached in MFS patients, because the carotid/brachial PP ratio, which is influenced by the geometry of the arterial system and its stiffness, is probably different between MFS and control subjects. However, an alternative calculation using carotid PP not calibrated with brachial BP yielded similar results (ie, that AsAo diameter was independently and positively associated with carotid PP in MFS patients and negatively in control subjects).

The negative relationship between AsAo diameter and PP, observed in the control subjects of the present study, is most likely a result of the increase in aortic compliance, which parallels the increase in aortic diameter and reduces wave reflections and thus central PP.6

**Arterial Stiffness of Aorta and Peripheral Arteries**

The increased arterial stiffness was confined to the aorta in MFS: The distensibility of the AbAo was only half the value of control subjects, but the distensibility of other arterial sites (CCA, CFA, and RA) was not significantly different between MFS and control subjects. These data thus provide additional information to previous studies in MFS showing an increased stiffness of the whole arterial tree7 by invasive methods and an increased stiffness of the AsAo8,10,11 and AbAo8 by noninvasive methods. The results of the present study are consistent with the histological finding that arterial abnormalities in MFS are largely confined to the aorta.4

**Clinical Implications of Findings**

Although the present study has a cross-sectional design and included a small number of patients, it suggests that MFS patients with high carotid PP are at high risk for AsAo dilation. Thus, carotid PP could be useful, in preference to

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>R² Increment</th>
<th>β Coefficient</th>
<th>t Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid PP</td>
<td>0.30</td>
<td>0.07</td>
<td>0.26±0.09</td>
<td>2.67</td>
<td>0.02</td>
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<tr>
<td>Age</td>
<td>0.45</td>
<td>0.20</td>
<td>0.26±0.05</td>
<td>4.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSA</td>
<td>0.73</td>
<td>0.27</td>
<td>34.4±6.6</td>
<td>5.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(adjusted global $R^2=0.58$)

<table>
<thead>
<tr>
<th>Control subjects</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid PP</td>
<td>−0.56</td>
<td>0.31</td>
<td>−0.20±0.07</td>
<td>−3.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.36</td>
<td>0.12</td>
<td>0.13±0.07</td>
<td>2.08</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BSA*</td>
<td></td>
<td></td>
<td></td>
<td>0.46</td>
<td></td>
</tr>
</tbody>
</table>

(adjusted global $R^2=0.47$)

*Not included in analysis.*
brachial PP and systolic BP, for evaluating the risk for subsequent aortic complications.

The present finding that local PP but not mean BP was a determinant of AsAo diameter adds to earlier studies showing that reducing dP/dt (the rate of change in the central BP with respect to time) was far more protective against aortic dissection than reducing mean BP.21 Thus, in addition to reducing heart rate and dP/dt, a primary therapeutic goal should aim at reducing the amplitude of central PP.

In conclusion, in patients with MFS, local PP, estimated from carotid PP, was a major determinant of AsAo diameter, whereas brachial PP was not. Increased arterial stiffness was confined to the aorta.

References
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