Decreased Aortic Elasticity in Children With Marfan Syndrome or Loeys-Dietz Syndrome

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Background: The characteristics of aortic elasticity are unclear in children with connective tissue disorders (CTDs) such as Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS), especially in those with a non-dilated aortic root (AoR). This study evaluated the aortic elasticity properties of pediatric MFS and LDS patients with either dilated or non-dilated AoR.

Methods and Results: The 31 children with MFS or LDS were classified into dilated (Z score of AoR diameter ≥2.5; n=17) or non-dilated (Z score of AoR diameter <2.5; n=14) AoR groups and compared with controls. Using transthoracic echocardiography, we analyzed the aortic elasticity parameters of distensibility, strain, and stiffness index at the levels of the AoR, sinotubular junction, ascending aorta, and descending aorta. Aortic distensibility and strain were significantly lower in both test groups than in controls at the AoR level. The Z score of AoR diameter significantly correlated with aortic distensibility (R=−0.63, P<0.001), strain (R=−0.54, P=0.002), and stiffness index (R=0.52, P=0.002) in the patients’ groups. Multivariate analysis revealed that aortic distensibility and the type of CTD were independently associated with AoR dilatation.

Conclusions: Aortic elasticity at the level of the AoR may be decreased in children with MFS or LDS even before AoR dilatation progresses. Less aortic distensibility and CTD type are considered important parameters in estimating AoR dilatation in these patients. (Circ J 2016; 80: 2369–2375)

Key Words: Aortic elasticity; Connective tissue disorders

Aortic root (AoR) dilatation and dissection are the main factors affecting prognosis in patients with connective tissue disorders (CTDs) such as Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS). Although aortic diameter has been the main predictor of aortic complications, aortic dissection can nonetheless occur in patients with AoR diameters below the indication for surgical intervention. Thus, the assessment of aortic diameter alone may not be sufficient to prospect clinical outcome. Aortic wall pathogenesis among the CTDs is similar, and includes fragmentation of elastic fibers and collagen deposition, leading to aortic stiffness. Nollen et al demonstrated that aortic stiffness could also be an independent predictor of progressive aortic dilatation in adult MFS patients. Increased aortic stiffness has been reported in children and adults with MFS, LDS, and other CTDs. However, the aortic elasticity properties in children with MFS or LDS have not been studied in detail, especially in patients without AoR dilatation.

The present study evaluated the elasticity of the aorta, including distensibility, strain, and stiffness index, using transthoracic echocardiography (TTE) in children with MFS and LDS with and without AoR dilatation.

Methods

This investigation was a retrospective review of patients’ clinical data at Shinshu University School of Medicine. The study protocol was approved by the institution’s Ethics Committee, and written informed consent was given by the parents of the children in the patient and controls groups enrolled in the study.

Subjects

Children with MFS or LDS who were followed as outpatients between 2007 and 2016 at Shinshu University Hospital were divided into 2 groups according to AoR diameter: the dilated group was defined as patients having an AoR diameter Z score...
>2.5<sub>12</sub> (n=17), and the non-dilated group contained patients with an AoR diameter Z score <2.5 (n=14). Demographic and clinical data were obtained from medical records. The revised Ghent nosology was used for the diagnosis of MFS.<sup>13</sup> All MFS patients harbored a fibrillin-1 (FBN1) mutation, while all LDS patients exhibited transforming growth factor-β receptor 2 (TGFBR 2) or SMAD 3 mutations and the clinical characteristics of LDS. We enrolled 15 subjects as controls; they presented with signs of heart disease or arrhythmia that were subsequently identified by further examination. None of the control subjects had a prior or family history of systemic disease.

**Measurement of Aortic Elastic Properties**

A trained physician (Y.A.) performed all TTE examinations with an iE33 device (Philips Healthcare, Andover, MA, USA). The diameters of the AoR and sinotubular junction (STJ) were measured at mid-systole and end-diastole using the inner-to-inner edge method in a 2D parasternal long-axis view according to the guidelines of the American Society of Echocardiography.<sup>14</sup> (Figure 1A). The diameter of the proximal ascending aorta (AAO) was measured at 2–3 cm from the valve at end-systole and end-diastole using the leading edge to leading edge principle in M-mode<sup>15</sup> (Figure 1B). The diameter of the descending aorta (DAO) was measured in a subcostal long-axis view at the level of the diaphragm<sup>14</sup> (Figure 1C). All echocardiographic measurements were averaged from 3 consecutive heartbeats. The Z scores for the AoR, STJ, AAO, and DAO were calculated using normative data.<sup>16,17</sup> Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the right arm by sphygmomanometer (ES-H55, Terumo Co, Tokyo, Japan) with the patient in a supine position. The mean of 3 measurements were averaged for ensuing calculations. The following 3 parameters of aortic stiffness were calculated at the levels of the AoR, STJ, AAO, and DAO:<sup>15,18,19</sup>

\[
\text{Aortic distensibility} = 2 \times \frac{(\text{AOs} - \text{AOd})}{\text{AOd}} \times (\text{SBP} - \text{DBP})
\]

\[
\text{Aortic strain} = 100 \times \frac{(\text{AOs} - \text{AOd})}{\text{AOd}}
\]

\[
\text{Aortic stiffness index} (\beta) = \frac{\ln(\text{SBP} / \text{DBP})}{(\text{AOs} - \text{AOd}) / \text{AOd}}
\]

Where AOs and AOd are the systolic and diastolic aortic dimensions, respectively, and \( \ln \) is the natural logarithm.

**Statistical Analysis**

Data are expressed as the mean±standard deviation (SD). In group comparisons, Student’s unpaired t-test was used for parametric variables and the Mann-Whitney U test was adopted for nonparametric variables. Categorical variables were analyzed using the Chi-square test. For comparisons of clinical characteristics and echocardiography parameters among the 3 groups, one-way analysis of variance and the post hoc Bonferroni test were performed. Spearman’s correlation analysis was used to assess for relationships between the Z scores of the aortic segments and aortic elasticity indexes. Multivariate regression analysis was also performed to determine the independent effect of aortic distensibility on aortic dilatation using independent variables potentially influencing aortic dilatation. Four factors (aortic distensibility, type of CTD [MFS was coded as 1 and LDS was coded as 0], age, SBP and DBP) were then entered into a multiple linear regression model. We chose the distensibility of the AoR because of its better correlation with AoR dilatation compared with both aortic strain and aortic stiffness index using univariate regression analysis. We chose other factors, including age, SBP, and DBP, that could be influencing factors for aortic dilatation and stiffness.<sup>20,21</sup> Intraobserver variability was assessed by one investigator (Y.A.) conducting off-line measurements on the same patients 4 weeks apart. Interobserver variability was assessed...
by a second investigator (N.M.) who was unaware of the previous results and performed the same measurements on 10 randomly selected study participants. Intra- and interobserver agreements were assessed using the intraclass correlation coefficient (ICC). Additionally, agreement between investigators was tested using Bland-Altman analysis by calculating the bias (mean difference) and 1.96 SD around the mean difference. A P value <0.05 was considered statistically significant. All
statistical analyses were carried out using SPSS version 23.0 software (SPSS, Inc, Chicago, IL, USA).

**Results**

**Study Subjects' Characteristics**

Table 1 shows the clinical characteristics of the 3 test groups, which were comparable with regard to age, sex, SBP, and DBP. CTD patients included 26 with MFS and 5 with LDS, and all were predominantly children (<18 years old; 84%). There were no LDS patients in the non-dilated group. Most CTD patients were receiving either β-blocker (atenolol) monotherapy or combination treatment using a β-blocker and angiotensin-receptor blocker (losartan). No significant difference was

![Graphs showing aortic distensibility, strain, and stiffness index in aortic root dilated group (AoR-D), aortic root non-dilated group (AoR-ND), and control subjects.](image)

Figure 2. Box-and-whisker plots showing aortic distensibility, aortic strain, and aortic stiffness index in aortic root dilated group (AoR-D), aortic root non-dilated group (AoR-ND), and control subjects. The horizontal line in the middle of each box indicates the median, the top and bottom borders of each box show the 75th and 25th percentiles, respectively, and the whiskers mark the 90th and 10th percentiles. NS, not significant.

![Graphs showing regression plots of relationships between aortic elasticity indexes and the Z score of the aortic root (AoR) diameter.](image)

Figure 3. Regression plots of relationships between aortic elasticity indexes and the Z score of the aortic root (AoR) diameter. (A) Aortic distensibility, (B) aortic strain and (C) aortic stiffness index. MFS, marfan syndrome; LDS, Loeys-Dietz syndrome.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>β</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>AoR distensibility</td>
<td>−0.37</td>
<td>0.011</td>
</tr>
<tr>
<td>Type of CTD</td>
<td>0.52</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>−0.28</td>
<td>0.087</td>
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<td>SBP</td>
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</tr>
<tr>
<td>DBP</td>
<td>−0.062</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Table 3. Multivariable Indicators of Aortic Dilatation in Pediatric Patients With MFS or LDS

Abbreviations as in Table 1.
observed between the dilated and non-dilated groups for use of medication. No subject had moderate or severe aortic regurgitation.

**Aortic Dimensions and Elastic Properties**

The data on aortic dimensions and stiffness at the levels of the AoR, STJ, AAO, and DAO are presented in Table 2. Both aortic distensibility and strain in the dilated group at all levels of the aorta apart from the DAO were significantly lower than in controls. The aortic stiffness index at the AoR and AAO levels in the dilated group was higher than in controls. Importantly, even in non-dilated patients, aortic distensibility, as well as strain, at the levels of the AoR and STJ was lower than in controls. At the AAO level in the non-dilated group, aortic strain was also lower as compared with controls (Table 2, Figure 2). Figure 3 presents the correlations between aortic elasticity parameters and the Z score of AoR diameter. Both aortic distensibility and aortic strain were negatively correlated (R=−0.63, P<0.001 and R=−0.54, P=0.002, respectively), and the aortic stiffness index positively correlated (R=0.52, P=0.002), with the AoR diameter Z score. These results indicated that lower aortic elasticity parameters at the AoR level correlated with aortic dilatation in young MFS and LDS patients not only in the dilated group, but also in the non-dilated group. At the AAO level, aortic strain was the only aortic elasticity index associated with the Z score of the AAO (R=−0.38). There were no significant correlations between the aortic elasticity indexes and aortic dilatation at the STJ and DAO levels. Multivariate regression analysis was conducted to identify the independent relevance of AoR dilatation in the patients’ groups. Calculations using aortic distensibility, type of CTD, age, SBP, and DBP as independent variables revealed that aortic distensibility and CTD type (larger Z score of the AoR in the LDS group than in the MFS group) were significantly correlated with the Z score of the AoR (Table 3).
Reliability of Aortic Measurements

Intra- and interobserver reproducibilities in the analysis of AOs and AOD at the 4 levels of the aorta were confirmed in 10 randomly selected participants by means of Bland-Altman analysis and ICC. Measurements of aortic diameters proved to be highly reproducible. Figure 4 shows the Bland-Altman plots for interobserver variability (bias ± limits of agreement), while Table 4 summarizes the intra- and interobserver reproducibilities from the Bland-Altman analysis and ICC.

Discussion

To our knowledge, this is the first report to demonstrate that: (1) children with MFS or LDS may already have decreased aortic elasticity even before AoR dilatation progresses, and (2) decreased aortic distensibility and CTD type are independent determinant factors of aortic dilatation in children with MFS or LDS. In agreement with previous reports, the segmental aortic elasticity parameters in MFS were significantly lower than in controls. Moreover, we demonstrated that aortic elasticity had already become reduced in children with MFS or LDS without AoR dilatation. An earlier study found that adult MFS patients with non-dilated AoR had increased pulse wave velocity because of diminished aortic elasticity, but did not describe impaired aortic elasticity in children with MFS or LDS in the early stage of disease. As aortic stiffness is related to disruption of the medial elastic fibers, it may represent a good marker of aortic medial pathology in both CTD patients and children with congenital heart disease.

Besides increased aortic stiffness, the type of CTD was an independent determinant factor of aortic dilatation in this study. We speculate that this result can be attributed to the histological characteristics of LDS, in which more severe medial elastic fiber disruption of the aortic wall leads to more rapid progression of aortic dilatation as compared with MFS.

BP levels were similar among the groups in this study despite higher aortic stiffness in the patients’ groups. There are contradictory results on the association of BP level and aortic stiffness in MFS. Teixido-Tura et al have reported that adult MFS patients with increased aortic stiffness showed higher BP than controls, whereas Hirata et al have showed no significant difference in BP between MFS and controls despite higher aortic stiffness in the MFS patients. We speculate this discrepancy might reflect the different stages in the disruption of the medial elastic fibers. Increased aortic stiffness by disrupting elastin in the aortic wall is associated with subsequent development of hypertension. Several clinical studies have showed that increased aortic stiffness in normotensive individuals is associated with subsequent BP progression. Children with MFS or LDS who have increased aortic stiffness may develop hypertension in adulthood if the disruption of the medial elastic fibers progresses.

Measurement of echocardiologic parameters to assess the elastic properties of the aorta, including distensibility, strain, and stiffness index, is a simple and repeatable method that can be incorporated into routine echocardiography. This noninvasive approach has been used for patients of various ages and diseases to evaluate aortic stiffness, and has been validated in coronary artery disease through comparisons with invasive methods. Although MRI is regularly used to assess aortic elasticity in CTD patients, routine testing can become expensive, time consuming, and traumatic for small children. In general, echocardiography is performed more frequently than MRI on patients with CTDs to follow aortic changes. Our current results confirmed that the measurement of aortic elasticity using echocardiography is useful and reliable in evaluating aortic impairment in children with CTDs.

Study Limitations

First, it was retrospective, cross-sectional, and included a small sample. Second, we were not blinded to the patients’ diagnoses. Third, we performed noninvasive brachial pressure measurement with a sphygmomanometer to determine aortic pressure even before AoR dilatation has progressed, because aortic stiffness may have already increased and contribute to medication resistance in the later stages.

Table 4. Reproducibility of Aortic Measurements in Pediatric Patients With MFS or LDS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interobserver variability</th>
<th>ICC</th>
<th>Intraobserver variability</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AoR sys</td>
<td>0.36±1.3</td>
<td>0.99</td>
<td>−0.26±1.2</td>
<td>0.99</td>
</tr>
<tr>
<td>AoR dia</td>
<td>0.27±1.1</td>
<td>0.99</td>
<td>−0.27±1.6</td>
<td>0.99</td>
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<tr>
<td>STJ sys</td>
<td>1.6±3.0</td>
<td>0.94</td>
<td>−0.54±1.8</td>
<td>0.98</td>
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<tr>
<td>STJ dia</td>
<td>0.90±3.4</td>
<td>0.95</td>
<td>−0.47±3.0</td>
<td>0.97</td>
</tr>
<tr>
<td>AAO sys</td>
<td>0.54±1.0</td>
<td>0.99</td>
<td>−0.04±2.2</td>
<td>0.97</td>
</tr>
<tr>
<td>AAO dia</td>
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<td>0.88</td>
<td>0.00±3.5</td>
<td>0.93</td>
</tr>
<tr>
<td>DAO sys</td>
<td>1.2±1.6</td>
<td>0.93</td>
<td>0.24±2.3</td>
<td>0.95</td>
</tr>
<tr>
<td>DAO dia</td>
<td>0.88±1.6</td>
<td>0.95</td>
<td>−0.11±3.8</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. AoR sys/dia, AoR diameter in systole/diastole; STJ sys/dia, STJ diameter in systole/diastole; AAO sys/dia, AAO diameter in systole/diastole; DAO sys/dia, DAO diameter in systole/diastole; ICC, intraclass correlation coefficient. Other abbreviations as in Table 1.
instead of direct measurement, although this method has been well correlated for distensibility of the AAO. As far as we know, segmental aortic stiffness and its relation to aortic dilation using echocardiography in children with MFS or LDS has not been described. Thus, this is the first report revealing that children with MFS or LDS with a non-dilated AoR already have decreased aortic elasticity, knowledge that may assist in the management of vascular complications in children with these CTDs.

In conclusion, the present study demonstrated that aortic stiffness as evaluated by echocardiography was increased in children afflicted by MFS or LDS, even before AoR dilation progresses.

Financial Support Statement / Disclosure

The authors have no conflicts of interest or financial relationships relevant to this article to disclose.

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6. Okamoto RJ, Xu H, Kouchoukos NT, Moon MR, Sundt TM 3rd. The authors have no conflicts of interest or financial relationships relevant to this article to disclose.

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