Aortic elasticity and size in bicuspid aortic valve syndrome

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Aims
To investigate the relation between aortic elastic properties and size in bicuspid aortic valves (BAVs).

Methods and results
127 BAV outpatients (121 males; age 23 ± 10 years) with no or mild valvular impairment, were recruited with 114 control subjects comparable for age, gender, and body size. Aortic distensibility (DIS) and stiffness index (SI) were derived by M-mode evaluation of the aortic root together with blood pressure measured by cuff sphygmomanometer. BAVs vs. controls had increased aortic diameter (P < 0.0001), higher systolic (P = 0.02) and pulse (P = 0.04) pressures. DIS was lower in BAVs than in controls (4.71 ± 3.67 vs. 7.44 ± 3.94 cm²dyne⁻¹, respectively; P < 0.0001) and SI was greater in BAVs (7.21 ± 4.93 vs. 3.57 ± 1.88, respectively; P < 0.0001). Definite impairment in aortic elasticity was present in 53 (42%) BAVs. Both DIS and SI were related (P < 0.0001) to aortic size in BAVs and controls. After adjusting for aortic size and blood pressure, the regression relations between SI and aortic diameter of BAVs were significantly different from controls (P = 0.0052).

Conclusion
Abnormal aortic elasticity is a common finding in BAVs with no or mild aortic valve impairment. However, impaired aortic stiffness is not due to aortic dilation. Simple assessment of aortic size may thus fail to identify early abnormal load bearing characteristics of the aortic wall in BAVs.

Keywords
Bicuspid aortic valve • Echocardiography • Aortic elasticity
diabetes; (iv) coronary artery disease (indicated by previous myocardial infarction, any surgical, or percutaneous revascularization, >50% coronary artery stenosis, or a positive result on ECG, perfusion or echocardiographic exercise, or pharmacological stress test); (v) familial hypercholesterolaemia; (vi) use of any cardiovascular drugs (including statins); (vii) any previous surgical or interventional cardiac or vascular procedure; (viii) association of any cardiomyopathy and/or genetic cardiovascular disease [including Marfan syndrome (MFS)]; and (ix) aortic aneurysm (defined as localized dilation of the aorta >1.5 times that of the expected normal diameter of any given aortic segment). One hundred and fourteen consecutive tricuspid aortic valve subjects (age 20.92 ± 9.85 years), without any of the previously described exclusion criteria, were prospectively recruited as controls.

Echocardiographic and Doppler analysis

Two-dimensional and Doppler echocardiograms were interpreted by the principal investigator (S.N.), an experienced echocardiographer. Aortic valve morphology was evaluated in the parasternal long and short axis views, and only those with a clearly defined aortic valve orifice and leaflets were included in the study. A congenital BAV was diagnosed when only two cusps were unequivocally identified in systole and diastole in the short axis view with a clear ‘fish mouth’ appearance during systole (Figure 1). Patients with dystrophic calcification, and/or with fusion of the commissures and/or any mitral valve abnormality attributable to rheumatic disease were not included in the study. Aortic size was assessed at four levels (annulus, Valsalva sinuses, sinotubular junction, and ascending aorta) as previously described at end-diastole, and normalized to body surface area. Left ventricular end-diastolic (EDVI) and end-systolic volume indexes (ESVI) were calculated with the biplane method of discs and normalized to body surface. The left ventricular EF was calculated as (EDVI – ESVI)/EDVI.

The presence of aortic regurgitation was assessed on colour Doppler by the use of standard criteria and graded as mild accordingly. Peak velocity was also assessed by continuous wave Doppler; aortic stenosis was considered mild when peak aortic velocity was <3 m/sec.

Calculation of aortic elasticity

Aortic elasticity was assessed using a two-dimensional guided M-mode evaluation of systolic (AoS) and diastolic (AoD) aortic diameters, 3 cm above the aortic valve; AoD was obtained at the peak of the R wave at the simultaneously recorded electrocardiogram, while AoS was measured at the maximal anterior motion of the aortic wall (Figure 2); for each diameter five measurements were averaged. The following indexes of aortic elasticity were calculated: aortic strain = 100(AoS – AoD)/AoD; DIS = [2(AoS – AoD)/AoD(P)] (10^-6 cm^2 dyne^-1); aortic stiffness index (SI) = ln(SBP/DBP)/[(AoS – AoD)/AoD] where SBP and DBP refer to brachial systolic and diastolic blood pressures, respectively, measured in mmHg; pulse pressure (PP) was calculated as SBP – DBP, and ln(SBP/DBP) refers to the natural logarithm of the relative pressure. Blood pressure was measured at the right arm by a purposely trained nurse unaware of the valve status of the patients, using a properly sized cuff sphygmomanometer, averaging three values. Phase 1 and Phase 5 Korotkoff sounds were used for SBP and DBP, respectively. AoD and AoS were evaluated off-line by the principal investigator blinded to the identity of the subject.

Statistics

Data are expressed as means ± standard deviations (SD) for controls, BAV subjects, BAV-AR, BAV-NF, separately; sex variable is expressed as percentage of males. Group mean values were compared through Generalized Linear Models procedure, after testing the homoscedasticity with the Levene’s test. Welch’s test was performed when this assumption was not met. Associations between groups of subjects defined and sex were investigated with the x^2 test. The relations between AoD and age, and between DIS, SI, aortic strain and age (controlling also for AoD, SBP, and PP) were evaluated by regression models and analysis of covariance (ANCOVA) in BAVs and control subjects. Three multivariate regression models were considered, to identify predictors of AoD, AoS, and AoS/AoD, respectively, in BAVs; predictors considered in each model were sex, age, BSA, DIS, SI, SBP, DBP, PP, and peak velocity. A logistic regression model was constructed considering the stepwise selection method, with
outcome BAV subjects vs. control subjects. Possible predictors considered in this model were AoS, AoD, AoS – AoD, SBP, DBP, PP, peak velocity (dichotomized considering the median value of its distribution), SI, and aortic strain. A further multivariate regression model was defined to study if BAV-NF and BAV-AR are independent predictors of SI and DIS, after controlling for age, sex, AoS, AoD, and AoS – AoD. A P-value <0.05 was considered statistically significant. Analyses were performed using SAS release 9.1.

Results

Baseline characteristics of overall BAVs, BAV-NF, BAV-AR, and controls are summarized in Table 1. All subjects were males except for seven BAVs and six controls. A familial BAV was documented in six patients; it was associated with thoracic aortic aneurysm in one relative and with aortic coarctation in another one. In three additional BAV patients, there was a family history of aortic valve replacement for aortic stenosis (aortic valve morphology unknown), and one more patient documented a family history of aortic dissection (aortic valve morphology unknown). The peak aortic pressure gradient in BAVs with aortic stenosis was 24.5 ± 6 mmHg (mean effective orifice area by continuity equation was 1.62 ± 0.15 cm²). AoD was significantly related to age both in BAVs and in controls (Figure 3); moreover, BAVs had significantly larger AoD after adjusting for age (P < 0.0001, ANCOVA). Similarly, significant findings were verified for aortic size at each aortic level (data not shown).

BAV-AR were significantly older than BAV-NF patients; SBP was higher in BAV-AR with respect to controls. EDVI was significantly smaller than in controls and BAV-NF. Peak velocity was higher in BAV-AR and BAV-NF with respect to control patients, and in BAV-AR than in BAV-NF. Aortic size, AoD and AoS were not significantly different in BAV-NF and BAV-AR, whereas AoS – AoD was significantly larger in BAV-AR than in BAV-NF.

Elastic properties

DIS was significantly lower in BAVs than in controls (Table 1; 3.32 ± 2.55 vs. 5.59 ± 2.96 10⁻⁶ cm² dyne⁻¹, respectively, P < 0.0001), SI was significantly greater in BAVs than in control subjects (7.49 ± 5.00 vs. 3.57 ± 1.88, respectively, P < 0.0001), and aortic strain was significantly lower in BAVs (10.28 ± 6.94 vs. 16.91 ± 7.38, P < 0.0001).

BAVs with DIS <5th percentile (i.e. 2.07 ± 10⁻⁶ cm² dyne⁻¹) of the distribution for DIS among controls, and with SI >95th percentile (i.e. 7.6) of the distribution for SI among controls, were considered as having a definite impairment in aortic elasticity (BAV-Abn). BAVs displaying both DIS and SI within the range of controls were classified as having normal elasticity (BAV-Nor). Fifty-three BAVs (42%) were considered BAV-Abn; another 72 (57%) were classified BAV-Nor. Two further patients had DIS <5th percentile and SI <95th percentile of the control group and were excluded from further analysis. BAV-Abn had larger body surface area, higher SBP, and PP, larger AoD and AoS – AoD than BAV-Nor (data not shown).

Aortic strain and DIS were significantly lower in BAV-AR and BAV-NF than in controls, whereas they were higher in BAV-AR with respect to BAV-NF. SI was significantly higher in BAV-AR and BAV-NF than in controls, and in BAV-NF with respect to BAV-AR (Table 1).

DIS was significantly related to age in both BAVs and controls (P < 0.0001 for both); after adjusting for age BAVs had significantly lower mean DIS than controls (P < 0.0001, ANCOVA; data not shown). SI was significantly related to age in controls (P = 0.0004 age) but...
mean SI than controls (\(P\) not in BAVs; after controlling for age BAVs had significantly higher Aortic elasticity and size in BAV

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Aortic strain (%) 16.91 ± 7.49

Heart rate (bpm) 68.25 ± 2.54 68.45 ± 2.60 68.05 ± 2.61 68.68 ± 2.63

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 114)</th>
<th>BAV (n = 127)</th>
<th>BAV-AR (n = 85)</th>
<th>BAV-NF (n = 36)</th>
<th>(P)-value controls vs. BAV</th>
<th>(P)-value controls vs. BAV-AR</th>
<th>(P)-value controls vs. BAV-NF</th>
<th>(P)-value BAV-AR vs. BAV-NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20.92 ± 9.85</td>
<td>23.14 ± 9.95</td>
<td>23.48 ± 9.69</td>
<td>19.81 ± 6.74</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.0405</td>
</tr>
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<td>Sex (% males)</td>
<td>94.7</td>
<td>94.5</td>
<td>94.1</td>
<td>97.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.76 ± 0.26</td>
<td>1.81 ± 0.20</td>
<td>1.82 ± 0.21</td>
<td>1.79 ± 0.19</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Blood pressure (mmHg)</td>
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</tr>
<tr>
<td>SBP</td>
<td>122.81 ± 10.06</td>
<td>126.17 ± 12.15</td>
<td>126.38 ± 11.38</td>
<td>123.67 ± 9.50</td>
<td>0.02</td>
<td>0.02</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP</td>
<td>75.05 ± 7.49</td>
<td>75.61 ± 6.81</td>
<td>76.09 ± 6.52</td>
<td>73.75 ± 6.69</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PP</td>
<td>47.75 ± 8.95</td>
<td>50.56 ± 12.02</td>
<td>50.28 ± 11.16</td>
<td>49.92 ± 9.98</td>
<td>0.04</td>
<td>0.04</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>End-diastolic volume index (mL/m²)</td>
<td>64.27 ± 10.67</td>
<td>72.20 ± 12.89</td>
<td>74.76 ± 13.46</td>
<td>67.42 ± 9.33</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td>0.0009</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>62.82 ± 3.25</td>
<td>62.93 ± 4.57</td>
<td>63.32 ± 4.46</td>
<td>62.28 ± 5.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Peak velocity (m/s)</td>
<td>1.25 ± 0.10</td>
<td>1.52 ± 0.29</td>
<td>1.50 ± 0.20</td>
<td>1.40 ± 0.18</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0107</td>
</tr>
<tr>
<td>AoS (cm)</td>
<td>2.75 ± 0.40</td>
<td>3.27 ± 0.49</td>
<td>3.24 ± 0.49</td>
<td>3.32 ± 0.50</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AoD (cm)</td>
<td>2.38 ± 0.44</td>
<td>2.99 ± 0.53</td>
<td>2.93 ± 0.53</td>
<td>3.08 ± 0.53</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AoS − AoD (cm)</td>
<td>0.38 ± 0.12</td>
<td>0.29 ± 0.16</td>
<td>0.31 ± 0.17</td>
<td>0.24 ± 0.13</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>&lt;0.0001</td>
<td>0.0309</td>
</tr>
<tr>
<td>Annulus (cm/m²)</td>
<td>1.20 ± 0.13</td>
<td>1.29 ± 0.16</td>
<td>1.30 ± 0.15</td>
<td>1.30 ± 0.17</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0006</td>
</tr>
<tr>
<td>Valsalva sinuses (cm/m³)</td>
<td>1.56 ± 0.21</td>
<td>1.80 ± 0.23</td>
<td>1.81 ± 0.23</td>
<td>1.80 ± 0.21</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sinotubular junction (cm/m³)</td>
<td>1.36 ± 0.17</td>
<td>1.56 ± 0.23</td>
<td>1.54 ± 0.22</td>
<td>1.59 ± 0.25</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ascending aorta (cm/m³)</td>
<td>1.39 ± 0.19</td>
<td>1.63 ± 0.35</td>
<td>1.65 ± 0.39</td>
<td>1.56 ± 0.23</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DIS (10⁻⁵ cm² dyne⁻¹)</td>
<td>5.59 ± 2.96</td>
<td>3.32 ± 2.55</td>
<td>3.67 ± 2.68</td>
<td>2.61 ± 2.13</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0374</td>
</tr>
<tr>
<td>SI</td>
<td>3.57 ± 1.88</td>
<td>7.49 ± 5.00</td>
<td>6.69 ± 4.59</td>
<td>9.06 ± 5.46</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic strain (%)</td>
<td>16.91 ± 7.38</td>
<td>10.28 ± 6.94</td>
<td>11.28 ± 7.03</td>
<td>8.38 ± 6.68</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise specified.
NS, not statistically significant. See manuscript for other abbreviations.

not in BAVs; after controlling for age BAVs had significantly higher mean SI than controls (\(P < 0.0001\), ANCOVA; data not shown). Aortic strain was significantly related to age in both BAVs and controls (\(P < 0.0001\) for both); adjusting for age, BAV subjects has significantly lower mean aortic strain values than controls (\(P < 0.0001\), ANCOVA; data not shown).

DIS was significantly related to AoD both in patients and in controls (\(P < 0.0001\) for both) (Figure 4A); notwithstanding considerable variation in DIS among BAVs, after controlling for AoD, SBP, and PP, the effect of group was not significant. SI was significantly related to AoD in patients and in controls (Figure 4B; \(P < 0.0001\) for both), with a large variation in SI in BAV subjects; in contrast to DIS, the effect of group was significant (\(P = 0.0052\)) even after controlling for AoD, SBP, and PP, and the regression relations between SI and AoD of patients and controls were significantly different. Aortic strain was also significantly related to AoD both in patients and in controls (\(P < 0.0001\) for both) (Figure 4C); however, the effect of group was not significant after controlling for AoD, SBP, and PP.

Reproducibility

Intra- and interobserver reproducibility, calculated as the standard deviation of the differences between measurements, and expressed as the percentage of the mean of the measurements, were determined after the re-evaluation of randomly selected images of 35 BAVs and 15 controls, and were: 2.8 and 2.9% for AoD, respectively, 3.5 and 3.4% for AoS, respectively, and 3.1% for SI.

Predictors of AoD, AoS, and AoS – AoD in BAV

Three multivariate regression models were defined, with outcomes AoD, AoS, and AoS – AoD, respectively (Table 2). After
stepwise removal of non-significant variables, the significant independent predictors of AoD were age, body surface area, DIS, and SI ($R^2 = 0.50$). Predictors of AoS were age, body surface area, and SI ($R^2 = 0.34$), whereas the independent variables related to change in aortic diameter ($\Delta$AoS - AoD) were body surface area, PP, DIS, and SI ($R^2 = 0.85$).

**Predictors of bicuspid aortic valve condition**

Significant predictors of the BAV condition were peak velocity, AoS, and SI (Table 3).

**Predictors of stiffness index and aortic distensibility**

After controlling for age, sex, AoD, AoS, $\Delta$AoS - AoD, BAV-NF, and BAV-AR (vs. controls), the presence of BAV-NF is an independent predictor of SI, although it was not a significant predictor in relation to DIS (Table 4).

**Discussion**

To our knowledge, this is the first study to evaluate the relation between aortic elastic properties and dilation in BAVs. Our data

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**Table 2 Predictors of aortic diastolic diameter, aortic systolic diameter and change in aortic diameter in BAV subjects, multivariate regression**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient estimate</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.869</td>
<td>0.394</td>
<td>0.0003</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.014</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.481</td>
<td>0.193</td>
<td>0.0140</td>
</tr>
<tr>
<td>Aortic distensibility</td>
<td>-0.052</td>
<td>0.016</td>
<td>0.0017</td>
</tr>
<tr>
<td>(cm² dyne⁻¹ 10⁻⁶)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stiffness index</td>
<td>0.021</td>
<td>0.010</td>
<td>0.0397</td>
</tr>
</tbody>
</table>

**Outcome: aortic systolic diameter ($R^2 = 0.34$)**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient estimate</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.505</td>
<td>0.334</td>
<td>0.0003</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.016</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.681</td>
<td>0.200</td>
<td>0.0009</td>
</tr>
<tr>
<td>Aortic stiffness index</td>
<td>0.022</td>
<td>0.007</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

**Outcome: change in aortic diameter ($\Delta$AoS - AoD) ($R^2 = 0.85$)**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient estimate</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.256</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.122</td>
<td>0.032</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>0.004</td>
<td>0.001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic distensibility</td>
<td>0.053</td>
<td>0.004</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(cm² dyne⁻¹ 10⁻⁶)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stiffness index</td>
<td>-0.008</td>
<td>0.002</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Table 3 Predictors of BAV subjects (vs. control), logistic regression model**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak velocity ($\geq 1.45$ m/s)</td>
<td>20.529</td>
<td>7.265–58.009</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AoS (cm)</td>
<td>6.172</td>
<td>2.323–16.400</td>
<td>0.0003</td>
</tr>
<tr>
<td>Aortic stiffness index</td>
<td>1.256</td>
<td>1.104–1.429</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Predictors considered in the model: AoS, AoD, AoS – AoD, SBP, DBP, PP, peak velocity, and SI. Stepwise selection method (see manuscript for abbreviations).
The impairment in aortic elasticity may be related to abnormal elastic fibers in the degenerated aortic medial layer of the BAV patients, which would have reduced capacity for elastic recoil and hence would permit the gradual plastic deformation and outward expansion of the aorta. Because this aortic dilatation would begin to unfold the crimped collagen within the aortic wall, the collagen fibers would consequently require less load and distension before they became unfolded completely and would bear load. This alteration in the material function of the tissue would be measurable as increased stiffness, but would be less evident from the diameters themselves.

**Comparison with Marfan syndrome**

Many previous studies have outlined the similarities between MFS and BAV. As found in the present study, the independency between impaired elasticity and aortic size has also been shown in MFS patients. Interestingly, Nollen et al. demonstrated that both aortic stiffness and size should be prospectively evaluated for optimal risk assessment and monitoring in MFS patients.

Our findings are also consistent with those by Okamoto et al., who demonstrated that DIS was reduced in aneurismal aortas from BAV and MFS patients independently from aortic size in the range of physiologic load. Quite notably, they found that the relative change in circumferential stretch ratio between the simulated diastolic and systolic states was significantly lower in patients with moderate-to-severe elastin fragmentation compared with those with mild elastin fragmentation. It should also be noted that our assessment of aortic strain, which is comparable to the circumferential stretch ratio, demonstrated a significant reduction in BAVs.

**Clinical implications and study perspectives**

Beta-blockers have been suggested to retard the progression of aortic dilatation in BAVs, although this positive effect has only been demonstrated in MFS. Moreover, aortic dilatation is quite prevalent in BAVs, even at a young age; thus, systematic employment of beta-blockers in such a large proportion of normotensive BAVs (most frequently young males) seems unfeasible in clinical practice. In a murine model of MFS, Habashi et al. demonstrated that losartan resulted into favourable effects on both aortic growth rate and aortic wall remodelling while propranolol-treated animals showed a lower rate of aortic growth without a significant effect on aortic wall thickness and elastic fibers architecture. If confirmed in humans, these findings might be relevant for BAVs, especially considering the good tolerance profile of angiotensin II type-1 antagonists.

Aortic size criteria have been identified for resection of aortic aneurysms during aortic valve replacement in BAVs. However, indications for aortic aneurysm surgery alone remain controversial. If abnormalities in connective tissue proteins account for the initiation of aortic dilatation in BAVs, it may be indicated to repair the aorta at a smaller size than in patients with normal valves, as for MFS. These indications are supported by recent findings by Neri et al. that aortic size per se served only a limited role in predicting acute type A aortic dissections, also in patients with an inherited connective tissue disorder (including BAV and MFS).

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**Table 4 Predictors of aortic stiffness index and distensibility, multivariate regression**

<table>
<thead>
<tr>
<th>Coefficient estimates</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>4.216</td>
<td>1.111</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.048</td>
<td>0.020</td>
</tr>
<tr>
<td>AoD (cm)</td>
<td>2.664</td>
<td>0.405</td>
</tr>
<tr>
<td>AoS − AoD (cm)</td>
<td>-15.852</td>
<td>1.199</td>
</tr>
<tr>
<td>BAV-NF subjects</td>
<td>1.378</td>
<td>0.537</td>
</tr>
<tr>
<td>BAV-AR subjects</td>
<td>0.676</td>
<td>0.390</td>
</tr>
</tbody>
</table>

Outcome: aortic stiffness index (R²: 0.69)
Outcome: aortic distensibility (R²: 0.79)

Predictors considered in each model: age, sex, AoS, AoD, AoS − AoD, BAV-AR (vs. control subjects), BAV-NF (vs. control subjects); see manuscript for abbreviations.

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It was particularly notable that SI, an index of arterial elasticity that is relatively independent of current distending pressure, was a significant predictor of the BAV condition by multivariate analysis. Moreover, the prevalence of (mild) aortic regurgitation did not cause the impairment in aortic elasticity in our patients. Interestingly, the ascending aortas of BAV-AR patients were more distensible and less stiff than those of the BAV-NF patients, in contrast to the findings reported by Murai et al. in non-BAV subjects. The elastic behaviour of the BAV-AR group, although still significantly stiffer than normal controls, may have permitted greater aortic root expansion and prevented full coaptation of the aortic valve leaflets.

The considerable variation in the degree of both DIS and SI among BAVs suggests that the load-bearing characteristics of the aortic wall are primarily altered in a group of BAV patients. This interpretation is consistent with the findings by Fedak et al., who demonstrated that a subset of BAVs have significantly reduced fibrillin-1 content of the aortic media; this fibrillin content did not show any relation with aortic diameter. Thus, the present study adds further support to the hypothesis that abnormalities of the aortic wall in BAVs are not secondary to abnormal valvular hemodynamics, and demonstrates that functional impairment of the ascending aorta can neither be attributed nor identified on aortic dilation.
patients). More recently, Pape et al.\textsuperscript{22} demonstrated that the majority of patients with acute type A dissection present with aortic size that falls below the limits set by current guidelines for elective aneurysm surgery. Furthermore, Davies et al.\textsuperscript{23} has shown that patients with ascending aortic aneurysms and unreplaced BAVs have similar rates of aortic complications in comparison with patients with tricuspid aortic valves, despite a faster rate of aortic growth. Thus, to identify patients with inherent aortic weakness before a life threatening complication occurs, there is great need for alternative methods that evaluate aortic function, as opposed to simply aortic size, to identify patients at risk for dissection.

Our data might be of clinical help to identify those patients in whom, due to increased aortic stiffness, medical and/or surgical therapy could be prescribed at an early stage of their natural history. Moreover, our findings suggest that in BAVs all factors potentially affecting aortic elasticity\textsuperscript{21,22} should be strictly monitored and adequately treated. Whether the herein described functional heterogeneity of the aortic root might have prognostic relevance should be, however, clarified in prospective studies evaluating both dimensions and functional characteristics of the ascending aorta, to establish whether aortic stiffness is linked to different rates of complications (i.e. aeurysm formation and/or dissection).

### Study limitations

Blood pressure was measured by cuff sphygmomanometry of the brachial artery and not invasively in the ascending aorta. However, the excellent correlation of the non-invasively assessed indexes of aortic function with indexes assessed from aortography has been previously reported.\textsuperscript{8,9} Additionally, calculation of the same indexes using the central PP as assessed by radial artery tonometry and pulse wave analysis instead of brachial artery PP same indexes using the central PP as assessed by radial artery et al demonstrated that patients with ascending aortic aneurysms and unreplaced BAVs have similar rates of aortic complications in comparison with patients with tricuspid aortic valves, despite a faster rate of aortic growth. Thus, to identify patients with inherent aortic weakness before a life threatening complication occurs, there is great need for alternative methods that evaluate aortic function, as opposed to simply aortic size, to identify patients at risk for dissection.

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### Conclusion

Abnormal aortic elastic properties are common in BAVs; however, functional heterogeneity in terms of aortic stiffness can neither be attributed nor identified solely based on aortic size. These data suggest the need to prospectively assess both aortic dimensions and aortic elasticity in BAV patients for an early detection of abnormal load-bearing characteristics of the aortic wall. The prognostic relevance of these findings must be, however, validated in follow-up studies.

### Conflict of interest

none declared.

### References


Conflict of interest: none declared.
Aortic elasticity and size in BAV