Objective—This study was undertaken to examine the association between bicuspid aortic valve (BAV) and aortic dilatation in the community. The association between BAV and aortic dilatation has been reported predominantly in retrospective studies in patients mostly with valvular dysfunction or selected surgical patients from tertiary referral centers. An independent association of BAV and aortic dilatation in a community-based study has not been demonstrated.

Methods and Results—In a geographically defined population of Olmsted County, Minnesota, residents with BAV (n =44, age 35±13 years) without hemodynamically significant obstruction or regurgitation and matched controls with normal tricuspid aortic valves were identified by transthoracic echocardiography. The two groups were compared with respect to measurements of the aorta. The BAV and control groups differed with respect to size of the aortic anulus (23.2±2.4 versus 21.6±2.4 mm; P =0.002), aortic sinus (33.5±4.6 versus 30.3±4.1 mm; P =0.0001), and proximal ascending aorta (33.3±6.5 versus 27.9±3.6 mm; P =0.0001). There was no difference in the size of the aortic arch (24.2±3.6 versus 25.3±3.4 mm; P =0.16). These differences were maintained when the groups were stratified by sex and blood pressure. The relationship between bicuspid aortic valve and aortic dilatation was maintained when adjusting for factors related to fluid mechanics and hemodynamics such as systolic blood pressure, diastolic blood pressure, left ventricular ejection time, and peak aortic valve velocity.

Conclusions—In a community-based study, BAV is associated with an alteration of aortic dimensions even in the absence of hemodynamically significant aortic valve stenosis or regurgitation. (Arterioscler Thromb Vasc Biol. 2003;23:351-356.)

Key Words: bicuspid aortic valve ■ aorta ■ dilatation ■ epidemiology ■ population-based study

Bicuspid aortic valve (BAV) disease is the most frequent congenital anomaly of the heart or great vessels.1 A congenital BAV may lead to premature development of significant aortic valve disease, such as aortic valve stenosis or regurgitation and endocarditis.1–3 Abnormalities of the aorta, such as aortic dilatation or dissection, have also been described in association with BAV. Previously, this association had been described largely in necropsy series in individuals with significant aortic stenosis or regurgitation or in individuals who had aortic coarctation or concomitant hypertension, a known risk factor for aortic dilatation and dissection.1,4–8 Moreover, other large necropsy series of aortic dissection found no association with BAV in the patients studied.9 Nonetheless, the presence of BAV in patients with fatal aortic dissections led to the speculation that BAV is a risk factor for abnormalities of the aortic wall, independent of concomitant valvular dysfunction, aortic coarctation, or hypertension.10,11 To this end, important antemortem echocardiographic studies12–15 as well as histological studies16,17 have suggested an independent association between BAV and aortic dilatation. However, some of these studies are retrospective and based on referred patients from tertiary centers mostly with hemodynamically significant aortic valve disease or surgical patients,12,13,16,17 raising the possibility of referral bias where patients with BAV and known aortic dilatation or aneurysm may have been referred for evaluation. In addition, some of the studies included only males and therefore are not applicable to females14 or did not measure all levels of the aortic root.15

The present epidemiologic study was undertaken to determine whether the association between BAV and aortic dilatation could be demonstrated by echocardiography in a geographically defined population of males and females at first diagnosis of BAV without significant stenosis or regurgitation.

Methods

Subjects
Bicuspid aortic valve cases were from a study entitled Initially Normally-Functioning Bicuspid Aortic Valve Project approved by
the Institutional Review Board at the Mayo Clinic, Rochester, Minnesota, where subjects gave informed consent to participate. The study comprises a database of subjects with bicuspid aortic valves seen at the Mayo Clinic.

The echocardiographic laboratory at the Mayo Clinic is the only laboratory providing echocardiographic services to the community of Olmsted County, and patients at first diagnosis of BAV confirmed by echocardiography were identified and included in this study. Excluded from this analysis were patients with evidence of aortic stenosis (aortic velocity $>2.5$ m/s), more than trivial aortic regurgitation by color Doppler, aortic coarctation, or mitral, pulmonic, or tricuspid valve disease, cardiomyopathy, pericardial disease, Marfan syndrome or a family history of Marfan syndrome, or any other form of congenital heart disease.

To each qualifying case, we matched one Olmsted County control who underwent echocardiography and was found to have a normal tricuspid aortic valve and a normal echocardiogram. The same exclusion criteria were applied to the control group. Controls were matched for age within 1 year and same sex; among potential controls, the one chosen had the body surface area closest in value to the case.

**Echocardiographic Methods**

Comprehensive 2D and Doppler echocardiographic examinations were performed by experienced echocardiogram technologists and reviewed by the echocardiographic laboratory physician. All echocardiograms were performed in a systematic manner by technologists who were blinded to the study. In addition to the assessment of cardiac chamber size and function, valve morphology, and function, a routine comprehensive echocardiographic examination includes measurements of the aortic dimensions. Aortic valve morphology was assessed in the parasternal long- as well as short-axis views. The diagnosis of bicuspid aortic valve was based on previously defined criteria\(^{18}\) as the presence of only 2 cusps clearly identified in systole and diastole in the short-axis view (Figure 1). Patients with fusion of the commissures attributable to rheumatic disease\(^{19,20}\) were not included as having BAV. Dimensions of the aortic anulus, the sinuses of Valsalva, and the proximal ascending aorta (measured 1 cm from the sino-tubular junction) were assessed in the parasternal long-axis view (Figure 2A). Measurements of the aortic arch were obtained from the suprasternal view (Figure 2B). Measurements were made perpendicular to the long axis of the aorta using the leading edge to leading edge method in views showing the largest aortic dimensions. Color Doppler was used to assess the presence and severity of aortic regurgitation,\(^{21}\) and aortic stenosis was excluded by both pulsed-wave and continuous-wave Doppler. Aortic stenosis was defined as present when the aortic peak velocity obtained by continuous-wave Doppler was $>2.5$ m/s.\(^{22}\)

Statistical Analysis

Continuous and categorical variables were compared between the BAV cases and their matched controls. Differences were assessed using the paired Student’s $t$ test for continuous variables and the McNemar’s test for binary variables. A 2-tailed probability value of $<0.05$ was considered to be statistically significant. Multiple regression analysis was performed to assess the independent association of hemodynamic parameters (systolic blood pressure, diastolic blood pressure, left ventricular ejection time, and aortic valve peak velocity) and presence of BAV with aortic dimensions.

**Results**

**Baseline Characteristics**

Forty-four BAV cases met the eligibility criteria. They were matched to an equal number of controls of the same age (mean, 35±13 years), sex (65% male), and body surface area (1.9±0.2 m\(^2\)). Some of the baseline characteristics of cases and controls are shown in Table 1. There were differences in indication for echocardiography regarding murmurs or clicks between cases and controls. Sixteen BAV cases versus 20 controls ($P=0.32$) complained of palpitations or atypical chest pain before echocardiography. No case or control had a history of diabetes, myocardial infarction, stroke, aortic dissection, or endocarditis. Four cases compared with 6 controls had been diagnosed with hypertension, but their systolic (122±17 versus 123±16 mm Hg; $P=0.67$) and diastolic (77±10 versus 72±8 mm Hg; $P=0.08$) blood pressures did not differ significantly. Likewise, there was no difference in the history of current (7 versus 2; $P=0.41$) or previous (6 versus 5; $P=0.41$) cigarette use. Four patients with BAV were known to have a family member with BAV compared with none in the control group ($P=0.13$), but no case or control had a family history of Marfan syndrome. Ten
cases compared with 2 controls \( (P=0.01) \) had a family history of coronary artery disease. There was no difference in laboratory data with regard to serum creatinine \( (1.0 \pm 0.2 \text{ mg/dL}; P=0.63) \), total cholesterol \( (211 \pm 66 \text{ mg/dL}; P=0.11) \), high-density lipoprotein \( (47 \pm 7 \text{ mg/dL}; P=0.47) \), or triglycerides \( (128 \pm 98 \text{ mg/dL}; P=0.99) \), except for slightly higher serum calcium levels in the cases \( (9.5 \pm 0.3 \text{ mg/dL}; P=0.03) \).

### Echocardiographic Results

There was no statistically significant difference between the BAV and control groups with respect to left ventricular ejection fraction \( (62 \pm 5\% \text{ versus } 62 \pm 4\%; P=0.94) \), left ventricular end-diastolic dimensions \( (51 \pm 5 \text{ mm} \text{ versus } 49 \pm 4 \text{ mm}; P=0.06) \), or left ventricular end-systolic dimensions \( (32 \pm 4 \text{ mm} \text{ versus } 31 \pm 3 \text{ mm}; P=0.30) \). The left ventricular mass was similar in both groups \( (98.6 \pm 26 \text{ g/m}^2 \text{ versus } 92.8 \pm 18 \text{ g/m}^2; P=0.4 \text{ or } 86 \pm 22 \text{ versus } 84 \pm 14 \text{ g/m}^2; P=0.9) \).

The peak aortic velocity was higher in the BAV patients compared with controls \( (1.7 \pm 0.4 \text{ versus } 1.2 \pm 0.2 \text{ m/s}; P=0.0002) \); however, no BAV case had a peak velocity \( >2.5 \text{ m/s} \). Left ventricular ejection time was the same in both groups \( (291 \pm 21 \text{ versus } 291 \pm 28 \text{ ms}; P=0.99) \).

### Aortic Dimensions and Subgroup Analyses

The dimensions of the aortic root were consistently larger in patients with BAV compared with controls (Table 2). Of the aortic root measurements compared, the largest difference between cases and controls was seen in the dimensions of the proximal ascending aorta \( (5.4 \text{ mm}) \), and this difference was more pronounced when only female cases and controls were considered \( (6.9 \text{ mm}) \) compared with the difference seen between male cases and controls \( (4.9 \text{ mm}) \). The smallest statistically significant difference between cases and controls was in the dimensions of the aortic anulus \( (1.6 \text{ mm}) \). However, the difference in the aortic anulus dimensions did not reach statistical significance when only males were compared in the BAV and control groups \( (P=0.06) \), although there was a trend toward a larger aortic anulus in the BAV group.

### Hemodynamic Parameters

Some hemodynamic parameters do correlate with aortic root dimensions (Table 4). Both systolic and diastolic blood pressure are correlated with dimensions of the ascending aorta and aortic arch. There is an inverse correlation between systolic blood pressure and aortic arch size.

### Table 1: Clinical Characteristics of Olmsted County, MN Residents With BAV and Their Age- and Sex-Matched Controls

<table>
<thead>
<tr>
<th></th>
<th>BAV</th>
<th>Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>35±13</td>
<td>35±13</td>
<td>1.00</td>
</tr>
<tr>
<td>Men, %</td>
<td>61</td>
<td>61</td>
<td>1.00</td>
</tr>
<tr>
<td>Body surface area, m(^2)</td>
<td>1.93±0.23</td>
<td>1.91±0.23</td>
<td>0.09</td>
</tr>
<tr>
<td>Indications for echocardiogram, n</td>
<td>5</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>Systolic murmur</td>
<td>19</td>
<td>13</td>
<td>...</td>
</tr>
<tr>
<td>LV function</td>
<td>1</td>
<td>9</td>
<td>...</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Rule out dissection</td>
<td>0</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>20</td>
<td>0.02</td>
</tr>
<tr>
<td>Physical examination before echo, n</td>
<td>40</td>
<td>40</td>
<td>1.00</td>
</tr>
<tr>
<td>Ejection click</td>
<td>17</td>
<td>3</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic ejection murmur</td>
<td>33</td>
<td>14</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 2: Aortic Dimensions by Sex Among Olmsted County, MN Residents With BAV and Their Age- and Sex-Matched Controls

<table>
<thead>
<tr>
<th></th>
<th>BAV</th>
<th>Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both sexes combined</td>
<td>44</td>
<td>44</td>
<td>...</td>
</tr>
<tr>
<td>Aortic anulus, mm</td>
<td>23.2±2.4</td>
<td>21.6±2.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic sinus, mm</td>
<td>33.5±4.6</td>
<td>30.3±4.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Proximal ascending aorta, mm</td>
<td>33.3±6.5</td>
<td>27.9±3.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Aortic arch, mm</td>
<td>24.2±3.6</td>
<td>25.3±3.4</td>
<td>0.16</td>
</tr>
</tbody>
</table>

### Table 3: Aortic Dimensions Stratified by Systolic Blood Pressure (SBP) Among Olmsted County, MN Residents With BAV and Their Age-, Sex-, and BSA-Matched Controls

<table>
<thead>
<tr>
<th></th>
<th>BAV</th>
<th>Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP&gt;120 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>17</td>
<td>...</td>
</tr>
<tr>
<td>Aortic anulus, mm</td>
<td>22.3±2.3</td>
<td>22.2±2.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Aortic sinus, mm</td>
<td>34.3±4.1</td>
<td>31.6±3.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Proximal ascending aorta, mm</td>
<td>32.9±5.5</td>
<td>29.2±3.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Aortic arch, mm</td>
<td>24.9±2.6</td>
<td>27.1±2.7</td>
<td>0.01</td>
</tr>
<tr>
<td>SBP≤120 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>26</td>
<td>26</td>
<td>...</td>
</tr>
<tr>
<td>Aortic anulus, mm</td>
<td>23.2±2.6</td>
<td>21.1±2.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Aortic sinus, mm</td>
<td>33.1±5.1</td>
<td>29.3±4.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Proximal ascending aorta, mm</td>
<td>33.5±7.4</td>
<td>26.8±3.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Aortic arch, mm</td>
<td>23.4±3.7</td>
<td>23.7±3.2</td>
<td>0.73</td>
</tr>
</tbody>
</table>
peak velocity and aortic anular dimensions in cases, and
ejection time is inversely correlated with dimensions of the
anulus and proximal ascending aorta in the control group. In
multiple regression analysis with factors related to fluid
mechanics as independent variables (systolic blood pressure, diastolic blood pressure, peak velocity, and left ventricular
erection time), the presence of a bicuspid aortic valve re-
ained a statistically significant independent predictor of aortic dimensions (aortic anulus, $P<0.0001$; aortic sinus,
$P=0.0002$; proximal ascending aorta, $P<0.0001$; aortic arch,
$P=NS$). Peak velocity was inversely related to dimensions of
the aortic anulus ($P=0.0009$) and proximal ascending aortic
dimensions ($P=0.02$). Systolic blood pressure, diastolic
blood pressure, and ejection time were not associated with
aortic dimensions in multiple regression analyses.

### Discussion

The present epidemiologic community-based echocardi-
ographic study shows that patients with a bicuspid aortic valve
without hemodynamically significant stenosis or regurgita-
tion have a larger aortic anulus, aortic sinus, and proximal ascending aorta compared with controls with normal tricuspid aortic valves. The two groups were matched with respect to age, sex, and body surface area to eliminate confounding, because these variables do influence aortic dimensions.\(^\text{25,26}\) In addition, none of the BAV cases or controls had Marfan syndrome or a family history of Marfan syndrome, and the prevalence of hypertension in each group was low. Both cases and controls are from a geographically defined population of Olmsted County, Minnesota, which helps eliminate geographic variation and reduce referral bias inherent in studies from tertiary medical centers. Importantly, none of the BAV patients were referred to the echocardiography laboratory because of aortic dilatation.

There is biologic rationale and data to support the idea of intrinsic aortic disease in the presence of BAV. The left ventricular outflow tract, aortic cusps, arterial media of the ascending aorta, and aortic arch and its branches are embryologically linked and originate from the neural crest.\(^\text{27-29}\) Disorders of the neural crest have been implicated in the development of cervicocephalic arterial dissections,\(^\text{30}\) and a familial cluster of aorto-cervicocephalic arterial dissection and BAV has also been described,\(^\text{29}\) raising the possibility of an underlying neural crest defect in the development of both conditions. Experimental mice deficient in endothelial NO synthase, which synthesizes endothelium-derived NO, were found to have a significantly high incidence of BAV (42%) compared with the control wild-type mice (0%).\(^\text{31}\) Endothelium-derived NO plays a role in cell growth and apoptosis as well as postdevelopmental vascular remodeling, angiogene-
sis, and limb vascular formation during embryogenesis.\(^\text{32,33}\) These data suggest that the genetic determinants of BAV are linked to the genetic determinants of arterial abnormalities. In addition, noninflammatory and nonatherosclerotic premature medial layer smooth muscle cell apoptosis was found and proposed to be a mechanism responsible for aortopathy in patients with BAV (mean age, 42±17 years) with or without aortic dilatation.\(^\text{16}\) Recently, various degrees of medial ab-
normalities of the ascending aorta determined by light and
electron microscopy were found to be common in patients
with BAV compared with controls with tricuspid aortic
valves in a study of great arterial walls in congenital heart
disease.\(^\text{17}\)

The peak aortic velocity was higher in the BAV patients
compared with controls (1.7±0.4 versus 1.2±0.2 m/s;
$P=0.0002$), raising the possibility of altered hemodynamic
factors, such as high-frequency vibrations, as the mechanism
for altered aortic dimensions in the BAV group.\(^\text{34}\) Turbulent
flow is known to cause disturbances in vascular endothelial
cells that eventually lead to apoptosis for the initiation of
atherosclerosis.\(^\text{35}\) Demonstration of whether turbulent flow is
important in initiating noninflammatory and nonatheroscle-
rotic medial layer smooth muscle cell apoptosis is beyond the
scope and design of the current study.\(^\text{16}\) In multiple regression
analysis adjusting for factors related to fluid mechanics,
however, the presence of a bicuspid aortic valve remained a
statistically significant independent predictor of aortic
dimensions.

Bicuspid aortic valve disease is a common congenital
cardiac disorder affecting ≈1% to 2% of the general popu-
lation,\(^\text{1}\) and its association with intrinsic aortic disease is
important given the complications of aortic dissection and
death. Prospective studies in patients with BAV are required
to determine the natural history and rate of progression of
aortic dilatation and to determine whether early intervention,
such as $\beta$-blocker therapy, is of any clinical and prognostic
significance.\(^\text{14}\) Management with $\beta$-blockers retards aortic
root dilatation and improves survival in patients with Marfan
syndrome.\(^\text{36,37}\) The present study shows that aortic root
dilatation in both males and females with BAV occurs in the
absence of hemodynamically significant aortic valve disease.
The aortic root dimensions in the BAV group, however, were
not markedly enlarged or aneurysmal, suggesting subclinical
disease. Multiple regression analyses maintain the association
between aortic root dimensions and the presence of bicuspid
aortic valve, even when factors related to fluid mechanics are

### Table 4. Pearson Correlations of Aortic Anulus, Aortic Sinus, Proximal Ascending Aorta, and Aortic Arch With Age, SBP, DBP, PV, and ET

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>SBP</th>
<th>DBP</th>
<th>PV</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic anulus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>-0.05</td>
<td>0.03</td>
<td>-0.04</td>
<td>-0.67*</td>
<td>-0.07</td>
</tr>
<tr>
<td>Control</td>
<td>0.10</td>
<td>0.12</td>
<td>0.26</td>
<td>-0.20</td>
<td>-0.34*</td>
</tr>
<tr>
<td>Aortic sinus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>0.41*</td>
<td>0.08</td>
<td>0.18</td>
<td>-0.24</td>
<td>0.31</td>
</tr>
<tr>
<td>Control</td>
<td>0.47*</td>
<td>0.29</td>
<td>0.21</td>
<td>-0.18</td>
<td>-0.25</td>
</tr>
<tr>
<td>Proximal ascending aorta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>0.51*</td>
<td>-0.04</td>
<td>-0.04</td>
<td>-0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>Control</td>
<td>0.54*</td>
<td>0.35*</td>
<td>0.34*</td>
<td>-0.16</td>
<td>-0.33*</td>
</tr>
<tr>
<td>Aortic arch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>0.63*</td>
<td>0.26</td>
<td>0.36*</td>
<td>0.56*</td>
<td>0.37</td>
</tr>
<tr>
<td>Control</td>
<td>0.27</td>
<td>0.33*</td>
<td>0.25</td>
<td>-0.002</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PV, peak velocity across the aortic valve; ET, left ventricular ejection time.

\(^*P<0.05\)
taken into consideration. We believe the demonstration of the association between BAV and aortic dilatation in a nonsurgical community-based study population of both males and females adds valuable data to the growing body of literature, supporting an intrinsic abnormality of the aorta in patients with BAV.

Limitations

Subjects for this study were not randomly identified from a cross-sectional sampling of the community of Olmsted County but were identified at the time of echocardiography. However, to randomly identify the 1% to 2% of BAV in the community and further limit it to those without hemodynamically significant disease is impractical. The Rochester Epidemiology Project allowed for capturing of relatively unselected cases at first presentation to primary medical care providers in a geographically defined population of Olmsted County. There was a difference in referral for echocardiography between cases and control, as shown in Table 1 (more clicks and systolic murmurs in the BAV group); however, this is a reflection of the bicuspid valve, and hemodynamically significant valve disease was excluded in the analysis. In addition, although referral bias (more clicks and systolic murmur in BAV versus control) was not completely eliminated, for reasons already mentioned, none of the BAV subjects were referred for echocardiography because of aortic dilatation, which would bias the association under study. Loss of statistical differences in anular dimensions in subgroup analysis (males only or SBP >120 mm Hg) could be secondary to a smaller number of patients in the subgroups.

Although below the value considered to define stenosis, the peak flow velocity across the aortic valve in the BAV group was higher compared with the control group. This raises the issue of poststenotic dilatation as a potential mechanism of the BAV subgroups.

In addition, multiple regression analysis confirmed the independent association of BAV and larger aortic dimensions. Patients with trivial aortic regurgitation (n=15) were included in this analysis because this degree of regurgitation is usually considered insignificant and does not modify the stroke volume in any significant way and therefore should not influence aortic dimensions. The present study design, however, does not discount turbulent flow as a potential trigger or aggravator of cellular events that ultimately manifest as aortic dilatation in BAV.

References


Bicuspid Aortic Valve Associated With Aortic Dilatation: A Community-Based Study

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