Bicuspid aortic valve (BAV) is the most common congenital lesion in adults. There is a high incidence of associated valvular lesions, including aortic valve prolapse, aortic regurgitation, and aortic stenosis due to intrinsic restriction and accelerated senile calcification. The natural history of the valvular lesions differs from that of lesions affecting normal tricuspid aortic valves in the rapidity of progression, with early onset of significant BAV disease in the third or fourth decade of life. Congenital anomalies of the aorta are associated with BAV, including coarctation and hypoplasia of the aorta. Aortic aneurysm and dissection are also more prevalent. Even in the absence of significant aortic pathology, proximal aortic root dilatation is more common in patients with bicuspid valves. These significant associations have given rise to the concept of an underlying congenital defect of both valvular and aortic structure in BAV patients.

The relative contributions of hemodynamic derangement from the underlying valvular disease and possible intrinsic aortic abnormalities have not been delineated. We undertook the present study to elucidate the contribution of valvular regurgitation, stenosis, and mixed valvular disease to aortic dilatation in patients with BAV. We sought to compare transthoracic data from patients with bicuspid valves with data from control patients with tricuspid aortic valves, matched for demographics and degree of valvular disease.

Methods and Results—Diameters of the left ventricular outflow tract, sinus of Valsalva, sinotubular junction, and proximal aorta were measured from transthoracic echocardiograms in 118 consecutive BAV patients. Annular area was measured by planimetry, and BAV eccentricity was expressed as the ratio of the right leaflet area to the total annular area. Seventy-seven control patients with tricuspid aortic valves were matched for sex and for combined severity of associated valvular lesions, including aortic valve prolapse, aortic regurgitation, and aortic stenosis due to intrinsic restriction and accelerated senile calcification. The natural history of the valvular lesions differs from that of lesions affecting normal tricuspid aortic valves in the rapidity of progression, with early onset of significant BAV disease in the third or fourth decade of life.

Methods

Patient Selection

We retrospectively reviewed the clinical echocardiography database at the Hospital of the University of Pennsylvania. This constitutes 41,000 inpatient and outpatient echocardiographic studies performed over a 4-year period from 1995 through 1999. Two hundred eleven consecutive patients with BAV were identified. Bicuspid valve morphology was confirmed by independent review of each echocardiogram by a single reviewer (T.P.).

Because of concerns regarding the accurate comparison of valvular lesions between transthoracic and transesophageal studies, we excluded 48 patients in whom only an intraoperative transesophageal echocardiogram was available. We also excluded all patients with documented coexistent proximal aortic pathology or congenital heart disease known to affect proximal aortic size. Therefore, thirty-eight patients were excluded, including patients with coarctation, acute aortic valve vegetation or abscess, history of prior aortic surgery.
aortic dissection, ventricular septal defect, tetralogy of Fallot, and supra-aortic stenosis. None of our BAV patients had a documented diagnosis of Marfan’s syndrome. Transthoracic echocardiograms were unavailable or inadequate for analysis in 7 patients, who were also excluded. The 118 remaining patients in whom measurements could be performed formed the study group.

Control patients were selected randomly from the database. Criteria for selection included the presence of a congenitally normal (tricuspid) aortic valve. These control patients were selected on the basis of the severity of aortic stenosis and regurgitation as well as sex, such that each control patient was individually matched with a patient in the BAV group. The presence of a morphologically tricuspid aortic valve was confirmed by offline review of all selected control patients by a single reviewer (T.P.).

Severity of Valvular Disease

The degree of aortic valvular disease for BAV patients and control patients was assessed by the interpreting physician at the time of the clinical echocardiographic study. Aortic regurgitation was graded on color Doppler by the assessment of regurgitant jet width and jet area in the parasternal long-axis view with the use of standard criteria. The severity of aortic stenosis was graded on the basis of the aortic valve area as calculated by the continuity equation. Valve area was considered mild (>1.5 cm²), moderate (1.0 to 1.5 cm²), or severe (<1.0 cm²).

Size of the Proximal Aorta

Measurements of the proximal aortic segments were made for both BAV and control patients in the parasternal long-axis view (Figure 1). Offline measurements were made by a single reviewer (T.P.), who used a Freeland Tomtec review station and a standard analysis package. Measurements were made perpendicular to the long axis of the aorta, during systole, from leading edge to leading edge, according to the standards of the American Society of Echocardiography. Four segments were measured for both BAV and control patients, including the left ventricular outflow tract, just proximal to the hinge points of the aortic valve cusps (Figure 1, arrow A), the midpoint of the sinuses of Valsalva (Figure 1, arrow B), the sinotubular junction (Figure 1, arrow C), and the proximal ascending aorta at 1 cm above the sinotubular junction (Figure 1, arrow D). All measurements were obtained for all study patients.

Valve Morphology

For bicuspid valve patients and control patients, the size of the aortic annulus was assessed. Planimetry was performed at the level of the valve commissures in parasternal short-axis views (Figure 2A) and was expressed as total annular area (areaT). For BAV, the area of the right cusp (areaR) was also assessed in the same frame (Figure 2B). The eccentricity of the bicuspid valves was expressed as a ratio: areaR/areaT.

Statistical Methods

Data were summarized as mean ± SD. One-way ANOVA was used for univariate comparisons of aortic size within the BAV group. Individual comparisons were subsequently made by Student unpaired t tests at a level of significance of 0.05. The Bonferroni correction was made for multiple comparisons. Linear regression techniques were used for multivariate analysis of aortic size at all levels. Paired Student t tests were used to compare aortic size in BAV patients with aortic size in the matched control patients.

Results

BAV Patients

A total of 118 patients with BAV constituted the study group. There was a preponderance of male subjects, with 79 men (67%) and 39 women (33%). This is consistent with the previously recognized male predominance of BAV. The
mean age of the group was 44.1±15.5 years. Only 10 patients with a preexisting history of BAV (8.5%) were referred for echocardiography. Indications for echocardiography in the remaining study patients included assessment of known or suspected aortic valve disease in 37 (31.3%), evaluation of murmur in 34 (28.8%), assessment of left ventricular function in 14 (11.9%), and evaluation of miscellaneous cardiac symptoms in the remaining patients.

The BAV patients demonstrated widely varying degrees of aortic valvular disease (Table 1). Eighteen patients had normal bicuspid valvular function, with neither regurgitation nor stenosis. Aortic regurgitation was present in 84 patients, ranging from mild (44 patients) to moderate (26 patients) and to severe (14 patients). Varying degrees of aortic stenosis was present in 48 patients, including 20 with mild stenosis, 12 with moderate stenosis, and 16 with severe or critical stenosis. Of the group of bicuspid patients with classified valvular disease, 32 patients had mixed degrees of regurgitation and stenosis (Table 1).

### Univariate Correlates of Aortic Diameters

#### With BAV

Aortic insufficiency was most strongly correlated with aortic size at all levels (Figure 3), as demonstrated by single-factor ANOVA ($P<0.0001$). Individual comparisons revealed that the most significant differences were between those with moderate or severe aortic insufficiency compared with those with nonregurgitant valves. However, linear regression demonstrated a highly significant trend for increasing aortic diameter across all levels of regurgitation ($P<0.0001$, $r=0.55$). Although aortic diameters at all levels were dilated in those with aortic stenosis (Figure 4), the severity of stenosis was not significantly associated with any recognizable trend in aortic size. The presence of increasing severity of aortic stenosis was associated with a significant and progressive diminution of left ventricular outflow tract diameter ($P<0.005$), consistent with the progressively severe left ventricular hypertrophy present in these patients. Male sex ($P<0.001$), advancing age ($P<0.005$), and increasing body surface area ($P<0.01$) were all associated with increasing diameter of the aorta at all levels measured. Valve eccentricity, the presence of a raphe, and diastolic blood pressure were not significantly associated with left ventricular outflow tract size or aortic size at any level.

### Multivariate Model of Bicuspid Aortic Size

Significant correlates from univariate analyses were included in a multivariate linear regression model of aortic diameter at each level. In this model, only the severity of aortic regurgitation ($P<0.001$) and advancing age ($P<0.01$) remained significantly associated with increasing outflow tract and aortic diameter at all 3 aortic levels. Male sex remained weakly associated with left ventricular outflow tract diameter ($P<0.05$) but was no longer associated with any of the aortic root diameters. Body surface area and systolic blood pressure were not associated with increasing aortic size in multivariate analysis.

### Matched Comparisons of Aortic Size

Control patients with congenitally tricuspid aortic valves were selected and were paired with 77 of the BAV patients. These pairs were matched for sex and for the degree of aortic regurgitation, stenosis, or combined aortic valve disease. We were unable to identify matched controls for 41 BAV patients, including 16 patients with severe aortic regurgitation and 15 patients with combined severe stenosis and regurgitation. A large number of potential tricuspid control patients screened for severe degrees of regurgitation could not be used because of concurrent Marfan’s syndrome, aortic dissections, or aortic aneurysms.

There were no significant differences between bicuspid and control patients with regard to body surface area or systolic or diastolic blood pressures (Table 2). Control patients were significantly older than their matched BAV patients because of the later onset of valvular disease in those with congenitally tricuspid valves.

## Table 1. Valvular Disease in BAV Patients

<table>
<thead>
<tr>
<th>Aortic Stenosis</th>
<th>Aortic Regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Values are number of patients.

![Figure 3](http://circ.ahajournals.org/Downloadedfromhttp://circ.ahajournals.org/)

*Figure 3.* Association between aortic regurgitation and aortic size in BAV patients. LVOT indicates left ventricular outflow tract; sinus, sinus of Valsalva; ST Jxn, sinotubular junction; and Prox Ao, proximal aorta. Increasing severity of aortic regurgitation was associated with increases in root dimensions.

*P* $<0.005$ and **P** $<0.001$ vs nonregurgitant valves.

![Figure 4](http://circ.ahajournals.org/Downloadedfromhttp://circ.ahajournals.org/)

*Figure 4.* Association between aortic stenosis and aortic size in BAV patients. All levels of proximal aorta were dilated in stenotic patients, without relation to stenosis severity. Progressive stenosis was associated with diminished size of left ventricular outflow tract. *P* $<0.005$ vs nonstenotic valves. Abbreviations as in Figure 3.
TABLE 2. Demographic Comparison of BAV Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Age, y</th>
<th>BSA, m²</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAV</td>
<td>43.9±15.8</td>
<td>1.88±0.21</td>
<td>126±19</td>
<td>71±12</td>
</tr>
<tr>
<td>Control</td>
<td>55.3±17.3</td>
<td>1.93±0.22</td>
<td>136±18</td>
<td>68±11</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td>0.10</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Values are mean±SD. BSA indicates body surface area; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

Figure 5. Comparison of aortic size. Size of aorta in BAV patients was larger at all levels compared with aortic size in matched controls with tricuspid aortic valves. *P<0.001 and **P<0.01. Abbreviations as in Figure 3.

Paired analysis demonstrated significant aortic dilatation at all levels measured in BAV patients compared with the matched controls with congenitally tricuspid valves (Table 3). There was also a trend toward a larger total annular area in the BAV patients. These differences in aortic size (Figure 5) were present despite the significantly older age of the control patients (55.3±17.3 years) compared with the BAV patients (43.9±15.8 years, P<0.001).

Discussion

The present study is the first to demonstrate proximal aortic dilatation at all levels measured in patients with BAV, beyond that attributable to associated valvular lesions. Previous studies have assessed BAV patients without significant valvular disease16 or have compared BAV patients with patients who were not matched as to the degree of valvular abnormalities.15 Matching patients with BAV with patients with tricuspid aortic valves with similar degrees of valvular disease reduces the influence of hemodynamic lesions associated with the BAV and thereby assesses the impact of BAV on aortic size independently.

Aortic regurgitation is independently associated with proximal aortic dilatation. We demonstrated that the increasing severity of regurgitation was associated with more severe dilatation in BAV patients and controls. Furthermore, the aortas of BAV patients were dilated beyond that expected from the degree of aortic regurgitation when they were compared with aortas of matched controls with comparable degrees of regurgitation. Similarly, patients with bicuspid valve stenosis have aortic root dilatation at all levels, which is not found in patients with congenitally tricuspid aortic valves and acquired aortic stenosis. The degree of aortic dilatation in BAV patients with aortic stenosis was similar to that seen in BAV patients with moderate to severe regurgitation, but there was no association between the degree of dilatation and severity of stenosis. Therefore, in our study population, we confirm the previous observation that poststenotic dilatation is a feature of BAV but not of congenitally normal valves.15 Similarly, those BAV patients with no evidence of valvular lesions had increased aortic dimensions. This aspect of our findings has been reported previously.15,16 The presence of a raphe and the eccentricity of the valve had no association with aortic root dimensions in the BAV group.

Our findings are consistent with the original hypothesis that intrinsic abnormalities of the aorta are in large part responsible for the development of aortic dilatation in the study population. Aortic root pathology has been previously reported in patients with BAV and appears to consist of a process similar to cystic medial necrosis19 but is characterized primarily by an extensive loss of elastic elements within the media.14,20 Apoptosis of neural crest derivatives has been implicated as a possible contributor to the process.21 Although shear stress from valvular lesions has been identified as a cause of cystic medial necrosis in patients with apparently normal aortas, the most likely explanation for our data is an intrinsic aortic abnormality in patients with BAV. Aortic regurgitation may play a role in facilitating the dilatation of the bicuspid root, superimposed on this intrinsic aortic pathology.

Several limitations of the present study should be acknowledged. First, patterns of referral for echocardiography may affect the overall demographics of the BAV study population. Despite the fact that a referral bias is likely to limit the number of normally functioning BAV valves, our series includes 18 BAV patients without stenosis or regurgitation. A second limitation arises from the fact that we were unable to match patients for age. Control patients with similar degrees of valvular disease could not be age-matched with BAV patients because of the prematurely advanced valvular lesions of BAV. However, significant differences in aortic size were found between BAV and control patients, despite the significantly older age of the controls. Age was associated with more severe aortic dilatation in both BAV and control patients. Therefore, the younger age of our BAV patients might have biased our results to underestimate the comparative extent of aortic dilatation.

TABLE 3. Aortic Root Comparisons of BAV Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Annular Area, cm²</th>
<th>Sinus Diameter, cm</th>
<th>Sinotubular Junction, cm</th>
<th>Proximal Aorta, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAV</td>
<td>9.89±3.00</td>
<td>3.74±0.54</td>
<td>3.54±0.53</td>
<td>3.61±0.55</td>
</tr>
<tr>
<td>Control</td>
<td>9.35±2.41</td>
<td>3.51±0.47</td>
<td>3.34±0.49</td>
<td>3.40±0.49</td>
</tr>
<tr>
<td>P</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean±SD.
We also were unable to match patients for duration and time course of their valvular disease. The duration of valvular regurgitation or stenosis before initial clinical recognition or onset of symptoms cannot be determined with certainty. In addition, our institution is a tertiary referral center, and serial echocardiograms are available for only a minority of patients. It is possible that despite the older age of our control patients, their hemodynamic lesions may have been present for fewer years. Future efforts will be directed toward establishing the time course of change in aortic dimension prospectively in a subset of BAV patients.

BAV is associated with an intrinsic abnormality of the proximal aorta resulting in dilatation out of proportion to the hemodynamic forces acting on the aorta. This conclusion raises an issue of potential importance to the physician undertaking aortic valve surgery, in reference to whether a mildly dilated aorta should be replaced at the time of valve replacement. The subject remains controversial in other disease states associated with concurrent aortic abnormalities and valvular disease, such as Marfan’s syndrome, in which the progression of proximal aortic dilatation is more clearly defined. Only longitudinal outcome data within the BAV population will allow definitive decision-making regarding this issue.

References
Bicuspid Aortic Valves Are Associated With Aortic Dilatation Out of Proportion to Coexistent Valvular Lesions
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