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# Aortopathy Is Prevalent in Relatives of Bicuspid Aortic Valve Patients

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**Objectives** This study aimed to determine the prevalence of dilation and abnormal elastic properties of aortic root in first-degree relatives (FDRs) of bicuspid aortic valve (BAV) patients.

**Background** Evidence indicates that BAV is a genetic disorder. Although FDRs of affected individuals have an increased prevalence of BAV, their risk of aortic root abnormalities is unknown.

**Methods** We studied dimensions as well as the elastic properties of the ascending aorta in 48 FDRs with morphologically normal tricuspid aortic valves, 54 BAV patients, and 45 control subjects using 2-dimensional echocardiography.

**Results** The prevalence of aortic root dilation was 32% in FDRs and 53% in BAV patients, whereas all control subjects showed normal aortic dimensions ($p < 0.001$). The FDRs and BAVs had significantly lower aortic distensibility ($1.7 \pm 1.4 \times 10^{-3}$ mm Hg and $1.4 \pm 2.0 \times 10^{-3}$ mm Hg vs. $2.5 \pm 1.6 \times 10^{-3}$ mm Hg, $p < 0.001$) and greater aortic stiffness index ($26.7 \pm 25.8$ and $55.9 \pm 76.8$ vs. $18.7 \pm 40.1$, $p = 0.001$) compared with control subjects. This difference remained significant in subjects without aortic root dilation or hypertension ($p = 0.002$ and $p = 0.004$, respectively).

**Conclusions** The aortic root is functionally abnormal and dilation is common (32%) in first-degree relatives of patients with BAV. Screening of FDRs by transthoracic 2-dimensional echocardiography should be considered for detection of aortic valve malformation and dilated ascending aorta. (J Am Coll Cardiol 2009;53:2288–95) © 2009 by the American College of Cardiology Foundation

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly, with an estimated incidence of 0.9% to 2% in the general population (1,2). Bicuspid aortic valve includes different morphologic phenotypes (3–6) characterized by various hemodynamic profiles. This valvular malformation is associated with aortic root dilation in affected patients (7,8), which is out of proportion to the severity of aortic valve dysfunction (8,9). Studies have shown reduced elastic properties of the proximal aorta in patients with BAV (10,11). This may be caused by a common developmental defect that is hypothesized to be responsible for the coexistence of BAV and aortic root enlargement (8,9).

Numerous studies using pedigree analysis have shown familial clustering of BAV (12–20). The prevalence of BAV among first-degree relatives (FDRs) of affected individuals is 9% to 21% (14,18–20). Statistical estimation of hereditary effect suggests that in this population, valve malformation is almost entirely genetic (19). In addition, autosomal dominant inheritance with reduced penetrance has been suggested by some investigators (17,18). Although FDRs of affected subjects are at increased risk of inheriting BAV and other cardiovascular malformations, there are limited data concerning the occurrence of aortic root abnormalities in this population (17–19).

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We hypothesized that aortic root morphologic and functional abnormalities are prevalent in relatives of BAV subjects. Using transthoracic echocardiography, we prospectively determined the prevalence of aortic root dilation as well as compared aortic root dimensions and aortic root elastic properties among 3 groups: 1) BAV patients; 2) FDRs with a normal tricuspid aortic valve; and 3) a control group.

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## Methods

Consecutive patients referred for echocardiography to our institution were recruited prospectively after the echocardiographic diagnosis of BAV. The BAV individuals hospitalized for aortic valve replacement or repair of an ascending aortic aneurysm were included if a pre-surgical transthoracic echocardiogram was available. Informed consent was obtained in accordance with our Institutional Review Board; all subjects had anthropometric measurements. Medical records were reviewed, and study subjects were questioned to determine any history of hypertension. Blood pressure was measured with commercially available digital sphygmomanometers, and was obtained after subjects sat at rest for at least 5 min. The FDRs with a diagnosis of BAV on screening echocardiography were included in the BAV group. For every newly affected individual identified during family screening, we attempted to recruit all of the FDRs of that individual. Subjects for the control group were enrolled from a cohort referred for echocardiography for various clinical indications, including screening after a diagnosis of hypertension. For this purpose we selected consecutive individuals without structural heart disease.

**Echocardiography.** Transthoracic echocardiograms were performed within 30 min of blood pressure measurement using state-of-the-art commercially available systems (ATL system upgraded to Philips HDI 5000 and iE33, Philips, Bothell, Washington). Multiple standard cardiac views were acquired with particular attention to the aortic valve and ascending aorta.

Measurements of the aortic root were made in the parasternal long-axis view, perpendicular to the long axis of the vessel, from leading edge to leading edge (21,22). Measurements of 4 segments, including the aortic annulus, sinuses of Valsalva, sinotubular junction, and proximal ascending aorta 1 cm above the sinotubular junction, were obtained from participants. All measurements were obtained during end systole and end diastole. Aortic dimensions were indexed by square root of body surface area. Observers performing aortic root measurements were blinded to the anthropometric and clinical data of participants.

The presence of aortic root dilation was determined with the use of data from a reference population relating normal aortic diameters to body surface area and age (22). The aortic root was considered dilated if the maximal dimension obtained at any of the 4 segments exceeded the 95% confidence interval of the diameter at sinuses of Valsalva of a normal reference population (21).

**Abbreviations and Acronyms**

AVA = aortic valve area
BAV = bicuspid aortic valve
FDR = first-degree relative

Aortic root elastic properties, including distensibility and stiffness index, were calculated at the sinuses of Valsalva level using the following formulas:

$$\text{aortic root distensibility (mm Hg} \times 10^{-3}) = 2 \times (\text{AoS} - \text{AoD})/\text{AoD} \times (\text{SBP} - \text{DBP}) \times 1,000 \text{ (23)}$$

$$\text{aortic root stiffness index} = \ln (\text{SBP}/\text{DBP})/(\text{AoS} - \text{AoD})/\text{AoD (24)}$$

where AoS is systolic aortic dimension, AoD is diastolic aortic dimension, SBP is systolic blood pressure, DBP is diastolic blood pressure, and ln is a natural logarithm.

Aortic regurgitation was graded as mild, moderate, or severe using an integrative approach (25–27). Aortic valve area (AVA) was calculated by the continuity equation. Valvular stenosis was graded as mild if AVA was $>1.5$ cm$^2$, as moderate if AVA was 1.0 to 1.5 cm$^2$, and severe when AVA was $<1.0$ cm$^2$.

**Definition of BAV.** Individuals who had aortic valves with 2 clearly defined cusps or with the characteristic systolic fish mouth appearance of the aortic valve cusps and 2 of 3 supportive features of BAV, including systolic doming or diastolic prolapse of the aortic valve cusps and eccentric valve leaflet closure, were considered to have a BAV (28). Bicuspid valve morphology was confirmed by independent review of each echocardiogram by 2 observers. In addition, subjects identified at the time of the aortic valve replacement surgery as having bicuspid valve morphology were included in the study. These study participants were considered to be probands.

**Exclusion criteria.** For probands, exclusion criteria were disagreement between observers concerning the diagnosis of BAV, incomplete diagnostic criteria of BAV (i.e., possible or probable BAV), coexistent coarctation of the aorta, discrete subaortic stenosis, tetralogy of Fallot, supra-aortic stenosis, or Marfan syndrome. For control subjects, exclusion criteria were congenital heart disease, greater than mild

**Table 1** The Clinical and Echocardiographic Characteristics of Subjects With a BAV, the FDRs, and Control Subjects

| | BAV Patients (n = 54) | FDRs (n = 48) | Control Subjects (n = 45) | p Value |
|---|---|---|---|---|
| Age (yrs) | 46.5 ± 14.8 | 41 ± 20.1 | 46.8 ± 17.9 | 0.210 |
| Male (%) | 66 | 48 | 52 | 0.162 |
| BSA (m$^2$) | 1.9 ± 0.2 | 1.8 ± 0.4 | 1.9 ± 0.3 | 0.144 |
| Systolic blood pressure (mm Hg) | 120.4 ± 12.7 | 120.4 ± 13 | 126.2 ± 18.2 | 0.126 |
| Diastolic blood pressure (mm Hg) | 67.2 ± 11.4 | 69 ± 10 | 72 ± 12.7 | 0.152 |
| Hypertension history (%) | 43* | 16 | 33 | 0.033 |

*$p < 0.05$ versus FDRs.
BAV = bicuspid aortic valve; BSA = body surface area; FDR = first-degree relative of a bicuspid aortic valve subject with a normal aortic valve.