

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 ± 25.8 and 55.9 ± 76.8 vs. 18.7 ± 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).

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

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

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

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 cm², as moderate if AVA was 1.0 to 1.5 cm², and severe when AVA was <1.0 cm².

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

Abbreviations and Acronyms

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

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.

valvular heart disease, abnormal left ventricular end diastolic dimension, segmental wall motion abnormality, left ventricular ejection fraction <50%, and greater than mild left ventricular hypertrophy (men ≥ 14 mm, women ≥ 13 mm) (21).

Statistical analysis. All analyses were performed with the statistical software program SPSS version 13.0 (SPSS Inc., Chicago, Illinois). Continuous data were presented as mean \pm SD. Categorical data were presented as an absolute number or percentages. The significance level was set at $p = 0.05$.

The 1-way analysis of variance was used for univariate comparison of baseline demographic, clinical, and echocardiographic characteristics among the 3 groups, that is, subjects with BAV, FDRs without BAV, and control subjects. A test of homogeneity of variances was performed for each individual variable. For multiple comparisons of mean value, the Bonferroni correction was used assuming equal variance and the Dunnett T3 was used where equal variance could not be used.

For comparison of categorical data among the 3 study groups, the Pearson chi-square test was used. Pairwise comparisons were performed between various study groups using the Fisher exact test, and p values were adjusted for multiple comparisons.

Interobserver variability was assessed between 2 independent observers for measuring aortic root diameter using a coefficient of variation. Interobserver variability for aortic diameter was assessed in 10 patients in both systole and diastole at the 4 levels by 2 independent observers. The overall variability was 8% for all levels during systole and diastole ($p = 0.63$). Variability for the annulus and sinus of Valsalva diameter was 7% ($p = 0.46$).

Results

From February 2004 to May 2008, we enrolled 49 BAV probands in the study. A total of 135 FDRs of affected individuals were contacted and invited to participate. Among those contacted, 53 FDRs participated in the study. On screening echocardiography, 5 of 53 FDRs (9.4%) were found to have a BAV, and were subsequently included in the BAV group. Echocardiograms of 45 consecutive individuals without structural heart disease were used as control subjects.

Baseline characteristics. As shown in Table 1, there was an insignificant difference in baseline characteristics as well as systolic blood pressure and diastolic blood pressure between the study groups.

Hypertension (history of hypertension treated by antihypertensive medications or history of repetitive high blood pressure measurements) was significantly different between FDRs and BAVs ($p = 0.045$); however, it was not significantly different for the other study groups.

There was a highly significant difference in the prevalence of aortic regurgitation (37% vs. 0% and 0%, $p < 0.001$) and

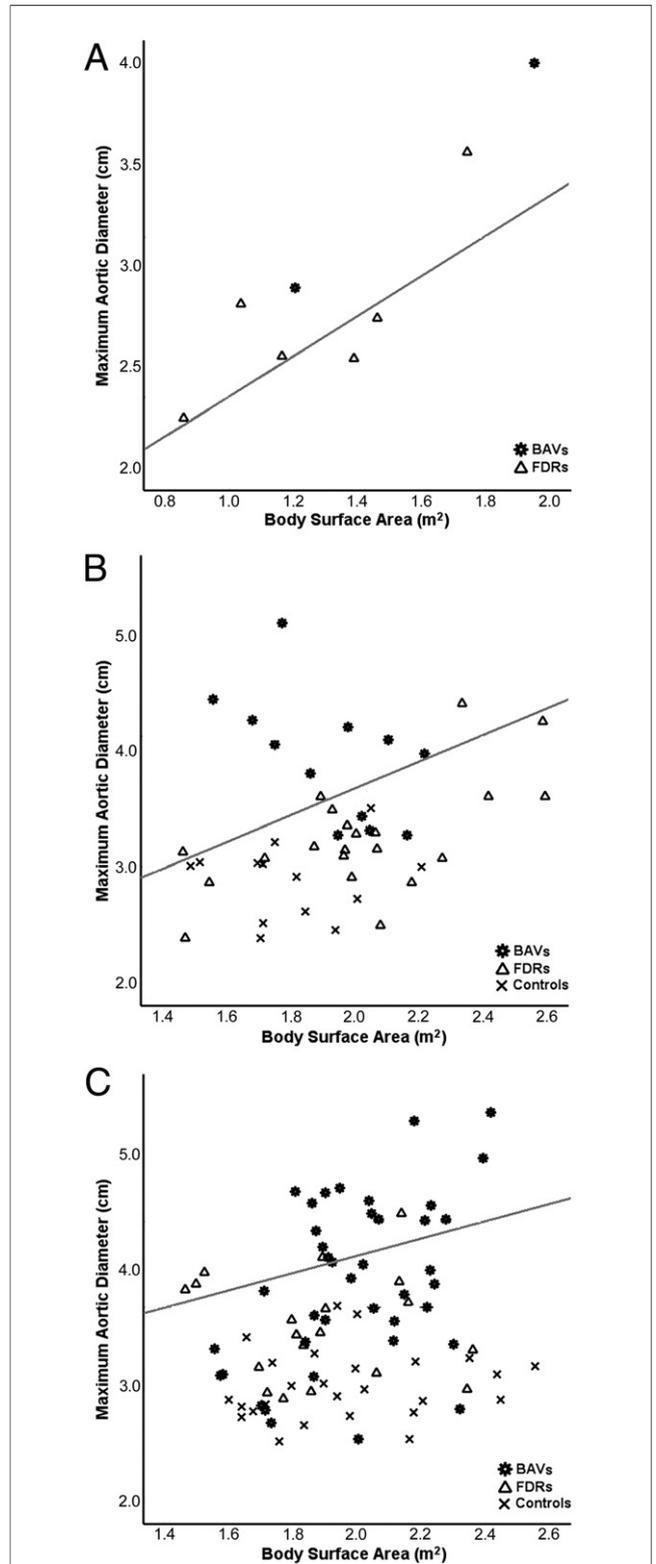


Figure 1 Aortic Root Dimension at Sinuses of Valsalva Plotted Against BSA of BAV Patients, FDRs, and Control Subjects

Oblique line represents upper limit of 95% confidence interval of the reference population ages: (A) ≤ 20 , (B) 20 to 39, and (C) ≥ 40 years. BAV = bicuspid aortic valve; BSA = body surface area; FDR = first-degree relative.

aortic stenosis (26% vs. 0% and 0%, $p = 0.001$) of greater than a mild degree in the BAV group compared with FDRs and control subjects.

Prevalence of aortic root dilation. Overall, 14 (32%) subjects in the FDR group and 29 (53%) BAV patients had a dilated aorta, defined as the maximal dimension obtained at 1 of 4 levels exceeding previously published data related to body surface area and age, whereas aortic dimensions of all control subjects were within the normal range ($p < 0.001$). The prevalence of dilated aorta in the FDR versus the BAV group was not statistically significant ($p = 0.12$).

Figure 1 shows that 12 (27%) of the FDRs with morphologically normal tricuspid aortic valves had dilated aortic root at the sinuses of Valsalva. In addition, 27 (51%) subjects in the BAV group had an aortic diameter beyond the upper limit of the 95% confidence interval at the sinuses of Valsalva.

Aortic root dimensions. As indicated in Figure 2, indexed aortic annulus dimensions (cm/m) were significantly different between FDRs, BAV patients, and control subjects (1.72 ± 0.17 vs. 1.95 ± 0.33 vs. 1.57 ± 0.13 , $p < 0.001$). The same was true for indexed diameters (cm/m) at the sinuses of Valsalva (2.77 ± 0.46 vs. 2.77 ± 0.46 vs. 2.18 ± 0.25 , $p < 0.001$). The dimensions at the sinotubular junction differed insignificantly among the 3 study groups ($p > 0.05$). The proximal ascending aorta (cm/m) was significantly larger in BAVs compared with both FDRs and control subjects (2.64 ± 0.59 vs. 2.20 ± 0.22 and 2.15 ± 0.22 , $p < 0.001$).

Morphology of dilated aortic root. We observed 2 major phenotypes of aortic root dilation. In type 1 (Fig. 3A), the diameter at the sinuses of Valsalva exceeds the ascending aorta, and in type 2 (Fig. 3B), the ascending aorta is larger than the diameter at the sinuses of Valsalva. Among FDRs with dilated aortas, types 1 and 2 dilation were observed in 86% and 14% of cases, respectively. The BAVs with an

enlarged aortic root had type 1 morphology in 72% and type 2 morphology in 28% of cases.

Elastic properties of aorta. As shown in Figure 4, the FDR and BAV groups had significantly reduced aortic root distensibility compared with the control group ($1.74 \pm 1.4 \times 10^{-3}$ mm Hg and $1.4 \pm 2.0 \times 10^{-3}$ mm Hg vs. $2.5 \pm 1.6 \times 10^{-3}$ mm Hg, $p < 0.001$). Moreover, there was no significant difference between FDRs and BAVs for this parameter. The aortic root stiffness index was also significantly higher in the FDR group and BAVs compared with control subjects (26.7 ± 25.8 and 55.9 ± 76.8 vs. 18.7 ± 40.1 , $p = 0.001$).

Aortic root elastic properties and aortic root size. Aortic distensibility was not significantly different ($p = 0.52$) between FDRs and BAVs with a dilated aortic root. In individuals with normal aortic root size, FDRs and BAVs showed reduced distensibility compared with control subjects ($1.5 \pm 1.16 \times 10^{-3}$ mm Hg and $1.3 \pm 1.16 \times 10^{-3}$ mm Hg vs. $2.4 \pm 1.66 \times 10^{-3}$ mm Hg, $p = 0.002$).

Similarly, in FDRs and BAVs the aortic root stiffness index of subjects with dilated aortic root was not significantly different ($p = 0.16$). In subgroups of participants with a normal-sized aorta, FDRs and BAVs also showed a greater aortic stiffness index compared with the control group (30.2 ± 37.1 and 46.5 ± 55.5 vs. 12.6 ± 9.4 , $p = 0.004$) (Figs. 5A and 5B).

Aortic root elastic properties and hypertension. Among participants without a history of hypertension, aortic root distensibility was significantly reduced in FDRs and BAVs compared with control subjects ($1.6 \pm 1.1 \times 10^{-3}$ mm Hg and $1.2 \pm 1.0 \times 10^{-3}$ mm Hg vs. $2.5 \pm 1.6 \times 10^{-3}$ mm Hg, $p = 0.001$). In addition, the stiffness index was greater in FDRs and BAVs compared with control subjects (25.7 ± 33.9 and 56.1 ± 75.7 vs. 11.2 ± 6.4 , $p = 0.005$). In a small subset of patients with a history of

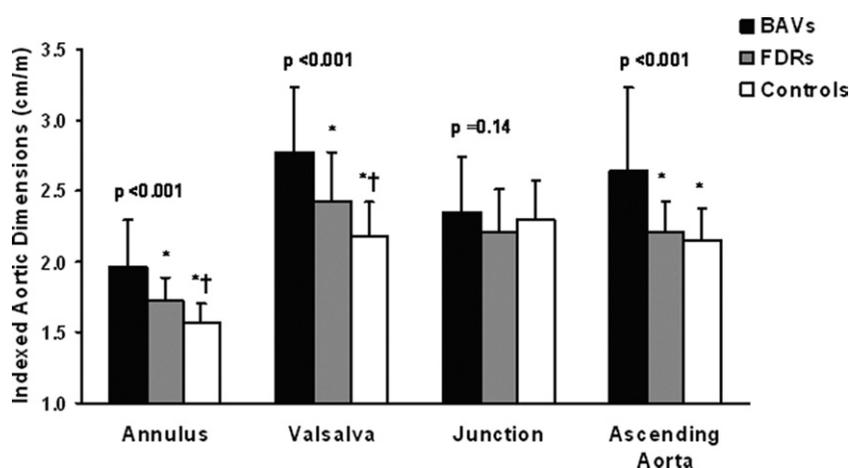


Figure 2 Indexed Aortic Root Dimensions of 3 Study Groups

At aortic root at annulus, sinuses of Valsalva, sinotubular junction, and proximal ascending aorta of BAV patients, FDRs, and control subjects. Analysis of variance results are shown as p values on the top of each group of black bars. * $p < 0.05$ versus BAV patients. † $p < 0.05$ versus FDRs. Abbreviations as in Figure 1.

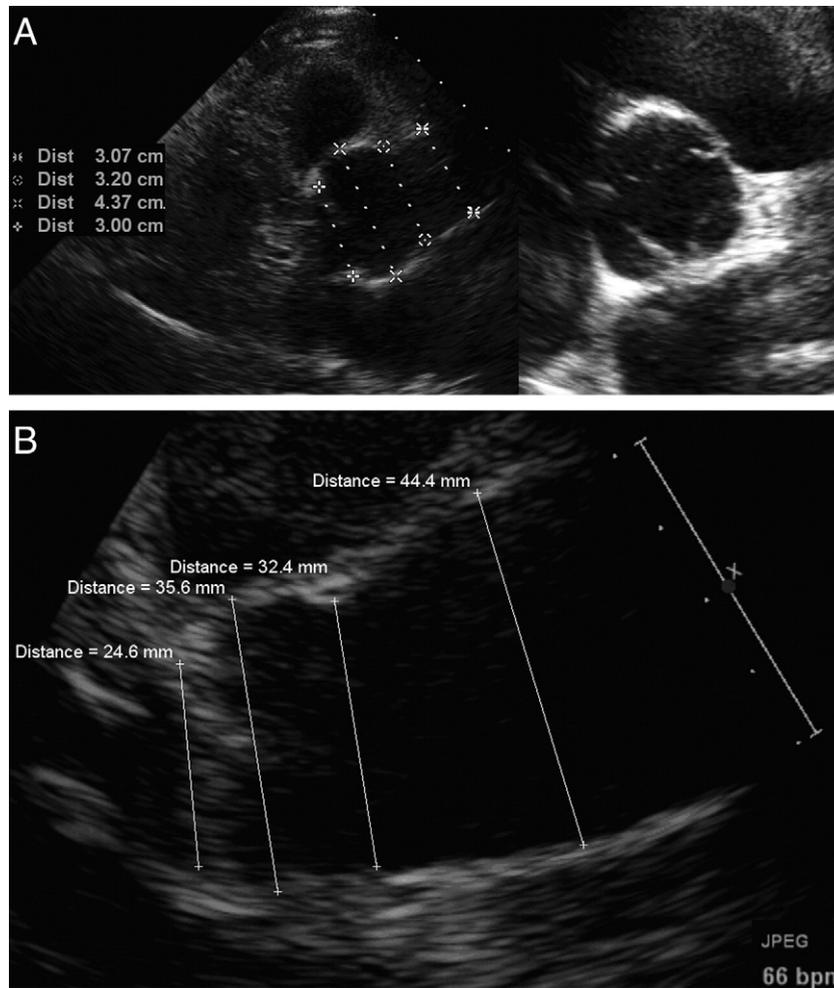


Figure 3 Morphologic Types of Aortic Root Dilatation

(A) Type 1 aortic root dilatation. (B) Type 2 aortic root dilatation.

hypertension, aortic root distensibility was significantly different in all of the 3 study groups ($0.5 \pm 0.1 \times 10^{-3}$ mm Hg vs. $1.0 \pm 0.9 \times 10^{-3}$ mm Hg vs. $2.1 \pm 1.4 \times 10^{-3}$ mm Hg, $p = 0.007$). In the same subgroup, the stiffness index was not different among FDRs, BAVs, and control subjects (50.5 ± 25.9 vs. 56.2 ± 64 vs. 15.3 ± 12.8 , $p = 0.08$). Because of the limited number of subjects with elevated blood pressure ($>140/90$ mm Hg) at screening echocardiography, separate analysis on these subjects was not performed.

Aortic root elastic properties in the surgical and medical cohort of BAV patients. A total of 27 (50%) patients in BAV group underwent aortic valve replacement and/or surgical repair of an ascending aortic aneurysm; the 27 remaining BAV patients were treated medically. Indexed aortic root dimensions (cm/m) were slightly but insignificantly larger at all levels in the surgical BAV cohort compared with the medical BAV cohort (annulus: 1.44 ± 0.31 vs. 1.38 ± 0.22 , $p = 0.47$; sinuses of Valsalva: $2.05 \pm$

0.39 vs. 1.94 ± 0.34 , $p = 0.31$; sinotubular junction: 1.76 ± 0.31 vs. 1.62 ± 0.28 , $p = 0.11$; ascending aorta: 1.97 ± 0.49 vs. 1.80 ± 0.35 , $p = 0.19$). Similarly, aortic root distensibility ($1.2 \pm 1.1 \times 10^{-3}$ mm Hg vs. $1.1 \pm 1.0 \times 10^{-3}$ mm Hg, $p = 0.7$) as well as stiffness index (50.9 ± 76.7 vs. 61.6 ± 77.4 , $p = 0.62$) differed insignificantly between the surgical and medical BAV cohorts.

Discussion

This study documents that aortic root dilatation is highly prevalent (32%) in FDRs of BAV patients with a normal tricuspid aortic valve phenotype. In addition, this is the first study to show that the aortic root dimensions at the annulus and sinuses of Valsalva level are significantly larger in FDRs of BAV subjects compared with control subjects. Moreover, it is the first demonstration that aortic root elastic properties, including distensibility and stiffness index, are abnormal in family members of BAV

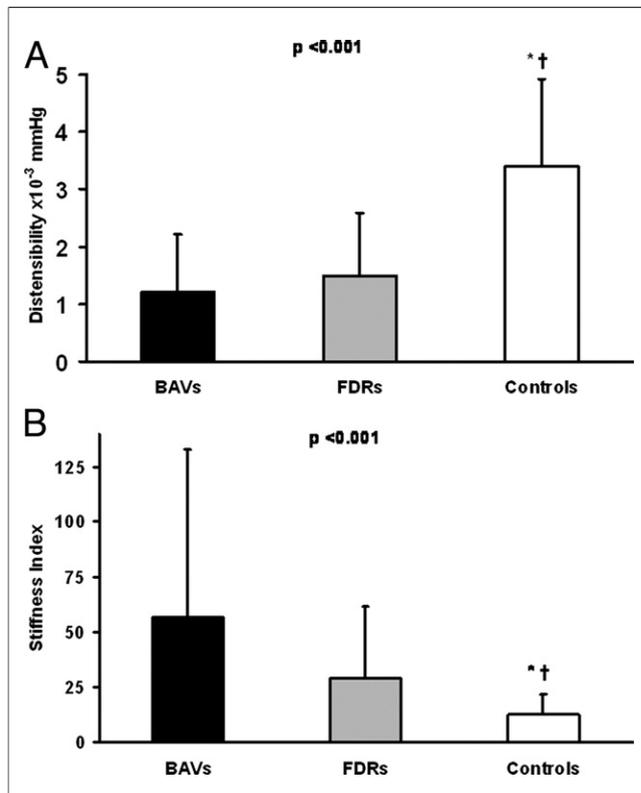


Figure 4 Comparison of Aortic Elastic Properties in 3 Study Groups

Both distensibility (A) and stiffness index (B) were significantly worse in the BAV patients and FDRs compared with the control subjects ($p < 0.001$). $*p < 0.05$ versus BAV patients. $\dagger p < 0.05$ versus FDRs. Abbreviations as in Figure 1.

patients. Reduced elasticity in FDRs and BAV patients is independent of aortic root diameter and is observed regardless of a history of hypertension. The degree of dilation and impaired elastic characteristics of the ascending aorta in FDRs without BAV are less prominent than in subjects with BAVs. The results of this study show the presence of an aortopathy in FDRs of BAV patients, resulting in both abnormal aortic root dilation and abnormal elastic properties.

The finding of an aortic root disorder in family members of patients with BAV is not unexpected. There is a general consensus that many patients with BAV have accelerated degradation of the aortic media and a loss of elastic tissue (29,30). Low fibrillin content and increased matrix metalloproteinase 2 activity of the dilated aortic root have been proposed as mechanisms for the ascending aortic abnormalities (31). Abnormal histology of the aortic wall is consistent with the evidence of reduced aortic elasticity as assessed by different imaging modalities in BAV patients (10,11). Abnormal wall structure and function may result in dilation of the aortic root or the ascending aorta even in the absence of hemodynamically significant valvular dysfunction (7–9). Conversely, there is growing awareness of a familial clustering of the BAV phenotype (12–20), indicating a strong genetic basis for this disease (17,19). Therefore, it is possible

that the elastic abnormalities and subsequent dilation of the aortic root in apparently healthy immediate relatives of BAV patients represents another manifestation of the same heritable disease.

Recently published observations by Loscalzo et al. (17) reported 13 families of patients with known ascending aortic aneurysms or prior aortic dissection or rupture. The investigators found a 35% prevalence of ascending aortic dilation with or without BAV being present among the relatives. Although the proband characteristics described by Loscalzo et al. (17) and our study are different, the segregation of BAV and a dilated ascending aorta among multiple family members is comparable. The coexistence of these 2 morphologic phenotypes within families suggests that these entities represent independent manifestations of a genetic disorder.

There are no large-scale studies evaluating the prevalence of ascending aortic dilation in relatives of BAV individuals as a primary end point. The current knowledge is based on publications evaluating familial clustering and the heritability of BAV (18,19). These studies focused attention on the detection of familial BAV and reported dilated ascending aortas and other cardiovascular abnormalities in FDRs as an

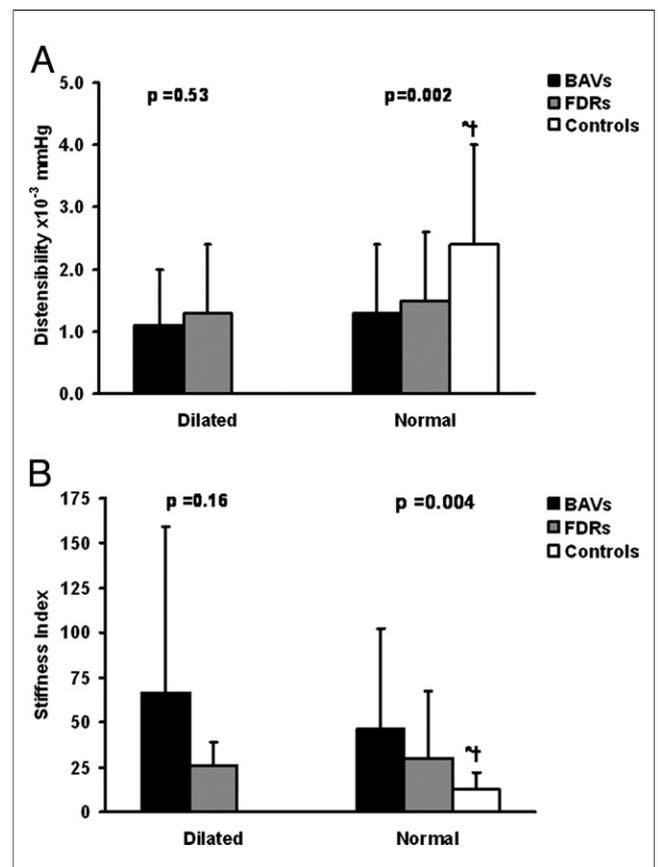


Figure 5 Aortic Elastic Properties in Individuals With Enlarged and Normal Aortic Root

Aortic distensibility (A) and stiffness index (B). $*p < 0.05$ versus BAV patients, $\dagger p < 0.05$ versus FDRs. Abbreviations as in Figure 1.

additional finding. The limitations of previous studies include the methodology of ascending aortic measurements and an unclear definition of aortic root dilation, as well as age differences in the study population.

Huntington et al. (18) evaluated the familial clustering of BAV and associated cardiac anomalies in 186 FDRs of 30 BAV patients. The investigators found that 5 of 169 (3%) had dilated ascending aortas among relatives without BAV. We observed a 32% rate of aortic root dilation, which is far greater than that described by Huntington et al. (18). This difference is likely to be the consequence of using a different methodology to perform aortic measurements. We detected root dilation at the sinuses of Valsalva level in the majority of cases using 2-dimensional echocardiography-guided measurements. The rate of aortic root dilation may have been underestimated by Huntington et al. (18), using a single aortic root dimension, with the location of the measurement in the ascending aorta not identified. Moreover, the investigators did not specify whether they used M-mode or 2-dimensional guided assessment. Measurements made by various echocardiographic modalities may yield substantially different results. Cyclic motion of the heart and resultant changes in the M-mode cursor location relative to the maximum diameter of the sinuses of Valsalva may result in systematic underestimation (by 2 mm) in the aortic diameter by M-mode in comparison with the 2-dimensional aortic diameter measurements (21). Therefore, 2-dimensional aortic root diameter measurements are preferable to those made by M-mode (21).

Cripe et al. (19) evaluated 77 children with BAV and 235 of their relatives. The FDR cohort consisted largely of siblings of probands ($n = 177$) with the definition of aortic root dilation not specified, whereas in our study only a small proportion of cases were from a population younger than age 18 years ($n = 6$). Cripe et al. (19) identified only 8 cases of aortic root dilation out of all 309 study subjects, including those with BAV. Other investigators reported the prevalence of aortic root dilation as high as 52% to 78% in adult BAV patients (7,8). This discrepancy between observations in children and adults suggests that aortic root size in BAV patients and their relatives is influenced by age significantly more than in a general population. The aortic root in this population is of normal dimension in childhood, and dilation develops over time in the adult age, possibly as a result of accelerated degradation of the media in the aortic wall, particularly if there is coexistent hypertension.

Study limitations. Although FDRs were apparently healthy, BAV subjects for this study were not randomly identified from a cross-sectional sampling of the community but were identified at the time of echocardiography in a referral center. Furthermore, 50% of probands had advanced valvular or aortic disease requiring surgery. Therefore, it is possible that their relatives represent families with high-risk genetic characteristics. The small proportion of FDRs relative to probands is another limitation of the study. Our recruitment rate was higher among family members with

BAV patients hospitalized for surgery than in family members with uncomplicated probands.

Clinical implications. Our findings suggest that FDRs of BAV patients should be screened for the presence of BAV and dilation of the ascending aorta. The natural history of FDRs with a mildly dilated aortic root and a tricuspid aortic valve phenotype will need to be determined in a long-term follow-up study of this population.

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