Valvular Heart Disease

Reduced Aortic Elasticity and Dilatation Are Associated With Aortic Regurgitation and Left Ventricular Hypertrophy in Nonstenotic Bicuspid Aortic Valve Patients

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Objectives	This study sought to assess elasticity and dimensions of the aorta and their impact on aortic valve competence and left ventricular (LV) function in patients with a nonstenotic bicuspid aortic valve (BAV).
Background	Intrinsic pathology of the aortic wall is a possible explanation for reduced aortic elasticity and aortic dilatation in patients with BAVs, even in the absence of a stenotic aortic valve. The relationship between aortic wall elasticity, aortic dimensions, aortic valve competence, and LV function in patients with BAVs has not previously been studied with magnetic resonance imaging.
Methods	Magnetic resonance imaging was performed in 20 patients with nonstenotic BAVs (mean ± SD, age 27 ± 11 years) and 20 matched control patients.
Results	The BAV patients showed reduced aortic elasticity as indicated by increased pulse wave velocity in the aortic arch and descending aorta (5.6 ± 1.3 m/s vs. 4.5 ± 1.1 m/s, p = 0.01; and 5.2 ± 1.8 m/s vs. 4.3 ± 0.9 m/s, p = 0.03, respectively), and reduced aortic root distensibility ($3.1 ± 1.2 × 10^{-3}$ mm Hg^{-1} vs. $5.6 ± 3.2 × 10^{-3}$ mm Hg^{-1}, p < 0.01). In addition, BAV patients showed aortic root dilatation as compared with control patients (mean difference 3.6 to 4.2 mm, p ≤ 0.04 at all 4 predefined levels). Minor degrees of aortic regurgitation (AR) were present in 11 patients (AR fraction 6 ± 8% vs. 1 ± 1%, p < 0.01). The LV ejection fraction was normal (55 ± 8% vs. 56 ± 6%, p = 0.61), whereas LV mass was significantly increased in patients (54 ± 12 g/m^2 vs. 46 ± 12 g/m^2, p = 0.04). Dilatation at the level of the aortic annulus (r = 0.45, p = 0.044) and reduced aortic root distensibility (r = 0.37, p = 0.041) correlated with AR fraction. Increased pulse wave velocity in the aortic arch correlated with increased LV mass (r = 0.42, p = 0.041).
Conclusions	Reduced aortic elasticity and aortic root dilatation were frequently present in patients with nonstenotic BAVs. In addition, reduced aortic wall elasticity was associated with severity of AR and LV hypertrophy. (J Am Coll Cardiol 2007;49:1660–5) © 2007 by the American College of Cardiology Foundation

The bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, occurring in 1% to 2% of the population (1–3). Intrinsic pathology of the aortic wall has been reported because of accelerated degeneration of the aortic media, indicating that BAV disease extends beyond the aortic valve (1,4). Given that serious complications like progressive aortic dilatation, aneurysm formation, and even aortic dissection will develop in at least one-third of patients

with BAVs, the bicuspid valve may be responsible for more deaths and morbidity than the combined effects of all other congenital heart defects (4).

Intrinsic aortic wall pathology in BAV disease is associated with aortic dilatation (2,4–7), but also may have a negative impact on aortic elasticity. In Marfan syndrome, increased aortic stiffness has been reported because of fragmentation of elastic wall components (8). Marfan syndrome and BAV disease have many histological and clinical similarities (4,5), reduced aortic elasticity may be present in BAV patients as well. Distensibility and pulse wave velocity (PWV) in the aorta are markers of vessel wall integrity because they are dependent on the elastic properties of the aorta (1,9). Previous reports have indicated the clinical importance of both parameters: reduced distensibility of the

Table 1	Characteristics of BAV Patients and Healthy Subjects	
Characteristics	Patients (n = 20)	Healthy Subjects (n = 20)
Male/female	13 (65)/7 (35)	13 (65)/7 (35)
Age at MRI (yrs)*	27 ± 11	27 ± 12
Height (cm)*	175 ± 8	174 ± 11
Weight (kg)*	69 ± 12	68 ± 15
Body surface area (m²)*†	1.8 ± 0.2	1.8 ± 0.3
Blood pressure, systolic (mm Hg)	128 ± 8	121 ± 11
Blood pressure, diastolic (mm Hg)	79 ± 7	70 ± 11
Heart frequency (beats/min)	71 ± 9	66 ± 11
New York Heart Association functional class I	20	20
Smoking (yes/no)	6/14	5/15

Unless otherwise indicated, data are number of patients, and data in parentheses are percentages.
*Data are mean ± SD. †According to the formula: $\sqrt{[\text{height (cm)} \times \text{weight (kg)}/3,600]}$.
BAV = bicuspid aortic valve; MRI = magnetic resonance imaging.

aortic root increases leaflet stress and therefore predisposes for aortic valve dysfunctioning and subsequent impaired left ventricular (LV) function (10–12). Additionally, aortic PWV is an independent predictor of progressive aortic dilatation in Marfan syndrome (8), and when increased, directly leads to an increased afterload for the LV (9). Because intrinsic aortic wall abnormalities in BAV disease may be associated with impaired distensibility and PWV, both parameters might have a negative impact on aortic valve and LV function in patients with BAV disease.

Recently, magnetic resonance imaging (MRI) has been established as an accurate noninvasive tool for assessment of aortic distensibility and PWV (13–16). To our knowledge, MRI has not been used previously to study the relationship between aortic wall elasticity, aortic dimensions, aortic valve competence, and LV function in patients with BAVs.

We hypothesized that intrinsic aortic wall pathology as measured by abnormal distensibility and PWV in nonstenotic BAV patients frequently occurs and that abnormal aortic elastic properties and aortic dilatation may negatively affect aortic valve and LV function. In the present study we excluded BAV patients with echocardiographic evidence of aortic valve stenosis to avoid the confounding effect on aortic elasticity of mechanical stresses placed on the aortic wall downstream of a stenotic valve (1,2).

Accordingly, the purpose of the current study was to assess aortic wall elasticity and aortic dimensions and their impact on aortic valve competence and LV function in patients with nonstenotic BAVs.

Methods

Patient population. Twenty patients with BAVs and 20 age- and gender-matched healthy subjects were prospectively studied with MRI at our institution (Table 1). Twenty patients with BAVs were recruited from our local congenital heart disease database (mean ± SD, age 27 ± 11 years). Inclusion criteria consisted of BAV as diagnosed by echocardiography. Exclusion criteria were evidence of aortic valve stenosis (aortic velocity >2.5 m/s on echocardiogra-

phy) (17), aortic coarctation and/or other forms of congenital heart disease, Marfan syndrome or a family history of Marfan syndrome, previous surgery or intervention, usage of medication such as beta-blockers, and general contraindications to MRI.

Age- and gender-matched healthy subjects were selected from our local database of subjects with an innocent heart murmur in the past, in whom congenital cardiac pathology had been excluded by physical examination and echocardiography. Characteristics and functional status as expressed as New York Heart Association class of the patients and healthy subjects were obtained from the patient records (Table 1). The local medical ethics committee approved the study, and informed consent was obtained from all participants before their enrollment in the study.

MR imaging. The MRI studies were performed with a 1.5-T system (NT 15 Gyroscan Intera, Philips Medical System, Best, the Netherlands).

Aortic diameters and cross-sectional aortic areas were measured from transaxial images obtained with a gated steady-state free-precession sequence. Scan parameters encompassed field-of-view 220 mm, rectangular field-of-view percentage 90%, repetition time 3.2 ms, echo time 1.23 ms, gate width 34.2 ms, flip angle 50°, acquired voxel size 1.25 × 1.25 × 6.00 mm, reconstructed voxel size 0.43 × 0.43 × 6.00 mm, trigger delay 600 ms after the R-peak. Individual slices were obtained at the level of the annulus of the aortic valve, the sinus of Valsalva, the sinotubular junction, and the proximal ascending aorta, the latter at the level of the pulmonary trunk (Fig. 1).

Aortic distensibility was measured at the level of the sinotubular junction. Distensibility (in mm Hg^{-1}) is calculated according to the following formula: $(A_{max} - A_{min})/(A_{min} \times [P_{max} - P_{min}])$, with A_{max} and A_{min} as maximal and minimal lumen area (in mm^2) of the sinotubular junction, and P_{max} and P_{min} as systolic and diastolic blood pressure (mm Hg) (15). Maximal lumen area is expected at the peak of aortic flow, and minimal lumen area is expected before the systolic flow curve (coinciding with the isovolumetric contraction phase) (16). Minimal and maximal lumen area MR imaging was performed after manually positioning the acquisition planes perpendicular to the aorta at the level of the sinotubular junction (Fig. 2), at time points of minimal and maximal flow through the aortic root, respectively (16). This approach enabled correction for through-plane motion of the aortic root during contraction (16). Scan parameters were identical to the diameter measurements; gate delay was individually applied for optimal timing of the acquisition (16). For timing of aortic flow, a phase-contrast sequence was used at the level of the sinotubular junction with scan parameters: field-of-view 300 mm, rectangular field-of-view percentage 90%, repetition
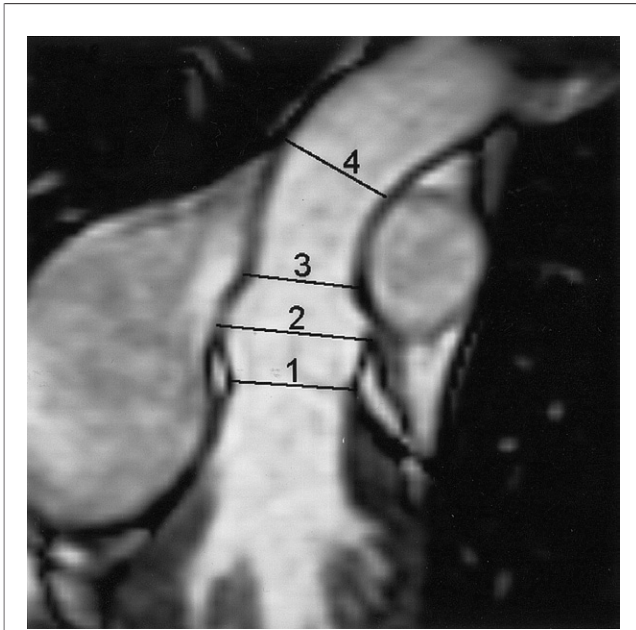
Figure 1 **Diameter Measurements of the Aortic Root**

Oblique coronal image showing the 4 diameter measurements of the aortic root: at the level of the annulus of the aortic valve (1), the sinus of Valsalva (2), the sinotubular junction (3), and the ascending aorta at the level of the pulmonary trunk (4).

time 4.8 ms, echo time 2.8 ms, flip angle 20°, acquired voxel size $2.34 \times 2.34 \times 8.00$ mm, reconstructed voxel size $1.17 \times 1.17 \times 8.00$ mm, using retrospective gating. Temporal resolution was approximately 10 ms depending on the heart rate. The sequence was encoded for a through-plane velocity up to 200 cm/s (16). The same acquisition was also used for assessment of aortic valve competence and measurement of peak flow velocity across the aortic valve. Aortic regurgitation (AR) fraction was considered significant if the regurgitant fraction was >5% of the systolic forward flow (16). Blood pressure was noninvasively obtained using a semiautomatic MRI-compatible sphygmomanometer (Invivo-Research-Inc. 3150, Orlando, Florida). In each patient, right brachial artery systolic and diastolic blood pressures were measured 3 times during the measurements for distensibility, and the average of the measurements was used for calculations (8).

The PWV was measured between the ascending and proximal descending aorta, and between the proximal descending aorta and aortic bifurcation (Fig. 3). A retrospectively electrocardiogram-gated gradient-echo pulse sequence with velocity encoding was applied at the level of the pulmonary trunk to measure through-plane flow in the ascending aorta and proximal descending aorta (Fig. 3). A second acquisition plane was positioned just above the bifurcation of the abdominal aorta (Fig. 3). Scan parameters were identical to the sequence used for the distensibility measurements. During the MRI acquisition, systolic and diastolic blood pressures were measured as described for the distensibility measurements. The PWV was calculated as:

$\Delta x/\Delta t$ (expressed in m/s), where Δx is the aortic path length between 2 imaging levels and Δt is the time delay between the arrival of the foot of the pulse wave at these levels (18).

Systolic LV function was assessed with a steady-state free-precession cine sequence. Scan parameters were: field-of-view 400 mm, rectangular field-of-view percentage 80%, repetition time 3.2 ms, echo time 1.6 ms, flip angle 70°, acquired voxel size $1.92 \times 2.41 \times 10.00$ mm, reconstructed voxel size $1.56 \times 1.55 \times 10.00$ mm, no slice gap (19). The following parameters were obtained after indexation for body surface area: LV end-diastolic volume, LV end-systolic volume, LV stroke volume, LV ejection fraction, and LV mass (16,19).

All images were quantitatively analyzed on a workstation with an Intel Pentium 4 processor (Intel, Santa Clara, California). The measurements for diameters and distensibility of the aortic root as well as the short-axis gradient-echo images of both ventricles were analyzed with the software package MASS (Medis, Leiden, the Netherlands) (16,19). Aortic velocity maps were analyzed with the analytic software package FLOW (Medis) (20). All contours and diameters were manually drawn by one observer (3 years of experience), and were subsequently checked by a radiologist who was blinded to the patient conditions (9 years of experience).

Statistical analysis. Statistical analysis was performed using SPSS for Windows (version 12.0.1, SPSS Inc., Chicago, Illinois). All data are presented as mean values ± 1 SD, unless stated otherwise. The Mann-Whitney *U* statistic was used to express differences in variables between the patients
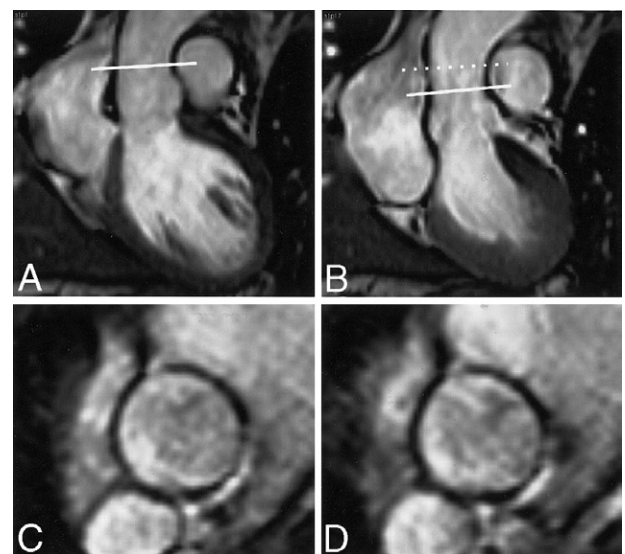
Figure 2 **Distensibility Measurements of the Aortic Root**

(A and B) Taken in the oblique coronal plane, these images show the slice positioning of the acquisition planes at minimal and maximal aortic flow for distensibility measurements, respectively, thus correcting for through-plane motion of the aortic root during contraction. Note the difference in position of the aortic root in both images, because of cardiac motion. **(C and D)** The corresponding area measurements in the double oblique transverse orientation.
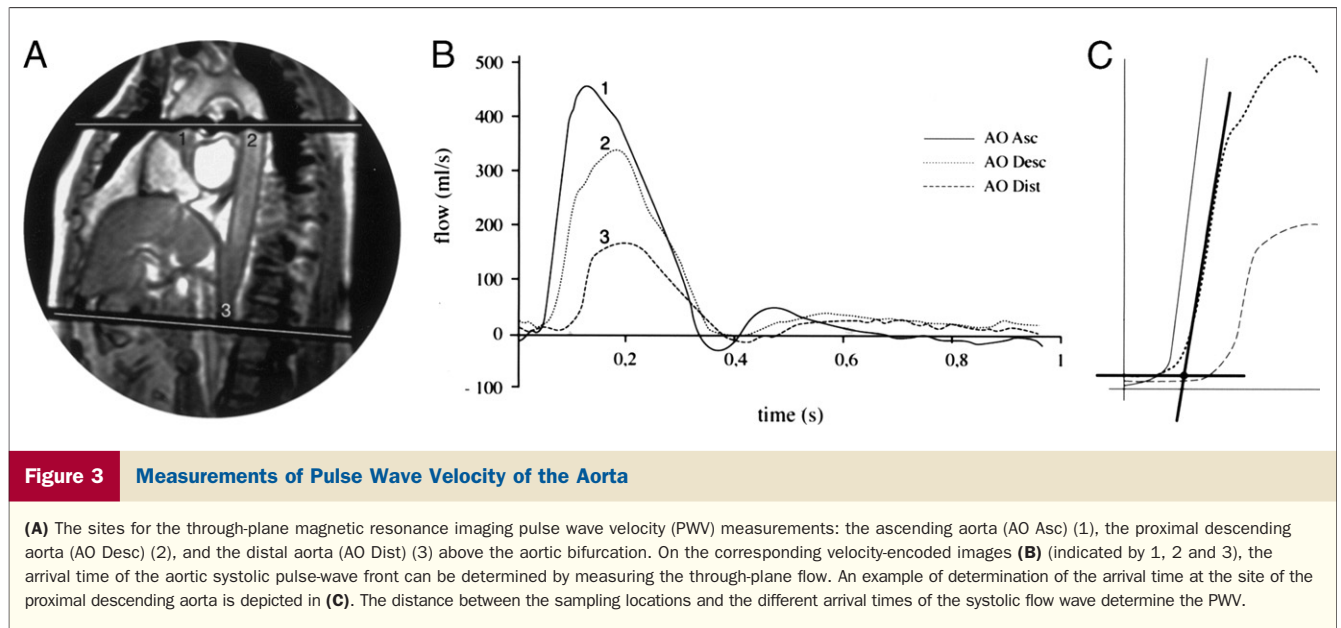
Figure 3   **Measurements of Pulse Wave Velocity of the Aorta**

(A) The sites for the through-plane magnetic resonance imaging pulse wave velocity (PWV) measurements: the ascending aorta (AO Asc) (1), the proximal descending aorta (AO Desc) (2), and the distal aorta (AO Dist) (3) above the aortic bifurcation. On the corresponding velocity-encoded images **(B)** (indicated by 1, 2 and 3), the arrival time of the aortic systolic pulse-wave front can be determined by measuring the through-plane flow. An example of determination of the arrival time at the site of the proximal descending aorta is depicted in **(C)**. The distance between the sampling locations and the different arrival times of the systolic flow wave determine the PWV.

and healthy subjects. Correlation between variables was expressed with the Spearman rank correlation coefficient. Linear regression analysis was used to identify predictors of variables with backward elimination procedures. Statistical significance was indicated by a p value of <0.05.

Results

Aortic dimensions and elasticity. Patients with BAVs showed significantly increased PWV in the aortic arch and descending aorta (Table 2, Fig. 2). In addition, distensibility at the level of the sinotubular junction was diminished in patients with BAVs as compared with the healthy subjects group (Table 2). Diameters and areas of the aortic root were significantly increased at all 4 levels in BAV patients as

compared with the healthy subjects (Table 2). Dilatation was most pronounced at the levels of the sinus of Valsalva and the proximal ascending aorta (Table 2). Dilatation at the level of the sinotubular junction was significantly correlated with decreased root distensibility (r = 0.56, p = 0.004) and increased PWV in the aortic arch (r = 0.45, p = 0.039). The presence of BAV and older age at time of MRI predicted reduced root distensibility and increased PWV in the aortic arch (r = 0.5 to 0.7, p ≤ 0.01 for all).

Aortic valve competence. Patients with BAVs were characterized by frequent minor degrees of AR, as 11 of 20 patients showed AR fraction ranging between 5% and 16%. In none of the healthy subjects did AR fraction exceed 5%. The AR fraction (expressed in percentages) (Table 2) was

Table 2   **Results in 20 BAV Patients and 20 Age- and Gender-Matched Healthy Subjects**

Parameters	Patients	Healthy Subjects	p Value	Mean Difference
Annulus diameter (mm)	30.1 ± 6.9	26.2 ± 3.3	0.03	3.9
Annulus area (cm^2)	7.4 ± 3.5	5.5 ± 1.4	0.03	1.9
Sinus of Valsalva diameter (mm)	33.4 ± 5.7	29.2 ± 3.2	<0.01	4.2
Sinus of Valsalva area (cm^2)	9.0 ± 3.4	6.8 ± 1.5	<0.01	2.2
Sinotubular junction diameter (mm)	30.4 ± 6.2	26.8 ± 3.4	0.04	3.6
STJ area (cm^2)	7.5 ± 3.5	5.7 ± 1.5	0.04	1.8
Ascending aorta diameter (mm)	30.0 ± 6.3	25.7 ± 3.1	<0.01	4.3
Ascending aorta area (cm^2)	7.4 ± 3.4	5.2 ± 1.3	<0.01	2.1
Distensibility (in 10^{-3} mm Hg^{-1})*	3.1 ± 1.2	5.6 ± 3.2	<0.01	
PWV aortic arch (m/s)	5.6	4.5	0.01	
PWV descending aorta (m/s)	5.2	4.3	0.03	
Aortic regurgitation fraction (%)	6 ± 8	1 ± 1	<0.01	
Peak-flow velocity at STJ (m/s)	1.68 ± 0.26	1.67 ± 0.33	0.97	
LV EF (%)	55 ± 8	56 ± 6	0.61	
LV EDV (ml/m^2)	101 ± 22	93 ± 16	0.29	
LV ESV (ml/m^2)	46 ± 17	41 ± 8	0.36	
LV mass (g/m^2)	54 ± 12	46 ± 12	0.04	

Data are expressed as mean $\pm$ SD. *Distensibility was measured at the level of the STJ.

BAV = bicuspid aortic valve; EDV = end-diastolic volume indexed for body surface area; EF = ejection fraction; ESV = end-systolic volume indexed for body surface area; LV = left ventricular; PWV = pulse wave velocity; STJ = sinotubular junction.

significantly correlated with dilatation at the level of the aortic annulus (r = 0.45, p = 0.044) and reduced aortic root distensibility (r = 0.37, p = 0.041). Peak flow velocities across the aortic valve were not increased in our patient group as compared with the healthy subjects (Table 2), supporting the fact that none of the patients had aortic valve stenosis.

LV function. Systolic function—expressed by LV ejection fraction and LV stroke volume—was not significantly different between patients with BAVs and healthy subjects (Table 2). Also, LV dimensions (LV end-diastolic and -systolic volume) were not significantly different between the 2 groups (Table 2). Mean LV mass of the patient group was significantly larger compared with that value in healthy subjects (Table 2). Increased LV mass was significantly correlated with increased PWV in the aortic arch (r = 0.42, p = 0.041), suggesting that LV hypertrophy results from an increased LV afterload. Linear regression showed that increased PWV in the aortic arch predicted increased LV mass (r = 0.5, p < 0.01).

Discussion

The purpose of the current study was to assess aortic wall elasticity and aortic dimensions and their impact on aortic valve competence and LV function in patients with nonstenotic BAVs. This study showed frequently reduced aortic elasticity and aortic root dilatation in patients with nonstenotic BAVs. In addition, reduced aortic wall elasticity was associated with the severity of AR and the degree of LV hypertrophy. Monitoring of aortic elasticity and aortic dimensions, in conjunction with aortic valve competence and LV function, seems therefore indicated in the long-term follow-up of patients with BAVs.

Aortic dimensions. Significant dilatation of the aortic root was present in our patient group with BAVs. Dilatation was most pronounced at the levels of the sinus of Valsalva and of the proximal ascending aorta, which is in agreement with previous ultrasound reports (21,22). Aortic dilatation may be caused by intrinsic pathology of the aortic wall, or hemodynamic factors caused by a stenotic aortic valve: high velocity and turbulent flow downstream of the stenosis place mechanical stress on the aortic wall (1). In this study only nonstenotic BAV patients were included, so aortic dilatation caused by stenotic mechanical stress was not suspected.

Intrinsic pathology of the aortic wall in patients with BAVs has been reported because of accelerated degeneration of the aortic media, indicating that BAV disease extends beyond the aortic valve (1,4). Inadequate production of fibrillin-1 during valvulogenesis may disrupt the formation of the aortic cusps, resulting in a bicuspid valve and a weakened aortic root (4). These lesions are similar in fibrillin-1–deficient aortas of patients with Marfan syndrome (4). The BAVs should therefore be considered a disease of the entire aortic root (1,4,7).

As a consequence of intrinsic aortic wall pathology, the presence of BAV has been reported to be an independent risk factor for progressive aortic dilatation, aneurysm formation, and even dissection (4,7). For the risk of aortic rupture and dissection, aortic root replacement is more aggressively recommended for patients with BAVs (i.e., 4 to 5 cm) than for those of patients with a tricuspid aortic valve (i.e., 5 to 6 cm) (4). Long-term surveillance of aortic dimensions is therefore required (4).

Aortic elasticity. Significantly reduced aortic elasticity in our patient group indicated that BAV disease is not only associated with aortic dilatation (2,4–7), but also with reduced aortic elasticity. In Marfan syndrome, increased aortic stiffness has been reported because of fragmentation of elastic wall components (8). Considering the many histological and clinical similarities between both entities (4,5), intrinsic aortic wall abnormalities in BAV disease are probably responsible for reduced aortic elasticity as well. Our patient group showed diminished elasticity of the entire aorta, suggesting not only that the proximal part of the aorta is affected in BAV disease (4,21), but also that aortic wall lesions extend into the entire aorta.

In patients with Marfan syndrome, aortic stiffness has proven to be an independent predictor of progressive aortic dilatation (8). Evaluation of the elastic properties of the ascending aorta in patients with BAVs might be used analogously to identify patients who are at risk of progressive dilatation of the aorta and other aortic sequelae. Future longitudinal studies are needed to investigate whether the same predictive value of aortic stiffness is applicable for patients with BAV disease.

Arterial stiffness has also been shown to be a cardiovascular risk factor on its own (9). Augmented arterial stiffening is associated with impaired coronary blood flow and LV dysfunction (9). In addition, a strong and independent association has been shown between increased arterial stiffness and the presence of coronary artery disease (23). Therefore, prognosis of patients with increased arterial stiffness in BAV disease may be worse as compared with healthy subjects because numerous other standard risk factors such as aging, smoking, lipid profiles, and gender are cumulative over a lifetime (9). Early detection of disturbances in arterial stiffness may allow for early therapeutic intervention (24). In Marfan patients, beta-adrenergic blockade has a beneficial effect on the progression rate of aortic dilatation with reduction of aortic complications (8,15). Whether this is applicable for BAV patients remains to be elucidated.

Aortic valve competence. In the current study, minor degrees of AR were a common finding in our patients with BAVs. Inherent structural weakness of the aortic valve cusps may lead to aortic valve prolapse and subsequent AR (4). In this study the degree of AR was correlated with dilatation of the aortic annulus and decreased aortic root distensibility. Dilatation of the aortic root has been reported to have the potential to cause AR (4,7,16). In addition, distensibility of the aortic root is crucial for aortic valve dynamics: aortic valve opening occurs in concert with root expansion during the beginning of systole (10,25). Disturbance of this inter-

relation greatly determines the stress on valve leaflets (10–12). We therefore hypothesize that reduced aortic root distensibility in patients with BAVs increases leaflet stress, and thus predisposes to aortic valve dysfunction in BAV disease.
LV function. The LV systolic function was adequately preserved in patients with BAVs. However, a significantly larger LV mass was observed in our BAV patients, indicating hypertrophy of the LV. Often LV hypertrophy is compensatory to increased LV afterload (26), which in this study was related to reduced elasticity of the proximal aorta. Myocardial stiffening may occur as a consequence of sustained LV hypertrophy, which has a negative effect on diastolic filling (26). Clinical studies have confirmed the detrimental effect of diastolic LV dysfunction, having a major contribution to congestive heart failure and diminished exercise performance (26,27). Diastolic LV dysfunction also may precede LV systolic dysfunctioning (26). Aging contributes to any diastolic dysfunction by increasing ventricular mass and loss of elastic myocardial properties over time (26,27). Therefore, LV hypertrophy might pose a future risk for LV dysfunction in our BAV patient group (26,27).

This study showed frequently reduced aortic elasticity and aortic root dilatation in patients with nonstenotic BAVs. In addition, reduced aortic wall elasticity was associated with severity of AR and degree of LV hypertrophy. Analogous to similar entities such as Marfan syndrome, intrinsic aortic wall abnormalities in BAV disease result in a negative cascade that affects aortic elasticity, aortic dimensions, aortic valve competence, and LV function. Monitoring of aortic elasticity and aortic dimensions, in conjunction with aortic valve competence and LV function, seems therefore indicated in the long-term follow-up of patients with BAVs. Future longitudinal studies are required to investigate the predictive value of aortic stiffness in patients with BAV disease.

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REFERENCES

1. Wilton E, Jahangiri M. Post-stenotic aortic dilatation. J Cardiothorac Surg 2006;1:7–18.
2. Nkomo VT, Enriquez-Sarano M, Ammash NM, Melton LJ III, Bailey KR, Desjardins V. Bicuspid aortic valve associated with aortic dilatation: a community-based study. Arterioscler Thromb Vasc Biol 2003;23:351–6.
3. Warren AE, Boyd ML, O'Connell C, Dodds L. Dilation of the ascending aorta in pediatric patients with bicuspid aortic valve: frequency, rate of progression and risk factors. Heart 2006;92:1496–500.
4. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. Circulation 2002;106:900–4.
5. Beroukhim RS, Roosevelt G, Yetman AT. Comparison of the pattern of aortic dilation in children with the Marfan's syndrome versus children with a bicuspid aortic valve. Am J Cardiol 2006;98:1094–5.
6. Beroukhim RS, Kruzick TL, Taylor AL, Gao D, Yetman AT. Progression of aortic dilation in children with a functionally normal bicuspid aortic valve. Am J Cardiol 2006;98:828–30.
7. Cecconi M, Nistri S, Quarti A, Manfrin M, Colonna PL, Molini E. Aortic dilatation in patients with bicuspid aortic valve. J Cardiovasc Med 2006;7:11–20.
8. Nollen GJ, Groenink M, Tijssen JG, van der Wall EE, Mulder BJ. Aortic stiffness and diameter predict progressive aortic dilatation in patients with Marfan syndrome. Eur Heart J 2004;25:1146–52.
9. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002;106:2085–90.
10. Schmidtke C, Bechtel J, Hueppe M, Noetzold A, Sievers HH. Size and distensibility of the aortic root and aortic valve function after different techniques of the ross procedure. J Thorac Cardiovasc Surg 2000;119:990–7.
11. Thubrikar M, Skinner JR, Aouad J, Finkelmeier BA, Nolan SP. Analysis of the design and dynamics of aortic bioprostheses in vivo. J Thorac Cardiovasc Surg 1982;84:282–90.
12. Thubrikar MJ, Nolan SP, Aouad J, Deck JD. Stress sharing between the sinus and leaflets of canine aortic valve. Ann Thorac Surg 1986;42:434–40.
13. Melina G, Rajappan K, Amrani M, Khaghani A, Pennell DJ, Yacoub MH. Aortic distensibility after aortic root replacement assessed with cardiovascular magnetic resonance. J Heart Valve Dis 2002;11:67–74.
14. Rogers WJ, Hu YL, Coast D, Vido DA, Kramer CM, Pyeritz RE. Age-associated changes in regional aortic pulse wave velocity. J Am Coll Cardiol 2001;38:1123–9.
15. Groenink M, de Roos A, Mulder BJ, et al. Changes in aortic distensibility and pulse wave velocity assessed with magnetic resonance imaging following beta-blocker therapy in the Marfan syndrome. Am J Cardiol 1998;82:203–8.
16. Grotenhuis HB, Westenberg JJM, Doornbos J, et al. Aortic root dysfunctioning and its effect on left ventricular function in Ross patients, assessed with MRI. Am Heart J 2006;152:975e1–8.
17. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–7.
18. Stevanov M, Baruthio J, Gounot D, Grucker D. In vitro validation of MR measurements of arterial pulse-wave velocity in the presence of reflected waves. J Magn Reson Imaging 2001;14:120–7.
19. van der Geest RJ, Reiber JH. Quantification in cardiac MRI. J Magn Reson Imaging 1999;10:602–8.
20. van der Geest RJ, Niezen RA, van der Wall EE, et al. Automated measurement of volume flow in the ascending aorta using MR velocity maps: evaluation of inter- and intraobserver variability in healthy volunteers. J Comput Assist Tomogr 1998;22:904–11.
21. Cecconi M, Manfrin M, Moraca A, Zanoli R, Colonna PL, Bettuzzi MG. Aortic dimensions in patients with bicuspid aortic valve without significant valve dysfunction. Am J Cardiol 2005;95:292–4.
22. La Canna G, Ficarra E, Tsagalau E, Nardi M, Morandini A, Chieffo A. Progression rate of ascending aortic dilation in patients with normally functioning bicuspid and tricuspid aortic valves. Am J Cardiol 2006;98:249–53.
23. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol 1994;140:669–82.
24. Franklin SS. Blood pressure and cardiovascular disease: what remains to be achieved? J Hypertens Suppl 2001;19:S3–8.
25. Thubrikar MJ, Heckman JL, Nolan SP. High speed cine-radiographic study of aortic valve leaflet motion. J Heart Valve Dis 1993;2:653–61.
26. Mandinov L, Eberli FR, Seiler C, Hess OM. Diastolic heart failure. Cardiovasc Res 2000;45:813–25.
27. Singh GK, Greenberg SB, Yap YS, Delany DP, Keeton BR, Monro JL. Right ventricular function and exercise performance late after primary repair of tetralogy of Fallot with the transannular patch in infancy. Am J Cardiol 1998;81:1378–82.