Elastic Properties of Aortic Wall in Patients With Bicuspid Aortic Valve by Magnetic Resonance Imaging

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Bicuspid aortic valve (BAV) is frequently associated with aortic wall abnormalities, including dilation of the ascending aorta and even dissection. We propose 2 new indexes of aortic wall biophysical properties, the maximum rates of systolic distension and diastolic recoil (MRSD and MRDR, respectively), in patients with BAV and matched control subjects. We evaluated 53 consecutive young patients with BAV (36 males, mean age 16 ± 4 years) with mild aortic valve disease and a control group of 22 age- and gender-matched healthy volunteers. All subjects underwent a cardiac magnetic resonance imaging study that included phase velocity mapping and cine acquisition at several aortic levels. The MRSD and MRDR were measured in the ascending aorta in both patients with BAV and controls. Of the 53 patients with BAV, 26 had enlarged ascending aortas (dilated BAV), and 27 had a normal aortic diameter (nondilated BAV). Compared to controls, the MRSD was significantly lower in the whole BAV group (4.37 ± 1.1 vs 9.1 ± 2.1), in patients with dilated BAV (4.5 ± 1.1 $p < 0.0001$), and in those with nondilated BAV (4.3 ± 1.0, $p < 0.0001$). The MRDR was greater in the whole BAV group (−4 ± 1.2 vs −7.6 ± 2.7, $p < 0.0001$), in the dilated BAV group (−3.9 ± 1.3, $p < 0.0001$), and in the nondilated BAV group (−4.1 ± 1.2, $p < 0.0001$). A receiver operating characteristic curve analysis of MRSD distinguished BAV from controls with 100% sensitivity and 95% specificity. In conclusion, MRSD and MRDR were slower in the patients with BAV than in the controls, regardless of the dimensions of the ascending aorta. **(Am J Cardiol 2011;108: 81–87)**

We propose 2 new magnetic resonance imaging (MRI) indexes of aortic elastic properties: the maximum rate of systolic distension (MRSD) and the maximum rate of diastolic recoil (MRDR). These indexes assess the velocities of aortic wall distension and recoil during the cardiac cycle. The purpose of the present study was to test these indexes in both patients with bicuspid aortic valve (BAV) and healthy controls and compare them with the other aortic wall biophysical property indexes currently available.

Methods

We enrolled 63 consecutive patients aged 8 to 25 years with a confirmed diagnosis of BAV. All patients underwent a comprehensive cardiac MRI study. Of the 63 patients, 10 were excluded from the analysis after the MRI examination because of significant aortic valve disease. Our final study population consisted of 53 patients (36 males; mean age 16 ± 4 years) with BAV and without significant aortic valve dysfunction. A total of 22 age- and gender-matched healthy volunteers (17 males; mean age 16 ± 4 years) were enrolled as controls. The patients with BAV were subdivided into 2 groups according to the ascending aortic diameter. The dilated BAV group consisted of patients with an ascending aortic diameter 2 SD greater than the average diameter of the control group, and the nondilated BAV group consisted of patients with a diameter ≤2 SD greater than the control group average.

The MRI studies were performed using a 1.5 T Signa CV/I MRI scanner (GE, Milwaukee, Wisconsin) using an 8-channel cardiac phased array coil. The thoracic aorta was visualized by acquiring sagittal-oblique cine images parallel to the major aortic axis using a breath-hold, electrocardiographic-triggered, steady-state free-precession (SSFP) pulse sequence with the following parameters: 400-mm field of view, 8-mm slice thickness, no gap, 1 number of excitations, 12 views per segment, echo time/repetition time 1.6/3.2 ms, flip angle 45°, matrix 224 × 224, and reconstruction matrix 256 × 256. The number of cardiac phases was set according to the heart rate to obtain an aortic wall excursion temporal resolution of approximately 10^{-3} seconds. Cross-sectional cine SSFP images with the same parameters were acquired at different aortic levels: (1) at the aortic valve plane to confirm the diagnosis of BAV; (2) at the aortic root; (3) at the sinotubular junction; (4) at the proximal ascending aorta (5 mm above the sinotubular junction) to measure the distensibility, MRSD, and MRDR; and (5) at the level of the maximum diameter of the ascending aorta. The left ventricular volumes and mass were obtained using the conventional approach. A gradient-echo velocity mapping

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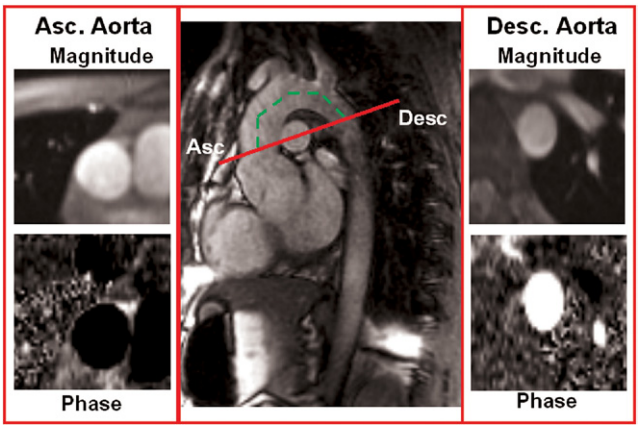

Figure 1. *(Middle)* SSFP images of thoracic aorta in patient with BAV. *Red line* represents phase velocity cine-MRI acquisition plane of ascending (Asc) aorta (5 mm above sinotubular junction) and proximal descending (Desc) aorta. Length of *green line* considered distance between ascending and descending aorta for evaluating flow wave propagation. *(Left)* Phase velocity cine-MRI magnitude image *(Upper)* and phase image *(Lower)* from ascending aorta. *(Right)* Phase velocity cine-MRI magnitude image (Upper) and phase image *(Lower)* acquired in descending aorta.

electrocardiographic-triggered sequence (phase velocity cine-MRI) was used to determine the blood flow and regurgitation volume. The through-plane flow was measured orthogonal to the vessels in the ascending aorta (5 mm over the sinotubular junction) and in the descending aorta (Figure 1). The following acquisition parameters were used: repetition time/echo time 12/5 ms, 20° flip angle, field of view 30, phase field of view 1, 192 × 192 matrix, 256 × 256 reconstruction matrix, 5-mm slice thickness, 1 excitation, 2 views per segment, and encoded velocity 250 cm/s. The number of cardiac phases was set according to the heart rate, as above. The systemic arterial pressure was noninvasively measured with an automatic manometer at the brachial artery level at each acquisition. The SSFP and phase velocity cine-MRI imaging sequences for the assessment of ventricular function, flow, and wall excursion were elaborated with commercially available software (Mass Plus and CV Flow, Leiden, The Netherlands). The diameters of the aortic root, sinotubular junction, and ascending aorta (at the maximum dimension level) were measured from the cine SSFP images. The flow through the aortic valve and the ascending and descending aorta was measured as described in a previous study.[1] The blood flow was calculated as the product of the aortic cross-sectional area and mean flow velocity for each cardiac phase. A volume/time curve was obtained for each section (aortic valve and ascending and descending aorta). The anterograde flow was measured as the area under the positive component of the curve, and the retrograde flow was the area under the negative component. The aortic regurgitation fraction was calculated at the level of the aortic valve plane as follows: retrograde flow/anterograde flow × 100, expressed as a percentage. The flow wave velocity propagation was defined as the time delay of the flow between the descending and ascending aorta (Figure 1) and was measured as previously reported.[1] Aortic wall distensibility in the ascending aorta was measured on the SSFP images, using a method described in previous studies.[1,2] In brief, aortic wall distensibility was then measured as (A max − A min)/[A min × (SP − DP)], where A max is the maximum (systolic) cross-sectional aortic area (in mm^2), A min is the minimum (diastolic) cross-sectional aortic area (in mm^2), SP is the systolic blood pressure (in mm Hg), and DP is the diastolic blood pressure (in mm Hg). We also defined MRSD and MRDR, 2 new indexes that describe the elastic properties of the aortic wall using cine-MRI in the ascending aorta. In brief, the cross-sectional area of the proximal ascending aorta (5 mm above the sinotubular junction) measured in each cardiac phase was indexed for the maximum end-systolic cross-sectional area and plotted against the time (relative cross-sectional area/time curve; Figure 2). In this curve, MRSD, the maximum rate of systolic distension of the ascending aorta cross-sectional area, was measured as the maximum systolic upslope, and MRDR, the maximum rate of diastolic recoil, was measured as the maximum diastolic downslope. The MRSD and MRDR were expressed as the percentile of the maximum area/10^{-3} seconds. The systemic vascular resistance was calculated using the cardiac output measured by phase velocity cine-MRI in the ascending aorta and the mean arterial pressure, assuming a right atrial pressure of 5 mm Hg in all patients. The measurement of aortic wall indexes was performed by 3 blinded expert investigators who were unaware of the clinical information of the patients and the presence of BAV.

The values are expressed as the mean ± SD (for normal distribution) or median and 25th to 75th percentile. The group means of numerical data were analyzed using a 2-sample Student's *t* test. Differences among the groups were analyzed using analysis of variance and Bonferroni tests, when appropriate. A simple linear correlation with Pearson's coefficient (r) was used to correlate the MRSD and MRDR with the cross-sectional area and systemic vascular resistance. A receiver operating characteristic analysis was used to compare the specificity and sensitivity of the aortic wall indexes to distinguish between BAV and controls. Observer agreement was quantified by using intraclass correlation coefficients.

Results

In 27 patients with BAV (17 males; the nondilated BAV group), the ascending aorta diameters were not significantly different from those of the healthy controls. In the remaining 26 patients with BAV (19 males; the dilated BAV group), the ascending aorta diameter was greater than the range measured in the controls (greater than the mean + 2 SD; Table 1). No significant differences were found in the left ventricle volumes and ejection fraction (Table 1) or the systemic vascular resistance (14.07 ± 4.3 vs 12.6 ± 5.8 Wood units, p = NS) in the patients with BAV and the controls. Figure 3 shows that the ascending aorta wall distensibility was significantly lower in those with BAV than in the controls (Table 2). Both groups of patients with BAV (dilated and nondilated BAV) had lower wall distensibility than did the controls. Flow wave propagation was significantly faster in the patients with BAV than in the controls (1.8 ± 0.75 vs 1.26 ± 0.4. mm/ms, $p < 0.05$), although the overlap was considerable (Figure 3). The patients with BAV

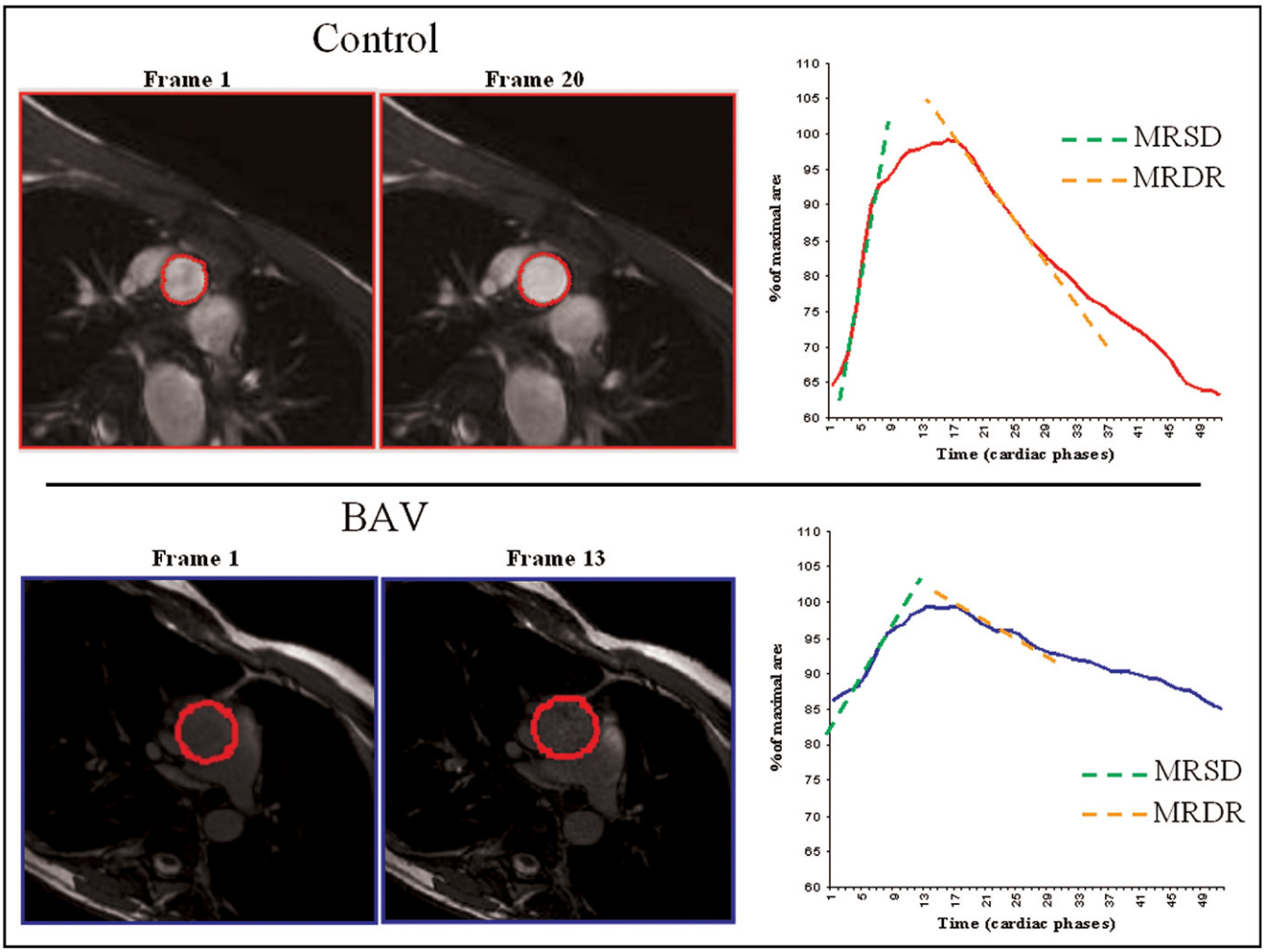

Figure 2. MRSD and MRDR in control subject *(Upper)* and patient with dilated BAV *(Lower). (A,B,D,E)* First SSFP frame and frame with largest cross-sectional area of ascending aorta of healthy patient and patient with BAV; *(C,F)* area/time curve of control and patient with BAV.

Table 1
Population characteristics

Variable	BAV	Nondilated BAV	Dilated BAV	Control	p Value		
					BAV vs Control	Nondilated BAV vs Control	Dilated BAV vs Control
Patients (n)	53	26	27	22			
Males (n)	36	17	19	17	0.41	1	0.44
Age (years)	16 ± 4	15 ± 4	19 ± 4	16 ± 4	0.9	0.39	0.012
Body surface area (m^2)	1.63 ± 0.3	1.51 ± 0.26	1.76 ± 0.2	1.62 ± 0.23	0.88	0.12	0.03
Diameter							
Aortic root	31.6 ± 5.5	30 ± 5.2	34 ± 5.7	29 ± 5.7	0.16	0.34	0.03
Aortic junction	28.2 ± 5.3	24.1 ± 4.3	31.2 ± 4.3	22 ± 5.3	0.0002	0.13	<0.0001
Ascending aorta	30.9 ± 6.8	24.3 ± 5.1	35.3 ± 5.3	23.8 ± 3.7	0.0002	0.6	<0.0001
End-diastolic volume index (ml/m^2)	92 ± 20	87 ± 21	96 ± 17	87 ± 15	0.38	0.99	0.06
End-systolic volume index (ml/m^2)	32 ± 12	29 ± 11	34 ± 12	31 ± 11	0.96	0.53	0.37
Ejection fraction (%)	67 ± 6	69 ± 7	66 ± 6	66 ± 6	0.57	0.12	0.99
Mass index (g/m^2)	74 ± 14	71 ± 14	76.5 ± 15	70 ± 12	0.39	0.35	0.9

had lower MRSD ($p < 0.0001$) than the controls (Table 2). The box-and-whisker plot in Figure 4 shows that only 1 healthy patient had an MRSD within the range of values found in the patients with BAV. No significant gender differences were found for MRSD in the controls (8.6 ± 2 vs 10 ± 2.5, male vs female, $p = 0.21$) or in those with BAV (4.2 ± 1.1 vs 4.6 ± 1.1, male vs female, $p = 0.76$). Both BAV groups (dilated and nondilated) had similar

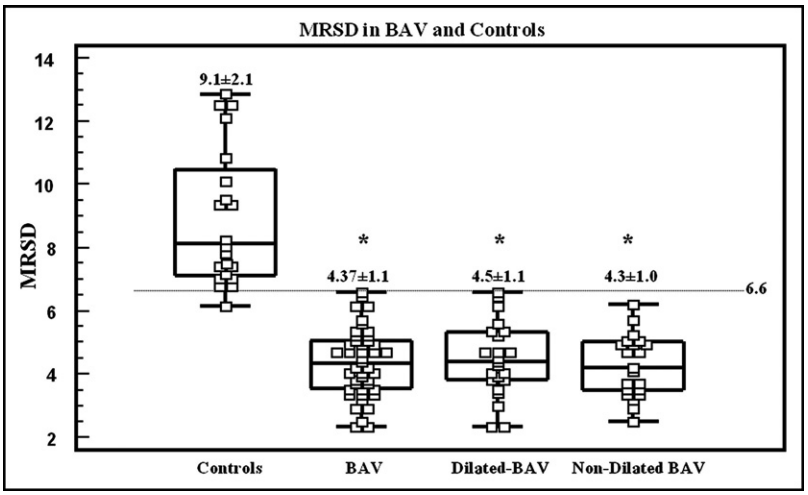

Figure 3. Box and whisker plot showing absence of overlap between MRSD values in controls, patients with BAV, and BAV subgroups (dilated BAV, those with ascending aorta dilation; and nondilated BAV, those without dilation). *Overall, patients with BAV with and without dilation had significantly lower MRSDs than did controls.

Table 2
Distensibility, flow wave velocity propagation, maximum rate of systolic distension (MRSD) and maximum rate of diastolic recoil (MRDR)

Variable	BAV	Nondilated BAV	Dilated BAV	Control	p Value		
					BAV vs Control	Nondilated BAV vs Control	Dilated vs Nondilated BAV
Ascending aorta distensibility	6.4 ± 3.0	6.4 ± 3.2	6.5 ± 2.9	8.7 ± 3.4	<0.05	0.02	0.9
Maximum rate of systolic distension	4.37 ± 1.1	4.3 ± 1.0	4.5 ± 1.1	9.1 ± 2.1	<0.0001	<0.0001	0.49
Maximum rate of diastolic recoil	−4 ± 1.24	−4.1 ± 1.2	−3.9 ± 1.3	−7.6 ± 2.7	<0.0001	<0.0001	0.56
Flow velocity propagation	2.37 ± 1.9	1.8 ± 0.7	2.2 ± 0.98	1.29 ± 0.4	0.03	0.004	0.09

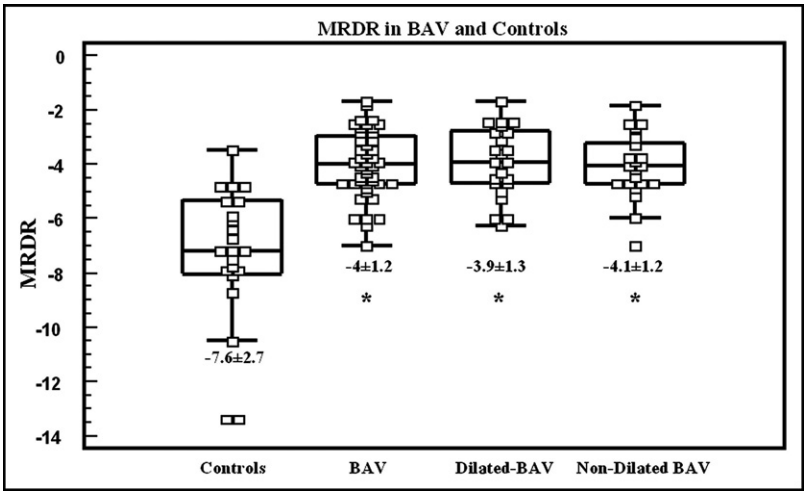

Figure 4. Box and whisker plot showing MRDR values in patients with BAV and controls. *Patients with BAV with and without ascending aorta dilation had greater MRDRs than did controls.

MRSD when evaluated separately; both were significantly lower than the MRSD in normal patients. The MRSD did not correlate with the systemic vascular resistance ($p = 0.79$). Similar results were found for MRDR. The patients with BAV had greater MRDR (greater values are less negative, indicating a slower rate) than the controls ($p < 0.0001$; Figure 5). No significant gender differences were found for MRDR in the controls (-7.2 ± 3.5 vs -7.9 ± 2.4, male vs female, $p = 0.47$) or in those with BAV (-3.7 ± 1.3 vs 4.3 ± 0.9, male vs female, $p = 0.18$). The MRDR was significantly greater in both BAV groups (nondilated and dilated) than in the healthy subjects. As with the MRSD, the MRDR did not correlate with systemic vascular resistance ($p = 0.98$). Receiver operating characteristic curve analysis

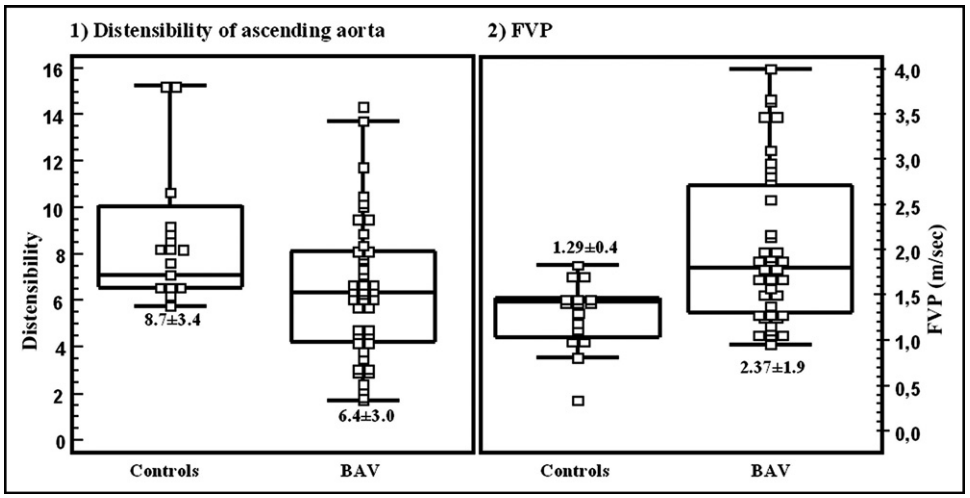

Figure 5. Box and whisker plots. *(1)* Distensibility of ascending aorta lower in patients with BAV than in controls. *(2)* Flow velocity propagation greater in patients with BAV than in controls.

Table 3
Receiver operating characteristic analysis comparisons

Variable	AUC	Standard Error	95% CI	p Value	
				MRSD	MRDR
Predicting BAV					
Ascending aorta distensibility	0.69	0.10	0.51–0.83	0.002	0.01
Flow velocity propagation	0.71	0.09	0.54–0.89	0.001	0.006
Maximal systolic distension rate	0.996	0.014	0.90–1	—	0.15
Maximal diastolic recoil rate	0.95	0.032	0.83–0.99	0.15	—
Predicting nondilated BAV					
Ascending aorta distensibility	0.67	0.11	0.45–0.85	0.004	0.006
Flow velocity propagation	0.66	0.11	0.45–0.84	0.003	0.007
Maximal systolic distension rate	1	0.0	0.86–1	—	0.29
Maximal diastolic recoil rate	0.97	0.025	0.82–1	0.29	—
Predicting dilated BAV					
Ascending aorta distensibility	0.71	0.11	0.48–0.87	0.01	0.07
Flow velocity propagation	0.78	0.11	0.56–0.92	0.04	0.1
Maximal systolic distension rate	0.992	0.01	0.84–1	—	0.15
Maximal diastolic recoil rate	0.935	0.05	0.75–0.99	0.16	—

showed that MRSD values >6.6 distinguished between those with BAV and the controls, with 100% sensitivity and 95% specificity. MRDRs with a cutoff of −4.8 identified patients with BAV, with 71.4% sensitivity and 90.9% specificity. Ascending aorta distensibility distinguished between the patients with BAV and controls (cutoff of 5.7), with 98% specificity and 40% sensitivity. Finally, flow wave propagation showed 71.8% specificity and 69.7% sensitivity. The receiver operating characteristic curves for MRSD and MRDR had a significantly greater area under the curve (AUC) compared to the ascending and descending aorta distensibility and flow wave velocity propagation (Table 3).

Good interobserver correlation was shown for MRSD (average difference 3.9 ± 18% of MRSD, coefficient 0.95) and MRDR (average difference 5.2 ± 8% of MRDR, coefficient 0.93) between the 2 observers.

Discussion

In the present study, we tested 2 new, noninvasive indexes of aortic wall elastic properties: MRSD and MRDR. MRSD is an expression of vessel distension during systole, and MRDR evaluates diastolic recoil. We found significant differences in MRSD and MRDR in patients with BAV and healthy controls. The patients with BAV had significantly lower MRSD and significantly greater MRDR than the controls, suggesting slower aortic wall distension during systole and slower recoil during diastole. However, the present study found that patients with BAV had significantly lower aortic distensibility and faster flow wave propagation velocities than the controls, confirming the findings from a previous report.[2] We selected patients with BAV with functionally normal or nearly normal valves in an attempt to exclude any confounding factors deriving from flow disturbances. In agreement with previous reports,[3] the aortic diameters of the patients with BAV in our study were significantly greater than those of normal age- and gender-matched controls. However, MRSD and MRDR results were significantly different from those of the controls, independent of aortic dilation, showing that these new indexes are not influenced by the aortic diameter. Bonderman et al[4]

recently demonstrated a massive focal apoptosis in the medial layers of patients with BAV, independent of aortic dilation. In the control patients, however, apoptosis was present in the aortic specimens of only those patients with a dilated aorta.[4] In contrast to MRSD and MRDR, distensibility is influenced by the degree of aortic dilation, particularly aortic diastolic size, as demonstrated by Jeremy et al.[5] Thus, the distensibility could be underestimated in patients with a normal aortic diameter, particularly in younger patients. Moreover, aortic dissection occurs at an earlier age in patients with BAV than in those with trileaflet aortic valve, and it is also linked to abnormalities of the biomechanical properties of the aortic wall.[6–8] Aortic dilation in BAV was demonstrated to be secondary to cystic medial necrosis caused by matrix disruption and smooth cells loss, similar to that found in patients with Marfan syndrome and in the fibrillin-1-deficient aorta model.[9,10] Specifically, altered or deficient fibrillin results in impaired elasticity of the vascular wall.[11] It has also been theorized that the abnormal elastic properties, dilation, and fragmentation of elastic components within the aortic walls of patients with BAV could be associated with increased expression of matrix-degrading proteins.[12] In fact, matrix metalloproteinase activity is increased in specimens obtained from BAV ascending aortic aneurysms.[13] MRSD and MRDR are expressions of the systolic and diastolic aortic strain rate. During the ejection phase of left ventricular contraction, the aorta is distended by blood flowing from the left ventricle, and kinetic energy from the left ventricle is transformed into potential energy stored in the aortic wall. During aortic wall recoil, this potential energy is converted to kinetic energy, favoring the diastolic flow in the peripheral vessel. Slow MRSD and MRDR velocities in the patients with BAV could reveal the impaired elasticity of aortic wall: a lower MRSD value means that the kinetic energy of systolic ejection is transformed more slowly into potential energy; a slower MRDR reflects a delayed conversion of potential energy to kinetic energy. The imbalance between the uptake and release of energy by the aortic wall, due to impaired elasticity, could slow the centripetal acceleration of the aortic wall, increasing aortic wall stress and progressively leading to dilation of the aortic wall. Our results have demonstrated that the aortic strain velocities in BAV were decreased without a significant overlapping of the MRSD values between those with BAV and the controls. Furthermore, all the patients with BAV had MRSD values of <6.6, confirming the presence of atypical aortic wall biomechanical properties in those with BAV. In contrast, a considerable overlapping of distensibility values was found between those with BAV and the controls in the present study (Figure 5), just as in previous reports.[2] When patients with extremely low distensibility values were excluded, most of our population with BAV showed intermediate values similar to those of the normal patients. A large variation in aortic distensibility was previously reported[14]; it could be partially explained because distensibility is influenced by aortic dimensions and systemic pressure. Furthermore, because the aortic biophysical properties change with increasing pressure owing to recruitment of the collagen fibers, the distensibility reflects only the mean of aortic elastic behavior in the physiologic pressure range.[15] Flow wave velocity propagation has been proposed as a valuable tool for evaluating the elastic properties of the aortic wall. Both patients with BAV and those with Marfan syndrome had significantly faster flow propagation than the controls.[16] The reduced aortic wall elasticity in those with BAV could be the cause of the increased flow velocity in the thoracic aorta. However, flow wave velocity propagation could be influenced by the hemodynamic status of the patients, potentially increasing under hyperdynamic conditions and decreasing in patients with left ventricular dysfunction or aortic disease. Hemodynamic perturbation in aortic coarctation, often associated with BAV in young patients, could alter the measurement of flow wave velocity propagation. Furthermore, normal variations in aortic arch anatomy imply great variations in the distance between the ascending and descending aorta, which would influence the flow wave velocity propagation measurements. A receiver operating characteristic curve comparison showed that MRSD was the better parameter for differentiating the aortic wall properties of BAV from those of healthy subjects. These results suggest that it is reasonable to consider these 2 new indexes as potential tools for evaluating the elastic properties of the aortic wall in BAV. Additional studies are needed to confirm these results.

The study limitations should be mentioned. First, the measurement of aortic distensibility implies the measurement of arterial systemic pressure. As in previous studies, the present study assessed the systemic arterial pressure using the brachial cuff pressure, instead of an invasively positioned catheter, because the patients enrolled were very young and asymptomatic. It has been shown that the pulse pressure measured at the brachial artery slightly overestimates the central pulse pressure.[17] Therefore, the peripheral brachial pressure might underestimate aortic distensibility, especially in younger subjects. However, other investigators have shown an excellent correlation between the calculated aortic distensibility using both invasive and noninvasive methods.[18] The new indexes we have proposed in the present study, the MRSD and MRDR, are both independent of the central aortic pressure. Therefore, this could encourage the clinical use of MRSD and MRDR.

1. 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;25:1146–1152.
2. Grotenhuis HB, Ottenkamp J, Westenberg JJ, Bax JJ, Kroft LJ, de Roos A. Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. *J Am Coll Cardiol* 2007;49:1660–1665.
3. Pachulski RT, Winberg AL, Chan KL. Aortic aneurysm in patients with functionally normal or minimally stenotic bicuspid aortic valve. *Am J Cardiol* 1991;67:781–782.
4. Bonderman D, Gharehbaghi-Schell E, Wollenek G, Maurer G, Baumgartner H, Lang IM. Mechanisms underlying aortic dilatation in congenital aortic valve malformation. *Circulation* 1999;99:2138–2143.
5. Jeremy RW, Huang H, Hwa J, McCarron H, Hughes CF, Richards JG. Relation between age, arterial distensibility, and aortic dilatation in the Marfan syndrome. *Am J Cardiol* 1994;74:369–373.
6. Gore I. Dissecting aneurysm of the aorta in persons under forty years of age. *Arch Pathol* 1953;55:1–13.
7. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. *J Am Coll Cardiol* 1991; 17:712–716.
8. Ward C. Clinical significance of the bicuspid aortic valve. *Heart* 2000;83:81–85.

9. Fedak PW, de Sa MP, Verma S, Nili N, Kazemian P, Butany J, Strauss BH, Weisel RD, David TE. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. *J Thorac Cardiovasc Surg* 2003;126:797–806.
10. Nataatmadja M, West M, West J, Summers K, Walker P, Nagata M, Watanabe T. Abnormal extracellular matrix protein transport associated with increased apoptosis of vascular smooth muscle cells in Marfan syndrome and bicuspid aortic valve thoracic aortic aneurysm. *Circulation* 2003;108(suppl 1):II329–II334.
11. Pereira L, Lee SY, Gayraud B, Andrikopoulos K, Shapiro SD, Bunton T, Biery NJ, Dietz HC, Sakai LY, Ramirez F. Pathogenetic sequence for aneurysm revealed in mice underexpressing fibrillin-1. *Proc Natl Acad Sci U S A* 1999;96:3819–3823.
12. LeMaire SA, Wang X, Wilks JA, Carter SA, Wen S, Won T, Leonardelli D, Anand G, Conklin LD, Wang XL, Thompson RW, Coselli JS. Matrix metalloproteinases in ascending aortic aneuryms: bicuspid versus trileaflet aortic valves. *J Surg Res* 2005;123:40–48.
13. Boyum J, Fellinger EK, Schmoker JD, Trombley L, McPartland K, Ittleman FP, Howard AB. Matrix metalloproteinase activity in thoracic aortic aneurysms associated with bicuspid and tricuspid aortic valves. *J Thorac Cardiovasc Surg* 2004;127:686–691.
14. Yin FCP, Brin KP, Ting CT, Pyeritz RE. Arterial hemodynamic indexes in Marfan's syndrome. *Circulation* 1989;79:854–862.
15. Savolainen A, Keto P, Hekali P, Nisula L, Kaitila I, Viitasalo M, Poutanen VP, Standertskjöld-Nordenstam GC, Kupari M. Aortic distensibility in children with the Marfan syndrome. *Am J Cardiol* 1991; 70:691–693.
16. Hirata K, Triposkiadis F, Sparks E, Bowen J, Wooley CF, Boudoulas H. The Marfan syndrome: abnormal elastic properties. *J Am Coll Cardiol* 1991;18:57–63.
17. Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London: Lea & Febiger; 1990:398–420.
18. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur Heart J* 1990;11:990–996.