Ascending Aorta and Myocardial Mechanics in Patients with “Clinically Normal” Bicuspid Aortic Valve

Insights from Cardiovascular Magnetic Resonance Tissue-Tracking Imaging

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Summary

Aortic valve dysfunction and aortic wall changes are well-known complications of bicuspid aortic valve (BAV) disease. The aim of the present study was to investigate whether a remodeling process of the left ventricle (LV) is present in patients with isolated BAV. Twenty-two consecutive patients (39 ± 15 years, 9 males) with clinically normal BAV and 18 age- and gender-matched control subjects (37 ± 10 years, 9 males) were included. Cardiovascular magnetic resonance (CMR) imaging was performed to evaluate LV function, aortic valve morphology, aortic orifice area, and ascending aorta (AA) dimensions. Tissue-tracking analysis was applied to assess LV systolic and diastolic myocardial mechanics in the longitudinal, circumferential, and radial direction and AA circumferential strain (CS). No significant difference was observed between BAV and controls regarding LV ejection fraction and LV mass index. Tissue-tracking analysis demonstrated that BAV patients had significantly impaired LV systolic and diastolic myocardial mechanics. BAV patients had also significantly lower AA CS compared with controls. At multivariate analysis, the presence of BAV was the only variable significantly and independently related to the impaired AA and LV systolic myocardial mechanics. In conclusion, LV myocardial deformation properties are impaired among BAV patients. The impairment of LV systolic mechanics observed in BAV patients appears to be related only to the congenital abnormality of the aortic valve itself.

(Int Heart J 2018; 59: 741-749)

Key words: Aortic wall, Deformation, Left ventricle, Magnetic resonance imaging, Myocardium, Strain

Aortic valve dysfunction and aortic wall changes are well-known complications of bicuspid aortic valve (BAV) disease and account for the increased incidence of cardiovascular morbidity and mortality in this population.¹⁻⁴⁾ While a genetic etiology of BAV disease is widely accepted,⁵⁾ hemodynamic, aortic tissue, and mechanical abnormalities are increasingly recognized as pathogenically responsible for disease progression and have significant implications for patient-tailored risk stratification and surgical planning.^{6,7)} Previous studies have indeed demonstrated regions of wall shear stress overload in BAV leaflets compared with tricuspid aortic valve leaflets,⁸⁾ altered blood flow with high wall shear stress along the aortic wall even in the presence of normally functioning BAVs and non-dilated ascending aorta (AA),⁹⁻¹¹⁾ extracellular matrix dysregulation and elastic fiber degeneration in AA regions exposed to increased wall shear stress,¹²⁾ and abnormal aortic elasticity that is independent from aortic valve dysfunction and AA dilatation.¹³⁾

Whether a remodeling process of the left ventricle (LV) is also independently present in BAV patients is still debated; studies to date are controversial concerning the LV myocardial deformation properties in patients with BAV disease and normal ejection fraction (EF), with results being flawed by the inclusion of patients with aortic valve dysfunction.¹⁴⁻¹⁶⁾ A better understanding of myocardial mechanics behavior in patients with “clinically normal” BAV (i.e., without aortic valve dysfunction and AA dilatation) appears to be clinically relevant because their intrinsic impairment could accelerate the development of LV dysfunction and heart failure once significant aortic valve dysfunction occurs in this population.^{2,17)} Hence, the aim of the present study was to investigate the LV myocardial mechanics in patients with isolated “clinically normal” BAV and to determine their relation with BAV morphology and AA dimensions and deformation properties. For this purpose, cardiovascular magnetic resonance (CMR) imaging was used to assess aortic valve morphol-

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Received for publication April 20, 2017. Revised and accepted September 12, 2017.

Released in advance online on J-STAGE June 6, 2018.

doi: 10.1536/ihj.17-230

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ogy and aortic root and AA dimensions, whereas CMR tissue-tracking imaging was used to derive AA and LV strain data directly from cine images.

Methods

Study population: From January 2015 to June 2016, a total of 22 consecutive asymptomatic BAV patients were diagnosed as having a “clinically normal” BAV, according to trans-thoracic echocardiography and CMR imaging results and were therefore included in the present study. “Clinically normal BAV” was defined according to the following criteria: 1) aortic valve velocity ≤ 1.5 m/second and 2) no more than trivial aortic regurgitation at trans-thoracic echocardiography, and 3) ascending aorta absolute diameter < 4.0 cm (or indexed diameter < 2.2 cm/m²) at any level at CMR imaging. All included patients were free of arterial hypertension, diabetes, cardiomyopathy, impaired LV systolic function (i.e., LVEF $< 55\%$), known coronary artery disease, genetic cardiovascular disease (including Marfan syndrome), and aortic coarctation. For comparison purpose, 18 volunteers matched for age and gender and without any of the previously listed exclusion criteria, served as a control group.

CMR imaging protocol: CMR studies were performed using a 1.5-Tesla scanner (Siemens Aera, Erlangen, Germany) with a cardiac-phased array receiver surface coil and electrocardiographic (ECG) gating. Vertical and horizontal long-axis slices, LV inflow-outflow slice, and a stack of contiguous short-axis slices from the atrioventricular ring to the apex were acquired using a cine steady-state free precession (SSFP) pulse sequence for the assessment of LV volumes and function and myocardial deformation (slice thickness = 7 mm, 3 mm interslice gap, TR/TE = 3.5/1.2 ms, temporal resolution = 30 frames per RR interval). To assess aortic valve morphology and aortic orifice area, cine SSFP imaging was performed carefully positioning multiple parallel thin image slices orthogonally to the aortic root at the level of the aortic valve leaflets, as previously described.¹⁸⁾ To assess AA dimensions and deformation properties, sagittal-oblique cine SSFP images parallel to the major aortic axis and cross-sectional cine SSFP images of the AA at the level of the pulmonary artery bifurcation were acquired.

CMR data analysis: All CMR analyses were performed offline by an experienced investigator using CMR⁴² (Circle Cardiovascular Imaging, Calgary, Canada) except angle measurements and assessment of the length of the proximal aorta (see below), for which Osirix software (Pixmeo SARL, Bernex, Switzerland) was used. LV volumes and function and LV mass were measured using the standard volumetric technique from the cine short-axis images; volume and mass measurements were indexed to body surface area. The angulation between the LV inflow long axis and the line through the center of the aorta (LV/Aorta angle), which has been hypothesized to be related to the development of aortopathy in BAV patients,¹⁹⁾ was measured in the LV outflow view. Aortic orifice area was assessed using the planimetry method, and BAV leaflets morphology was classified according to the type of leaflet fusion, as described by Schaefer, *et al.*,²⁰⁾ type 1 indicates fusion

between the right and left coronary cusp, type 2 indicates fusion between the right and non-coronary cusp, whereas type 3 indicates fusion between the left and non-coronary cusp. Aortic diameters were measured at the level of sinuses of Valsalva, sinotubular junction, and ascending aorta at the level of the pulmonary artery bifurcation using the inner edge to inner edge technique at end-diastole; all aortic diameters were indexed for body surface area to account for the wide range of body size. The length of the proximal aorta was measured as the distance (indexed for body surface area) from the level of aortic annulus to the origin of the brachiocephalic trunk, as previously described.²¹⁾

Tissue-tracking analysis: The assessment of myocardial and AA mechanics was performed using a dedicated CMR tissue-tracking software (Tissue Tracking module, CVI⁴²⁾, Circle Cardiovascular Imaging, Calgary, Canada).

Myocardial mechanics Following uploading of the cine basal and apical short-axis images, the brightness was optimized to ensure optimal endocardial/blood pool discrimination; the mitral valve annular plane and the position of LV apex were manually identified at end-diastole. The LV endocardial and epicardial borders (excluding papillary muscles and trabeculae) were then manually traced on the end-diastolic frame on long-axis and short-axis cine images; the software automatically propagated the contour and followed its features throughout the remainder of the cardiac cycle. Adjustment of contour tracking was done after visual assessment during cine loop playback to ensure that the LV segments were tracked appropriately. As the LV myocardial architecture consists of longitudinally and circumferentially orientated fibers located predominantly in the epicardium/endocardium and mid-wall, respectively, longitudinal, circumferential, and radial strain are reflective of subendocardial, mid-wall, and transmural myocardial functions, respectively.²²⁾ Peak systolic global longitudinal strain (GLS) and global longitudinal strain rate during early filling (eGLSr) were derived from the long-axis cine images analysis, whereas peak systolic global circumferential strain (GCS), global circumferential strain rate during early filling (eGCSr), peak systolic global radial strain (GRS), and global radial strain rate during early filling (eGRSr) were derived from the short-axis cine images analysis (Figure 1).

AA mechanic The same approach was applied to the cross-sectional cine SSFP image of the AA acquired at the level of the pulmonary artery bifurcation to measure the AA peak systolic circumferential strain (CS). Before processing, a cine loop playback was previewed to visually confirm the adequate tracking of the aortic wall throughout the cardiac cycle. If tracking of the aortic wall was deemed as unsatisfactory, a manual adjustment was performed. Figure 2 shows examples of AA CS in a control subject and a BAV patient.

A single experienced investigator (GN) performed the tissue-tracking analysis. In 15 randomly selected subjects, measures were repeated by both this investigator and a second investigator (JM) to assess inter- and intra-observer agreement for measures.

Statistical analysis: Continuous variables are expressed as mean and standard deviation (SD). Categorical data are

Figure 1. Color-coded left ventricular (LV) peak systolic longitudinal and circumferential strain on a 4-chamber steady-state free precession image (A) and on the mid-section of a short-axis view (B) using tissue-tracking software. The LV global longitudinal (C), circumferential (D), and radial (E) strain curves as well as the LV global longitudinal (F), circumferential (G), and radial (H) strain rate curves are also shown. *S* in the strain curves indicates the peak systolic strain, whereas *e* in the strain rate curves indicates the strain rate during early filling.

Figure 2. Color-coded ascending aorta (AA) peak systolic circumferential strain (CS) in a control subject (A, B) and a patient with bicuspid aortic valve (C, D). Peak AA CS in the control subject was 15.9%, whereas peak AA CS in the patient with bicuspid aortic valve was 6.3%.

presented as absolute numbers and percentages. Differences in continuous variables between groups were assessed with the Student's *t* test or Mann-Whitney *U* test, where appropriate. Chi-square or Fisher's exact test,

where appropriate, was computed to assess differences in categorical variables. Linear regression analyses were performed to evaluate the relation between AA and myocardial mechanics. Univariate and multivariate linear regres-

Table I. Demographic, Clinical, and Baseline Echocardiographic Characteristics of the Study Population

	Control subjects (n = 18)	BAV patients (n = 22)	P
Age (years)	37 ± 10	39 ± 15	0.60
Male gender	9 (50%)	9 (41%)	0.75
Body surface area (m ²)	1.82 ± 0.20	1.93 ± 0.29	0.19
Heart rate (beats per minute)	75 ± 19	72 ± 14	0.69
Left ventricular end-diastolic diameter (mm)	47.0 ± 2.5	49.0 ± 5.1	0.12
Left ventricular end-systolic diameter (mm)	30.2 ± 2.5	31.1 ± 5.2	0.49
Interventricular septum thickness (mm)	8.8 ± 1.1	8.9 ± 1.5	0.82
Posterior wall thickness (mm)	8.8 ± 0.9	9.0 ± 1.4	0.55
Left ventricular end-diastolic volume (mL)	96 ± 6	94 ± 11	0.46
Left ventricular end-systolic volume (mL)	35 ± 4	34 ± 7	0.42
Left ventricular ejection fraction (%)	63 ± 3	64 ± 6	0.60

Data are expressed as mean ± standard deviation or median (interquartile range) and n (%).

Table II. Proximal Aorta Dimensions, Aortic Valve, and Left Ventricular Parameters as Assessed by CMR Imaging in the Control Subjects and BAV Patients

	Control subjects (n = 18)	BAV patients (n = 22)	P
Sinus of Valsalva (mm/m ²)	16.3 ± 1.8	16.9 ± 3.0	0.40
Sino-tubular junction (mm/m ²)	13.3 ± 1.5	14.3 ± 2.4	0.14
Ascending aorta (mm/m ²)	14.1 ± 1.6	15.2 ± 3.3	0.17
Aortic orifice area (cm ² /m ²)	2.1 ± 0.43	1.97 ± 0.41	0.47
BAV morphology			
type 1	-	15 (68%)	
type 2	-	7 (32%)	
Left ventricular-aorta angle (°)	46.7 ± 8.0	55.3 ± 8.1	0.002
Proximal aortic length, mm/m ²	42.2 ± 6.1	43.0 ± 5.2	0.66
Left ventricular end-diastolic volume (mL/m ²)	77.5 ± 10.7	75.2 ± 17.3	0.62
Left ventricular end-systolic volume (mL/m ²)	23.2 ± 5.7	21.5 ± 6.8	0.41
Left ventricular ejection fraction (%)	70.3 ± 6.3	71.3 ± 6.7	0.64
Left ventricular mass index (g/m ²)	41.5 ± 7.2	45.9 ± 12.0	0.17

Data are expressed as mean ± standard deviation or median (interquartile range) and n (%).

sion analyses (using the forward stepwise model selection procedure) were performed to determine the independent correlates of AA and LV mechanics; age and gender were entered into the multivariate model independently of their probability value by univariate analysis and were kept fixed throughout the stepwise selection procedure. Regarding the remaining variables, only those with a probability value < 0.10 by univariate analysis were entered as covariates in the multivariate model. Intra- and inter-observer reproducibility of AA and myocardial deformation parameters were assessed using the within-subject coefficient of variation, which provides a dimensionless measure of data dispersion, consequently allowing comparison between variables with different units or scales.²³⁾ Two-tailed tests were considered statistically significant at the 0.05 level. Statistical analysis was performed using the SPSS (SPSS 22; SPSS Inc., Chicago, IL) and MedCalc (MedCalc 15, Mariakerke, Belgium) software packages.

Results

Demographic, clinical, and baseline echocardiographic characteristics of the study population are summarized in Table I. By the study design, control subjects and BAV patients were well matched concerning age (37 ± 10 versus 39 ± 15 years; *P* = 0.60) and gender (9 males, 50% versus 9 males, 41%; *P* = 0.75). Aortic dimensions, aortic valve, and LV parameters as assessed by CMR imaging in the two groups are shown in Table II. No significant differences in AA dimensions, aortic orifice area, LV volumes, LVEF, and LV mass were observed between BAV patients and controls, whereas LV/Aorta angle was significantly larger in the BAV patients (*P* = 0.002). A total of 15 (68%) BAV patients presented type 1 leaflets morphology and 7 (32%) presented type 2 leaflets morphology; type 3 was not observed in any patient.

The tissue-tracking analysis was feasible in all patients. Intra- and inter-observer agreement for the measurements of LV myocardial and AA mechanics are shown in Table III. Of note, all strain measurements had good re-

Table III. Intra- and Inter-Observer Reproducibility of Left Ventricular Myocardial and Ascending Aorta Mechanics

	Intra-observer CV (%)	Intra-observer CV (%)
Left ventricular global longitudinal strain	1.7	2.6
Left ventricular global circumferential strain	1.6	2.7
Left ventricular global radial strain	2.4	3.5
Left ventricular global longitudinal strain rate during early filling	4.1	5.2
Left ventricular global circumferential strain rate during early filling	4.4	5.3
Left ventricular global radial strain rate during early filling	5.4	6.8
Ascending aorta circumferential strain	3.3	4.0

Figure 3. Ascending aorta circumferential strain (A), left ventricular myocardial strains in the three directions (longitudinal, B, circumferential, C, and radial, D) and left ventricular myocardial strain rates during early filling in the three directions (longitudinal, E, circumferential, F, and radial, G) in the control subjects and BAV patients. AA indicates ascending aorta; CS, circumferential strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; and LV, left ventricular.

producibility.

Myocardial and vascular mechanics: Of note, a significant impairment of LV systolic and diastolic myocardial mechanics in all the three vectors was observed among the BAV patients (LV GLS: $-19.0 \pm 2.1\%$ versus $-20.5 \pm 2.0\%$; $P = 0.026$; LV GCS: $-21.1 \pm 2.6\%$ versus $-23.1 \pm 2.5\%$; $P = 0.021$; LV GRS: $41.1 \pm 8.9\%$ versus $49.1 \pm 10.9\%$; $P = 0.015$; LV eGLSr: 0.92 ± 0.22 1/second versus 1.23 ± 0.22 1/second; $P < 0.001$; LV eGCSr: 1.22 ± 0.37 1/second versus 1.63 ± 0.40 1/second; $P = 0.002$; LV eGRSr: -2.52 ± 0.72 1/second versus -3.20 ± 0.86 1/second; $P = 0.010$. Figure 3). As expected, BAV patients had significantly lower AA CS compared with

control subjects ($10.7 \pm 5.4\%$ versus $18.0 \pm 5.6\%$; $P < 0.001$. Figure 3). No significant difference in AA and myocardial mechanics were observed between BAV patients with type 1 versus type 2 leaflets morphology (AA CS: $9.4 \pm 4.2\%$ versus $13.5 \pm 6.9\%$; $P = 0.10$; LV GLS: $-19.0 \pm 2.0\%$ versus $-19.2 \pm 2.4\%$; $P = 0.86$; LV GCS: $-20.9 \pm 2.2\%$ versus $-21.6 \pm 3.7\%$; $P = 0.60$; LV GRS: $40.3 \pm 7.9\%$ versus $42.9 \pm 11.2\%$; $P = 0.53$; LV eGLSr: 0.96 ± 0.22 1/second versus 0.83 ± 0.22 1/second; $P = 0.18$; LV eGCSr: 1.28 ± 0.40 1/second versus 1.08 ± 0.24 1/second; $P = 0.23$; LV eGRSr: -2.55 ± 0.78 1/second versus -2.44 ± 0.64 1/second; $P = 0.75$).

As shown in Figure 4, a significant relationship was

Figure 4. Relation between ascending aorta (AA) circumferential strain (CS) and left ventricular (LV) global longitudinal strain (GLS; **A**), global circumferential strain (GCS; **B**), global radial strain (GRS; **C**), global longitudinal strain rate during early filling (eGLSr; **D**), global circumferential strain rate during early filling (eGCSr; **E**), and global radial strain rate during early filling (eGRSr; **F**) in the study population. White circles: control subjects. Black circles: BAV patients.

Table IV. Correlates of Ascending Aorta Circumferential Strain and Left Ventricular Systolic and Diastolic Myocardial Mechanics

	AA CS		LV GLS		LV GCS		LV GRS		LV eGLSr		LV eGCSr		LV eGRSr	
	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Age (years)	0.18	0.26	-0.15	0.37	-0.21	0.20	0.15	0.35	-0.42	0.007	-0.37	0.018	0.24	0.13
Male gender	-0.028	0.86	0.12	0.45	0.14	0.38	-0.13	0.41	-0.22	0.17	-0.19	0.24	-0.020	0.90
BAV versus controls	-0.562	<0.001	0.35	0.026	0.37	0.021	-0.38	0.015	-0.57	<0.001	-0.48	0.002	0.41	0.010
Ascending aorta diameter (mm/m ²)	0.14	0.39	-0.046	0.78	-0.23	0.15	0.17	0.29	-0.28	0.083	-0.075	0.65	0.034	0.84
Aortic orifice area (cm ² /m ²)	0.18	0.26	0.016	0.92	0.002	0.99	-0.010	0.95	-0.009	0.96	0.042	0.80	-0.13	0.43
Left ventricular-aorta angle (°)	-0.20	0.22	0.20	0.21	0.25	0.12	-0.27	0.096	-0.57	<0.001	-0.67	<0.001	0.47	0.002
AA CS (%)	-	-	-0.37	0.020	-0.33	0.036	0.29	0.074	0.36	0.022	0.35	0.029	-0.26	0.11

observed between systolic and diastolic LV longitudinal and circumferential mechanics and AA mechanics (LV GLS: $\beta = -0.37$, $P = 0.020$; LV GCS: $\beta = -0.33$, $P = 0.036$; LV GRS: $\beta = 0.29$, $P = 0.074$; LV eGLSr: $\beta = 0.36$, $P = 0.022$; LV eGCSr: $\beta = 0.35$, $P = 0.029$; LV eGRSr: $\beta = -0.26$, $P = 0.11$). Table IV shows the results of the univariate linear regression analysis aiming to identify significant correlates of AA and LV myocardial mechanics. At multivariate analysis, the presence of BAV was the only variable significantly and independently related to AA CS ($\beta = -0.59$, $P < 0.001$), LV GLS ($\beta = 0.38$, $P = 0.018$), LV GCS ($\beta = 0.40$, $P = 0.011$), and LV GRS ($\beta = -0.41$, $P = 0.010$). Age ($\beta = -0.41$, $P = 0.001$), male gender ($\beta = -0.32$, $P = 0.006$), and the presence of BAV ($\beta = -0.57$, $P < 0.001$) were significantly and independently related to LV eGLSr, whereas the presence of BAV and LV-Aorta angle were significantly and independently related to LV eGCSr ($\beta = -0.28$, $P = 0.027$ and $\beta = -0.52$, $P < 0.001$) and LV eGRSr ($\beta = 0.26$, $P = 0.030$ and $\beta = 0.45$, $P = 0.008$).

Discussion

The results of the present study can be summarized as follows: 1) AA mechanics are significantly impaired among patients with “clinically normal” BAV; 2) patients with “clinically normal” BAV have a significant impairment of LV systolic and diastolic myocardial mechanics, and finally 3) the impairment of LV systolic mechanics observed in BAV patients appears to be independently related to the congenital abnormality of aortic valve itself. These findings are hypothesis-generating and could explain, at least in part, the demonstrated premature clinical heart failure in BAV disease.²⁾

BAV disease is known to be frequently associated with dilatation of the aorta and an increased risk of aortic dissection.¹³⁾ Subclinical AA remodeling processes have been described in these patients using a number of imaging modalities; previous studies, using M-mode echocardiography, have indeed demonstrated abnormal aortic elasticity in BAV patients, despite the presence of normally

functioning BAV and non-dilated AA.^{13,14,24} These abnormalities are explained by the extracellular matrix dysregulation and elastic fiber degeneration determined by the altered blood flow and high wall shear stress along the aortic wall of BAV patients and commonly precede the development of aortic dilatation.¹²

Trans-thoracic echocardiography, while being the most commonly used noninvasive modality, presents significant inherent limitations in the assessment of the AA. These include the frequent inability to visualize the entire vessel, and the lack of three-dimensional morphological information; these limitations hold true also for the most recently introduced ultrasound tissue-tracking imaging, which can assess vascular deformation and strain.^{25,26} In contrast, CMR imaging can provide full three-dimensional visualization of the aorta and has also been established as an excellent method for the accurate evaluation of aortic valve morphology and aortic root and AA dimensions.²⁷ Furthermore, cross-sectional cine SSFP images of the aorta can be used for reliable assessment of vascular mechanics.^{28,29} Using this technique, Grotenhuis, *et al.* observed reduced aortic elasticity in patients with nonstenotic BAVs,²⁸ whereas Aquaro and colleagues found a significant impairment of systolic aortic distension and diastolic recoil, regardless of the aortic dimension;²⁹ importantly, the approach used to determine the vascular mechanics demonstrated good inter-observer agreement.²⁹ In the present study, a novel CMR tissue-tracking imaging technique was applied to investigate the AA mechanics; we demonstrated this approach to be feasible and reproducible and confirmed the significant impairment of AA strain in “clinically normal” BAV patients.

Whether a concomitant intrinsic impairment of LV mechanics is also present in BAV patients is still debated, with conflicting results provided by previous echocardiographic studies.¹⁴⁻¹⁶ Zhang and colleagues did not observe any significant difference in LV strain between 8 patients with normally functioning BAV and 20 healthy volunteers.¹⁶ Conversely, Santarpia, *et al.*¹⁴ and Kurt, *et al.*¹⁵ reported impaired LV strains in BAV patients. However, patients with mildly dysfunctional BAVs were included in the last two studies, potentially introducing a bias; it is indeed known that subclinical myocardial dysfunction starts early in the aortic valve disease process (especially in the setting of aortic stenosis) with reduced function of subendocardial fibers.³⁰ In the current study, CMR tissue-tracking imaging, which allows obtaining LV strain data directly from cine images with good accuracy and reproducibility and overcomes important limitations of LV strain assessment by speckle-tracking echocardiography (e.g., acquisition angle, acoustic window, and operator dependence),³¹ was for the first time used to investigate the LV mechanics in patients with “clinically normal” BAV (i.e., without aortic stenosis or regurgitation and without associated AA dilatation). A significant impairment of systolic and diastolic myocardial deformation in all the three vectors (longitudinal, circumferential, and radial) was observed. Importantly, the observed impairment of LV systolic mechanics was independent of potentially confounding factors, including AA dimension and strain, suggesting that BAV disease may be not only a disease of the aortic

valve and of the aortic wall but inherently of the LV myocardium, as well. Previous studies have established the genetic etiology of BAV disease;⁵ therefore, one hypothetical explanation for the subclinical myocardial dysfunction in BAV patients could be related to the underlying genetic disorder. For instance, mutations of Notch1 gene (a signaling transmembrane receptor) have been reported in BAV patients;⁵ recent data indicate that Notch1 signaling also plays a critical role in cardioprotection.³² The increased plasma concentration of matrix metalloprotein-2 observed in BAV patients may explain our observations as well; matrix metalloprotein-2 has been indeed documented not only in tissue excised from the proximal aortas of BAV patients but also in the pulmonary trunk, and raised plasmatic levels have been reported as well, indicating a more widespread pathology.³³⁻³⁶ Interestingly, an association between circulating levels of matrix metalloprotein-2 and cardiac dysfunction has been demonstrated by clinical studies in other scenarios (including hypertrophic cardiomyopathy and ischemic heart disease),^{37,38} and experimental studies have demonstrated that matrix metalloprotein-2 is a direct determinant of the development of LV contractile impairment.³⁹ Because of the lack of follow-up data, the clinical significance and implications of these findings are still unknown at this time. It is conceivable that the intrinsic impairment of LV contractility may accelerate the ominous LV remodeling pathways occurring after the development of significant aortic valve dysfunction, partially explaining the observed premature occurrence of congestive heart failure in BAV patients compared with the general population.^{2,17}

This study has some limitations that should be acknowledged. First, the study population was relatively small; consequently, multivariate analyses were exploratory, and their results need to be confirmed by further studies with larger sample size. Second, four-dimensional flow CMR, which has recently demonstrated altered AA hemodynamics in patients with normally functioning BAVs and non-dilated AA,^{10,11} was not part of the study protocol; consequently, no information can be provided about the relationship between AA hemodynamics and vascular and myocardial mechanics. Third, T1 mapping, which may allow detection of extracellular volume expansion because of interstitial fibrosis,⁴⁰ was not performed; further studies are therefore required to determine the value of this novel CMR technique in BAV patients. Fourth, clinical follow-up data were not available; consequently, no information can be provided about the prognostic role of AA and LV strain in BAV disease. To this end, larger studies with long-term follow-up are necessary.

Disclosures

Conflicts of interest: The authors report no relationships that could be construed as a conflict of interest.

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