FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Aortic Strain in Bicuspid Aortic Valve: an analysis

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE CARDIOLOGIA

Trabalho realizado sob a orientação de:

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NOVEMBRO/2020

Aortic strain in bicuspid aortic valve: an analysis

Análise de strain aórtico em bicuspidia aórtica

Trabalho final do 6ºano do Mestrado Integrado em Medicina com vista à atribuição do grau de Mestre

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ABSTRACT

Introduction: Bicuspid aortic valve (BAV) is frequently related to aortic valve disease and aortopathy and it is usually monitored by transthoracic echocardiography and computed tomography (CT) angiography. However, early markers of disease progression are not currently available. Speckle-tracking echocardiography (STE) has shown consistent results among other cardiac pathologies. The present study evaluated STE aortic and left ventricle (LV) strain prognostic value, their discriminative power and their correlation with the degree of valvular regurgitation.

Methods: We retrospectively followed forty-eight adult patients with BAV and twenty gender and age matched controls for a median period of approximately twenty months, all with LV ejection fraction > 50% and without wall-motion abnormalities or poor acoustic window. We measured LV and aortic classic and STE parameters and we analysed their statistically significant differences, as well as their discriminative power of BAV presence. Hereinafter, we assessed their correlation with the primary cardiac outcome - aortic valve replacement (AVR) - through a COX regression analysis. Finally, our population with BAV was divided according to their severity of aortic regurgitation (AR) in none, mild, moderate or severe, and we evaluated: a) their echocardiographic parameters' differences throughout the disease; and b) which values predicted the existence of at least moderate AR.

Results: In our sample, values of LV dimensions and aortic diameter were higher in BAV population. Regarding their mechanics, LV global longitudinal strain (GLS) was impaired ($p<0.001$) and aortic global circumferential strain (GCS) did not differ among the two groups. Aortic GLS was significantly increased ($p=0.027$) and was a reliable discriminator of BAV presence, though aortic diameter was better (area under the curve = 0.92). In BAV patients with AR, aortic GCS decreased with the increment of severity ($p=0.004$) and severe AR had an exponentially augmented aortic GLS (45.2 ± 32.3%). Aortic valve replacement was the only outcome observed and its only predictor was LV end-diastolic volume (indexed).

Discussion: BAV patients had impaired LV contraction, despite having preserved LV ejection fraction. Our population had pronounced aortic dilatation, which caused a distortion in strain calculation, with high values of aortic GLS. Increasing severity of AR caused a reduction in aortic GCS, partly reflecting its significant vascular wall impairment throughout the disease.

Conclusion: STE aortic strain was not a reliable predictor of surgery in BAV patients.

KEYWORDS

Bicuspid Aortic Valve | Speckle-Tracking Echocardiography | Strain | Aortic Valve Insufficiency | Prognosis

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital heart disease[1–4] and it is present at birth in approximately 1-2% of the global population.[5,6] It has a male predominance of 3:1[7] and it is widely accepted to occur due to genetic anomalies[8] (mainly directly or indirectly related to NOTCH pathway[9]) that lead to an abnormal valvulogenesis during embryonic development.[7,10] BAV is also associated with other anomalies, such as coarctation of the aorta (25%-85%), Turner syndrome (10-34%), interrupted aortic arch (27%)[11] and hypoplastic left heart syndrome.[7] There are 3 types of BAV disease: type 1 refers to a right-left cusps fusion (>70% of the cases[6]), type 2 to a fusion of the right and non-coronary cusps, and type 3 to a fusion of the left and non-coronary cusps.[1,2,8] The site of fusion can have a prognostic implication since type 1 is more related with aortic stenosis and type 2 with earlier disease.[12] It can also be categorized in Sievers 0-2 according to the number of raphes present in the fused cusp.[11]

Although it is usually considered a benign disease,[13] with none or mild symptoms, its clinical presentation may be very variable, ranging from asymptomatic elderly patients to severe aortic stenosis in children (only 2%).[14] A large proportion experiences related complications, and at earlier ages, when compared to the normal tricuspid aortic valve population.[15] These include aortic stenosis, aortic regurgitation (AR), infective endocarditis, aortopathy, heart failure and cardiac surgery.[3,7,13] Aortic stenosis is the most common complication associated with BAV[11] and, as Rodrigues *et al*. described, it usually emerges 5-10 years sooner than in the healthy population.[1] This manifests because, in patients with BAV, there is a stress overload on both leaflets, more precisely on the site of fusion, which, therefore, makes it prone to accelerated degeneration of the valve.[5] Grotenhuis *et al.* also hypothesized that the reduced elasticity of the aortic root present in patients with BAV also increases leaflets' stress.[16] Furthermore, some authors[2,5,15] consider BAV a chronic stenotic valve since its opening is restricted *per se*. This causes turbulent flow through the valve, with irregularities in its opening-closure mechanism, which predisposes to fibrosis and calcification.[15] AR is usually secondary to infective endocarditis, aortic root dilatation, or coarctation of the aorta and is present in about 7-20% of the cases.[11] Aortopathy is also common among this population, some authors even suggesting that BAV is as much an aortic disease as it is a valve disease.[17] These patients have, indeed, a higher risk of aortic dilatation (usually at mid-ascending aorta[18]), dissection (8 times higher[19]) and aneurysm formation.[1,8,10] Two main theories explain this finding: genetic and hemodynamic. The first one postulates that there is a common developmental defect involving both the aortic valve and the aortic wall, leading to cystic media necrosis,[20] whilst the second posits that the altered hemodynamic forces on the aortic wall, produced by the eccentric flow through the morphologically stenotic valve, are the cause of the vascular disorder.[2,17] Although 50-70% of patients develop ascending aorta aneurysm[5] and 3% have infective endocarditis,[21] their survival is not significantly different from the rest of the population.[1,3,19,22] However, nearly all patients with BAV will require surgery during their lifetime.[21]

This population is usually monitored by transthoracic echocardiography and computed tomography (CT) angiography to detect its common complications.[7] Though BAV's pathophysiology is well established, in clinical practice, early markers of disease progression are not currently available. Speckle-tracking echocardiography (STE) has emerged as a reliable measurer of left ventricle (LV)

systolic function[23] due to its fast, accurate, angle-independent and offline processing of myocardial deformation.[24,25] It has already been proved as an important initial predictor of LV dysfunction in aortic valve diseases through the measurement of global longitudinal strain (GLS).[26] Since 2008, STE has also been used to evaluate vascular wall properties of proximal elastic arteries.[25,27] It assesses the circumferential and longitudinal deformation that an artery undergoes during the cardiac cycle. Its values, in particular circumferential ascending aortic strain and its rate, have been described as important complementary parameters to the classic echocardiographic evaluation of patients with aortic stenosis.[27]

The aim of our study was to assess both left ventricular and ascending aortic strain values through STE in adult BAV patients and controls. We sought to analyse their discriminative power, prognostic value (namely time to surgery) and correlation with the degree of valvular regurgitation.

METHODS

Study population

We conducted a retrospective analysis of a prospectively enrolled cohort of 48 patients diagnosed with BAV and 20 gender and age matched controls. Patients with less than 18 years old, segmental wall-motion abnormalities, left ventricular ejection fraction (LVEF) < 50%, or poor acoustic window were excluded.

The study was approved by the institutional scientific and bioethical committees and was performed in accordance with the Declaration of Helsinki.

Study procedures

We analysed the epidemiologic, clinical, analytical, and echocardiographic data (namely, 2D-STE strain analysis) of the selected population. The cohort was followed-up during a median period of 19.9 months (IQR 12.9–25.2), and outcomes (hospital admission for heart failure (HF), aortic valve replacement (AVR), and death) were determined.

ECHOCARDIOGRAPHIC DATA

Echocardiographic examination included STE analysis of left ventricular function and aortic strain analysis, as previously described.[28] We used a Vivid 7 (GE Healthcare, Horten, Norway) cardiovascular ultrasound device, with a 1.7/3.4-MHz tissue harmonic transducer. Standard echocardiographic views were obtained with 60–80 fps in 2D imaging. Echocardiographic data were analysed offline using specific software (EchoPAC 16.0, GE Healthcare, Horten, Norway).

Left ventricular dimensions and function

We followed the current recommendations[29,30] to measure LV size and systolic and diastolic functions. Peak LV global longitudinal strain (LV-GLS) was assessed by STE using a 16-segment model.[28,31]

Aortic strain analysis

Global ascending aortic wall deformation was also assessed by STE. In the analysis, a line was manually drawn along the inner side of the aortic wall in the short and long axis, with high frame rate pictures of the ascending aorta. The software, then, automatically generated additional lines near the outer side of the vessel wall. The first systolic frame was usually chosen as the frame of interest to include the maximal wall aortic expansion for strain calculation, as previously suggested.[27,32] The tracking process and conversion to Lagrangian strains were performed offline using dedicated software (EchoPAQ, GE Healthcare). Through the analysis of the curves, we obtained maximal and minimal longitudinal aortic strain values [Ao-LSmax (positive value) and Ao-LSmin (negative value), respectively], as well as maximal and minimal circumferential aortic strain values [Ao-CSmax (positive value) and Ao-CSmin (negative value), respectively]. Global longitudinal aortic strain (Ao-GLS, the sum of Ao-LSmax and Ao-LSmin) and global circumferential aortic strain (Ao-GCS, the sum of Ao-CSmax and Ao-CS min), represented as absolute values, were also determined.

STATISTICAL ANALYSIS

Normality of continuous variables was assessed by histogram observation and Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation and categorical variables as a percentage. Student's t-test or ANOVA were used for group comparisons. Individual variables were assessed for homogeneity of variance using Levene's test. For categorical variables, the chi-square or Fisher's exact test were used, as appropriate.

A receiver operating characteristic (ROC) curve analysis was performed to compute the discriminative power of several continuous variables in BAV patients and controls. A comparison of ROC curves was executed using the Delong method.

Relationships between different parameters were assessed by correlation analysis: Pearson's method for continuous and normally distributed variables, and Spearman's method for continuous but skewed variables.

Survival analysis was performed using Kaplan-Meier curves, with the date of entry into the study defined as the date of the diagnosis (first echocardiography). Patients that did not die were censored at the end of the study.

Univariate Cox's proportional hazards analysis was used to identify independent predictors of outcomes in the overall BAV population. Significant variables ($p<0.05$) were subsequently entered into a multivariate analysis.

A P-value (two-sided) < 0.05 indicated statistical significance. Stata (Stata IC for Windows, version 13, Lakeway Drive, TX, USA) was used for the statistical analysis.

RESULTS

Study population

After excluding patients with LVEF < 50%, age < 18 years, wall-motion abnormalities or poor acoustic window, a total of 48 patients with BAV and 20 controls were included in our study. The mean patient age was 46.6 ± 15.5 years and 81% were male (39 patients). The mean control age was 45.3 ± 13.8 years (p=0.12) and 75% were male (p=0.08). According to the current European Society of Cardiology guidelines,[33] among those with BAV, 27 had AR: 8 with mild, 11 with moderate and 8 with severe disease. Besides that, in our BAV cohort, 3 had aortic stenosis: 1 with moderate and 2 with severe disease.

The echocardiographic data is present in **Table 1**.

Echocardiographic analysis in BAV patients and controls

Among classic echocardiographic parameters, LV end-diastolic volume indexed (LVEDVi) (72.5 ± 26.3 vs 52.5 ± 7.5 mL/mm^2, p=0.002), LV end-diastolic diameter (LVEDD) (56.3 ± 11.1 vs 46.6 ± 5.1 mm, p<0.001), interventricular septum (IVS) thickness (10.8 ± 6.7 vs 7.5 ± 1.2 mm, p=0.041) and aortic diameter (40.4 ± 7.9 vs 28.8 ± 3.5 mm, p<0.001) were significantly augmented in BAV patients compared to the control population. Regarding STE measurements, LV-GLS (-16.0 ± 2.8 vs -19.0 ± 1.9, p<0.001) was decreased in BAV population, whereas Ao LSmax (18.4 ± 17.4 vs 9.0 ± 9.4, p=0.031) and |Ao-GLS| (28.8 ± 18.8 vs 17.7 ± 15.7, p=0.027) were increased. Circumferential aortic strain did not differ between groups **(Table 1)**.

Table 1. Echocardiographic data in BAV patients and controls

	BAV	**Controls**	***P-value***
LVEF (± SD, %)	60.7±6.6	62.2±4.2	0.357
LVEDVi (± SD, mL/m^2)	72.5±26.3	52.5±7.5	**0.002**
LVEDD (± SD, mm)	56.3±11.1	46.6±5.1	**<0.001**
IVS (± SD, mm)	10.8±6.7	7.5±1.2	**0.041**
LV-GLS (± SD, %)	-16.0±2.8	-19.0±1.9	**<0.001**
Ao LSmax (± SD, %)	18.4±17.4	9.0±9.4	**0.031**
Ao LSmin (± SD, %)	-10.4±8.2	-8.7±14.0	0.534
|Ao-GLS| (± SD, %)	28.8±18.8	17.7±15.7	**0.027**
Ao CSmax (± SD, %)	6.3±4.8	6.8±4.8	0.700
Ao CSmin (± SD, %)	-4.2±4.8	-3.1±3.3	0.379
|Ao-GCS| (± SD, %)	10.5±6.3	9.9±4.2	0.724
Ao Diameter (± SD, mm)	40.4±7.9	28.8±3.5	**<0.001**

Statistically significant values are represented in bold. Ao, aorta; Ao CSmax, aortic circumferential strain (maximum); Ao CSmin, aortic circumferential strain (minimum); Ao-GCS, aortic global circumferential strain; Ao-GLS, aortic global longitudinal strain; Ao LSmax, aortic longitudinal strain (maximum); Ao LSmin, aortic longitudinal strain (minimum); BAV, bicuspid aortic valve; IVS, interventricular septum; LV-GLS, left ventricular global longitudinal strain; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume (indexed); LVEF, left ventricular ejection fraction.

Comparing classic and STE left ventricular and aortic parameters, the best discriminator of BAV presence was aortic diameter, with an area under the curve (AUC) of 0.92, a specificity of 94.7% and a sensitivity of 85.4% (p<0.001). |Ao-GLS| was also a reliable discriminator, with AUC = 0.87, specificity = 93.9% and sensitivity = 82.3% (p<0.001) **(Table 2)**.

Table 2. Discriminative power of echocardiographic parameters in BAV

	AUC	95% CI	*P-value*	Sensitivity	Specificity	Criterion
LVEF (± SD, %)	0.53	0.40-0.65	0.679	89.5	25.0	<58
LVEDVi (± SD, mL/m^2)	0.77	0.65-0.86	**<0.001**	52.1	94.8	**>62**
LVEDD (± SD, mm)	0.84	0.73-0.92	**<0.001**	83.3	73.7	**>49**
IVS (± SD, mm)	0.79	0.69-0.85	**0.023**	79.2	94.7	**>8**
LV-GLS (± SD, %)	0.82	0.71-0.90	**<0.001**	72.9	79.0	**>-18**
Ao LSmax (± SD, %)	0.71	0.58-0.81	**0.005**	76.6	63	**>8.9**
|Ao-GLS| (± SD, %)	0.87	0.78-0.94	**<0.001**	82.3	93.9	**>24**
Ao Diameter (± SD, mm)	**0.92**	**0.83-0.97**	**<0.001**	**85.4**	**94.7**	**> 33**

Statistically significant values are represented in bold. Ao, aorta; Ao CSmax, aortic circumferential strain (maximum); Ao CSmin, aortic circumferential strain (minimum); Ao-GCS, aortic global circumferential strain; Ao-GLS, aortic global longitudinal strain; Ao LSmax, aortic longitudinal strain (maximum); Ao LSmin, aortic longitudinal strain (minimum); AUC, area under the curve; BAV, bicuspid aortic valve; IVS, interventricular septum; LV-GLS, left ventricular global longitudinal strain; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume (indexed); LVEF, left ventricular ejection fraction.

BAV and aortic regurgitation

The prevalence of AR in our population with BAV was 56.3%, with the majority presenting moderate AR (11 patients). **Table 3** shows the echocardiographic data in BAV patients, according to their degree of AR (none, mild, moderate and severe). All LV parameters had significant differences with the increasing severity of AR, even though patients without AR revealed worse values when compared to those with mild AR. LV-GLS absolute value decreased as the disease progressed, demonstrating a lessening in LV contraction (severe AR with LV-GLS = -13.6 ± 2.0% vs no AR with LV-GLS = -16.3 ± 3.4%, p=0.045). Regarding ascending aortic parameters, |Ao-GLS| in moderate AR was lower than in mild AR and had its maximum value in severe valve incompetence (no AR = 22.4 ± 10.0% vs mild AR = 31.8 ± 23.5% vs moderate AR = 28.2 ± 11.7% vs severe AR = 45.2 ± 32.3%, p<0.001). Aortic global circumferential strain (|Ao-GCS|) decreased throughout the disease (no AR = 11.7 ± 8.5% vs mild AR = 11.1 ± 4.0% vs moderate AR = 8.9 ± 3.7% vs severe AR = 8.9 ± 3.6%, p=0.004) (**Table 3**).

Amid our population with BAV, the best discriminator of the existence of at least moderate AR was |Ao-GLS|, with AUC = 0,76, specificity = 65% and sensitivity = 100% (p=0.021). All patients with moderate or severe AR had |LV-GLS| > 15% (**Table 4**).

Table 3. Echocardiographic data in BAV patients according to the degree of aortic regurgitation

	None (n=21)	Mild (n=8)	Moderate (n=11)	Severe (n=8)	*P-value*
LVEF (± SD, %)	59.9±8.7	62.1±5.4	62.4±3.5	58.9±4.6	**0.013**
LVEDVi (± SD, mL/m^2)	65.3±20.2	60.1±12.3	70.2±16.1	106.8±35.6	**0.025**
LVEDD (± SD, mm)	55.4±10.1	47.1±14.5	58.3±4.8	65.1±9.9	**0.026**
IVS (± SD, mm)	9.8±1.5	15±16.2	9.9±2.1	10.3±0.9	**<0.001**
LV-GLS (± SD, %)	-16.3±3.4	-17.3±1.9	-16.3±1.6	-13.6±2.0	**0.045**
Ao LSmax (± SD, %)	12.9±8.8	20.4±24.1	17.4±13.6	33.8±26.3	**0.001**
Ao LSmin (± SD, %)	-9.5±6.6	-11.4±9,5	-10.8±10.4	-11.4±8.9	0.367
|Ao-GLS| (± SD, %)	22.4±10.0	31.8±23.5	28.2±11.7	45.2±32.3	**<0.001**
Ao CSmax (± SD, %)	7.1±6.1	5.4±4.1	6.3±4.1	5.1±2.8	0.112
Ao CSmin (± SD, %)	-4.6±5.6	-5.6±5.3	-2.5±2.8	-3.8±3.8	0.129
|Ao-GCS| (± SD, %)	11.7±8.5	11.1±4.0	8.9±3.7	8.9±3.6	**0.004**
Ao Diameter (± SD, mm)	41.7±9.2	38.2±10.2	40.5±5.1	39.2±5.4	0.099

Statistically significant values are represented in bold. Ao, aorta; Ao CSmax, aortic circumferential strain (maximum); Ao CSmin, aortic circumferential strain (minimum); Ao-GCS, aortic global circumferential strain; Ao-GLS, aortic global longitudinal strain; Ao LSmax, aortic longitudinal strain (maximum); Ao LSmin, aortic longitudinal strain (minimum); BAV, bicuspid aortic valve; IVS, interventricular septum; LV-GLS, left ventricular global longitudinal strain; LVDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume (indexed); LVEF, left ventricular ejection fraction.

Table 4. Discriminative power of echocardiographic parameters in BAV with at least moderate regurgitation

	AUC	95% CI	*P-value*	Sensitivity	Specificity	Criterion
LVEF (± SD; %)	0.53	0.38-0.67	0.763	11.1	76.2	<55
LVEDVi (± SD; mL/m^2**)**	0.63	0.48-0.76	0.115	70.4	52.4	>59
LVEDD (± SD, mm)	0.61	0.46-0.75	0.208	63.0	67.0	>55
LV-GLS (± SD, %)	0.56	0.40-0.70	0.538	81.5	38.1	>-18
Ao LSmax (± SD, %)	0.65	0.50-0.78	0.066	69.2	61.9	>12.4
|Ao-GLS| (± SD, %)	**0.76**	**0.65-0.89**	**0.021**	**100**	**65**	**>15**
Ao Diameter (± SD, mm)	0.56	0.41-0.70	0.500	66.7	55.4	<41

Statistically significant values are represented in bold. Ao, aorta; Ao CSmax, aortic circumferential strain (maximum); Ao CSmin, aortic circumferential strain (minimum); Ao-GCS, aortic global circumferential strain; Ao-GLS, aortic global longitudinal strain; Ao LSmax, aortic longitudinal strain (maximum); Ao LSmin, aortic longitudinal strain (minimum); BAV, bicuspid aortic valve; IVS, interventricular septum; LV-GLS, left ventricular global longitudinal strain; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume (indexed); LVEF, left ventricular ejection fraction.

Survival and event-free rate analysis

The cohort was followed-up for a median period of 19.9 months (IQR 12.9-25.2) and surgery with AVR was the only outcome observed. There was no HF hospitalization or death in our population of study. Univariate and multivariate COX regression analysis are demonstrated in **tables 5 and 6**. Kaplan-Meier surgery-free survival curves are depicted in **figures 1 and 2**.

On univariate analysis, LVEF, LV-GLS and LV dimensions were predictors of surgery (aortic strain measures were not) (**Table 5**). On multivariate analysis, only LVEDVi was a predictor of surgery (p=0.001) (**Table 6**).

AVR was progressively more performed as months of follow-up went on. At 20 months, approximately 27% were submitted to surgery (**Figure 1**). We separated them into patients with more and less than LVEDVi = 70 mL/m^2. Those with LVEDVi ≥ 70 mL/m^2 were substantially more referred to surgery in a shorter period (**Figure 2**).

Table 5. Univariate Cox regression analysis (Outcome: time to surgery – AVR)

Predictor	HR (95% CI)	*P-value*
LVEF (± SD; %)	0.89 (0.84-0.96)	**0.001**
LVEDVi (± SD; mL/m^2**)**	1.04 (1.02-1.06)	**<0.001**
LVEDD (± SD, mm)	1.11 (1.05-1.17)	**<0.001**
LV-GLS (± SD, %)	1.24 (1.03-1.50)	**0.024**
|Ao-GLS| (± SD, %)	1.02 (0.97-1.08)	0.354
|Ao-GCS| (± SD, %)	0.98 (0.90-1.05)	0.546
Ao Diameter (± SD, mm)	1.07 (0.99-1.16)	0.076

Statistically significant values are represented in bold. Ao, aorta; Ao-GCS, aortic global circumferential strain; Ao-GLS, aortic global longitudinal strain; AVR, aortic valve replacement; LV-GLS, left ventricular global longitudinal strain; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume (indexed); LVEF, left ventricular ejection fraction.

Table 6. Multivariate Cox regression analysis (Outcome: time to surgery – AVR)

Predictor	HR (95% CI)	*P-value*
LVEF (± SD; %)	0.92 (0.84-1.00)	0.070
LVEDVi (± SD; mL/m^2**)**	1.04 (1.01-1.06)	**0.001**
LV-GLS (± SD, %)	1.02 (0.81-1.30)	0.856

Statistically significant values are represented in bold. AVR, aortic valve replacement; LV-GLS, left ventricular global longitudinal strain; LVEDVi; left ventricular end-diastolic volume (indexed); LVEF, left ventricular ejection fraction.

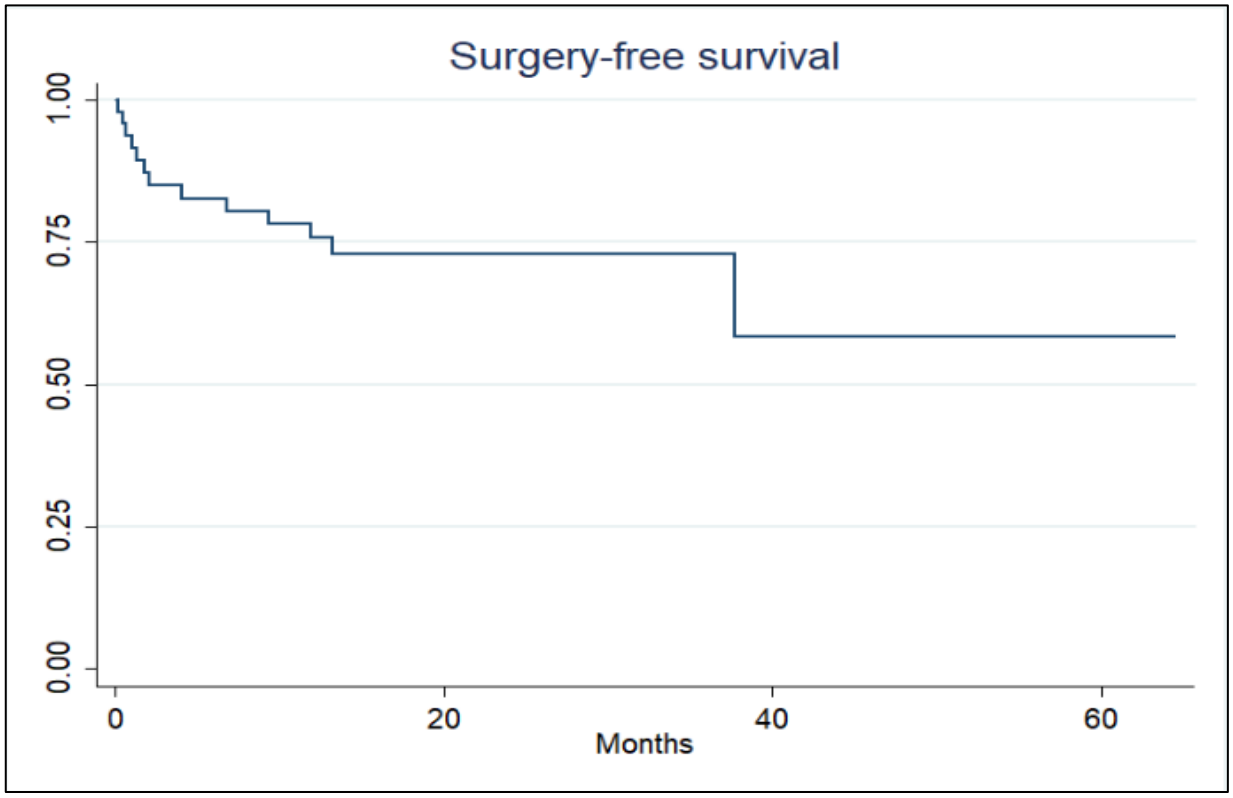

Figure 1 - Overall surgery-free survival of BAV patients.

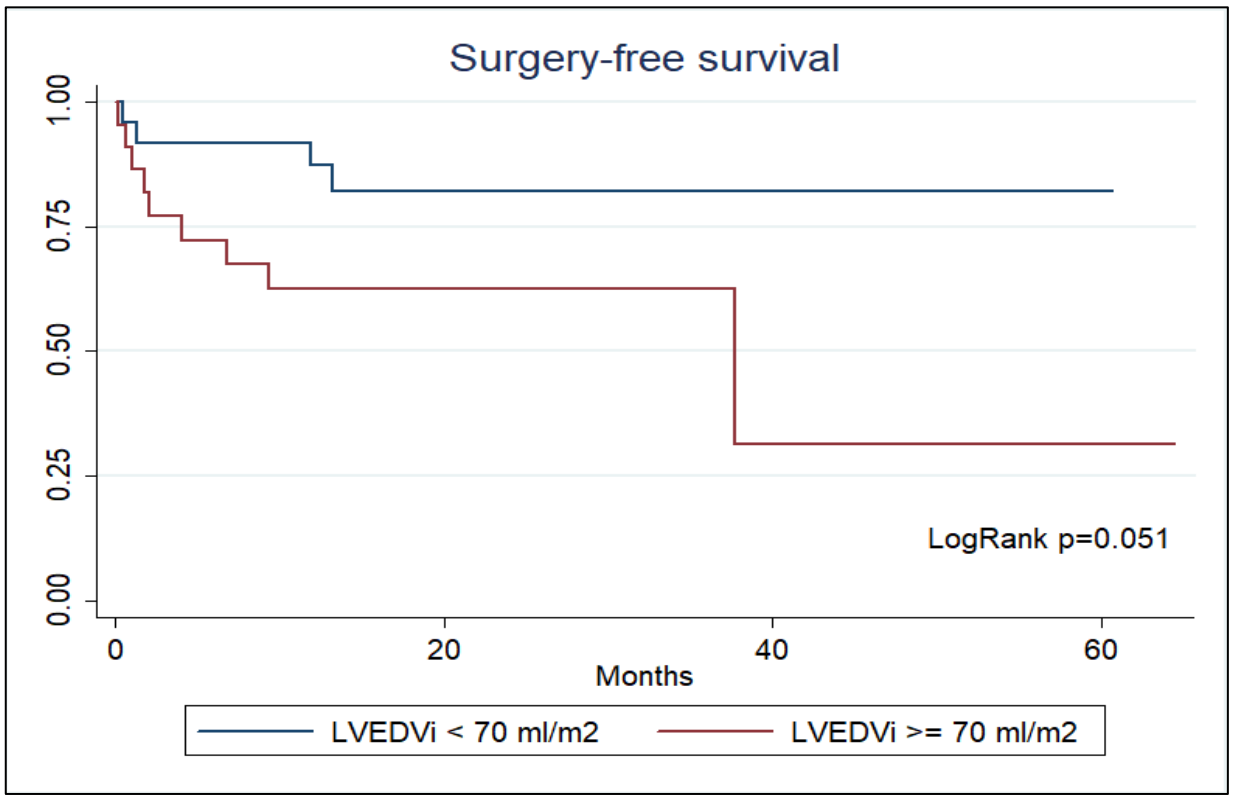

Figure 2 - Surgery-free survival of BAV patients, in relation to the left ventricle end-diastolic indexed volume.

DISCUSSION

To the best of our knowledge, this is just the second study to analyse aortic strain in BAV, using STE.

We described LV and ascending aortic function in patients with BAV. In our study, both classic and speckle-tracking echocardiographic parameters were generally altered in BAV. Among them, we also assessed the importance of valvular regurgitation on the quantification of their values. Moreover, we observed that aortic diameter was the best discriminator of BAV disease and that LVEDVi was the main predictor of time to surgery in our BAV cohort.

Amid our population, AR was the most common valvular complication associated, despite its prevalence being inferior to aortic stenosis.[11] Classic LV echocardiographic parameters were altered in comparison to the control population, with larger LV and IVS dimensions, even though they all had preserved LVEF. This LV remodeling is predominantly explained by the reduced aortic valve area and increased ascending aortic stiffness described in BAV patients.[10] Besides that, the existence of AR induces volume and pressure overload, that leads to an even superior LV mass and dilatation.[23]

LV-GLS was diminished in BAV, reflecting a subclinical impaired contraction of the LV. It corroborates previous studies that stated that LV mechanics were altered in BAV disease, with decreased longitudinal, circumferential and radial strain, even with mild valvular disease or in the absence of aortic stenosis, AR or aortopathy.[4,8,10] A recent research used LV-GLS to predict cardiac outcomes in patients with BAV (with or without valvular incompetence) and observed that, for every 1% reduction in its value, there was a 9% increment on the probability of achieving its end-point (mostly aortic valve surgery).[23] Nevertheless, in our study, we noted that LV-GLS was not a reliable predictor of our primary outcome (time to surgery – AVR).

It is well established that BAV is frequently associated with ascending aorta dilatation, a finding that was also observed in our study, with aortic diameters ranging from 32.5 to 48.3mm (aortic dilatation in BAV > 40mm, according to the current European Society of Cardiology guidelines[6]). As a matter of fact, a cut-off value of aortic diameter > 33mm was the best discriminator of the presence of a patient with BAV. Contrary to a previous study,[8] |Ao-GCS| had no differences between the two populations, which may derive from the fact that they did not have any patient with BAV complications. As Teixeira *et al.* concluded in patients with aortic stenosis, |Ao-GCS| correlates with LVEF and vascular flow's alterations (positively with stroke volume index) and not so much with vascular wall properties.[32] Furthermore, they also observed that |Ao-GCS| did not differ in patients with tricuspid aortic valve and different levels of AR, despite having an increased stroke volume index.[25] They attributed it to a significant vascular wall impairment caused by the disease. Opposed to what they stated, we noticed that its value decreased as the severity of AR in BAV accrued. Perhaps, we can explain this finding because, although being subject to a similar stroke volume index and pressure overload, BAV patients' ascending aortas already have underlying altered mechanics generated by chronic increased wall stress, in addition to the impairment caused singly by AR. Moreover, there was also a significant decline in LVEF throughout the disease, contributing to a reduction in vascular flow.

Ascending aorta in BAV has reduced distensibility and is stiffer compared to the healthy

population,[4,10] even with normal aortic diameter.[34] It partially explains its tendency to rupture/dissection, since a stiffer aorta has an impaired deformation capacity when undergoing different sources of stress.[35] Aortic longitudinal strain was suggested to be a good parameter to evaluate aortic distensibility.[36] Following this reasoning, our population with BAV had contradictory significantly greater distensibility than the control one, using solely |Ao-GLS| values. In contrast to Longobardo *et al.*[36] and Li *et al.*[4], our patients had more marked dilatation of the ascending aorta (40.4 vs 37.4 vs 36.4mm). This can contribute to an abnormal distensibility of the aorta with distortion of longitudinal strain calculations. Besides that, our population had more cases of severe AR. A prior study referred that ascending aorta of patients with BAV and AR was more distensible and less stiff than those with BAV and normofunctional valve.[37] Therefore, analysing |Ao-GLS| values throughout the increment of AR severity, we can observe that it decreases from mild to moderate AR and then it exponentially augments when severe AR is present. Thus, we hypothesize that, in more serious cases of valvular regurgitation in BAV, longitudinal strain values are abnormally high. This may explain why |Ao-GLS| was the best discriminator of at least moderate AR, with all patients having |Ao-GLS| > 15%. Moreover, this finding also supports the fact that aortic strain is not an adequate predictor of time to surgery (AVR), due to the unpredictability of its values.

During our follow-up, we observed no HF hospitalizations nor deaths related to BAV. 13 patients were subject to AVR, totaling a further 27.1% of our study population. The main indications for AVR in BAV are: a) ascending aorta dilatation > 50mm (with risk factors such as a family history of aortic dissection); b) symptomatic severe AR; or c) asymptomatic severe AR with impairment of LVEF (≤50%) or severely dilated LV.[33] In fact, when assessing our single outcome (time to surgery), LVEDVi emerged as the only significant predictor. Thereafter, we divided our patients in LVEDVi less or greater than 70mL/m^2 and we found important differences. Those with severe LV dilatation (LVEDVi ≥ 70mL/m^2) were called up to surgery in a shorter period.

Our study has some limitations, namely regarding the fact we did not observe any HF hospitalizations or deaths. Consequently, we were not able to analyse properly the prognosis role these STE values may have. Hence, we suggest further studies to have a larger follow-up time in order to relate this type of events. Moreover, we analysed aortic distensibility using only |Ao-GLS|, as advocated by a previous study. It would be important we also had aortic distensibility measured to strengthen our research findings.

CONCLUSION

In our study, LV mechanics were altered in BAV patients, even though they had preserved ejection fraction. Aortic strain, more precisely its longitudinal value, showed an acceptable power in identifying the presence of BAV population and, among them, patients with at least moderate AR. We also observed that higher aortic diameters could distort aortic longitudinal strain calculations. Concerning classic and STE parameters, we did not find any reliable early prognosis marker, besides LVEDVi. However, our only outcome was refferal to surgery (AVR). Further studies could focus on assessing aortic strain worth in other end-points, such as HF hospitalization or death related to BAV.

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