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Bicuspid Aortic Valve: Prolapse and Aortic Valve Calcification are Markers of Significant Valve Dysfunction and Major Cardiovascular Events at 5 Years

Válvula aórtica bicúspide: El prolapso y la calcificación valvular aórtica son marcadores de disfunción valvular significativa y de eventos cardiovasculares mayores a 5 años

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ABSTRACT

Background: Bicuspid aortic valve (BAV) is a congenital heart disease that can be associated with aortic and/or valve complications. It is important to identify risk groups for a closer follow up and timely intervention.

Objective: The aim of this work is to analyze the impact of clinical and morphological valve characteristics in the development of moderate/severe (significant) aortic valve dysfunction and in the incidence of major cardiovascular events in adults with BAV.

Methods: Consecutive patients with diagnosis of non-syndromic BAV (2010-2019) followed up at our institution were incorporated in the study. Clinical and echocardiographic information was prospectively collected. Univariate and multivariate analyses were performed to identify clinical and morphological characteristics that predict significant valve dysfunction and major cardiovascular events (death/surgery/aortic syndrome). A p value <0.05 was considered significant.

Results: Three-hundred patients (44.3 ± 15.3 years, 71% men), the majority with type I BAV and presence of raphe (79.6% and 77%, respectively) were included. Mean age at diagnosis was 36.3 ± 16.2 years, and 84 patients (31.2%) presented significant aortic valve dysfunction at the onset of the study.

Twenty-three patients required cardiac surgery (7.7%) and 3 died (1%) during a follow-up of 4.9 ± 1.7 years. At the end of the follow-up period, 101 (33.6%) patients had significant aortic valve dysfunction. The presence of at least 1 of the following factors: valve prolapse, baseline aortic valve calcification > 1 and age > 50 years were associated with lower significant aortic valve dysfunction and major cardiovascular event-free survival.

Conclusions: In our cohort, we observed a high incidence of events associated with BAV. Among the variables analyzed, the presence of at least 1 risk factor was associated with lower event-free survival and significant dysfunction at 4.9 years.

Keywords: Bicuspid aortic valve- Aortic valve regurgitation- Aortic stenosis- Aortic valve replacement

RESUMEN

Introducción: La válvula aórtica bicúspide (VAB) es una cardiopatía congénita que puede asociarse a complicaciones aórticas y/o valvulares. Resulta importante identificar los grupos de riesgo para realizar un estrecho seguimiento e indicar la intervención a tiempo. Este trabajo propone analizar el impacto que tienen las características clínicas y morfológicas valvulares en el desarrollo de la disfunción valvular aórtica moderada/grave (significativa) y en la incidencia de eventos cardiovasculares mayores en adultos con VAB.

Material y métodos: Se seleccionaron pacientes consecutivos con diagnóstico de VAB no sindrómica (2010-2019) en seguimiento en el ICSI. Se recabó información clínica y ecocardiográfica de manera prospectiva. Se realizó análisis uni y multivariado para identificar las características clínicas y morfológicas predictoras de disfunción valvular significativa y de eventos cardiovasculares mayores (muerte, cirugía, síndrome aórtico). Una p menor a 0,05 fue considerada significativa.

Resultados: Se siguieron 300 pacientes (44,3 ± 15,3 años, 71% varones). La mayoría con VAB tipo I y con presencia de rafe (79,6% y 77%, respectivamente). La edad media de diagnóstico fue de 36,3 ± 16,2 años. Hubo 84 pacientes (31,2%) que presentaban disfunción valvular aórtica significativa al momento del inicio del estudio.

Con un seguimiento de 4,9 ± 1,7 años, 23 pacientes requirieron cirugía cardíaca (7,7%) y 3 fallecieron (1%). Al final del seguimiento 101 pacientes (33,6%) presentaban disfunción valvular aórtica significativa. La presencia de al menos uno de los siguientes factores: prolapso valvular, calcificación valvular aórtica basal > 1 y edad > 50 años, se asoció a menor sobrevida libre de disfunción valvular aórtica significativa y de eventos mayores.

Conclusiones: En nuestra cohorte, observamos una alta incidencia de eventos asociados a VAB. Dentro de las variables analizadas, la presencia de al menos un factor de riesgo se asoció a menor sobrevida libre de eventos mayores y disfunción significativa a 4,9 años.

Palabras clave: Válvula aórtica bicúspide- Insuficiencia aórtica- Estenosis aórtica- Reemplazo valvular aórtico

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Abbreviations

AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
BSA	Body surface area

IQR	Interquartile range
LVEF	Left ventricular ejection fraction
TTE	Transthoracic Doppler echocardiography

INTRODUCTION

Bicuspid aortic valve (BAV) is a frequent congenital heart disease that affects 0.8% to 2% of the population. (1) It is a clinically relevant entity due to both aortic and valve complications that may occur during its progression, so it is currently described as a valve-aortopathy. (2)

A high percentage of patients present major cardiovascular events associated with BAV during their lifetime (3). Moreover, this pathology constitutes the first cause of aortic valve replacement in patients below 65 years of age. (4) Symptomatic severe aortic stenosis and symptomatic severe aortic regurgitation constitute the first two causes of surgical intervention in patients with BAV. (5-7)

Surgical or percutaneous intervention in valvulopathies has an optimal timing in which the risk of disease progression (sudden death, heart failure, or irreversible left ventricular dysfunction) exceeds that of intervention. When severe aortic valvulopathy is intervened too late, the prognosis is worse. The establishment of symptoms is usually associated with rapid clinical deterioration and an ominous prognosis in the absence of early intervention. (8) In many cases, myocardial damage is present before the onset of symptoms. (9) It is therefore important to identify risk groups with valve dysfunction, for a closer follow up and timely surgical intervention. (10)

Although an association between the degree of aortic valve calcification and the development of aortic stenosis has been described, there is currently scarce information to predict the evolution of the patient's valve dysfunction with BAV diagnosis. (6, 7)

Our working team believes that there are certain initial characteristics that would allow detecting those patients who will develop significant regurgitation and/or stenosis and would therefore require closer follow-up.

The aim of this work was to analyze clinical and morphological valve characteristics, identifying those variables that have an impact on the development of stenosis and significant aortic regurgitation and on major event-free survival.

METHODS

Population

Consecutive asymptomatic patients with confirmed BAV diagnosis (2010-2019), followed up by the valvulopathy team of our health network, which includes second and third level complexity institutions (ICSI Las Lomas, ICSI Nordelta and ICSI Pilar) with access to electronic medical records, were included in the study.

All patients, underwent a baseline clinical examination and baseline characteristics were recorded (age, gender, height, weight, major cardiovascular risk factors, first-degree family history of BAV and/or aortopathy, symptoms: dyspnea according to the New York Heart Association classification, chest pain and/or syncope, associated injuries, age of BAV diagnosis, usual medication, blood cholesterol and creatinine).

The inclusion criterion was BAV verified with transthoracic Doppler echocardiography (TTE), defined from short axis left parasternal projection of large vessels as an elliptic aortic valve opening with identification of 2 leaflets in mesosystole and 2 commissures, and eccentric valve closure and/or dome opening of the aortic valve. In case of doubt, another diagnostic imaging method was required to confirm BAV. All studies were verified by the coordinators of the research group (MCC and PS).

All included patients signed an informed consent approved by our Institution. Patients under 18 years of age, previously operated for BAV, and/or with complex congenital heart diseases were excluded from the study.

Study protocol and endpoints

All procedures followed the principles of the Declaration of Helsinki and good clinical practice regulations.

All patients underwent baseline TTE and follow-up imaging studies according to the degree of valve dysfunction and aortic dilation:

- Patients without aortic valve dysfunction and non-dilated aorta: biannual.
- Patients with mild or moderate aortic valve dysfunction and non-dilated aorta: annual.
- Patients with severe aortic valve dysfunction and/or dilated aorta: semi-annual.

The entire population underwent at least a baseline TTE and a conventional and complete follow-up TTE with a 2 to 4 MHz transducer (Vivid S5 (GE® Vingmed Ultrasound, Israel and Vivid T8, GE® Medical Systems, China), performed by a team of 5 university cardiologists specialized in echocardiography and trained in aortic measurement (Level III).

Routine echocardiographic measurements were performed in all patients. The degree of valvulopathy, was classified according to current guidelines at the beginning of the BAV study. (13, 14), Aortic regurgitation in BAV normally presents difficult to quantify eccentric jets, so it was classified as mild, moderate and severe using a comprehensive diagnostic approach that incorporated quantitative and semi-quantitative criteria. (15, 16) A moderate or severe valve dysfunction was considered significant.

Bicuspid aortic valve was classified according to Schaefer et al as: I, fusion of coronary leaflets, II, fusion of right coronary and non-coronary leaflets and III: fusion of non-coronary and left coronary leaflets. (6) The presence or absence of raphe and the degree of calcification was classified from 0 to 3 according to the echocardiographic classification of Rosenhek et al (absent, mild, moderate or severe). (9) Grade 2 or 3 calcification was considered significant. The presence of aortic valve prolapse was evaluated in all patients, defined as valve

protrusion ≥ 1 mm through the plane of the aortic annulus in the left parasternal view or in the five-chamber view. (11)

Aortopathy was defined as diameter ≥ 40 mm and/or ≥ 21 mm/m² and aortic aneurysm was defined as diameter ≥ 45 mm, according to published studies. (3, 18) Aortopathy was classified into 3 types: I, dilation of the tubular portion and of the sinus portion; II, dilation of the tubular portion and III, dilation of the sinus portion. (2, 19)

A subgroup of patients underwent multislice computed angio-tomography and/or cardiac magnetic resonance imaging, according to current BAV management recommendations, and to unify criteria the same cut-off points as for TTE were considered.

The incidence of major cardiovascular events defined as aortic regurgitation, aortic or combined surgery, aortic dissection and/or death was documented. Death was defined as due to cardiovascular or non-cardiovascular causes according to autopsy review (1 case), discussion with an attending physician (2 cases) and/or review of the medical history (all 3 cases). Also, in deaths of cardiovascular cause, it was determined whether they were due to the valve disease or other cardiac conditions.

The indication for surgical intervention was taken by the treating team in all cases and was mainly carried out in the presence of symptoms. In asymptomatic patients surgical decision was made based on evidence of left ventricular dysfunction (left ventricular ejection fraction (LVEF) $\leq 55\%$, left ventricular end-diastolic diameter ≥ 75 mm) or with aortic diameters ≥ 55 mm. (14, 16, 20)

Statistical analysis

Continuous variables were compared with Student's two-tailed t test and categorical variables with the chi-square test with Yates correction or Fisher's exact test, as appropriate. Continuous variables were expressed as mean \pm standard deviation, median and interquartile range (IQR) or frequency (in percentage), as appropriate. Kaplan Meier estimates are expressed with standard error (SE) Univariate analysis of all recruited parameters was performed to predict the incidence of major cardiovascular events during follow-up. A multivariate analysis was then performed and the criteria for introducing variables were clinical relevance and statistical significance in the univariate analysis.

Kaplan Meier curves were built to analyze major cardiovascular event-free survival. In the subgroup of patients without significant valve dysfunction at the beginning of follow-up, significant aortic valve dysfunction-free survival was analyzed. Total survival data were considered based on the follow-up cut-off point of February 2019 and/or the occurrence of a major cardiovascular event.

Statistical analysis was performed using Windows Sofastat and GraphPad Prism 8 software packages. A p value < 0.05 was considered significant.

Ethical considerations

The study was evaluated and approved by the institutional Ethics Committee. An informed consent, authorized by a relative or person responsible was requested for each patient included in the study.

RESULTS

Baseline population characteristics

A total of 300 patients with confirmed diagnosis of non-syndromic BAV at our institution (2010-2019)

were included in the study. Mean age was 44.3 ± 15.3 years, 6.5% had family history of BAV, and follow-up was 4.9 ± 1.7 years. Follow-up could not be completed in 7% of the patients (21 cases). Baseline computed tomography/magnetic resonance imaging was performed in 98 patients (32.6%).

Table 1 shows baseline clinical characteristics of the 300 patients. Table 2 describes baseline echocardiographic characteristics according to valve phenotype. The predominant type of BAV was fusion of coronary leaflets. There were almost no cases of BAV due to fusion between non-coronary leaflet and left coronary leaflet, so they were not included in subsequent analyses. Aortopathy was identified at the beginning of follow-up in 1 every 2.6 patients (38%). There were 84 patients (31.2%) who presented significant aortic valve dysfunction at the time of inclusion in the study.

Major cardiovascular events and significant aortic valve dysfunction

There were 24 major combined cardiovascular events registered. During follow-up, 3 deaths were recorded (mean age: 64 ± 5.1 years), all of cardiovascular cause. Of these, two occurred in relation to cardiac surgery (1 in the postoperative period of aortic valve replacement due to severe symptomatic aortic stenosis and another during surgery of prosthetic endocarditis). The third one was found by necropsy, also due to cardiovascular cause unrelated to BAV (acute coronary syndrome in a patient with mild valve dysfunction).

Twenty-three cardiac surgeries (7.7%) were indicated and performed during follow-up. The causes of surgical indication can be seen in Figure 1. Dyspnea was the most frequent symptom (90.4%). The main

Table 1. Patient baseline clinical characteristics

	Total (n=300)
Age, years	44.3 ± 15.3
Men, n (%)	213 (71)
Hypertension, n (%)	55 (18.3)
Diabetes mellitus, n (%)	15 (5)
Smoking, n (%)	41 (13.6)
Dyslipidemia, n (%)	36 (12)
BAV as finding, n (%)	173 (71.2)
Age at diagnosis, years	36.3 ± 16.2
Weight (kg)	77.1 ± 15.2
Height (cm)	171.4 ± 13.5
BSA - Dubois (m ²)	1.9 ± 0.25
LVEF, %	63.7 ± 3.1
LAVoli (ml/m ²)	28.7 ± 9.6
Creatinine (mg/dL)	0.92 ± 0.20
Total cholesterol (mg/dL)	191.4 ± 32.2

BAV: Bicuspid aortic valve. BSA: Body surface area. LVEF: Left ventricular ejection fraction. LAVoli: Left atrial volume indexed by body surface area. The results are expressed as mean \pm SD, absolute number and frequency in percentage, as appropriate.

indication for surgery was severe symptomatic aortic stenosis (13 patients, mean gradient: 41 ± 15.7 mmHg, LVEF: $61.7 \pm 9.6\%$). Severe symptomatic aortic stenosis was significantly more frequent in women (53% women) ($p < 0.01$). The second cause of cardiac surgery was severe symptomatic aortic regurgitation (7 patients, all men, with end diastolic diameter 5.6 ± 0.5

cm, LVEF: $63.8 \pm 9.1\%$). Also, 3 patients underwent prophylactic intervention due to aneurysmal aortic dilation (mean aortic diameter 5.4 ± 0.3 cm) with surgical criteria before valve dysfunction. In the 3 cases Bentall de Bono surgery was performed with mechanical aortic valve prosthesis.

The rate of aortic growth was 0.6 mm (0.35-0.83

	Type I BAV (n=234)	Type II BAV (n=35)	p
LV end-diastolic diameter (cm)	4.98±0.62	4.92±0.54	NS
LV end-systolic diameter (cm)	3.06±0.21	2.85 ±0.35	NS
Interventricular septum thickness (cm)	1.03±0.22	0.99±0.20	NS
Posterior Wall thickness (cm)	0.94±0.13	0.94±0.12	NS
LVEF (%)	64.8±7.1	63.5±4.6	NS
Baseline annulus (cm)	2.23±0.30	2.32±0.31	NS
Valsalva sinuses (cm)	3.60±0.63	3.84±0.70	NS
Sinotubular junction(cm)	3.07±0.51	3.39±0.61	0.04
Aortic arch (cm)	2.66±0.48	2.72±0.44	NS
Proximal descending aorta (cm)	1.99±0.37	2.16±0.44	NS
Raphe	193 (82.4)	28 (80)	NS
Baseline aortic stenosis			
Mild	34 (14.5)	7 (18)	NS
Moderate	16 (7)	5 (13)	NS
Severe	9 (4)	1 (3)	NS
Baseline aortic regurgitation			
Mild	114 (49)	14 (37)	NS
Moderate	44 (19)	11 (29)	NS
Severe	9 (4)	1 (3)	NS
Significant baseline valve dysfunction	71 (29)	13 (37)	NS
Baseline valve calcification			
Absent	86 (36)	10 (26)	NS
Mild	112 (47)	19 (50)	NS
Moderate	23 (10)	5 (13)	NS
Severe	16 (7)	4 (11)	NS
Baseline aortopathy (4 cm and/or >2.1 cm/m ²)	88 (37)	16 (42)	NS
Aortic valve prolapse	39 (16)	6 (17)	NS

Dimensions, degree of valve disease and baseline aortic measurements are shown according to the presence of Schaefer's phenotype I or II. BAV: Bicuspid aortic valve. LV: Left ventricular. LVEF: Left ventricular ejection fraction.

Table 2. Baseline echocardiographic characteristics according to valve phenotype

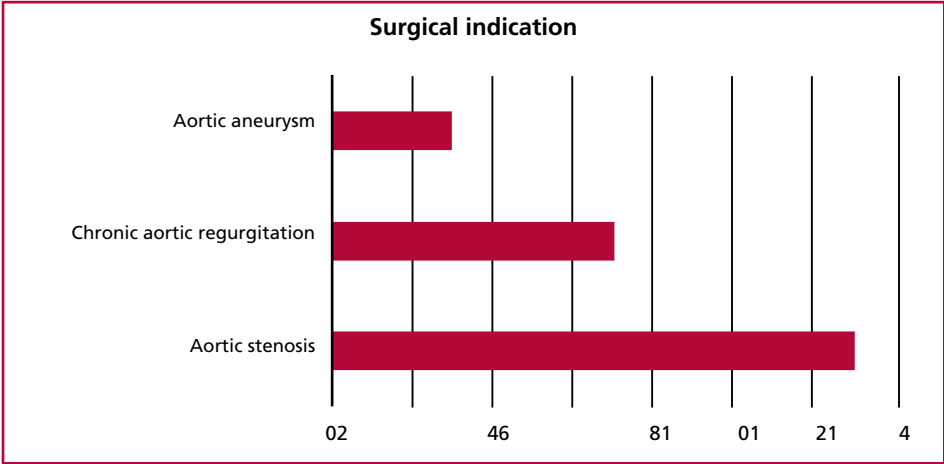


Fig. 1. Causes for cardiac surgery indication. The main cause was symptomatic severe aortic stenosis.

mm) per year at sinus level and 0.3 mm (0.09 to 0.53 mm) at the proximal ascending aorta level.

Infective endocarditis was diagnosed in 6 patients (2%), 5 of which (83%) required emergency surgical treatment for severe aortic regurgitation and heart failure.

At the end of the follow-up period, 101 (33.6%) patients presented significant aortic valve dysfunction; with moderate/severe aortic regurgitation in 64 cases (63.3%) and moderate/severe aortic stenosis in 37 cases (36.6%).

Predictors of significant aortic valve dysfunction and major cardiovascular events

The univariate analysis revealed that the presence of significant baseline aortic valve calcification (2 and 3 of the Rosenhek classification) and age over 50 years were associated with a higher incidence of major cardiovascular events (Table 3).

On the other hand, the presence of significant baseline aortic valve calcification (2/3 of the Rosenhek classification), age over 50 years and aortic valve prolapse were associated with a higher incidence of aortic valve dysfunction during follow-up (Table 4).

Survival

Major cardiovascular event-free survival was significantly lower in patients with at least one risk factor for aortic valve dysfunction, as shown in Figure 2 (chi square log-rank test=12.6, $p=0.0002$).

About 8.7% patients without significant valve dysfunction at the time of diagnosis progressed to moderate or severe regurgitation and/or stenosis. In addition, significant aortic valve dysfunction-free survival was notably lower in patients with at least one of the aforementioned risk factors, as shown in Figure 3 (chi square log-rank test=23.5, $p<0.0001$).

DISCUSSION

In our study we present the contemporary evolution of a longitudinal adult cohort with BAV in our institution. As a first aspect, the incidence of major cardiovascular events, at the expense of cardiovascular surgery is high. Although mortality is low, the morbidity generated by this pathology throughout life is decisive. There is no local literature reporting the incidence of cardiovascular surgery in young adults at 5 years of follow-up. A recent study published in Brazil reported an average annual incidence of valve surgery of 4.75 per 100,000 inhabitants in the general population, especially due to rheumatic disease. (11) In the United States, the annual incidence of aortic valve replacement surgery is 8.33 per 100,000 Medicare beneficiaries under 65 years. (12) In the same work, the total annual incidence of aortic valve interventions was 88.9 per 100,000 Medicare beneficiaries (including transcatheter aortic valve implantation (TAVI) and elderly patients). (12) Compared with these values, we can say that patients with BAV have a much higher incidence of valve replacement than the general population.

Regarding the incidence of events in series of young adult patients with BAV, our cohort results are similar to those published in developed countries. The incidence of cardiac surgery is high, mainly due to aortic valve replacement, with short or mid-term mortality comparable to the general population. (13, 14) However, in congenital heart disease with prolonged life expectancy, a long-term follow-up is necessary to reliably assess the impact of the pathology on total mortality and life expectancy.

Considering the predictors of cardiovascular events and valve dysfunction, there is controversy about the role of raphe and valve phenotype as event predictors. The study of Fernandes et al. which included pediatric

Table 3. Predictors of major cardiovascular events (cardiac surgery/death/acute aortic syndrome)

	OR (95% CI)	p
Age over 50 years	6.2 (2.5-15.8)	<0.0001
Baseline aortic valve calcification	11.3 (4.6-28.0)	<0.0001
Baseline aorta >40 mm	2.06 (0.90-4.69)	0.08
Aortic valve prolapse	2.14 (0.56-8.2)	0.3
Male gender	1.38 (0.57-3.32)	0.48

Univariate analysis of predictors of major cardiovascular events. Variables indicating significant association are shown in bold.

Table 4. Predictors of significant aortic valve dysfunction during follow-up (moderate/severe aortic regurgitation and/or stenosis)

	OR (95% CI)	p
Age over 50 years	2.23 (1.26 – 3.93)	0.005
Baseline aortic valve calcification	6.05 (3.21-11.4)	<0.0001
Aortic valve prolapse	3.05 (1.58-5.9)	0.0007
Male gender	NS	0.66
Presence of raphe	NS	0.59
Baseline aorta >40 mm	NS	0.49

Univariate analysis of predictors of significant valve dysfunction. Variables indicating significant association are shown in bold.

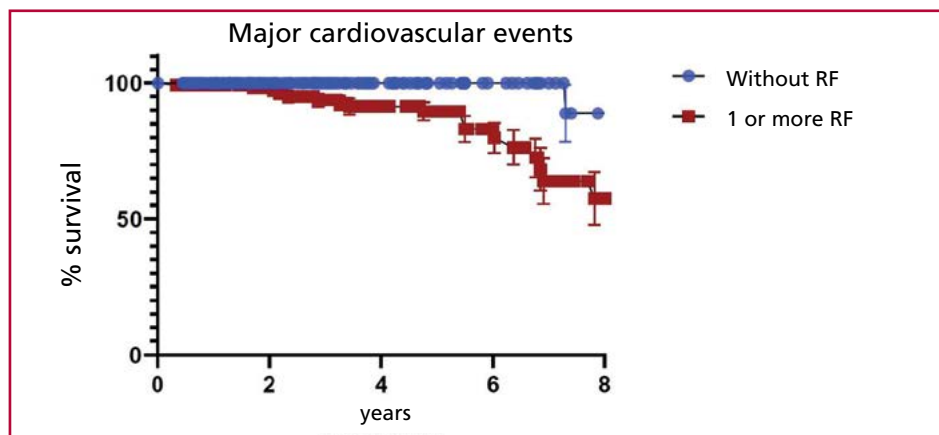


Fig. 2. Kaplan-Meier curve showing major cardiovascular event-free survival (death, cardiovascular surgery and/or acute aortic syndrome) in patients with and without aortic valve dysfunction risk factors (aortic valve prolapse, aortic valve calcification and/or age ≥ 50 years). Patients with at least one risk factor presented lower major cardiovascular event-free survival (chi-square log-rank test: 13.79, $p=0.0002$). Vertical bars indicate standard error. RF: Risk factors.

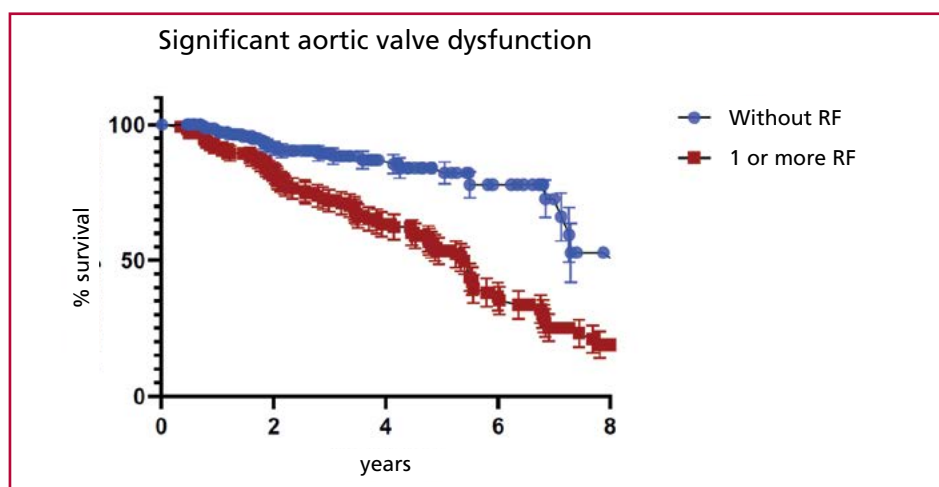


Fig. 3. Kaplan-Meier curve showing significant aortic valve dysfunction-free survival (death, cardiovascular surgery and/or acute aortic syndrome) in patients with and without aortic valve dysfunction risk factors (aortic valve prolapse, aortic valve calcification and/or age ≥ 50 years). Patients with at least one risk factor presented lower event-free (dysfunction) survival (chi-square log-rank test: 23.5, $p=0.0001$). Vertical bars indicate standard error. RF: Risk factors.

patients with BAV found a higher incidence of events in patients with type II BAV. (15) Moreover, Kong et al. recently reported a higher incidence of events in BAV with raphe. (16) The Catalan group of Evangelista et al. recently published an association between the presence of raphe and progression of aortic stenosis (17) In the series by Kong et al., patients with raphe were significantly older, and it is difficult to separate the impact of age as a predictor of events from the presence of raphe as a possible confounder. However, in the independent analysis of event predictors, neither the Mayo Clinic nor the Canadian group have found a clear association of either valve phenotype or raphe as predictors of events in their publications. (13, 14) An independent association between the presence of raphe and/or valve phenotype and the incidence of major cardiovascular events was not found in our cohort, although follow-up is still short to rule out such association.

Concerning the degree of aortic valve calcification as predictor of valve dysfunction, we report a signifi-

cant association between these two variables, similarly to other authors. The degree of valve calcification has been associated with rapid progression of aortic stenosis, especially in patients with degenerative aortic stenosis. (6, 7, 19, 19) However, in young patients with BAV, the information published is scarce. Particularly, the identification of aortic valve calcification in patients with BAV identifies the subgroup of patients who present a higher risk of major events and development of significant aortic stenosis with a 5-year surgery requirement. Also, this finding is more frequent in women.

On the other hand, in relation to aortic valve prolapse, there is only one work recently published by the Catalan group that has reported the same association as ours (17). Significant aortic regurgitation in BAV occurs predominantly in men and valve asymmetry associated with greater valve prolapse could play a role in its progression. Since prolapse can be identified with TTE and could be a predictor of significant events and dysfunction, we believe it is relevant to de-

termine its presence and include its description in the echocardiographic reports of patients with BAV.

Finally, it is important to highlight that aortic dilation is prevalent in these patients. (19, 20) In patients with BAV, aortic dilation is more frequent than in the general population (19). Its finding can be decisive in the evolution, either due to contraindication of certain sporting activities, to the need for closer monitoring or to the need for surgery owing to the significant increase in the diameters with greater risk of rupture and/or aortic dissection. In our study, surgical indication was decided by aortic diameters in three patients, rather than by valve dysfunction. The annual aortic growth rate in patients with BAV is significant considering that it is a congenital heart disease. In the era of prophylactic surgical indication, the rate of acute aortic syndromes is lower than that reported in previous studies. (20, 21) Although in our cohort no acute aortic syndromes were observed, the incidence is probably lower due to the prophylactic surgical indication when the risk of dissection is high (diameter greater than 5.5 cm in the absence of risk factors). In addition, a longer follow-up would allow evaluating the real incidence of this complication.

Limitations and strengths

We consider that as it is a congenital heart disease, the short follow-up is a study limitation. However, conducting prospective longitudinal studies in our country is difficult and we believe the information provided by the study is valuable, even with 5 years of follow-up. These results reflect the first years of the cohort follow-up, which still continues.

Moreover, we did not include pediatric patients, since our center receives patients over 18 years of age. All patients were asymptomatic at the time of inclusion in the study and the follow-up/intervention conduct was taken independently.

On the other hand, less than half of the patients underwent computed tomography and/or cardiac magnetic resonance imaging, so the prevalence of aortic dilation could be underestimated, since TTE has limitations to evaluate the entire thoracic aorta.

The detection of risk groups in patients with a pathology that requires lifelong follow-up allows health resources to be used more judiciously. Close monitoring would also allow determining the moment of surgical indication, with its consequent impact on the patient's prognosis.

CONCLUSIONS

The results of our study with 4.9 years of follow-up show a high incidence of significant aortic valve dysfunction and major cardiovascular events (at the expense of aortic valve replacement surgery) in young adult patients with BAV.

Patients with one or more of the following factors: aortic valve prolapse, significant aortic valve calcification and/or over 50 years of age had a higher

incidence of significant aortic valve dysfunction and major events during follow-up. These findings would identify risk subgroups and intensify their cardiologic follow-up.

Future directions

Our group is currently conducting a substudy to evaluate the usefulness of cardiac multislice computed tomography combined with TTE for the quantification of calcium and early identification of valve characteristics in adults with BAV. We also plan to validate the predictive value of the risk factors proposed in a cohort of patients with BAV from another institution.

Conflicts of interest

All the authors of this work have contributed to the study and accepted the Editorial Committee conditions, confirming no direct or indirect conflicts of interest.

(See authors' conflicts of interest forms on the website/Supplementary material)

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