Fate of mild-to-moderate bicuspid aortic valve disease untreated during ascending aorta replacement

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Abstract

Background: Bicuspid aortic valve (BAV) is the most common congenital heart defect and it is responsible for an increased risk of developing aortic valve and ascending aorta complications. In case of mild to moderate BAV disease in patients undergoing supracoronary ascending aorta replacement, it is unclear whether a concomitant aortic valve replacement should be performed. Methods: From June 2002 to January 2020, 75 patients with mild-to-moderate BAV regurgitation (± mild-to-moderate stenosis) who underwent isolated supracoronary ascending aorta replacement were retrospectively analyze. Clinical and echocardiographic follow-up was 100% complete (mean: 7.4±3.9 years, max 16.4). Kaplan Meier estimates were employed to analyze long-term survival. Cumulative incidence function for time to re-operation, recurrence of aortic regurgitation (AR)[?]3+ and aortic stenosis (AS) greater than moderate, with death as competing risk, were computed. Results: There was no hospital mortality and no cardiac death occurred. Overall survival at 12 years was 97.4+-2.5%, 95% CI [83.16-99.63]. At follow-up there were no cases of aortic root surgery whereas 3 patients underwent AV replacement. At 12 years the CIF of reoperation was 2.6+-2.5%, 95% CI [0.20-11.53]. At follow up, AR 3+/4+ was present in 1 pt and AS greater than moderate in 3. At 12 years the CIF of AR>2+/4+ was 5.1+-4.98% and of AS>moderate 6.9+-3.8%. Conclusions: In our study mild to moderate regurgitation of a BAV did not significantly worse at least up to 10 years after isolated supracoronary ascending aorta replacement.

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Running head: BAV disease untreated during AAR

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Abstract

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Methods: From June 2002 to January 2020, 75 patients with mild-to-moderate BAV regurgitation (± mild-to-moderate stenosis) who underwent isolated supracoronary ascending aorta replacement were retrospectively analyze. Clinical and echocardiographic follow-up was 100% complete (mean: 7.4±3.9 years, max 16.4). Kaplan Meier estimates were employed to analyze long-term survival. Cumulative incidence function for time to re-operation, recurrence of aortic regurgitation (AR)[?]3+ and aortic stenosis (AS) greater than moderate, with death as competing risk, were computed.

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Abbreviations and acronyms

AAR: ascending aorta replacement

AKI: acute kidney injury

AVR: aortic valve replacement

BAV: bicuspid aortic valve

CIF: cumulative incidence function

CPB: cardiopulmonary bypass

EF: ejection fraction

LCOS: low cardiac output syndrome

STJ: sino-tubular junction

TAVI: transcatheter aortic valve implantation

Introduction

Bicuspid aortic valve (BAV) is the most frequent congenital cardiac anomaly, with a prevalence of 1-2%[1] in the general population. Aortic valve dysfunction and thoracic aortic disease are the most common complications associated with BAV. Within thoracic aortic aneurysms in BAV patients, supra-coronary aneurysm is the prevalent phenotype (60-70% of dilatated aortas)[2,3]. In patients with normal functioning BAV and supracoronary ascending aorta aneurysm the 2017 European Guidelines[4] advise for isolated ascending aorta replacement , and two recent studies confirm good long-term function of the BAV [5,6,7]. However, in patients undergoing supracoronary ascending aorta replacement with concomitant mild-to moderate BAV diseases, the indication to aortic valve replacement (AVR) is still a matter of debate. The aim of this study is to assess the long-term evolution of untreated mild and moderate BAV disease after isolated ascending aortic replacement.

Materials and methods

Study population and follow-up

A retrospective review of our Institutional, prospectively maintained, database was carried out to identify patients with BAV and mild to moderate aortic regurgitation who underwent elective ascending aorta replacement from June 2002 to January 2020. Patients with acute aortic dissections and aortic root pathology were excluded. Bicuspid aortic valve morphology was preoperatively characterized by means of trans-thoracic or trans-esophageal echocardiography and subsequently intraoperatively confirmed. Patients charts were then analyzed to obtain details about pre-operative characteristics, intra-operative variables and in-hospital outcomes. All operations were performed using conventional cardio-pulmonary by-pass and mild hypothermia through a median sternotomy. The final decision to preserve the BAV was taken intraoperatively by the operating surgeon according to the degeneration degree of the aortic leaflets. Usually the native BAV was preserved because the leaflets appeared relatively free from fibrosis or calcification. The size of the aortic vascular graft, and the subsequent degree of sino-tubular junction (STJ) remodeling, was decided by the operating surgeon according to the anatomical finding. In case of moderate aortic regurgitation, type Ia according to the El-Khoury classification[8], a smaller graft was employed to restore a more physiological annulus/STJ ratio and decrease the grade of aortic regurgitation. Transesophageal echocardiography was performed after weaning from the CPB to assess the BAV function. Survival and echocardiographic follow-up were carried on querying the informatic hospital system for out-patients visit and echocardiographic examinations. If follow up information were not present in the hospital system, patients were reached via phone call or the referring cardiologist was contacted. The Ethical Committee of our Institution approved the study and individual informed consent for this retrospective analysis was not requested.

Statistical analysis

All analysis were performed with Stata software version 15. Categorical data were described as absolute and percentage (%) values. Continuous normal distributed variables were expressed as mean +-standard deviation (SD), while continuous not-normal variables were reported as median and [25th percentile; 75th percentile]. To assess normal distribution Shapiro-Wilk test was employed. Kaplan-Meier estimates were used to analyze long-term survival. Cumulative incidence function (CIF) was computed for recurrence of aortic valve regurgitation ([?]3+), aortic valve stenosis ([?]3+), with death as competing risk. Spaghetti plots were used to support visual assessment of the longitudinal trajectory of the degree of Aortic valve regurgitation and Aortic valve stenosis for each individual over time. In particular, a spaghetti plot shows for each patient the values for the repeated outcome measure (aortic valve stenosis and aortic valve regurgitation on vertical axis) versus time (horizontal axis) and connects the dots chronologically, using lines of uniform color and intensity for each subject. A p-value of less than 0.05 was employed to define statistical significance.

Results

Patients characteristics and in hospital results

During the study period 666 consecutive BAV patients underwent elective thoracic aortic surgery. Of these

591 patients underwent root replacement (both valve sparring root replacement and Bentall procedure) or ascending aortic replacement combined with AVR and were excluded. The remaining 75 patients represent the focus of the study. Mean age was 56 +- 12 years. Most of the patients were male (N=42 75%) and had hypertension (56%). The mean left ventricular ejection fraction (EF) was 50,0 +- 5,27 and median left ventricular EDD was 60,0 [57,0-65,0]. Preoperative characteristics of the patients are listed in Table 1. The mean Valsava sinuses and STJ diameter were respectively 39,7 +- 4,01 mm and 35,9 +- 4,90 mm. A total of 33/75 patients (44%) had moderate aortic regurgitation, while 42/75 (56%) had mild aortic regurgitation. Mild aortic valve stenosis was detected in 5/75 (6,7%) patients and 3/75 (4%) patients had moderate aortic valve stenosis. These three patients were elderly and with a relative high surgical risk, the aortic gradients were at the inferior limit (mean gradient between 25 and 28 mmHg in all 3 patients) and intraoperatively the valve was relatively free of significant calcification, and for all these reasons the operating surgeon decided not to proceed with surgical AVR. The most common aortic valve phenotype in our patients was BAV type 0 antero-posterior (55/75, 73%), followed by BAV type 1 left-right (17/75, 23%) and BAV type 1 right-non coronary (3/75, 4%). Mitral valve repair, as concomitant procedure, was performed in 2 patients (2,5%) and coronary artery bypass grafting in 2 patients (2,5%). The median postoperative length of stay was 6 [4,5-7.5] days, no patient presented stroke or required re-exploration for bleeding and there were no in-hospital deaths, as shown in Table 2. Before discharge, all patients underwent trans-thoracic echocardiography and no significant differences in the degree of aortic regurgitation or stenosis were found.

Long term outcomes

Clinical and echocardiographic follow-up was 100% complete (mean follow-up: 7.4+-3.9 years, max 16.4; median 6.8 years [4.5-10.8]). During the follow-up 2 patients died for non-cardiac causes whereas no cardiac deaths occurred. Overall survival at 12 years was 97.4+-2.5%, 95% CI [83.16-99.63] (Fig. 1). Aortic root surgery was not necessary in any patient. Three patients underwent aortic valve replacement. One patient needed reoperation for endocarditis 149 months after the intervention. The others two patients developed severe aortic valve stenosis: one underwent surgical AVR after 154 months, and the other to transcatheter aortic valve implantation (TAVI), after 84 months. Interestingly, both patients didn't show any grade of aortic stenosis at the preoperative echocardiography in which only some degree of regurgitation had been detected. None of the 3 patients with moderate aortic stenosis at baseline did require aortic valve replacement for significant disease progression. At 12 years the CIF of reoperation with death as competing risk was 2.6 +-2.5%, 95% CI [0.20-11.53] (Fig. 2). At the echocardiographic follow up the median EF was 55 [55-60], aortic regurgitation 3+/4+ was present in 1 patient and aortic stenosis greater than moderate in 3 (Fig. 3,4). At 12 years the CIF of aortic regurgitation >2+/4+ was 5.1+-4.98% and of aortic stenosis >moderate 6.9+-3.8% (Fig. 5).

Comment

BAV is the most common congenital cardiac anomaly[1] and its correlation with thoracic aortic disease is well established, so as to be defined "BAV aortopathy"[9,10]. Within thoracic aortic aneurysm, supracoronary ascending aorta dilatation results to be the prevalent phenotype[2,3,11]. In our cohort the most relevant BAV phenotype were BAV type 0 antero-posterior (55/75, 73%) and BAV type 1 left-right (17/75, 23%), these results do not differ from the findings by Sievers and coworkers[12] who had previously investigated the association with BAV phenotype and aortic configuration. Michelena and coworkers, analyzing a cohort of 212 patients with normal functioning BAV[13], reported that 20 years after the diagnosis 5 +- 2% of the patients required ascending aorta surgery for aneurysmal degeneration, while AVR was required in 24 +- 4 % of the patients. Similarly, Russo and coworkers[5,6] analyzing a cohort of 40 patients undergoing supra-coronary ascending aorta replacement with normally functioning BAV reported that , after a mean follow-up 93 +- 50 months, only 4 patients required AVR, 3 for aortic regurgitation and 1 for aortic stenosis and at 10-years, they reported that freedom from cardiac death was 83 +- 16%. Likewise, Vinholo and coworkers[7]published the long-term (mean echocardiography follow up 4,50 +- 4,09 years) results of 23 patients with none or trace of aortic regurgitation or stenosis who underwent ascending aorta replacement without aortic valve replacement. In this group, 5 patients showed a progression of the aortic regurgitation or stenosis from

none to mild and 2 patients from none to severe. Only 1 patient required aortic valve replacement during follow up. Differently, we analyzed the evolution of the BAV disease in patients undergoing supracoronary ascending aorta replacement who, at the time of aortic surgery, already presented moderate (33/75, 44%) or mild (42/75, 56%) aortic regurgitation. During the follow up, only 1 patient presented a worsening of the AR, while 3 patients developed aortic stenosis more than moderate. Of these 2 needed AVR: 1 surgical and 1 trans-catheter. Moreover 1 patient required re-operation for endocarditis. These data showed good durability of the BAV preserved during supracoronary ascending aorta replacement.

No patients required reoperation for aortic root dilatation, as reported in previous studies[14,15]. No cardiac deaths occurred.

Limitations

This study presents numerous limitations: it is a single center retrospective study and has all the limitations related to this model of analysis, the lack of echocardiography details about the Color Doppler measures (vena contracta and jet width), the mechanism of aortic regurgitation and the grade of STJ remodeling during surgery. For these reasons further studies with larger number of patients and more echocardiographic features are necessary to better understand the real nature and evolution of this disease.

Conclusion

In conclusion in our study, mild to moderate regurgitation of a BAV did not significantly worse after isolated supracoronary ascending aorta replacement. When progression of the BAV disease occurs, the evolution seems to be more commonly towards a higher degree of stenosis. Despite this, the need of reoperation due to severe BAV disease is low and this finding is reassuring particularly when dealing with elderly patients. TAVI could be a subsequent possible therapeutic strategy in this case[16]. Our data can help the decision-making process in this controversial setting, although larger series and longer follow-ups are needed.

Acknowledgments

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Table 1: Preoperative/Intraoperative characteristics

Age (mean+ SD)	55,9 ±12
Male (n,%)	57 (75,0)
Hypertension (n,%)	42 (56,0)
Diabetes (n,%)	3 (4,0)
Creatinine, mg/dL (median, IQR)	0,9 [0,7-0,9]
Valsalva sinuses, mm (mean+ SD)	39,7 ± 4,01
Sino-tubular junction, mm (mean+ SD)	35,9 ± 4,90
Aortic tubular tract, mm (mean+ SD)	50,5 ± 3,15
Aortic valve stenosis (n,%) none mild moderate	67 (89,3) 5 (6,7) 3 (4)
Aortic valve regurgitation (n,%) mild moderate	42 (56,0) 33 (44,0)
BAV phenotype (n,%) AP LR RNC	55 (73,3) 17 (22,7) 3 (4)
Left ventricle EDD, mm (median, IQR)	60,0 [57,0-65,0]
EF, % (mean + SD)	50,0 ± 5,27
Concomitant procedure (n,%) MV surgery CABG	2 (2,50) 2 (2,50)

AP: antero-posterior, BAV: bicuspid aortic valve, CABG: coronary artery bypass grafting, EDD: end diastolic diameter, EF: ejection fraction, IQR: interquantile range, LR: left-right, MV: mitral valve, RNC: right-non coronary, SD: standar deviation

Table 2: Postoperative data

Length of stay, days (median, IQR)	6 [4,5-7,5]

Length of stay, days (median, IQR)	6 [4,5-7,5]
LCOS (n, %)	4 (5,3)
AF (n, %)	10 (13,3)
AKI (n, %)	1 (1,3)
Stroke (n, %)	0
Re-exploration for bleeding (n, %)	0
In-hospital deaths (n, %)	0

AF: atrial fibrillation, AKI: acute kidney injury, LCOS: low cardiac output syndrome

Figure Legends

Figure 1: Overall survival al 12 years. Dotted lines represent 95% confidence intervals.

Figure 2: CIF of reoperation at 12 years. Dotted lines represent 95% confidence intervals.

Figure 3: Aortic regurgitation evolution at the follow up.

Figure 4: Aortic stenosis evolution at the follow up.

Figure 5: CIF of aortic stenosis >moderate. Dotted lines represent 95% confidence intervals.