ORIGINAL PAPER

Therapeutic approach comparison in bicuspid aortic valve aortopathy and clinical practice implications

CIPRIAN NICUȘOR DIMA^{1,2)}, CAIUS GLAD STREIAN^{1,2)}, MARIAN GAȘPAR^{1,2)}, SILVIU CRISTIAN SUCIU³⁾, CONSTANTIN CARAION⁴⁾, ELIAN OCTAVIAN BOLDU²⁾, SIMONA CERBU⁵⁾, EMIL RADU IACOB⁶⁾, CONSTANTIN TUDOR LUCA^{2,7)}, LUCIAN PETRESCU^{2,7)}

¹⁾Department of Cardiovascular Surgery, Victor Babeș University of Medicine and Pharmacy, Timișoara, Romania

²⁾Department of Cardiovascular Surgery, Institute of Cardiovascular Diseases, Timișoara, Romania

³⁾Department of Microscopic Morphology, Victor Babeș University of Medicine and Pharmacy, Timișoara, Romania

⁴⁾Department of Functional Sciences, Victor Babeș University of Medicine and Pharmacy, Timișoara, Romania

⁵⁾Department of Radiology and Medical Imaging, Victor Babeș University of Medicine and Pharmacy, Timișoara, Romania

⁶⁾Department of Pediatric Surgery, Victor Babeș University of Medicine and Pharmacy, Timișoara, Romania

⁷⁾Department of Cardiology, Victor Babeș University of Medicine and Pharmacy, Timișoara, Romania

Abstract

Bicuspid aortic valve (BAV) is the most common heart valve malformation, and it may be associated with the development of long-term complications, such as aortic stenosis (AS) secondary to valvular calcification and aortic insufficiency (AI), with or without ascending aortic aneurysm (AAA). This study was performed at the Institute of Cardiovascular Diseases, Timișoara, Romania, from 2015 through 2018 and included a total of 105 patients with BAV. Out of the 105 BAV patients, 14 displayed AAA, alongside either AS or AI, and were selected to undergo aortic valve replacement (AVR) alongside surgical replacement or aortoplasty of the ascending aorta, and the elastic fiber loss in the ascending aortic wall was evaluated for each patient. Two surgical interventions used alongside AVR in BAV patients with AAA and AS or AI were compared in this study: reduction ascending aortoplasty (RAA) and ascending aorta replacement (AAR). Postoperative follow-ups have shown RAA is useful short-term but that, in contrast to AAR, it leads to aortic redilatation over time. These results can contribute to a major future meta-analysis with the goal of improving the current clinical practice guidelines for BAV aortopathy.

Keywords: bicuspid aortic valve, aortopathy, aortic stenosis, aortic insufficiency, reduction ascending aortoplasty.

Introduction

Bicuspid aortic valve (BAV) is the most frequent congenital heart abnormality, with a prevalence of approximately 1% in the general population [1]. The associated pathologies can be aortic stenosis (AS), aortic insufficiency (AI), ascending aortic aneurysm (AAA), and infectious endocarditis [2–5]. A lot of disorders associated with aortopathy have been observed in BAV patients [6, 7]. A BAV may develop progressive calcification similar to a tricuspid aortic valve, but the calcification of the bicuspid valve is more pronounced than that of the tricuspid valve [8, 9]. BAV appears to be a genetic disease, with data from the literature suggesting a prevalence of 9% among first-degree relatives [10]. According to other authors, among patients who needed surgery, there were more cases of AI in men and more cases of AS in women [11, 12].

BAV has a heterogeneous clinical appearance, and the surgical approach should be adjusted according to its different clinical forms [13].

Studies have shown that over 30% of BAV patients will develop severe complications, BAV being the main cause for AS in all age groups and for AI with or without infection in young adults, and only 20% of BAV patients can

live a life free of cardiovascular complications secondary to the disease [14, 15].

Aim

This study aims to compare two surgical treatments of BAV patients with AAA, namely reduction ascending aortoplasty (RAA) and ascending aorta replacement (AAR), and at the same time find correlations between different clinical characteristics, which can lead to the identification of risk factors in BAV patients and therefore have an impact on the clinical practice guidelines by offering new therapeutic options.

Patients, Materials, and Methods

Selection of patients

This study was conducted within the Institute of Cardiovascular Diseases, Timișoara, which serves the western region of Romania. The study included patients hospitalized from January 2015 through January 2020.

Patients with Marfan syndrome, coronary artery disease, congenital heart disease, coarctation of the aorta, and other disorders that could be related to BAV and considerably lower patient life expectancy, such as oncological diseases,

were excluded from this study. Biological, clinical, and imaging tests have been performed for comprehensively evaluating the aorta and its different anatomic variations.

AVR was performed for all 105 BAV patients included in this study. The 14 BAV patients that displayed AAA additionally underwent AAR or RAA.

Both the morphology and function of the aortic valve were evaluated by preoperative two-dimensional transthoracic echocardiography (2D TTE) and three-dimensional transesophageal echocardiography (3D TEE) in all 105 BAV patients. Histological testing of the ascending aortic wall was conducted for the 14 BAV patients with AAA to evaluate elastic fiber loss compared to patients with tricuspid aortic valves.

Patients from all groups underwent postoperative visits at fixed time intervals after the intervention, namely at six weeks, 12 weeks, and then yearly. All 14 BAV patients with AAA were present at each postoperative follow-up, while approximately 10% of BAV patients without AAA have been excluded from the follow-up results, as they had not been consistent in attending the postoperative follow-ups on time.

This study was evaluated and approved by the Research Ethics Committee of the Victor Babeș University of Medicine and Pharmacy, Timișoara, Romania.

Echography

Echocardiography was performed using a Philips ultrasound machine (Philips Medical Systems). Preoperative 2D TTE and intraoperative 3D TEE have been used to quantify left ventricular function, to measure the aortic annulus, aortic lumen, and aortic arch diameters, examine the aspect and regurgitation, and to assess aortic valve function and BAV morphology, which can be either Type A, representing the fusion of the right and left coronary leaflets, Type B, representing the fusion of the right coronary and non-coronary leaflets, and Type C, representing the fusion of the left coronary and non-coronary leaflets.

Surgical procedures

Surgical procedures were conducted by an experienced surgeon, median sternotomy was performed, and patients were hypothermic at 30°C. Cardiopulmonary bypass was established, and the ascending aorta was clamped at the level of the emerging brachiocephalic trunk. St. Thomas crystalloid cardioplegia was administered intermittently at 20-minute intervals.

Figure 1 – Intraoperative aspect of the bicuspid valve. The two leaflets (cusps) as well as massive calcifications can be observed.

Histopathology exams

Samples were washed with saline and fixed in 10% neutral buffered formalin for 48 hours. The samples were dehydrated, cleared, and paraffin embedded. Five μ m thick sections were taken from each paraffin block and mounted on salinized slides. Conventional microscopy was employed for the morphological and histochemical interpretation of the stained slides, using an AxioCam 506 camera (Zeiss, Jena, Germany). Images were generated by scanning the slides using the Panoramic Viewer system (3DHISTECH, Hungary).

Results

Preoperative and intraoperative results

This study included 105 BAV patients with a mean age of 54 ± 15 years, out of which 64 (61%) patients were men and 41 (39%) women. Approximately 2/3 of patients came from rural areas. Of the 105 BAV patients included in this study, 14 (13.3%) were diagnosed with AAA and underwent AVR alongside either AAR or RAA, while the remaining 91 (86.7%) patients underwent only AVR. The 14 BAV patients with AAA had a mean age of 53.8 years, and this predisposition was found mostly in men (78.6% of cases). Of these 14 BAV patients with AAA, nine (64.29%) had severe AS and five (35.71%) had AI. BAV patients with AAA that presented both AS and AI have been grouped considering the pathology that was most dominant.

All BAV patients underwent surgery to replace the aortic valve, while those also presenting AAA additionally underwent AAR or RAA. RAA was performed on the ascending aorta in 50% of cases and AAR surgery was performed in the remaining 50%.

Intraoperatively, the size of each graft was selected based on echocardiographic measurements and the BAVs were replaced with either mechanical or biological prostheses. Figures 1 and 2 show the intraoperative bicuspid valve aspect of the youngest patient enrolled in this study, a 27-year-old male.

BAV patients with AAA displaying an aortic lumen diameter of 5–5.5 cm underwent RAA, which entailed resecting an oval section of the ascending aortic wall and performing aortorrhaphy using a 4-0 Prolene double-armed suture. The aortic lumen was reduced to a maximum of 4 cm.

Figure 2 – Intraoperative aspect of valvular replacement using a mechanical prosthesis.

For BAV patients with AAA displaying an aortic lumen diameter ≥ 5.6 cm, the ascending aortas were replaced with tubular prostheses made of synthetic material (Dacron).

The type of prosthesis was selected based on patient age, *i.e.*, biological prostheses for patients aged over 65 and mechanical prostheses for the rest, as described in Figure 3. RAA was the type of surgical intervention used in elderly patients with severe cardiovascular disease, due to the high intraoperative risk, as well as in other patients depending on the degree of aortic dilatation and classification of the ascending aortic wall, intraoperatively

Figure 3 – Type of intervention directly correlated with age. AAR: Ascending aorta replacement; AVRb: Aortic valve replacement using biological prosthesis; AVRm: Aortic valve replacement using mechanical prosthesis; RAA: Reduction ascending aortoplasty.

Figure 5 – Schematic showing diagnosis, type of intervention, and postoperative follow-up for each group of patients. AAA: Ascending aortic aneurysm; AAR: Ascending aorta replacement; AI: Aortic insufficiency; AS: Aortic stenosis; AVR: Aortic valve replacement; BAV: Bicuspid aortic valve; RAA: Reduction ascending aortoplasty.

evaluated by the surgical team. The degree of dilatation was directly correlated with aortic lumen diameter and a high degree indicated an aortic wall unsuitable for RAA, as shown in Figure 4. All AVR, RAA, and AAR procedures performed in BAV patients with AAA have met the criteria that the aortic lumen diameter was ≥ 50 mm.

These patients have been grouped accordingly, and a detailed map showing the diagnosis, type of intervention, and postoperative follow-up for each group can be seen in Figure 5.

Figure 4 – Type of intervention directly correlated with aortic lumen diameter. AAR: Ascending aorta replacement; AVRb: Aortic valve replacement using biological prosthesis; AVRm: Aortic valve replacement using mechanical prosthesis; RAA: Reduction ascending aortoplasty.

No surgical re-interventions have been performed nor did any subsequent aortic complications, such as dissection or rupture, occur.

Histopathological study

Macroscopic examination of the heart valves showed their uneven deformation and thickening, with irregular edges, areas of calcification and intense sclerosis (Figure 6).

Figure 6 – Macroscopic aspect of the bicuspid valves showing degenerations.

The heart valves and areas of the excised aortic artery wall were fixed in 10% neutral buffered formalin solution for 72 hours, embedded in paraffin, and then examined under an optical microscope. In our study, we used two classical stainings: Hematoxylin–Eosin (HE) and Goldner–Szekely (GS) light green trichrome.

For the immunohistochemical (IHC) study, we used anti-cluster of differentiation 34 (CD34) antibodies (monoclonal mouse anti-human CD34 Class II, clone QBEnd-10, 1/50 dilution, Dako) to highlight the micro-vascularization of the heart valves, anti-alpha-smooth

muscle actin (α -SMA) (monoclonal mouse anti-human SMA, clone 1A4, 1/100 dilution, Dako) to highlight the myofibroblasts in the valve structure and anti-cluster of differentiation 68 (CD68) (monoclonal anti-human CD68, clone KP1, 1/100 dilution, Dako) to highlight the macrophage cells participating in the heart valve remodeling processes.

Microscopic examination revealed at the level of the heart valves the presence of a dense connective tissue, with thick collagen fibers, arranged disorderly and with numerous fibroblastic type connective cells. In some areas, inhomogeneous calcifications of the valve structure have been highlighted (Figures 7 and 8). Calcium deposits were of various sizes and shapes and were identified throughout the valve area (Figures 9 and 10). In the structure of the heart valves, small areas rich in loose connective tissue were identified, with numerous inflammatory cells and blood vessels (capillaries, arterioles, and venules) with a disordered arrangement, similar to those in a granulation tissue.

IHC examination showed extremely low vascularization of the valves in areas with sclerotic tissue, but in areas with lax connective tissue, vascularization was intense

(Figures 11 and 12). Myofibroblasts and macrophage cells were absent in areas with sclerotic tissue of the heart valves but were present in large numbers in areas with lax connective tissue (Figures 13 and 14).

Histological examination of excised aortic wall samples showed interlamellar degeneration with mucoid replacement, loss and fragmentation of elastic fibers (Figures 15 and 16).

Postoperative monitoring

Each postoperative follow-up consisted of clinical assessment, chest X-ray, electrocardiogram (ECG), TTE, and blood testing aimed at detecting complications, *i.e.*, prosthetic thrombosis, bioprosthetic failure, paravalvular leaks, hemolysis, and heart failure. Antithrombotic therapy, personalized based on the prosthesis used and patient-related risk factors, was prescribed lifelong for all mechanical prostheses or during the first three post-operative months for biological prostheses.

The mean follow-up time was 39 ± 12 months and it included both BAV patients that underwent AVR only and those who also benefited from RAA or AAR alongside AVR.

Figure 7 – Microscopic image of an area of the heart valve, rich in fibroblast collagen fibers, and calcium salt deposits (HE staining, $\times 100$). HE: Hematoxylin–Eosin.

Figure 8 – Image of heart valve with intensely calcified areas (GS trichrome staining, $\times 100$). GS: Goldner–Szekely.

Figure 9 – The area of the heart valve consists of dense connective tissue, partially calcified (HE staining, $\times 100$).

Figure 10 – Cardiac valve area, rich in loose connective tissue, with numerous blood vessels and small deposits of calcium salts (GS trichrome staining, $\times 100$).

Figure 11 – Image of heart valve with a sclerotic area, poor in blood vessels, and a lax connective tissue area, well vascularized (Immunostaining with anti-CD34 antibody, $\times 100$). CD34: Cluster of differentiation.

Figure 12 – Cardiac valve area, rich in lax connective tissue, with numerous blood vessels (Immunostaining with anti-CD34 antibody, $\times 40$).

Figure 13 – Microscopic image of a heart valve area, rich in lax connective tissue with numerous myofibroblasts (Immunostaining with anti- α -SMA antibody, $\times 100$). α -SMA: Alpha-smooth muscle actin.

Figure 14 – The area of the heart valve, rich in loose connective tissue, blood vessels and macrophages (Immunostaining with anti-CD68 antibody, $\times 100$). CD68: Cluster of differentiation 68.

Figure 15 – Ascending aortic wall including intima and media. Note the presence of interlamellar degeneration with mucoid replacement (HE staining, $\times 100$).

Figure 16 – Ascending aortic wall showing changes of the elastic lamellae with partial and focal loss of the elastic component and the persistence of chromophobic spaces located at irregular intervals between the elastic lamellae (Orcein staining, $\times 100$).

At three years post-operation, there was no need for surgical re-interventions. BAV patients with AAA and AS who underwent AVR and RAA developed aortic redilatation over time, in contrast to BAV patients with AAA and AS who underwent AVR and AAR. Aortic redilatation occurred in four out of seven BAV patients with AAA that underwent AVR and RAA, namely three out of three patients with AI and one out of four patients with AS. Postoperatively, their aortic lumen mean diameter was 33.8 ± 5 mm, while at three years after surgery it was 34.6 ± 5 mm, therefore

showing an approximately 0.24% increase over the three-year period. None of the BAV patients with AAA that underwent AVR and AAR suffered aortic redilatation during the same three-year period. Table 1 encompasses the pre-operative, postoperative, and follow-up echocardiographic measurements of aortic lumen diameter for the 14 BAV patients with AAA. These results show that, although RAA can be useful short-term, it causes aortic redilatation and therefore requires more thorough monitoring than AAR, which does not cause aortic redilatation.

Table 1 – Preoperative, postoperative, and follow-up echocardiographic measurements of aortic lumen diameter for the 14 BAV patients with AAA

Patient No.	Gender	Age [years]	Preoperative aortic lumen diameter [mm]	AS	AI	Interventions	Postoperative aortic lumen diameter [mm]	Aortic lumen diameter at three years follow-up [mm]
1.	M	27	55		*	AVRm + RAA	36	37.9
2.	M	72	62.5		*	AVRb + AAR	28	28
3.	M	42	59		*	AVRm + AAR	28	28
4.	M	74	58		*	AVRb + AAR	28	28
5.	F	51	52		*	AVRm + RAA	35.5	38.8
6.	M	52	56		*	AVRm + AAR	28	28
7.	M	37	51		*	AVRm + RAA	37.2	39.5
8.	M	59	65		*	AVRm + AAR	32	32
9.	M	42	52		*	AVRm + RAA	38.4	39.4
10.	M	29	57		*	AVRm + AAR	34	34
11.	M	64	55		*	AVRm + RAA	40	42.3
12.	M	62	55		*	AVRm + RAA	39	39.8
13.	F	69	51		*	AVRb + RAA	38.5	38.9
14.	F	74	59		*	AVRm + AAR	30	30

AAA: Ascending aortic aneurysm; AAR: Ascending aorta replacement; AI: Aortic insufficiency; AS: Aortic stenosis; AVRb: Aortic valve replacement using biological prosthesis; AVRm: Aortic valve replacement using mechanical prosthesis; BAV: Bicuspid aortic valve; F: Female; M: Male; RAA: Reduction ascending aortoplasty.

The results also show that BAV patients with AAA and AI that underwent AVR and RAA developed aortic redilatation much faster and, therefore, will require surgical re-intervention much sooner than BAV patients with AAA and AS that underwent the same procedures.

For the 91 BAV patients without AAA that underwent AVR, no significant aortic modifications have been reported at three years post-operation and, therefore, these patients did not require a yearly follow-up.

Discussions

In BAV patients with AAA, surgical treatment is challenging and there is currently controversy related to the therapeutic act [16, 17]. There is a large phenotypic variety in BAV [6, 7, 18]. Therefore, the surgical method needs to be adapted to the pathogenic mechanisms of the different BAV phenotypes [19]. A review published in 2017, following the collection of clinical/scientific data from literature published over the course of a year, shows that clinical studies that compared results of BAV patients after the sole replacement of the aortic valve agree regarding the existence of an increased risk for severe aortic complications in patients with AI compared to those with AS [13].

Surgical guidelines for AAR in BAV patients are supported by the argument that BAV aortopathy is more similar to Marfan syndrome aortopathy than to the aortopathy secondary to tricuspid valve degenerative diseases [14]. Multiple international clinical practice guidelines from 1998–2014 take a stance either for RAA or the more aggressive technique of AAR [20–22].

The results in this study show most BAV patients with AAA that underwent AVR and RAA (four out of seven) have suffered aortic redilatation over time, while none of the same group of patients that underwent AVR and AAR displayed redilatation.

A study from 2016 has shown that pathogenic mechanisms at the level of the proximal aorta are similar in BAV patients with AS and patients with tricuspid valvulopathy [23]. BAV accompanied by AI has been found to develop aortic complications at some point up to 15 years from the AVR intervention [24]. In this study, echocardiographic results up to three years post-operation have not shown any considerable modifications prompting reoperation for any of the 105 patients, but the indication of echocardiographic monitoring has stayed in place, with more thorough follow-ups for patients that underwent RAA.

The RAA method is an alternative to AAR and is chosen as a surgical treatment for patients with high perioperative risk or those with cases of borderline ascending aorta dilatation [25, 26].

AAR has been associated with increased perioperative mortality and morbidity rates [27, 28]. Moreover, RAA requires a shorter aortic clamping time, duration of cardiopulmonary bypass time, and intensive care stay [29, 30].

In BAV patients with AAA that had both AS and AI, the behavior of the disease was influenced by the dominant component, either stenosis or insufficiency, and the impairment was more severe in patients with dominant insufficiency. Therefore, in cases where patients presented both AS and AI, the most dominant pathology was considered.

BAV patients with AI are known to present aortic aneurysms much sooner than BAV patients with AS or tricuspid valvulopathy [13]. Accordingly, there were differences between BAV patients enrolled in this study with AAA and AS *versus* AAA and AI, *i.e.*, BAV patients with AAA and AI have shown redilatation of the ascending aorta sooner than the BAV patients with AAA and AS following the RAA intervention.

Recent studies also support the idea that BAV patients with AI may develop a more severe form of dilatation of the ascending aorta compared to BAV patients with AS [31, 32]. There are also new studies that have analyzed mutations of the gene encoding fibrillin-1 (*FBNI*) and made comparisons between aortic dilatations in young adults [33]. Histological studies have correlated aortic aneurysm/dilatation to potential risk factors, and BAV has been identified as a risk factor in 13% of cases [34]. Recent studies have shown the analysis of structural changes require a consensus in establishing a surgical management plan for aortic pathology with inflammatory or non-inflammatory etiology [35].

Furthermore, studies have reported a significant loss of elastic fibers in the ascending aortic wall in approximately half of BAV patients with AAA and AI, compared to just 10% of BAV patients with AAA and AS [36].

Although it is generally believed that elder patients are more susceptible to mid ascending aortic dilatation, while younger patients are more likely to show dilatation of the annulus and aortic root, there is not a consensus regarding the correlation of age and dilatation, with some studies recommending a customized surgical intervention for each patient [37, 38].

According to a recent study, postoperative monitoring of up to 15 years is required in order to see aortic affections following AVR and RAA or AVR only [39].

There are potential limitations of this study, such as the limited number of patients (only 13% of all patients with BAV underwent AAR or RAA) or the lack of genetic data and testing.

✉ Conclusions

For patients with BAV and AAA, RAA is efficient for the short-term but redilatation occurs over time, which provides a rationale for the necessity of long-term monitoring. None of the BAV patients with AAA and either AI or AS developed redilatation subsequent to AAR during the three-year monitoring period; however, most of them have developed redilatation subsequent to RAA during the same period. Following RAA, redilatation is faster in BAV patients with AAA and AI compared to BAV patients with AAA and AS and, therefore, AAR has better long-term results in BAV patients with AAA and AI. This study can have long-term implications and can contribute to a major international meta-analysis focused on improving the clinical practice guidelines currently used in BAV aortopathy.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Ciprian Nicușor Dima and Caius Glad Streian equally contributed to this article.

References

- [1] Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. *J Am Coll Cardiol*, 2004, 44(1):138–143. <https://doi.org/10.1016/j.jacc.2004.03.050> PMID: 15234422
- [2] Verma S, Siu SC. Aortic dilatation in patients with bicuspid aortic valve. *N Engl J Med*, 2014, 370(20):1920–1929. <https://doi.org/10.1056/NEJMra1207059> PMID: 24827036
- [3] Braverman AC. Aortic involvement in patients with a bicuspid aortic valve. *Heart*, 2011, 97(6):506–513. <https://doi.org/10.1136/hrt.2009.183871> PMID: 21339321
- [4] Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol*, 2010, 55(25):2789–2800. <https://doi.org/10.1016/j.jacc.2009.12.068> PMID: 20579534
- [5] Michelena HI, Prakash SK, Della Corte A, Bissell MM, Anavekar N, Mathieu P, Bossé Y, Limongelli G, Bossone E, Benson DW, Lancellotti P, Isselbacher EM, Enriquez-Sarano M, Sundt TM 3rd, Pibarot P, Evangelista A, Milewicz DM, Body SC; BAVCon Investigators. Bicuspid aortic valve: identifying knowledge gaps and rising to the challenge from the International Bicuspid Aortic Valve Consortium (BAVCon). *Circulation*, 2014, 129(25):2691–2704. <https://doi.org/10.1161/CIRCULATIONAHA.113.007851> PMID: 24958752 PMCID: PMC4145814
- [6] Cotrufo M, Della Corte A. The association of bicuspid aortic valve disease with asymmetric dilatation of the tubular ascending aorta: identification of a definite syndrome. *J Cardiovasc Med (Hagerstown)*, 2009, 10(4):291–297. <https://doi.org/10.2459/JCM.0b013e3283217e29> PMID: 19242284
- [7] Schaefer BM, Lewin MB, Stout KK, Gill E, Prueitt A, Byers PH, Otto CM. The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. *Heart*, 2008, 94(12):1634–1638. <https://doi.org/10.1136/hrt.2007.132092> PMID: 18308868
- [8] Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation*, 2005, 111(7):920–925. <https://doi.org/10.1161/01.CIR.0000155623.48408.C5> PMID: 15710758
- [9] Mathieu P, Bossé Y, Huggins GS, Della Corte A, Pibarot P, Michelena HI, Limongelli G, Boulanger MC, Evangelista A, Bédard E, Citro R, Body SC, Nemer M, Schoen FJ. The pathology and pathobiology of bicuspid aortic valve: state of the art and novel research perspectives. *J Pathol Clin Res*, 2015, 1(4):195–206. <https://doi.org/10.1002/cjp.2.21> PMID: 27499904 PMCID: PMC4939890
- [10] Huntington K, Hunter AGW, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *J Am Coll Cardiol*, 1997, 30(7):1809–1812. [https://doi.org/10.1016/s0735-1097\(97\)00372-0](https://doi.org/10.1016/s0735-1097(97)00372-0) PMID: 9385911
- [11] Novaro GM, Tiong IY, Pearce GL, Grimm RA, Smedira N, Griffin BP. Features and predictors of ascending aortic dilatation in association with a congenital bicuspid aortic valve. *Am J Cardiol*, 2003, 92(1):99–101. [https://doi.org/10.1016/s0002-9149\(03\)00480-6](https://doi.org/10.1016/s0002-9149(03)00480-6) PMID: 12842261
- [12] Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. *Mayo Clin Proc*, 1999, 74(1):14–26. <https://doi.org/10.4065/74.1.14> PMID: 9987528
- [13] Guzzardi DG, Verma S, Fedak PWM. Bicuspid aortic valve aortopathy: mechanistic and clinical insights from recent studies. *Curr Opin Cardiol*, 2017, 32(2):111–116. <https://doi.org/10.1097/HCO.0000000000000359> PMID: 28182589
- [14] Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM, Pellikka PA, Tajik AJ, Enriquez-Sarano M. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation*, 2008, 117(21):2776–2784. <https://doi.org/10.1161/CIRCULATIONAHA.107.740878> PMID: 18506017 PMCID: PMC2878133
- [15] Braverman AC, Güven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. *Curr Probl Cardiol*, 2005, 30(9):470–522. <https://doi.org/10.1016/j.cpcardiol.2005.06.002> PMID: 16129122
- [16] Bonow RO. Bicuspid aortic valves and dilated aortas: a critical review of the ACC/AHA practice guidelines recommendations. *Am J Cardiol*, 2008, 102(1):111–114. <https://doi.org/10.1016/j.amjcard.2008.01.058> PMID: 18572047

- [17] Etz CD, Homann TM, Silovitz D, Spielvogel D, Bodian CA, Luehr M, DiLuozzo G, Plestis KA, Griep RB. Long-term survival after the Bentall procedure in 206 patients with bicuspid aortic valve. *Ann Thorac Surg*, 2007, 84(4):1186–1193; discussion 1193–1194. <https://doi.org/10.1016/j.athoracsur.2007.03.057> PMID: 17888968
- [18] Della Corte A, Bancone C, Quarto C, Dialetto G, Covino FE, Scardone M, Caianiello G, Cotrufo M. Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression. *Eur J Cardiothorac Surg*, 2007, 31(3): 397–404; discussion 404–405. <https://doi.org/10.1016/j.ejcts.2006.12.006> PMID: 17236783
- [19] Girdauskas E, Rouman M, Borger MA, Kuntze T. Comparison of aortic media changes in patients with bicuspid aortic valve stenosis versus bicuspid valve insufficiency and proximal aortic aneurysm. *Interact Cardiovasc Thorac Surg*, 2013, 17(6): 931–936. <https://doi.org/10.1093/icvts/ivt406> PMID: 24006478 PMID: PMC3829512
- [20] Hardikar AA, Marwick TH. The natural history of guidelines: the case of aortopathy related to bicuspid aortic valves. *Int J Cardiol*, 2015, 199:150–153. <https://doi.org/10.1016/j.ijcard.2015.06.059> PMID: 26197400
- [21] Girdauskas E, Rouman M, Disha K, Fey B, Dubsclaff G, Theis B, Petersen I, Gutberlet M, Borger MA, Kuntze T. Functional aortic root parameters and expression of aortopathy in bicuspid versus tricuspid aortic valve stenosis. *J Am Coll Cardiol*, 2016, 67(15):1786–1796. <https://doi.org/10.1016/j.jacc.2016.02.015> PMID: 27081018
- [22] Girdauskas E, Rouman M, Disha K, Espinoza A, Dubsclaff G, Fey B, Theis B, Petersen I, Borger MA, Kuntze T. Aortopathy in patients with bicuspid aortic valve stenosis: role of aortic root functional parameters. *Eur J Cardiothorac Surg*, 2016, 49(2):635–643; discussion 643–644. <https://doi.org/10.1093/ejcts/ezv123> PMID: 25855595
- [23] Wang Y, Wu B, Li J, Dong L, Wang C, Shu X. Impact of aortic insufficiency on ascending aortic dilatation and adverse aortic events after isolated aortic valve replacement in patients with a bicuspid aortic valve. *Ann Thorac Surg*, 2016, 101(5):1707–1714. <https://doi.org/10.1016/j.athoracsur.2015.10.047> PMID: 26794893
- [24] Girdauskas E, Disha K, Rouman M, Espinoza A, Borger MA, Kuntze T. Aortic events after isolated aortic valve replacement for bicuspid aortic valve root phenotype: echocardiographic follow-up study. *Eur J Cardiothorac Surg*, 2015, 48(4):e71–e76. <https://doi.org/10.1093/ejcts/ezv259> PMID: 26224339
- [25] Feindt P, Litmathe J, Börgens A, Boeken U, Kurt M, Gams E. Is size-reducing ascending aortoplasty with external reinforcement an option in modern aortic surgery? *Eur J Cardiothorac Surg*, 2007, 31(4):614–617. <https://doi.org/10.1016/j.ejcts.2007.01.028> PMID: 17306983
- [26] Carrel T, von Segesser L, Jenni R, Gallino A, Egloff L, Bauer E, Laske A, Turina M. Dealing with dilated ascending aorta during aortic valve replacement: advantages of conservative surgical approach. *Eur J Cardiothorac Surg*, 1991, 5(3):137–143. [https://doi.org/10.1016/1010-7940\(91\)90212-3](https://doi.org/10.1016/1010-7940(91)90212-3) PMID: 2025439
- [27] Yun KL, Miller DC, Fann JI, Mitchell RS, Robbins RC, Moore KA, Oyer PE, Stinson EB, Shumway NE, Reitz BA. Composite valve graft versus separate aortic valve and ascending aortic replacement: is there still a role for the separate procedure? *Circulation*, 1997, 96(9 Suppl):II-368–375. PMID: 9386126
- [28] Malashenkov AI, Rusanov NI, Muratov RM, Movsesian RA, Fursov BA, Bykova VA, Tsoukerman GI. Eight years clinical experience with the replacement of the ascending aorta using composite xenopericardial conduit. *Eur J Cardiothorac Surg*, 2000, 18(2):168–173. [https://doi.org/10.1016/s1010-7940\(00\)00500-5](https://doi.org/10.1016/s1010-7940(00)00500-5) PMID: 10925225
- [29] Belov IV, Stepanenko AB, Gens AP, Savichev DD, Charchyan ER. Reduction aortoplasty for ascending aortic aneurysm: a 14-year experience. *Asian Cardiovasc Thorac Ann*, 2009, 17(2): 162–166. <https://doi.org/10.1177/0218492309103302> PMID: 19592547
- [30] Zhang H, Lu F, Qu D, Han L, Xu J, Ji G, Xu Z. Treatment of fusiform ascending aortic aneurysms: a comparative study with 2 options. *J Thorac Cardiovasc Surg*, 2011, 141(3):738–743. <https://doi.org/10.1016/j.jtcvs.2010.05.031> PMID: 20584536
- [31] Girdauskas E, Disha K, Secknus M, Borger M, Kuntze T. Increased risk of late aortic events after isolated aortic valve replacement in patients with bicuspid aortic valve insufficiency versus stenosis. *J Cardiovasc Surg (Torino)*, 2013, 54(5): 653–659. PMID: 24002396
- [32] Girdauskas E, Disha K, Raisin HH, Secknus MA, Borger MA, Kuntze T. Risk of late aortic events after an isolated aortic valve replacement for bicuspid aortic valve stenosis with concomitant ascending aortic dilation. *Eur J Cardiothorac Surg*, 2012, 42(5):832–837; discussion 837–838. <https://doi.org/10.1093/ejcts/ezs137> PMID: 22466700
- [33] Seike Y, Minatoya K, Matsuda H, Ishibashi-Ueda H, Morisaki H, Morisaki T, Kobayashi J. Histologic differences between the ascending and descending aortas in young adults with fibrillin-1 mutations. *J Thorac Cardiovasc Surg*, 2020, 159(4):1214–1220.e1. <https://doi.org/10.1016/j.jtcvs.2019.01.126> PMID: 30905418
- [34] Butcovan D, Mocan V, Haliga RE, Ioan BG, Danciu M, Tinica G. Sub-classification of non-inflammatory and inflammatory surgical aortic aneurysms and the association of histological characteristics with potential risk factors. *Exp Ther Med*, 2019, 18(4): 3046–3052. <https://doi.org/10.3892/etm.2019.7903> PMID: 31572544 PMID: PMC6755460
- [35] Halushka MK, Angelini A, Bartoloni G, Basso C, Batoroeva L, Bruneval P, Buja LM, Butany J, d'Amati G, Fallon JT, Gallagher PJ, Gittenberger-de Groot AC, Gouveia RH, Kholova I, Kelly KL, Leone O, Litovsky SH, Maleszewski JJ, Miller DV, Mitchell RN, Preston SD, Pucci A, Radio SJ, Rodriguez ER, Sheppard MN, Stone JR, Suvarna SK, Tan CD, Thiene G, Veinot JP, van der Wal AC. Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology: II. Noninflammatory degenerative diseases – nomenclature and diagnostic criteria. *Cardiovasc Pathol*, 2016, 25(3):247–257. <https://doi.org/10.1016/j.carpath.2016.03.002> PMID: 27031798
- [36] Roberts WC, Vowels TJ, Ko JM, Filardo G, Hebel RF Jr, Henry AC, Matter GJ, Hamman BL. Comparison of the structure of the aortic valve and ascending aorta in adults having aortic valve replacement for aortic stenosis versus for pure aortic regurgitation and resection of the ascending aorta for aneurysm. *Circulation*, 2011, 123(8):896–903. <https://doi.org/10.1161/CIRCULATIONAHA.110.972406> PMID: 21321157
- [37] Merlanti B, De Chiara B, Maggioni AP, Moreo A, Pileggi S, Romeo G, Russo CF, Rizzo S, Martinelli L, Maseri A; VAR Study Group. Rationale and design of GISSI OUTLIERS VAR Study in bicuspid aortic valve patients: prospective longitudinal, multicenter study to investigate correlation between surgical, echo distinctive features, histologic and genetic findings in phenotypically homogeneous outlier cases. *Int J Cardiol*, 2015, 199:180–185. <https://doi.org/10.1016/j.ijcard.2015.06.182> PMID: 26197404
- [38] Stock S, Mohamed SA, Sievers HH. Bicuspid aortic valve related aortopathy. *Gen Thorac Cardiovasc Surg*, 2019, 67(1): 93–101. <https://doi.org/10.1007/s11748-017-0821-x> PMID: 28856517
- [39] Liu S, Shi Y, Liu R, Tong M, Luo X, Xu J. Early prognosis of reduction ascending aortoplasty in patients with aortic valve disease: a single center's experience. *Ann Thorac Surg*, 2017, 103(2):511–516. <https://doi.org/10.1016/j.athoracsur.2016.06.005> PMID: 27570157

Corresponding authors

Emil Radu Iacob, Lecturer, MD, PhD, Department of Pediatric Surgery, Victor Babeș University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timișoara, Timiș County, Romania; Phone +40745–614 590, e-mails: radueiacob@umft.ro, radueiacob@yahoo.com

Simona Cerbu, Assistant, MD, PhD, Department of Radiology and Medical Imaging, Victor Babeș University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timișoara, Timiș County, Romania; Phone +40749–276 265, e-mail: cerbusimona@yahoo.com