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Bicuspid Aortic Valve Disease: New Insights

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ABSTRACT

Bicuspid aortic valve (BAV) is the most common cardiac congenital abnormality and can be associated with significant valvulopathy or aortopathy. Current active areas of BAV research include prediction of development of valve dysfunction and aortopathy, and the various surgical valvular strategies with or without ascending aortic replacement. There is also increasing interest in the emerging role of transcatheter aortic valve replacement (TAVR) even though it is listed as a relative contraindication in current TAVR recommendations. Although there are clearly established guidelines in the clinical management and surgical techniques for the management of BAV with or without aortopathy, many of these newer surgical techniques have shown excellent post-surgical results but need to be directly compared against "standard" guidelines recommended treatment. As such, this creates new controversies regarding the clinical and surgical management of BAV. In this review, we have summarized the current understanding of the pathophysiology of BAV valvulopathy and aortopathy, various newer surgical therapies, and gaps in our scientific knowledge that require further research.

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KEYWORDS Bicuspid aortic valve; diagnosis; therapy

Introduction

Bicuspid aortic valve (BAV) is the most frequent congenital heart disease with an incidence of about 13 per 1000 live births.[1] However, the exact prevalence of BAV is unclear as it is often diagnosed in a variety of clinical situations across patient populations of different age groups. From 21,417 autopsies, Larson and colleagues reported a prevalence of 1.37%.[2] Echocardiographic screening of all newborns would provide a more accurate estimate of BAV prevalence but is unlikely to be practical or affordable. In addition, BAV is a heterogeneous disease presenting with different phenotypes and clinical complications.

Different classifications for BAV morphologies have been proposed that are based on description of cusp position, cusp size, aortic sinus characteristics, and commissural position and presence and characteristics of raphe.[3,4] The Sievers and Schmidtke classification system has garnered significant popularity due to its simplicity and practicality.[5] Type 0 consists of two leaflets without any raphes (fusion of two leaflets), Type 1 consists of a single raphe due to fusion of the left coronary cusp with either the right or the non-coronary cusp, and Type 2 consists of two raphes with fusion of the left coronary cusp with both the right and non-coronary (Figure 1). The proposed classification system is advantageous as it combines all the possible BAV anatomical variations (i.e. the number of raphes, and spatial positioning of cusp fusion) with the functional consequences of BAV associated valvulopathy (i.e. predominant stenosis, predominant regurgitation, balanced stenosis and regurgitation, or normal functioning valve). Several non-functional complications of BAV also exist (valve dysfunction, aortic dissection, and endocarditis) and have prompted research groups to investigate the predisposing factors to these conditions.

The functional and non-functional complications of BAV have led to a number of unanswered clinical questions which can be summarized as follows: (1) how to predict the development of valvular dysfunction (i.e. who develops aortic stenosis [AS] or aortic regurgitation [AR]); (2) how to predict the development of aortopathy; and (3) what and when is the best therapeutic approach to these complications (aortic valve replacement [AVR] or sparing [AVS] with or without concomitant replacement of the aortic root or ascending aorta). In addition, the advent of transcatheter aortic valve replacement (TAVR) and its inevitable spread to intermediate and low risk populations has opened the question of the safety and efficacy of this treatment modality in patients with BAV. The present review article summarizes the evidence to address these questions and provides an overview on the recently obtained insights into BAV.

BAV and valvular dysfunction

To determine the natural history of BAV and the true incidence of AS or AR, one should ideally follow a large number of patients from a young age. However, such long-term

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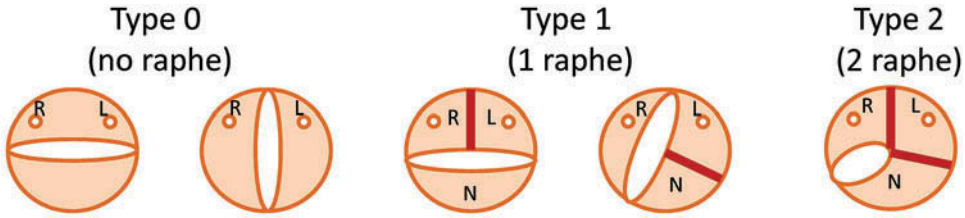

Figure 1. The Sievers and Schmidtke classification system for bicuspid aortic valve. (Reprinted from *The Journal of Thoracic and Cardiovascular Surgery*, 133, H.-H. Sievers and C. Schmidtke, A classification system for the bicuspid aortic valve from 304 surgical specimens, 1226–1233, © 2007, with permission from Elsevier.). The ostia of the right and left coronary arteries are represented. Abbreviations: L = left; R = right; N = non-coronary.

longitudinal studies are not always practical. Instead, researchers are often reliant on cross-sectional observational studies.

Valvular stenosis

Aortic stenosis requiring AVR surgery is the most frequent complication of BAV. In the largest multicenter observational BAV registry to date, which included 2118 patients, Kong and colleagues showed that up to 37% BAV patients had moderate to severe AS at the time of initial transthoracic echocardiography.[6] Surgical data suggested that almost 50% of patients with severe AS undergoing replacement surgery had congenital BAV.[7] In addition, among patients with BAV referred for AVR surgery, severe AS is the indication for surgery in 65%.[4,8]

The natural history of BAV-associated severe AS has also been described. In a large population-based study, Michelena and colleagues identified 212 patients (average age 32 years) with minimally dysfunctional BAV (i.e. absent or mild stenosis or regurgitation), of which 196 (97%) patients were available for follow-up.[4] After a mean follow-up of 15 ± 6 years, 13% of patients developed isolated severe AS requiring surgical AVR. In a small study of 75 BAV patients, Beppu and colleagues demonstrated that aortic sclerosis tends to occur during the second decade of life. They observed increasing valve thickness progressing with age, and eventual calcium deposition occurring in the fourth decade.[9] The peak aortic valve gradient increased by 18 mmHg per decade of life for the entire study cohort.[9] In addition, a gender difference in the development of AS has been found, with women more likely to present with moderate to severe AS than men.[10]

However, there is conflicting data regarding the association of BAV leaflet morphology and the potential for AS. Beppu and colleagues reported that BAV with left-right cusp fusion was more likely to be associated with rapid development of AS. [9] In contrast, Kong and colleagues indicated that BAV patients with right-noncoronary cusp fusion had a higher incidence of moderate to severe AS (Figure 2).[6] Furthermore, the presence of raphes (i.e. type 1 and 2 based on the Sievers and Schmidtke classification system) were more likely to be associated with moderate to severe AS compared to absence of raphes (i.e. type 0) (Figure 3). Finally, in the population-based longitudinal observational study by Michelena and colleagues, they failed to identify any relationship between leaflet morphology and AS on follow-up.[4] Thus, the issue of the relation of BAV leaflet morphology and aortic stenosis remains uncertain.

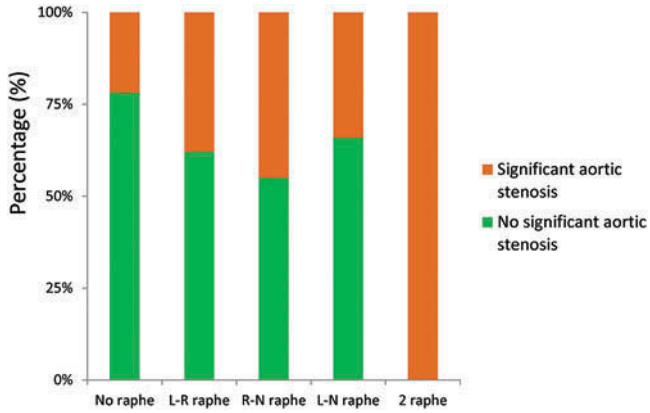

Figure 2. Prevalence of moderate to severe aortic stenosis in bicuspid aortic valve based on leaflet morphology. (Reproduced with permission from JAMA Cardiology. 2017. 2(3):85–92. © 2017 American Medical Association. All rights reserved.).

Valvular regurgitation

The incidence of AR is lower than that of AS in BAV patients.[4,6,8] In the population-based study by Michelena and colleagues, only 3% of patients with previously minimally dysfunctional BAV eventually developed isolated severe AR necessitating AVR surgery (compared to 13% who required surgery for isolated severe AS). When "significant" AR was defined as moderate to severe, Tzemos and colleagues observed an overall 20% incidence in 642 BAV patients.[8] However, in that cohort AVR surgery was only performed in 6% of patients for symptomatic severe AR or progressive left ventricular dysfunction.[4,8] Finally, in the largest multicenter BAV registry to date, the prevalence of moderate to severe AR was 32%.[6] Furthermore, men were more likely to have associated moderate-severe AR as compared to women.

The association between BAV leaflet morphology and development of AR is unknown. In the study by Kong and coworkers, moderate and severe AR was slightly more common among BAV patients with 2 raphes.[10] However, the incidence of significant AR was similar across patients with type 0 BAV and type 1 regardless of the raphe location (Figure 4). In contrast, an association between the type of aortopathy and AR has been described. The presence of AR was independently associated with both an isolated dilated aortic root and isolated dilated tubular ascending aorta.[11] Thus, it is currently unclear which BAV patients will develop significant valvular dysfunction on follow-up and current prediction models are less than ideal.

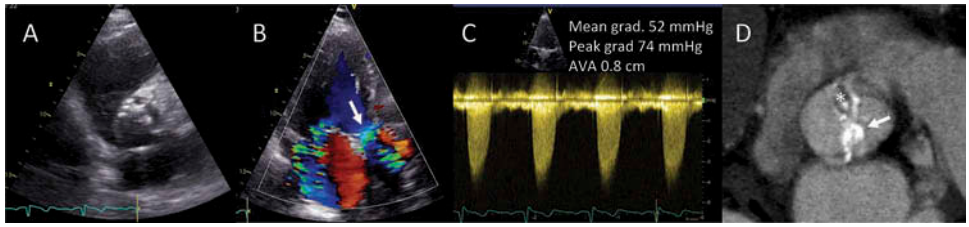

Figure 3. Bicuspid aortic valve stenosis. Example of a 75-year-old female complaining of dyspnea. On transthoracic echocardiogram, the parasternal short-axis view showed a calcified aortic valve with probable bicuspid morphology (panel A). On the apical 3-chamber view, a turbulent systolic flow through the aortic valve was observed (panel B, arrow) and the continuous wave Doppler showed a dense spectral signal with a peak velocity of 4.2 m/s and calculated mean and peak gradients of 52 mmHg and 74 mmHg, respectively (panel C). The aortic valve area (AVA) is 0.8 cm^2. On multi-detector row computed tomography (panel D), the anatomy of the aortic valve was better delineated, showing a type 0 bicuspid aortic valve with a calcified commissure (arrow) and a small opening (asterisk). Abbreviations: AVA = aortic valve area.

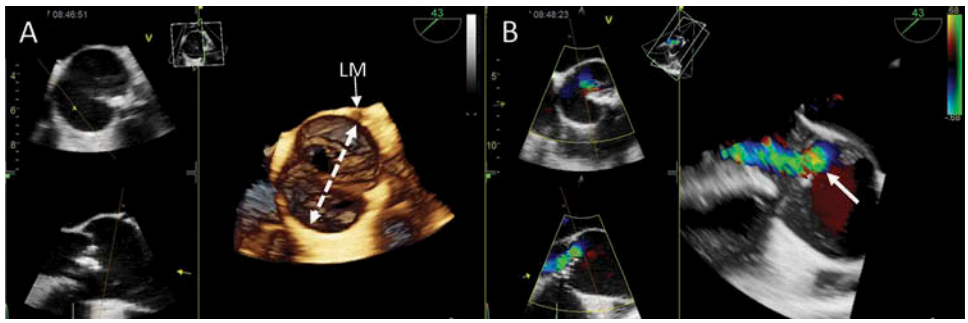

Figure 4. Bicuspid aortic valve regurgitation. Three-dimensional transesophageal echocardiography of a patient with type 0 bicuspid aortic valve. Panel A shows the biplane view of the aortic valve with the short- and long-axis views. The reconstructed 3-dimensional volume rendered image is visualized from the aortic side. Note the dilatation of the aortic root (59 mm, double arrowhead). Three-dimensional color Doppler flow data show the regurgitant jet (arrow) with a planimetered 3-dimensional vena contracta area of 0.6 cm^2 indicating severe aortic regurgitation. Abbreviations: LM = left main.

BAV and aortopathy

Thoracic aortic aneurysm is the second most frequent complication in patients with BAV.[12] Dilatation of the ascending aorta in BAV can start at a very young age and progressively worsen throughout childhood.[13] A study by Holmes and colleagues evaluated the rate of ascending aortic dilatation in children aged <19 years by converting measurements of aortic root, ascending aorta, height/weight, and systolic/diastolic blood pressure into z scores based on normative data.[14] A z score of –2 to 2 was defined as normal, 2 to 4 as dilated, and >4 as markedly dilated. In this study, the mean z score of ascending aorta gradually increased with age, from mean z score of 0.98 for children <1 years old to mean z score of 2.4 for the 15–18 years age group.[14] Increased aortic dimensions, but not aneurysms, were noted in the majority of BAV patients in early adulthood.[15] Three types of aortic dilatation in BAV have been described (Figure 5).[12,16] Type 1 is the root phenotype which involves isolated aortic root dilatation with sparing of the ascending aorta. Type 2 is isolated dilatation of the ascending aorta with relative sparing of the aortic root. Type 3 involves the dilatation of both the ascending aorta and aortic root, and is the most common type of aortic dilatation in BAV. Several factors are associated with progressive aortic dilatation and include age, hypertension, male gender, aortic valve disease, and valve morphologies.[8,16,17] Evaluation of the aortic dimensions in BAV patients is mandatory. In a prospective community study from Olmsted County, Minnesota, USA, aortic aneurysm (an ascending aorta ≥45 mm) was identified in 7.7% of BAV patients at baseline with a mean age of 55 years.[18] The 15-year risks of aortic surgery and aortic dissection were 46% and 7% respectively. In 384 patients without baseline aneurysms, 49 developed an aneurysm at follow-up, corresponding to an incidence of 84.9 cases per 10,000 patient years. The 25-year risk of aneurysm formation was 26% (95% CI, 18.2–33.8%), 86 times the risk of the general population.

The possible association between BAV and aortopathy may be due to both genetic and hemodynamic factors that affect the structural support and elasticity of the aortic wall. Mutations of transforming growth factor β receptor (*TGFBR1* and *TGFBR2*) and smooth muscle cell α actin (*ACTA2*) have been linked to abnormalities of the vessel smooth muscle cells of the ascending aorta media in BAV patients. These genetic factors predispose to aortic media degeneration with vessel smooth muscular cell apoptosis, elastin fragmentation and increased degradation of collagen and elastin. However, these genetic abnormalities are neither specific for BAV patients nor are consistently documented.[19,20] Other circumstantial evidence supporting the genetic influence on BAV-associated aortopathy includes the higher observed incidence of aortopathy in first-degree relatives of BAV patients,[21,22] and progressive ongoing aortic dilatation in some BAV patients after AVR surgery.[23]

Altered hemodynamics (flow patterns) caused by the BAV may increase wall shear stress in specific regions of the aortic wall which may exacerbate the progression of the aortopathy. Four-dimensional flow cardiovascular magnetic resonance (CMR) has permitted characterization of aortic

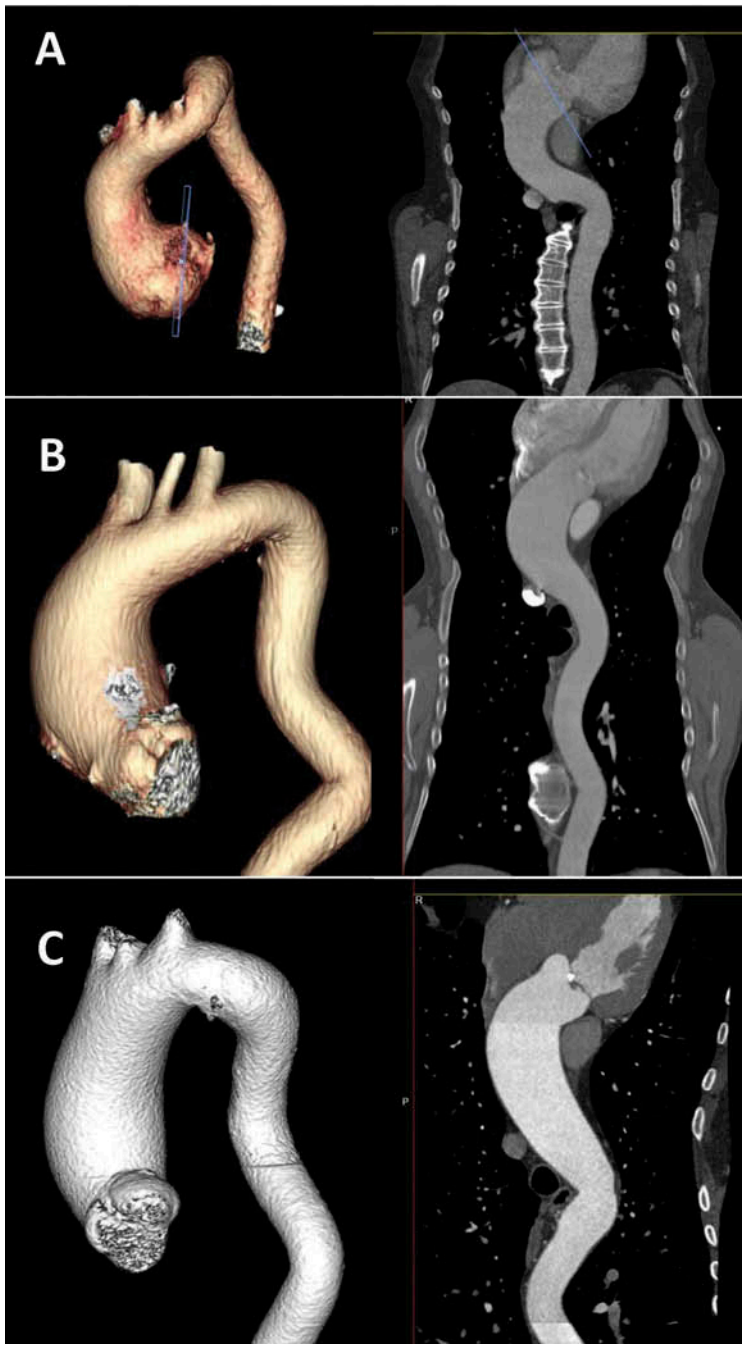

Figure 5. Type of aortic root and ascending aorta dilatation in BAV patients. Type 1 is isolated aortic root dilatation with sparing of the ascending aorta (panel A). Type 2 is isolated dilatation of the ascending aorta with relative sparing of the aortic root (panel B). Type 3 is dilatation of both the ascending aorta and aortic root (panel C).

flow and the measurement of regional wall shear stress in patients with BAV (Figure 6).[24] Previous study measuring regional wall stress has suggested that specific BAV morphologies were associated with specific dilated aorta phenotypes.[24] In patients with right and non-coronary cusp fusion, the right-posterior aortic wall showed the highest wall shear stress and patients frequently had dilatation of either the entire ascending aorta and aortic arch (type 1) or isolated dilatation of the aortic root only (type 3). In contrast, patients with left-right coronary cusp fusion had maximal wall shear stress in the right-anterior wall of the aorta, and frequently had isolated dilatation of the ascending aorta (type 2).[24] Guzzardi and colleagues also evaluated 20 BAV patients who underwent 4D flow CMR and subsequent resection of the ascending aorta, which enabled correlation of the regional maps of wall shear stress with histology.[25] The regions of the aorta with the highest wall shear stress exhibited greater medial elastin degradation with increased *TGFB1* and metalloproteinase activity. However, an increase in aortic wall shear stress was observed in all BAV patients independently of valve morphology and grade of stenosis or regurgitation, suggesting that even patients with BAV and normal aortic valve function may be at risk of developing aortopathy.

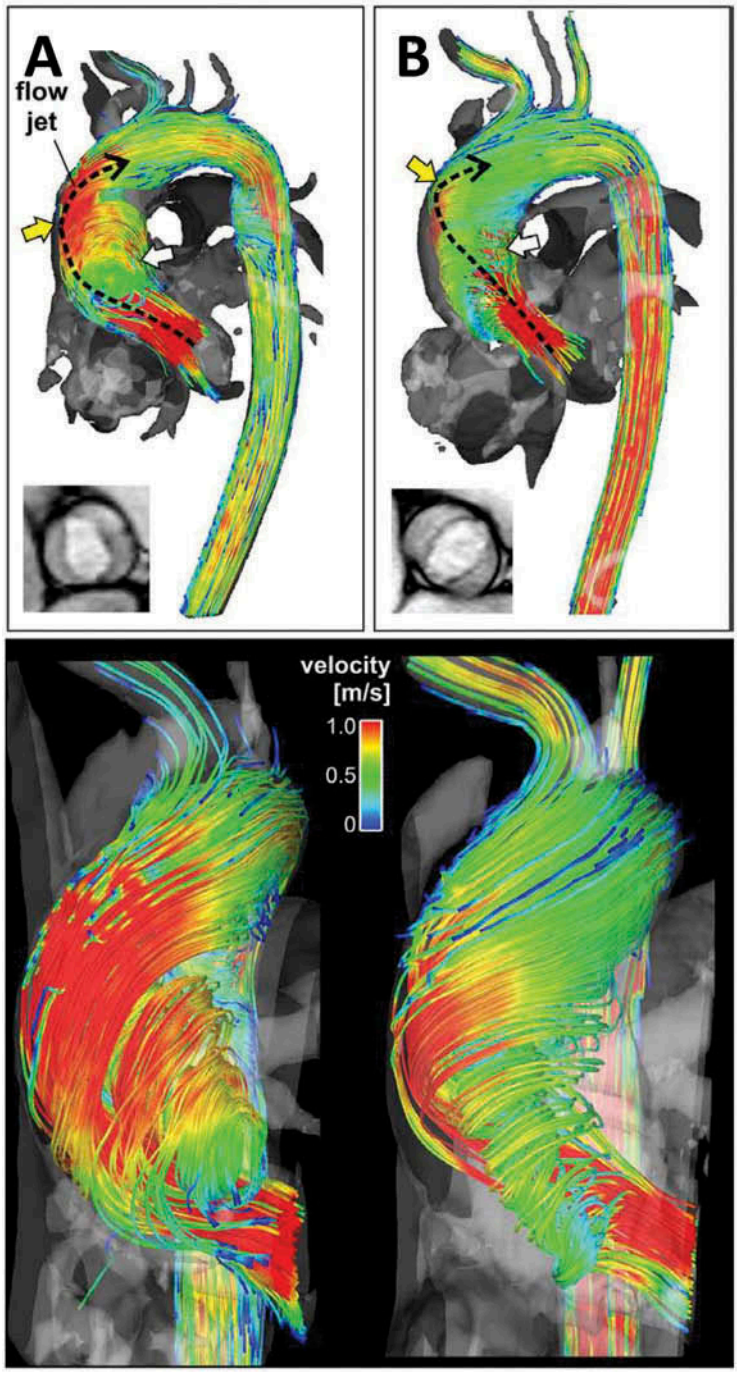

Figure 6. Altered aortic flow patterns in bicuspid aortic valve resulting in increased wall shear stress and resultant aortic dilatation as characterized by 4-dimensional flow cardiovascular magnetic resonance imaging. In panel A, an example of a bicuspid aortic valve (BAV) with fusion between the right and the left coronary cusps is shown. In panel B, a type 0 BAV with orientation of the commissures anteroposterior is shown. The 3-dimensional streamline visualization of the peak systolic blood flow (dashed lines) indicate different wall impingement zones of the outflow jets (yellow arrows) for the different morphologies of BAV. The 3-dimensional flow patterns are presented in the panels below. (Reproduced from R. Mahadevia et al., Bicuspid Aortic Cusp Fusion Morphology Alters Aortic Three-Dimensional Outflow Patterns, Wall Shear Stress, and Expression of Aortopathy, *Circulation*, 129(6), © 2014, with permission from Wolters Kluwer Health, Inc.).

Therefore, current research suggests that both genetic factors and valve-related hemodynamics are associated with the development of BAV-associated aortopathy. Predicting which BAV patients will develop aortopathy is challenging and the precise pathophysiological mechanisms are not completely understood. Due to the risk of progressive aortic dilatation and potentially life-threatening complications, BAV patients require systematic and accurate evaluation of their aorta, with regular follow-up of the aortic dimensions regardless of the valve morphology and function.

Bicuspid aortic valve and ascending aortic interventions

Although AVR is the most common surgical approach for severe bicuspid AS, TAVR has been shown to be feasible and safe in inoperable and high risk populations. For severe AR secondary to aortopathy, valve sparing techniques may be preferable in young patients provided that the repair is durable. Beyond bicuspid valvular dysfunction, the presence of aortopathy will have an influence on the surgical approach.

Thoracic aortic aneurysm repair

In patients with BAV-associated aortic root/ascending aortic aneurysm with or without concomitant valvulopathy, the Bentall procedure, applying a prosthetic valve and conduit combination, has been the "standard" surgical therapy for decades.[26] However, aortic valve sparing (AVS) operations are gaining popularity, whereby the native aortic valve is preserved during surgery for aortic root aneurysm and surgery for ascending aortic aneurysms with associated AR. Compared to AVR surgery for severe AR in tricuspid valves, AVS surgery is associated with less valve-related complications.[27] Similarly in BAV patients, the 10-year freedom from reoperation with aortic valve sparing surgery was 81% and was considerably lower than aortic valve replacement surgery in patients of similar age.[27,28]

There are two types of AVS operations: remodeling of the aortic root as described by Sarsam and Yacoub,[29] and reimplantation of the aortic valve within a Dacron graft as described by David and coauthors.[30,31] In remodeling of the aortic root, the aortic sinuses are excised, leaving behind a 4–5 mm rim of aortic root wall attached to the annulus. A tubular Dacron graft is then tailored to create three new neoaortic sinuses and is sutured to the rim of aortic root wall. Finally, the coronary arteries are reimplanted into the Dacron graft. A subcommissural annuloplasty is often performed to reduce the annular size, improve leaflet coaptation, and reduce the tension on any concomitant leaflet correction.[29,32] Remodeling of the aortic root is theoretically physiologically superior to reimplantation of the aortic valve. Previous echocardiographic study showed that the presence of sinuses of Valsalva is important for normal cusp motion and reduction of cusp stress.[33] Similarly, CMR using time-resolved 3-dimensional phase contrast imaging showed that using an anatomically correct Dacron graft with three aortic sinuses generated flow vortices similar to normal volunteers.[34] However, patients with a repairable BAV and a dilated aortic annulus (≥28 mm diameter) often do not do well with a simple subcommissural annuloplasty.[35] In a large surgical series of 316 BAV patients who underwent aortic root remodeling surgery, Aicher and colleagues demonstrated that a larger aortic annular diameter, BAV leaflet configuration, younger age, a lower effective height (i.e. measure of coaptation line to the annulus), and need for cusp repair using a pericardial patch, were all independent risk factors for reoperation.[35] This was likely because a subcommissural annuloplasty may be inadequate at stabilizing the aortic annulus and halt the progressive BAV-associated aortopathy. Therefore, stabilization of the aortic annulus with AVS root reimplantation may constitute a more appropriate surgery in this subset of patients.

In reimplantation of the aortic root, the aortic sinuses are similarly excised and the coronary arteries detached. However, the aortic annulus is further freed from the surrounding structures, and the aortic valve is reimplanted inside a Dacron graft by securing it above and below the aortic annulus. Compared to remodeling of the aortic root, reimplantation results in a more durable repair, higher freedom from reoperation, and freedom from moderate to severe AR on follow-up.[36]

Against the backdrop of AVS surgeries, it should be noted that composite aortic root replacement (i.e. Bentall operation) is well established and has excellent survival compared to an age- and gender-matched US population.[26] It eliminates the risk of aortic root dilatation or dissection. With the advent of TAVR valve-in-valve procedure, it would theoretically add another 10 years to young patients with a bioprosthetic valve undergoing the Bentall procedure. Future studies will have to compare such hybrid Bentall surgery with bioprosthetic AVR and subsequent follow-up TAVR valve-in-valve procedure, against AVS surgery.

In addition, although current guidelines recommend aortic surgery in BAV patients when the aortic root and/or ascending aorta dimension is >55 mm or >50 mm if there are associated risk factors,[37] the appropriate strategy for patients undergoing aortic valve surgery who have aortic dimensions between 45–50 mm is still debated. Previous retrospective study has shown that BAV patients with aortic dimensions >45 mm or aortic cross-sectional area/height ratio >10 cm2/m undergoing aortic valve replacement surgery, concurrent aortic repair can be safely performed and is associated with better late survival and less aortic events.[38] Therefore, future prospective randomized trials are required to establish the indication for concurrent aortic repair in BAV patients undergoing valve surgery when the aortic dimension is smaller than 50 mm.

Transcatheter aortic valve replacement

TAVR is an established treatment modality for high risk patients with severe AS. However, current guidelines list BAV as a relative contraindication for TAVR,[37,39,40] and all pivotal trials to date have specifically excluded BAV patients.[41,42] This was primarily due to concerns about: (1) asymmetrical leaflet configuration and heavy calcification that may hinder valve positioning and expansion, and subsequent risk of paravalvular regurgitation, aortic annular rupture and coronary artery obstruction (Figure 7); (2) BAV-associated aortopathy that may increase the risk of aortic dissections or ruptures; and (3) uncertain long-term durability as a significant proportion of patients will have progressive root dilatation as part of BAV-associated aortopathy. However, off-label use of TAVR in bicuspid AS is increasingly performed as experience with the techniques accumulates and improves.[43–45]

The Bicuspid Transcatheter Aortic Valve Replacement Registry is the largest international, multicenter, observational registry that enrolls all consecutive patients with bicuspid AS from Europe, North America, and Asia-

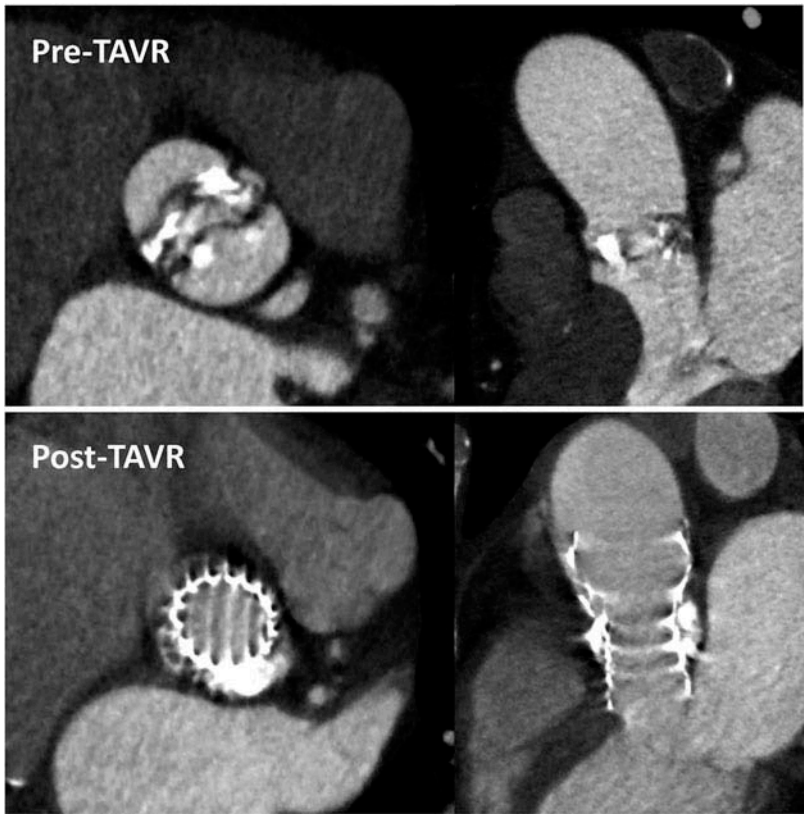

Figure 7. Transcatheter aortic valve replacement in bicuspid aortic valve. Example of type 0 bicuspid aortic valve and heavy calcifications at the edge of the cusps and commissures visualized on the double oblique transversal and sagittal views. After implantation of a CoreValve system, multi-detector row computed tomography shows circular deployment of the transcatheter valve, displacing away the calcifications.

Pacific regions.[44,45] In the published studies, TAVR devices were divided into early generation (Sapien XT, Edwards Lifesciences, Irvine, California; CoreValve, Medtronic, Minneapolis, Minnesota) versus new generation devices (Sapien 3, Edwards Lifesciences, Irvine, California; Lotus, Boston Scientific, Marlborough, Massachusetts; Evolut R, Medtronic, Minneapolis, Minnesota). Implantations of new generation devices were less likely to result in residual moderate to severe paravalvular leak, annulus rupture or second valve-in-valve implantation.[44] Furthermore, when compared to TAVR in patients with tricuspid aortic valves, there were no differences in procedural complications with these new generation devices when implanted in BAV patients. Cumulative event rates for all-cause mortality were similar between bicuspid and tricuspid aortic valves.[45]

Despite the foregoing data, selection bias nearly always exists whereby TAVR was generally performed in high-risk or inoperable bicuspid AS patients. In addition, bicuspid AS patients are more likely to be younger,[43–45] and the long-term implications of age-related progressive aortic dilatation and its complications need to be included in the decision-making process. Therefore, expanding TAVR indications to include bicuspid AS patients, especially those who are young and at lower operative risk, should proceed with caution until further evidence accumulates supporting and confirming its long-term success and durability.

Conclusions

There are still large gaps in understanding the pathophysiology of BAV-associated valvulopathy and aortopathy. Most recent cross-sectional and longitudinal observational studies have frequently produced conflicting findings regarding the subsequent development of BAV valvulopathy. Neither the prevalence, appearance, nor relation to valve morphology has been defined with certainty. The relative contribution of genetic factors and hemodynamic stresses to the aortopathy of BAV remains undefined. Novel imaging modalities such as 4-dimensional flow CMR and wall shear stress provided valuable insights into valve-mediated hemodynamics and progression of BAV aortopathy. Although our understanding of aortopathy is complemented by genetic and molecular studies, they have been at times contradictory and require further investigations. Finally, there is a trend towards TAVR and AVS surgeries for BAV-associated valvulopathy and aortopathy respectively. These "newer" therapies will need to be compared against the "traditional" Bentall surgery, and likely hybrid procedures such as Bentall surgery with bioprosthetic AVR and subsequent follow-up TAVR valve-in-valve procedure.

Disclosure Statements

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