Chapter

Bicuspid Aortic Valve: Current Therapeutic Strategies

Syed Usman Bin Mahmood, Prashanth Vallabhajosyula and Rita Milewski

Abstract

Bicuspid aortic valve (BAV) is the most common congenital valvular pathology with an incidence of 1–2% in the general population. It is associated with an ascending aortic aneurysm phenotype in 26–50%, and aortic root (+/− ascending aneurysm) phenotype in up to 20–32% of patients. Bicuspid aortic valve patients present with a spectrum of valvular, ascending, and aortic root aneurysmal pathophysiologies. This variable spectrum has mandated the development of an array of surgical procedures to be able to tailor an individualized approach to BAV syndrome for a typically younger BAV population in which long-term outcomes are especially relevant . This chapter will delineate the current evidence-based surgical therapeutic strategies for patients with a BAV syndrome of aortic valve stenosis or insufficiency phenotype and aortic phenotype pathophysiology and include aortic valve replacement, aortic valve repair, aortic valve and supracoronary ascending aorta replacement (AVRSCAAR), Bentall procedure, and valve-sparing root reimplantation.

Keywords: bicuspid aortic valve, aortic valve replacement, aortic valve repair, aortic root replacement, valve sparing root reimplantation, Bentall, supracoronary ascending aorta replacement

1. Introduction

Bicuspid aortic valve (BAV) is the most common congenital anomaly of the cardiac valves. It occurs in approximately 1–2% of the general population [1–5]. Its incidence is known to be higher in Caucasian males and lower in female or non-Caucasian populations [6]. BAV syndrome is a heterogeneous disease that can manifest with various valvular, ascending aortic, and aortic root pathophysiologies. The bicuspid aortic valve can be functionally normal, or it may be insufficient or stenotic. Asymptomatic BAV patients with no other hemodynamic deficiencies have good long-term survival; however, valvular degeneration, either aortic stenosis or insufficiency, may develop with time and require close surveillance [7]. This heterogeneity of BAV syndrome has mandated the development of varied surgical procedures to address the valvular/aortic root pathophysiologies as delineated in **Figure 1** [4]. Therefore, definitive management of BAV syndrome requires a personalized approach according to patient-specific pathophysiology. Therapeutic management strategies for valvular

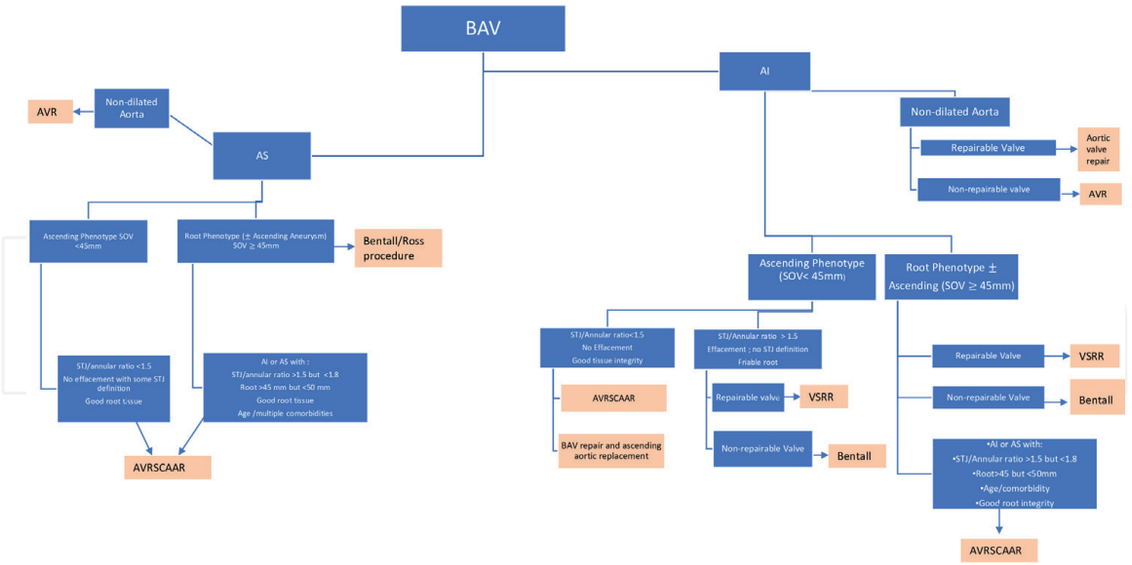

Figure 1.
Bicuspid aortic valve surgical management according to aortic phenotypes.

phenotype and aortic phenotype utilizing a specific algorithmic approach for variable aortic valve, aortic root, and ascending aorta pathophysiologies in BAV syndrome can provide good long-term functional and clinical results [4] (**Figure 1**).

2. BAV syndrome pathology and pathophysiology

The bicuspid aortic valve morphology has been characterized by raphe number and the position of cusps and raphes [8]. This morphology includes complete or partial leaflet fusion. The most common morphology in BAV patients is fusion of left and right coronary cusps. The next most common morphology in BAV patients is fusion of right coronary cusp with noncoronary cusp [8, 9]. The morphology of the bicuspid aortic valve has been described by various classification systems, most notably the Sievers classification [8–10]. Sievers Type 0 BAV has an incidence of 7% in the original Sievers and Schmidtke series and a BAV valve geometry of no raphe and 2 valve cusps [8, 11]. Sievers Type 1 BAV morphology is the most common and has an incidence of 88% in the original series with a BAV valve geometry of a single raphe and 2 valve cusps [8, 11]. Sievers Type 2 BAV has an incidence of 5% in the original series and is the rarest morphology of the three types in this classification with a BAV valve geometry of 2 raphe and 2 valve cusps [8, 11].

Patients with BAV are known to have high rates of various valvular pathologies in adult life [7], particularly aortic stenosis (especially in males) [12], aortic regurgitation [13], and infective endocarditis involving the aortic valve [14]. BAV is three to four times more frequent in men than in women. Approximately, 50–75% of patients with BAV will require aortic valve replacement procedure during their lifetime and up to 25% may require an aortic procedure often concurrent with their valve replacement [15].

BAV syndrome pathophysiology is associated with dilation of the aorta [2]. BAV may be associated with an ascending aortic aneurysm phenotype in around 26–50% patients or a root phenotype in up to 20–32% of patients [2, 3, 16]. These distinct phenotypes have been stratified into three categories. Type 1 is dilation of ascending

aorta along its convexity and can involve root dilation. Type 2 is arch dilation and ascending aortic dilation with sparing of the root. Type 3 involves an isolated root phenotype and has been associated with a genetic causality [16–18]. BAV associated with aortic dilation increases the risk of dissection as the aorta dilates further. In BAV patients, aortic dissection has been observed to occur almost 5–10 times more commonly than trileaflet aortic valve population [19].

Aortic dilatation and aneurysm formation in BAV patients has been attributed to two different mechanisms: hemodynamic stress and the inherent aortic wall tissue abnormality. Hemodynamically, shear stress on the aortic wall due to blood flowing through a stenotic valve has been hypothesized to cause early dilatation of the aorta [20]. Abnormal flow patterns have been noted due to the configuration of the BAV even in absence of stenosis [21].

Dysregulation of the aortic wall can also contribute to aneurysmal dilation. Human and animal studies have identified that extracellular matrix dysregulation along with dysfunctional signaling pathways can contribute to hemodynamic effects observed in calcific aortic valve disease and regurgitation [22]. A recent study demonstrated newborns with BAV having aortopathy and dilated aorta even in the presence of relatively normal velocities across the valve [23] and this suggests inherent aortic tissue dysregulation as a factor which may impact the population of patients with BAV.

3. Embryology and genetics of BAV and associated aortic aneurysm

The aortic valve develops from endocardial cushions within the maturing heart tube and begins to form around the fifth week of embryonic development. In normal cardiac development, these cushions later divide into three distinct aortic valve leaflets. In patients with BAV disease, the cushions either fail to divide or fuse leading to the characteristic bicuspid morphology. It has been postulated that multifactorial variables including genetic/embryologic factors impact the formation of the bicuspid aortic valve.

There is a recognized genetic component to bicuspid aortic valve disease. It may occur sporadically or as an autosomal dominant disorder with variable penetrance [24]. And, it has been noted that some family members of BAV patients may present with isolated BAV, some with associated aortic (ascending/root) aneurysms and some may be carriers with no manifest disease. The spatial and anatomical sequences in development of congenital heart disease (CHD) continues to be defined. Outflow tract defects specifically those involving the aortic valve have been difficult to categorize as they appear to be multifactorial in origin with many signaling and transcriptional gene anomalies possible for the outcome. Autosomal dominant inheritance pattern has been described for BAV specifically involving the NOTCH1 gene pathway however, this is not exclusive [25].

The genetic mechanism for a majority of BAV cases remains unknown. Although these cases may seem 'sporadic' there is still a 10% increase in risk of having BAV in siblings and offspring based on epidemiological studies [26]. There is a similar rate of incidence of aortic aneurysms in family members with or without BAV demonstrating some role of shared environmental or genetic causes [27]. High number of genetic variants, associated with structural variation and mixed inheritance patterns of the disease have complicated the discovery of the BAV-associated genes [28]. Chromosomal mutations involving 9q have been linked to BAV disease [29]. Mutations at various loci on chromosomes 5, 15, and 18 are linked to familial BAV and aortic syndromes [24].

The occurrence of aortic aneurysm and coarctation in patients with BAV underlines a possible common genetic pathway for these disease entities. Microscopic examination of BAV associated aneurysm tissue has demonstrated non-inflammatory medial degeneration also known as cystic medial necrosis [30]. Dysregulation of the canonical (Smad2/Smad3) TGF-B signaling genes has been implicated to be a possible common defect for BAV and aneurysm formation. TGF-B signaling plays a role in cell migration and valvulogenesis that are pivotal in proper valve formation and functioning [30]. Similarly, Loeys-Dietz syndrome (LDS) is caused by mutations in genes encoding for TGF-B receptors. BAV along with thoracic aortic aneurysms are commonly found in patients with LDS.

With these multifactorial variables that impact BAV syndrome presenting as familial clusters and variable penetrance, screening is recommended in first degree relatives of patients with BAV disease [31]. An echocardiogram is commonly utilized to monitor the bicuspid aortic valvular pathophysiology. A CTA or MRA may also be utilized for monitoring the bicuspid aortic valve aortic phenotype.

4. Genetic syndromes with BAV

BAV is associated with several complex valvuloaortopathies and specific syndromes. Approximately 30–50% of patients with coarctation of the aorta have BAV [32–34].

Turner Syndrome is one of the most common genetic syndromes involving patients having a BAV phenotype [34]. The syndrome is associated with X chromosome monosomy in females. Approximately 30% of females with Turners can have a BAV [35]. The frequency of aortic aneurysms associated with BAV is also known to be higher in this group [36]. This observation along with the male predominance of BAV has led to the hypothesis that the X chromosome reduction maybe related to BAV incidence [37]. Generally short statured females with coarctation of the aorta should raise suspicion and lead to surveillance for BAV disease [38].

Loeys-Dietz Syndrome (LDS) is the second most common syndrome associated with BAV with approximately 10% of these patients manifesting the BAV phenotype [39]. TGF-B pathway gene mutations are known to be associated with the LDS. These mutations are common in non-syndromic thoracic aortic aneurysmal disease as well demonstrating a possible common pathway. Compared to non-syndromic patients, the LDS patients tend to present earlier in their life usually with symptomatic aortic regurgitation due to accelerated aortic dilation. Increased arterial tortuosity in major blood vessels and male sex have been determined to be associated with a higher risk of dissection in these patients [40].

Velocardiofacial Syndrome (DiGeorge Syndrome) is caused by deletions in gene 22; this syndrome involves cleft palate, immune deficiency, hypoparathyroidism, ventricular septal defect (VSD), and conotruncal defects of the heart (truncus arteriosus and tetralogy of Fallot). BAV and aneurysmal disease is more prevalent in this set of patients compared to the non-syndromic population [41]. The syndrome itself is a combination of genetic defects that are found in BAV disease demonstrating the multigenetic components that are involved in the BAV phenotype.

5. Surveillance of the aorta in BAV disease

BAV syndrome is a heterogenous disease presenting with variable aortic and valvular pathology over a spectrum of age groups. Asymptomatic BAV may be an

incidental finding on imaging [32, 33, 38]. Patients with BAV syndrome require individualized treatment according to the degree of involvement of the aortic and valvular apparatus with patient comorbidities and age considerations. BAV patients should therefore undergo routine, periodic surveillance, to delineate the optimal timing of therapeutic intervention.

Surveillance for BAV syndrome patients is performed based on the pathophysiology of the aortic valve phenotype or aortic phenotype. Surveillance requires serial echocardiography for valvulopathy. The growth rate of the aorta in BAV patients can be 0.2–2.3 mm/year [16, 42, 43], and serial CTA or MRI should be performed to monitor the growth rate. For patients with ascending aortic and root dimensions within normal limits, imaging can be done every 3–5 years [35]. For dimensions ranging from 40 to 49 mm, imaging should be performed annually. For BAV patients with an aorta measuring 50–54 mm or with family history of aortic dissection or rapid growth of the aorta, imaging should be performed every 6–12 months [44].

5.1 Family screening

Current guidelines suggest family screening with echocardiography for all first-degree relatives with BAV probands. Relatives found to have BAV should have complete evaluation and CTA or MRA imaging [45]. When multiple signs of a disorder are present, genetic testing should be conducted for BAV patients especially those in their early years of life. Other high-risk features that should lead to genetic testing are family history of dissection or sudden death, congenital heart lesions, or other aneurysmal disease. Once identified, genetic counseling plays an important role in the holistic care for BAV patients. Due to the variable expression of causative genes, parents of BAV patients may not have a bicuspid aortic valve. Lifetime follow-up and aortic surveillance is also important as the timing of incidence of valve or aortic disease may be different amongst different family members.

6. Therapeutic strategies for bicuspid aortic valve syndrome

6.1 Aortic dilatation/aneurysm

The 2022 ACC/AHA guidelines for the diagnosis and management of aortic disease delineate the threshold for aortic repair in BAV patients without any other comorbidity or valvular dysfunction to be ≥50 mm [44, 46]. BAV patients who require cardiac surgery for any other pathology should undergo aortic repair if the diameter is ≥45 mm [44].

7. Aortic regurgitation

BAV has become the most common cause of isolated primary aortic regurgitation in the developed world. There may be mixed aortic regurgitation and stenosis; however, in approximately 5–10% of patients will have moderate-severe isolated primary aortic regurgitation [13]. Pathophysiology for aortic regurgitation in BAV usually includes leaflet deformities (size variation, prolapse, fenestrations, thickening or immobility), aortic root dilation (root phenotype), endocarditis or aortic dissection.

Patients with BAV syndrome are a younger population and therefore the long-term durability of surgical procedures and minimization of associated complications are critical outcome goals [4]. Decisions regarding the therapeutic interventions are based on aortic valve phenotype and ascending aortic/root phenotype (**Figure 1**).

Valve choice is an important decision. Currently, fewer patients are willing to alter their lifestyle or take the anticoagulation required for mechanical prosthesis, especially with TAVR options as a bridge. Equally important, consideration of therapeutic options and anticoagulation must be assessed for BAV women of childbearing age [4]. For these reasons a better understanding of the optimal surgical technique for BAV ascending/root aortic aneurysm disease is critical.

The **Figure 1** delineates the anatomic and pathophysiologic criteria utilized for decision making.

7.1 Aortic insufficiency (AI) phenotype

Indications for aortic valve intervention for AI and AS are delineated in the 2020 ACC/AHA Guideline [47]. Surgical aortic valve replacement currently includes either bioprosthetic or mechanical valve [4, 10].

There has also been a trend toward more reparative surgical approach for bicuspid aortic insufficiency. Primary cusp repair for patients with appropriate cusp pathology, although technically more complex than prosthetic aortic valve replacement, is becoming an attractive option as it may reduce the risk of Major Adverse Valve-Related Event (MAVRE) [4, 48]. Long-term outcome and follow-up studies will be important to monitor these patients.

7.2 Aortic insufficiency with aortic phenotype

For BAV syndrome patients with Aortic Valve Insufficiency phenotype and aortic root phenotype with sinus of Valsalva (SOV) measuring ≥45 mm, the **Figure 1** delineates the therapeutic options. The mechanical Bentall procedure has been a gold standard for multiple root pathologies with low morbidity and mortality [4, 49]. However, mechanical valves do not always carry 100% freedom from reoperation or a survival similar to age-matched controls [4]. Good long-term results for patients with a biologic composite root have been shown in a recent study and a meta-analysis of the Bentall procedure and revealed an annual linearized rate for late mortality of 2.02%, reoperation of 0.46%, bleeding of 0.64%, thromboembolic events of 0.77%, and MAVRE of 2.66% [4, 50]. This procedure can be performed for BAV aortic root and valvular pathologies with good long-term results [4]. A recent study in BAV patients undergoing Bentall procedure revealed a 5 and 10-year survival of 93% and 89% respectively, with freedom from reoperation of 100% and 1.9% stroke rate at 6 years [4, 51].

For patients with BAV aortic valve insufficiency phenotype and aortic root phenotype with a valve that is repairable, a valve sparing root replacement (VSRR) can be employed [4, 52, 53]. A study by de Kerchove reported 98.3% 5-year survival and 100% freedom from reoperation at 6 years in BAV patients undergoing VSRR [54]. Similarly, Kari reported 99% survival and 6-year 90% freedom from reoperation for BAV VSRR [55]. DeNino et al. demonstrated a lower aortic valve gradient and similar postoperative complication rates in the VSRR group compared to bioprosthetic valve conduit [56]. A study by Vallabhajosyula et al., in the isolated BAV insufficiency subpopulation noted a 5-year freedom from reoperation and survival for Bentall

and VSRR at 98% and 100% versus 100% and 98% respectively [53]. These studies support the findings that primary repair with VSRR can be selectively utilized to treat BAV AI with root aneurysm [52–56]. This decision should be weighed against the risk of recurrent AI. The VSRR patients have been shown to have significantly lower mortality, stroke, and MAVRE compared to mechanical Bentall [4]. The results of recent studies may be utilized to inform young BAV patients interested in biologic conduit or repair options, especially those averse to taking anticoagulation and open to transcatheter valve options in the future. Long-term 15-to-20-year data will be important to better understand the role of biologic versus mechanical valves in BAV aortic root complex focused procedures. In patients with a non-repairable valve, Bentall procedure remains the standard of care [4].

7.3 AS and AI with mild-moderate root phenotype

For both BAV aortic stenosis and aortic insufficiency valve phenotype and mild-moderate root phenotype with ascending aneurysm and moderate dilatation (SOV 40–45 mm), the fate of the retained sinus segment and the effect of valvular pathology on post-operative sinus growth had been undefined. It has been proposed that the sinus segment in BAV aortopathies is at risk for future aortic events. Therefore, it has been advocated, by some, for removal of all aortic segments in patients with aortopathies despite moderate dilation [4]. A recent swing in the pendulum has occurred advocating for retention of the sinus of Valsalva for moderate root aneurysms [56, 57]. This change results from studies reporting a slower growth rate for the sinus segment and a less aggressive aortic event rate for the preserved moderately dilated aortic root [4, 56–58]. Peters et al. found the sinus segment growth rate was only between 0.27 mm and 0.5 mm per year requiring an average of 29.1 years for the sinus segment to become aneurysmal after AVRSCAAR Please do not use an abbreviation without first defining it [58]. For patients with either BAV aortic stenosis and aortic insufficiency with ascending aneurysm and moderate dilatation (40–45 mm) AVRSCAAR can be performed as a therapeutic option with good long-term results (Consort Diagram **Figure 1**) [4, 56–58].

7.4 Aortic stenosis

Aortic valve stenosis occurs in approximately 50% of adult patients with BAV valve phenotype that requires aortic valve replacement [12, 59]. Progression to critical aortic stenosis pathophysiology resulting in therapeutic intervention in BAV patients often occurs at a younger age than patients with trileaflet aortic valves.

7.5 Aortic stenosis valve phenotype

For patients with aortic valve phenotype, but no aortic aneurysm phenotype, aortic valve replacement with a prosthetic aortic valve is the therapeutic option (**Figure 1**). Additional trials are needed to delineate the optimal anatomy, sizing, and implantation techniques for TAVR [60, 61].

The Ross procedure (pulmonary autograft to replace the aortic valve and homograft to replace pulmonic valve) can also be considered as an option to replace the stenotic aortic valve. In patients with the appropriate pulmonary and aortic annular anatomy, good long-term durability has been noted [62].

7.6 Aortic stenosis with root phenotype

In patients with BAV aortic stenosis phenotype an unrepairable valve and aortic root phenotype with a sinus of Valsalva ≥45 mm, a mechanical or bioBentall procedure is a therapeutic option (**Figure 1**). This involves replacing the aortic valve and ascending/root aorta as a composite and reimplanting the coronary arteries to the tubular graft. This can be either mechanical or bioprosthesis (BioBentall).

For patients with BAV aortic stenosis phenotype an ascending aortic aneurysm and moderate sinus of Valsalva (SOV) dilation (40–45 mm), aortic valve replacement and supracoronary ascending aortic replacement (AVRSCAAR) can be performed thereby preserving the root. Studies have shown that the aortic root remains stable over long-term [4, 56].

Figure 1 delineates the surgical procedure for AS phenotype and the associated aortic phenotypes.

8. Management of BAV in pregnancy

Patients with known BAV should be counseled regarding the risks of heritable disease, risk of aneurysm dissection or rupture during pregnancy, and complications of valve related disease. Valve related management is achieved keeping in mind the risk of anticoagulation during and after pregnancy. Pregnant patients with BAV and aneurysm disease are at a higher risk of spontaneous aortic dissection or rupture [63]. Pregnancy associated hemodynamic changes are associated with this increased risk along with the inherent intima media weakness attributed to BAV patients. The highest risk is during the 3rd trimester or postpartum [63]. Aortic aneurysm >40 mm and increase in aortic size during pregnancy have been demonstrated to be common factors in patients who had Type A dissections pre- or post-partum [64]. Contemporary management of BAV and ascending aortic disease has reduced the significant maternal and fetal risk associated with these entities. Contemporary guidelines suggest surveillance of any aortic dilatation in pregnant patients with echocardiography every month during pregnancy if the diameter is >40 mm and every 12 weeks if there is dilation of the aorta but the diameter does not exceed 40 mm [65]. Current guidelines recommend avoidance of pregnancy if the known aortic diameter is >50 mm in BAV patients [65, 66]. Blood pressure control is the mainstay for general management in pregnant females with any thoracic aortic dilation. Surgery during pregnancy is generally avoided due to the high maternal and fetal risk involved; however, it would be indicated in severe valve dysfunction if transcatheter approaches are not an option.

9. Conclusion

1. BAV syndrome presents variable aortic valve phenotype and aortic phenotype.

2. Bicuspid aortic valve patients present with a spectrum of valvular, ascending aortic, and aortic root aneurysmal pathologies.

3. This variable spectrum has mandated the development of an array of surgical procedures to be able to tailor an individualized approach to BAV syndrome for a typically younger BAV population in whom long-term outcomes are especially relevant.

4. Patients with bicuspid aortic valve syndrome require personalized management based on the level of involvement of the aorta and age at presentation. Care can be provided an utilizing an algorithm-based approach delineated in **Figure 1**.

5. For patients who undergo isolated valve surgery for BAV related structural valve disease surveillance is important for ascending aortic disease in the future.

6. Family surveillance of known BAV patients requiring surgical care is also important with consideration of heritable characteristics of this disease.

Author details

Syed Usman Bin Mahmood, Prashanth Vallabhajosyula and Rita Milewski*
Division of Cardiac Surgery, Yale School of Medicine, New Haven, CT, United States

*Address all correspondence to: rita.milewski@yale.edu

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