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STATE-OF-THE-ART PAPER

Bicuspid Aortic Valve Disease

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Bicuspid aortic valve (BAV) disease is the most common congenital cardiac defect. While the BAV can be found in isolation, it is often associated with other congenital cardiac lesions. The most frequent associated finding is dilation of the proximal ascending aorta secondary to abnormalities of the aortic media. Changes in the aortic media are present independent of whether the valve is functionally normal, stenotic, or incompetent. Although symptoms often manifest in adulthood, there is a wide spectrum of presentations ranging from severe disease detected in utero to asymptomatic disease in old age. Complications can include aortic valve stenosis or incompetence, endocarditis, aortic aneurysm formation, and aortic dissection. Despite the potential complications, 2 large contemporary series have demonstrated that life expectancy in adults with BAV disease is not shortened when compared with the general population. Because BAV is a disease of both the valve and the aorta, surgical decision making is more complicated, and many undergoing aortic valve replacement will also need aortic root surgery. With or without surgery, patients with BAV require continued surveillance. Recent studies have improved our understanding of the genetics, the pathobiology, and the clinical course of the disease, but questions are still unanswered. In the future, medical treatment strategies and timing of interventions will likely be refined. This review summarizes our current understanding of the pathology, genetics, and clinical aspects of BAV disease with a focus on BAV disease in adulthood. (J Am Coll Cardiol 2010;55:2789–800) © 2010 by the American College of Cardiology Foundation

Bicuspid aortic valve (BAV) disease (Fig. 1) is the most common congenital heart defect, with a prevalence estimated between 0.5% and 2% (1–5). There is a male predominance of approximately 3:1. In adulthood, complications are common (6,7), and therefore, the burden of disease from BAV disease is more significant than any other congenital cardiac lesion. Despite its importance, our understanding of BAV disease is incomplete and questions remain unanswered about this common condition. Although much of the original focus centered on the abnormal bileaflet valve, the disease is significantly more complex. BAV disease is not only a disorder of valvulogenesis, but also represents coexistent aspects of a genetic disorder of aorta and/or cardiac development. This review will summarize our current understanding of the pathology, genetics, and clinical aspects of BAV disease with a focus on BAV disease in adulthood.

The bicuspid valve is typically made of 2 unequal-sized leaflets. The larger leaflet has a central raphe or ridge that results from fusion of the commissures, and these fused commissures are susceptible to disruption as occurs with balloon valvuloplasty. The morphologic patterns of the bileaflet valve vary according to which commissures have fused, with the most common pattern involving fusion of the right and left cusps. Fusion of the right and left coronary cusps is associated with coarctation of the aorta. Fusion of the right and noncoronary cusps is associated with cuspal pathology. Rarely, the leaflets are symmetrical or there is no raphe ("pure" bicuspid valve). A number of classifications have been used that pertain to the orientation of the leaflets (2,8–10).

Nonvalvular findings occur in up to 50% of adults with BAV. The most common abnormality is dilation of the thoracic aorta. In 1928, Abbott (11) first described the association between BAV and aortic disease, and in 1972, McKusick (12) reported on the association between BAV and Erdheim cystic medical necrosis. Whereas some changes may be secondary to flow dynamics, so-called post-stenotic dilation, more recent studies have shown that structural abnormalities occur at the cellular level independent of the hemodynamic lesion (13–16). The thoracic aorta shows decreased fibrillin, elastin fragmentation, and apoptosis (17–19). Deficient fibrilin-1 results in smooth muscle cell detachment, matrix disruption, and cell death (17). Increases in matrix metalloproteinases (endopeptides involved in cell matrix turnover) are thought to contribute to this process (18,20,21). The pulmonary trunk shows some

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Abbreviations and Acronyms

ACC = American College of Cardiology

AHA = American Heart Association

BAV = bicuspid aortic valve

similar structural abnormalities in patients with BAV, but the clinical significance of this finding is less clear (18,22).

BAV and associated thoracic aortic aneurysms are thought to be manifestations of a single gene defect (23). BAV disease is also known to coexist with other congenital vascular defects; the most common of which is coarctation of the aorta. Of patients with coarctation, approximately 50% to 75% have BAV (24). BAV is also associated with and genetically related to left-sided lesions such as hypoplastic left heart syndrome (25–27). There are a number of syndromes whose cardiac involvement includes BAV and left-sided obstructive lesions: Shone's syndrome with multiple left-sided lesions of inflow and outflow obstruction (28), Williams syndrome with supravalvular stenosis, and Turner syndrome with coarctation of the aorta (29). Other congenital lesions that have been associated with BAV include ventricular septal defects, patent ductus arteriosus, or atrial septal defects, suggesting a more global disorder of cardiac development as a basis for the disorder. Finally, some reports have suggested involvement of the coronary arteries including single coronaries or reversal of coronary dominance (30–32).

Cardiac and valve morphogenesis occur early in fetal development. Initially, the extracellular matrix thickens and forms an endocardial cushion that ultimately develops into the 4 cardiac valves. The actual events that lead to abnormal valvulogenesis and the formation of a BAV are not known. Earlier theories proposed that abnormal blood flow across the developing valves would result in failure of cusp separation. More recent theories involve cell migration, signaling pathways, and genetic susceptibility. Abnormal neural crest migration resulting in fusion of valve cushions has been suggested as a possible explanation by which BAV disease develops in humans (33–36). Aortic aneurysms, cervicocephalic aneurysm, and intracranial aneurysms, all of neural crest origin, are reported in the BAV population (37,38). Others have suggested the extracellular matrix proteins play a pivotal role in valvulogenesis and BAV development. Endothelial nitric oxide is important in vascular and valve formation, and knockout mice without endothelial nitric oxide synthase can develop BAV (39).

Genetics

There have been a number of reports of familial clustering of BAV disease (40,41). Glick and Roberts (41) reported a prevalence of aortic valve disease of 24% in families with more than 1 person with aortic disease, suggesting a Mendelian pattern of inheritance. However, determining the genetics of BAV is complex, and recent studies have demonstrated that BAV is likely due to mutations in different genes with dissimilar patterns of inheritance (42). To date, only a few of these pathways have been identified. Mutations in the signaling and transcriptional regulators *NOTCH1* (gene map locus 9q34.3) result in abnormal aortic valve development (BAV) and later to de-repression of calcium deposition (43,44). This important finding provides linkage between the genetic abnormality, abnormal morphogenesis, and subsequent disease progression. Regions 18q, 5q, and 13q are reported to contain genes responsible for BAV and/or associated cardiovascular malformations (45). The region 10q contains the *ACTA2* gene, which encodes for smooth muscle alpha-actin (*ACTA2*), and mutation in this gene can result in thoracic aneurysm and, in some instances, BAV (46). The ubiquitin fusion degradation 1-like gene, expressed in the outflow tract during embryogenesis is down-regulated in BAV tissue when compared with trileaflet valve tissue. Although more studies are required before genetic screening will have a role, clinical studies have reported a 9% prevalence of BAV in first-degree relatives of patients with BAV (42,47), and based on this data and expert opinion, the current American College of Cardiology (ACC)/American Heart Association (AHA) adult congenital heart disease guidelines suggest echocardiographic screening for BAV in first-degree relatives of patients with BAV (48).

Diagnosis

Auscultatory findings include an ejection sound best heard at the apex. There may be associated murmurs of aortic stenosis, incompetence, or coarctation of the aorta when these lesions are present. In the current era, transthoracic echocardiograms usually confirm the diagnosis. When adequate echocardio-

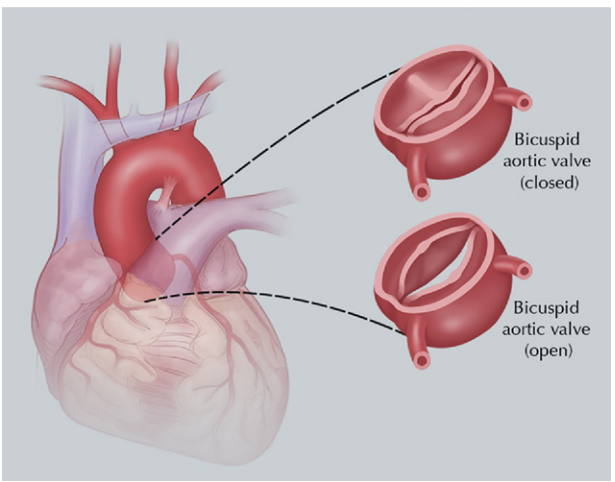

Figure 1 Schematic of the Bicuspid Aortic Valve

Depicted is the abnormal bicuspid valve. Other aspects of the disease include abnormalities of the media in the proximal ascending aorta with resultant dilation of the ascending aorta, abnormalities in the media of the proximal pulmonary artery, and, in some cases, variations in coronary anatomy. Figure illustration by Rob Flewell.

graphic images are obtained, sensitivities and specificities of 92% and 96% are reported for detecting BAV anatomy. The echocardiographic diagnosis can be difficult in patients with heavily calcified valves (49). Differentiating severe bicuspid aortic stenosis from severe unicuspid unicommissural aortic stenosis can also be difficult, but this is particularly important when considering aortic valvuloplasty. In order to establish the diagnosis, the valve must be visualized in systole in the short-axis view. During diastole, the raphe can make the valve appear trileaflet. In diastole, the orifice has a characteristic "fish mouthed" appearance. In the long-axis view, the valve often has an eccentric closure line and there is doming of the leaflets. If there is uncertainty in diagnosis, a transesophageal echocardiogram can improve visualization of the leaflets. In some instances, alternative cardiac imaging such as cardiac magnetic resonance imaging or computer tomography will help to confirm BAV anatomy, but more commonly, these imaging modalities are used to visualize the thoracic aorta (Figs. 2A to 2D).

Clinical Course

Although the clinical presentation of patients with BAV can vary from severe valve disease in infancy to asymptomatic valve or thoracic aortic disease in old age, symptoms typically develop in adulthood. The clinical manifestations relate to the function of the aortic valve (stenosis or incompetence), the aortopathy (dissection), and acquired complications such as endocarditis.

In childhood, BAV disease is commonly asymptomatic. It is estimated that only 1 in 50 of children have clinically significant valve disease by adolescence (50). Aortic stenosis due to a small valve orifice size can present in children with BAVs. Similarly, pure aortic incompetence secondary to a prolapsed leaflet may occur in childhood. Earlier studies of the unoperated clinical course in children were from the era of cardiac catheterization. The unoperated clinical course and late outcomes in children with BAV, but without valve dysfunction, have not been well studied.

Eventually during adulthood, the abnormal shear stress leads to valve calcification and, in some, there is further aortic root dilation (51,52). Estimates of the prevalence of these complications and outcomes have varied depending on the era of the study, the cohort selected, and the method used to diagnose BAV (clinical exam vs. cardiac catheterization vs. echocardiography). Two large recent series have helped to better define the unoperated clinical course of BAV in the modern era (6,7) (Table 1). Estimates of late cardiac events (medical and surgical complications) were

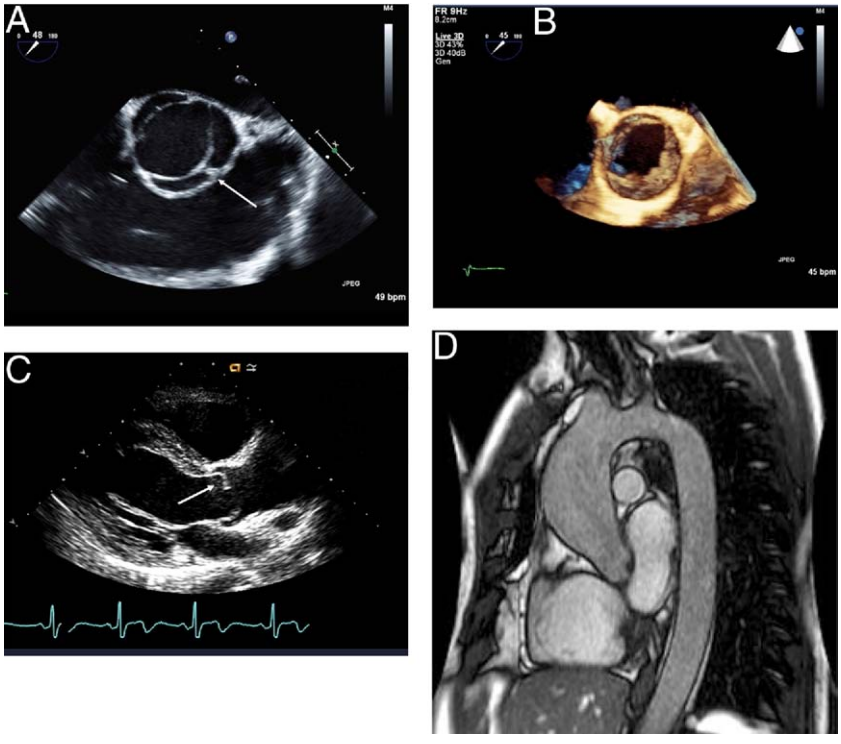

Figure 2 Images of the BAV and Aorta

(A) Transesophageal short-axis view of a bicuspid aortic valve (BAV). There is fusion of the right and left cusps. The **arrow** points to the raphe. **(B)** Transesophageal 3-dimensional image of a BAV. The valve is seen in diastole with the characteristic fish mouth appearance of the valve orifice. **(C)** Transthoracic long-axis view of the aortic valve and aortic root. There is doming of the aortic valve leaflets **(arrow)** and dilation of the aortic sinus and ascending aorta. **(D)** Sagittal oblique cine magnetic resonance image of the thoracic aorta. There is dilation of the ascending thoracic aorta.

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Table 1 Late Outcomes in Adults With BAV Disease

	Patients With BAV and No Significant Aortic Valve Dysfunction (n = 212)*	Patients With BAV With a Spectrum of Valve Function (n = 642)†
Mean follow-up, yrs (range)	15 ± 6 (0.4–25)	9 ± 5 (2–26)
Mean age at baseline, yrs	32 ± 20	35 ± 16
Outcomes		
Overall survival	90 ± 3% at 20 yrs	96 ± 1% at 10 yrs
Cardiac deaths		3 ± 1%
Aortic valve or ascending aorta surgery	27 ± 4%‡	22 ± 2%
Cardiovascular medical events	33 ± 5%	NA
Aortic dissection	0	2 ± 1%
Hospital admission for heart failure	7 ± 2%	2 ± 1%
Endocarditis	2%	2%
Predictors of outcomes		
Predictors of cardiac events (medical and surgical)	Age ≥50 yrs Valve degeneration	Age >30 yrs Moderate or severe aortic stenosis Moderate or severe aortic regurgitation

*Adapted from Michelena et al. (6). Cardiovascular medical events = cardiac death, congestive heart failure, new cardiovascular symptoms (dyspnea, syncope, anginal pain), stroke, and endocarditis. Surgical events = aortic valve surgery (aortic valve replacement, repair, or valvulotomy) and surgery of the thoracic aorta (for aneurysms, dissection, or coarctation). †Adapted from Tzemos et al. (7). Primary cardiac events = surgery on the aortic valve or ascending aorta, percutaneous aortic valvotomy, aortic complications (dissection or aneurysm development), congestive heart failure requiring hospital admission, or cardiac death. ‡Includes surgery for coarctation of the aorta.
BAV = bicuspid aortic valve.

approximately 25% at a mean age of 44 years in the study from Toronto (7) and 40% at a mean age of 52 years in the Olmsted County study (6). Cardiac event rates were higher if 1 or more of the following risk factors were present: age >30 years, moderate or severe aortic stenosis, and moderate or severe aortic incompetence (Fig. 3). Importantly, in both of these series, fatal events were rare. Most surgical procedures involved aortic valve and aortic root replacements. In the Olmsted County series (6), 27% of adults with BAV and no significant valve disease at baseline required cardiovascular surgery within 20 years of follow-up. Twenty-two percent of the patients in the Toronto cohort (7) required intervention within 9 years of follow-up. In both studies, age was an important determinant of outcomes supporting the notion held by many that eventually most patients with BAV would require some form of intervention.

Aortic Stenosis

A common complication of BAV disease is aortic stenosis. Although the fetus may survive with severe aortic stenosis because the right heart can carry the full cardiac output in utero, after birth these infants are at risk for cardiovascular deterioration. Pre-natal diagnosis and treatment are now

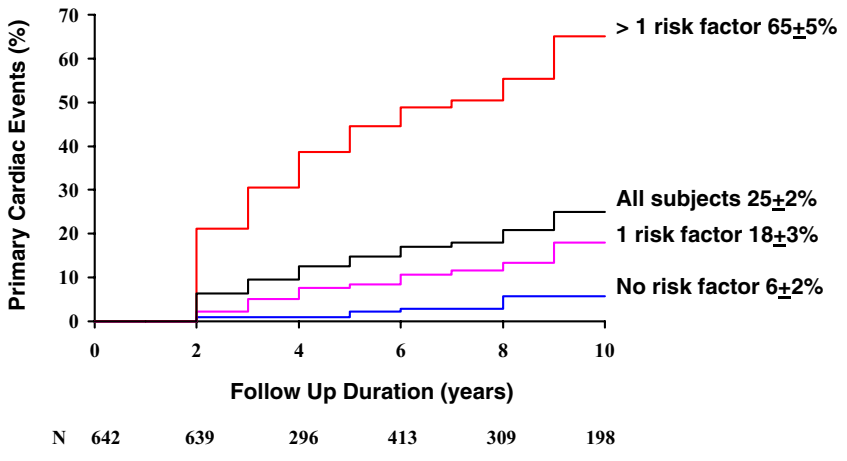

Figure 3 Frequency of Adverse Cardiac Events in Adults With Bicuspid Aortic Valve Disease Stratified According to Risk Profile

Risk factors identified in this study included: age >30 years, moderate or severe aortic regurgitation, and moderate or severe aortic stenosis. Reprinted, with permission, from Tzemos et al. (7).

possible (53). While not unique to BAV disease, myocardial fibrosis can be seen in children with significant aortic stenosis and is partially reversible after relief of the obstruction (54,55). Children who present with aortic stenosis in infancy have more severe disease and poor outcomes (56–58). Because there is often very little calcification during childhood, balloon valvuloplasty is the treatment of choice for severe aortic stenosis in this age cohort.

In the Joint Study of the Natural History of Congenital Heart Defects, one-third of the children in the cohort had increases in catheterization gradients during the 4- to 8-year follow-up period (59). However, only a subgroup of children had follow-up, and the group of children with repeat catheterizations may not be representative of the entire BAV population. In the follow-up study, children with baseline peak left ventricular to aortic gradients >50 mm Hg were at risk for serious cardiac events at a rate of 1.2% per year (60). However, even in children with less valve involvement in early childhood, the disease can progress. Of the children with gradients <25 mm Hg, 20% required intervention in follow-up. Similarly, in the United Kingdom cohort <20% of children with mild aortic stenosis at baseline had mild disease after 30 years of follow-up (61). Age was the primary determinant of valvular disease progression.

In adults, the development of aortic stenosis is often due to leaflet calcification, which occurs in a similar fashion to that seen in patients with trileaflet leaflet calcification. This process is felt to be an active process, perhaps initiated by endothelial dysfunction and involving inflammation, lipoprotein deposition, calcification, and ossification of the aortic side of the valve leaflets (62). The folding and creasing of the valves and the turbulent flow are felt to contribute to development of fibrosis and calcification (63). The combination of these processes results in an accelerated disease progression. Calcification is often present by 40 years of age. In 1 series (64), more rapid progression in aortic valve gradients occurred in patients with anteroposteriorly located cusps. In children, aortic valve disease is more significant in patients with right and noncoronary cusp fusion (65). However, not all studies have found this association, and the 2 large studies in adults have not identified leaflet orientation as a risk factor for late adverse events (6,7). This finding that valve orientation was not predictive of outcomes in adults may reflect the modifying role of atherosclerosis risk factors and/or more advanced degenerative process encountered in adults. Indeed, the Olmsted County study (6) identified a composite index of valve degeneration, which incorporated valve thickening, calcification, and mobility, that was an independent predictor of long-term cardiac events in a population of adults with no baseline valve dysfunction. The predictive role of both morphology and function in adults with BAV parallels that observed in series examining older adults with aortic stenosis mostly of acquired basis (66–68).

Aortic Incompetence

In childhood, aortic incompetence can develop in the setting of redundant or prolapsing cusps, endocarditis, or after balloon valvuloplasty (69,70). With age, aortic incompetence may also develop secondary to dilation of the ascending aorta. Although adults with BAV often have some degree of aortic regurgitation, the actual prevalence of pure aortic incompetence has varied, with some suggesting it is rare and others suggesting that it is common (3,71,72). In 1 large surgical series, 13% of surgically excised valves at the time of aortic valve replacement were for pure aortic incompetence (9). In the Olmstead county echocardiographic study of asymptomatic adults (6), 47% had some degree of aortic incompetence at baseline; however, interventions for severe aortic incompetence were relatively uncommon, occurring in only 3% of the cohort during follow-up. In the Toronto study (7), 21% of the population had moderate or severe aortic incompetence at baseline; however, only 6% had an intervention for symptomatic aortic incompetence or progressive left ventricular dysfunction. Despite variations in prevalence, moderate or severe aortic incompetence is clinically important and is an independent predictor for late adverse cardiac events.

Aortopathy and Aortic Dissection

Aortic root dilation has been documented in childhood, suggesting that this process begins early in life (73–75). Furthermore, children with BAV have greater increases in aortic dimensions than do children with trileaflet valves (73). In both children and adults, progressive dilation of the aorta is more common in patients with larger aortas at baseline (76–78). In BAV disease, the aortic annulus, sinus, and proximal ascending aorta are larger than those found in adults with trileaflet valves (79–81). These differences persist even after adjusting for blood pressure (systolic and diastolic), peak aortic velocities, and left ventricular ejection time (79). Our group reported a prevalence of aortic sinus dilation of 28% (mean age 35 ± 16 years), and after 9 years of follow-up, the prevalence had increased to 45% with a median increase in the aortic sinus dimension of 0.2 mm/year (7). In the Olmsted County study (6), the prevalence of ascending aorta dilation (>40 mm) was 15% and in the subset of patients with repeat measurements, the prevalence increased to 39% at study completion. Dilation of the ascending aorta was an independent risk factor for ascending aorta surgery. Although there are a number of risk factors associated with dilation of the ascending aorta including increased systolic blood pressure, male sex, and significant valve disease, the most important variable is likely age (7,79,82,83). Aortic root size is shown to be related to valve morphology and the presence of significant valve disease (82,84). Specifically, the increased stroke volume from aortic incompetence is felt to result in stress on the diseased aorta and subsequent aortic dilation (82,85,86).

Changes in the aortic media during pregnancy may predispose to subsequent aortic dilation, but this has not been confirmed by prospective studies.

The most feared complication is aortic dissection, primarily due to the high associated mortality rate; however, the actual incidence of this complication is debated. Although the prevalence varies depending on the cohort studied, a pooled estimate of cases of dissection associated with BAV was 4% (4,87–89). Recent studies suggest a lower risk. In the Toronto series (7), the prevalence of dissection was 0.1% per patient-year of follow-up, and in the Olmsted County study (6), there were no cases of dissection. Despite the low rates of dissection, the increased prevalence of BAV disease relative to Marfan syndrome make dissections due to BAV equal to or more common than dissections due to Marfan syndrome (90). Dissection in BAV, when it occurs, typically involves the ascending aorta, but involvement of the descending aorta has been reported in older patients (2). Distal aortic disease may be related to BAV or may be secondary to other risk factors commonly found in older individuals. Although dissection is more common in patients with dilated aortas, there are reports of dissection in normal-sized aortic roots and after valve replacement (91). Risk factors for dissection have included aortic size (92,93), aortic stiffness (94), male sex (95), family history (96), and the presence of other lesions such as coarctation of the aorta (95) or Turner syndrome (97).

Endocarditis

Endocarditis can lead to valve perforation or destruction and result in severe aortic incompetence. When this occurs acutely, it is poorly tolerated. Endocarditis risk, based on earlier case series, was estimated to range between 10% and 30% (3). However, high rates were likely due to reporting bias in earlier studies, and more recent estimates of the incidence of endocarditis are much lower at 2% or 0.3%/year (6,7). Because the risk of endocarditis is felt to be low, the ACC/AHA practice guidelines no longer suggest bacterial endocarditis prophylaxis in patients with straightforward BAV disease, except in patients with a prior history of endocarditis (98). Because these guidelines are a significant departure from the prior recommendations, physicians and/or patients accustomed to the routine use of endocarditis prophylaxis may be hesitant to apply these new recommendations.

Survival

Despite these complications, 2 large series have confirmed that in the current era, life expectancy in adult patients with BAV disease is not shortened when compared with the general population. In asymptomatic adults with BAV with a spectrum of valve function, the 10-year survival was 96 ± 1% (7), and in asymptomatic adults with BAV without significant valve dysfunction, the 20-year survival was 90 ± 3% (6) (Fig. 4).

Surveillance

In order to follow disease progression, serial transthoracic echocardiograms should be performed in all patients. At a minimum, annual cardiac imaging is recommended for patients with significant valve lesions or those with aortic root diameters ≥40 mm. In those patients without significant valve lesions and aortic roots diameters <40 mm,

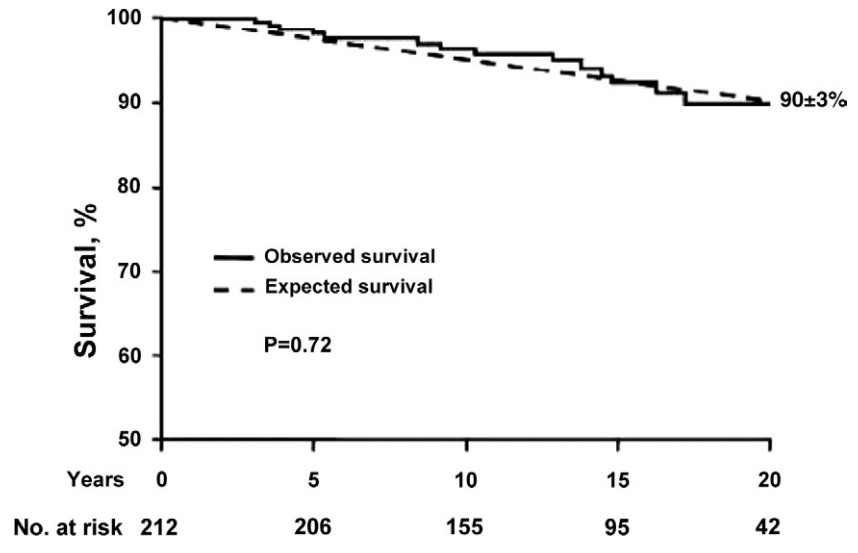

Figure 4 Survival in Adults With Bicuspid Aortic Valve With No Significant Aortic Valve Dysfunction

Dashed line represents subjects with bicuspid aortic valve disease compared with an age- and sex-matched control population **(solid line)**. Reprinted, with permission, from Michelena et al. (6).

cardiac imaging every 2 years may be adequate (48,50). Aortic root size should be referenced to body surface area, especially in patients where body size is important, such as women and patients with Turner syndrome. An aortic sinus dimension of 2.1 cm/m^2 is considered the upper limit of normal (99,100). Complete imaging of the thoracic aorta should be performed periodically for surveillance. Because computer tomography scans are associated with significant radiation exposure, they should only be performed in this young population if needed and if other imaging modalities are not available. Other parameters, such as compliance of the aorta, can be measured with echocardiography or magnetic resonance imaging. Aortic elasticity is reduced in patients with BAV and aortic regurgitation and, in the future, these physiologic measures may have a role in risk stratification (94,101). Measures of systemic endothelial dysfunction, such as brachial flow-mediated vasodilation to hyperemia and carotid-femoral pulse wave velocity, have been shown to be abnormal in patients with BAV, suggesting that BAV perhaps represents a generalized vascular process (102).

In the future, biomarkers may be useful for assessment of the valve, the response of the ventricle to the valve disease, and the aortic root disease. For example, in degenerative aortic valve disease, brain natriuretic peptide has been shown to be prognostically important (103–105). Serum markers such as matrix metalloproteinase, aminoterminal propeptide of type III collagen, fibrinogen, and markers of inflammation are elevated in subjects with abdominal aortic aneurysms (106). Little information is available on these or other serum biomarkers in BAV disease. We have demonstrated that ascending aortic dilation was associated with increased serum matrix metalloproteinase 2 in young men with nonstenotic BAV (102). The clinical utility of these and other serum markers requires further study.

Medical Therapy

At a minimum, high blood pressure should be aggressively treated in patients with BAV disease. In Marfan-associated aortopathy, treatment with beta-blockers to slow the rate of progression is the standard of care at many centers, although debate exists about their effectiveness (107,108). Some clinicians have extrapolated this practice to the treatment of aortopathy associated with BAV disease. The ACC/AHA guidelines for the management of adult congenital heart disease and guidelines for the management of patients with valvular heart disease suggest that it is reasonable to use beta-blockers in this population (Class IIa recommendation) (48,109). There are emerging data in animal models and in 1 small study in humans supporting the use of angiotensin II receptor blockers to decreased aortic root dilation in Marfan syndrome (110,111). Whether these agents will have a role in BAV aortopathy has not yet been demonstrated. Finally, long-term vasodilator therapy in BAV disease with aortic regurgitation is only recommended if there is concomitant systemic hypertension (48).

The relationship between risk factors for atherosclerosis and the development and progression of degenerative aortic valve disease has been well studied (112). However, the role of treatment with cholesterol-lowering agents is unresolved. Although some studies (113,114) have demonstrated slowing of the progression of aortic valve disease, 1 large prospective randomized trial (115) found that treatment did not stop disease progression in calcific aortic stenosis. Two additional prospective studies addressing this issue are still in progress. The use of lipid lowering agents specifically in young patients with BAV has not been studied, and the current ACC/AHA guidelines for the management of patients with valvular heart disease do not endorse the use of statins to slow the degenerative process in this population (50).

Interventions

When rheumatic disease is excluded, a significant portion of adults undergoing surgery for aortic valve disease will have a congenitally malformed valve (116). In many cases, indications for surgery are similar to that in patients with tricuspid valve disease or "degenerative aortic valve disease" (50). However, some features are unique to this population and require consideration.

During childhood, insertion of a prosthetic valve is suboptimal because of the continuing growth of the child. Fortunately, at this stage, the aortic valve is usually not calcified and valvuloplasty can successfully disrupt the commissural fusion and relieve obstruction. Valvuloplasty is the interventional strategy of choice in children and in some young adults with BAV and aortic stenosis. In the current era, surgical valvotomy has been replaced by balloon valvuloplasty. Thresholds for interventions differ in part because valvuloplasty is felt to be a relatively low-risk procedure and because the population is somewhat different than the adult with aortic stenosis. Symptomatic aortic stenosis is an indication for intervention, similar to standard indications for degenerative trileaflet valve disease. However, in the pediatric setting, indications include children with peak-to-peak gradients >50 mm Hg who develop ST- or T-wave changes at rest or with exercise or who are interested in participating in athletics. An additional indication includes asymptomatic children with peak-to-peak gradients >60 mm Hg (50,117). Mid-term results after balloon valvuloplasty are good at experienced centers (118–120). In instances when aortic incompetence develops after balloon valvuloplasty, aortic valve replacement may be necessary.

In adulthood, aortic valve replacement is the most common intervention for either aortic valve stenosis or incompetence, and valvuloplasty is rarely performed (7). Surgery for BAV disease occurs at an earlier age than surgeries for degenerative tricuspid aortic disease (116).

In the Olmsted County series (6), the average age for BAV surgery was 40 ± 20 years versus 67 ± 16 years for patients with tricuspid aortic valve. The usual surgical options include valve replacement (bioprosthetic or mechanical valves), Ross operations (native pulmonary valve moved to the aortic position and a homograft placed in the pulmonary position), or valve repair for those with aortic incompetence (121). Indications of interventions for aortic stenosis or incompetence are similar to those described for tricuspid aortic valve disease in the ACC/AHA guidelines for the management of patients with valvular heart disease (50). BAV disease involves younger patients and involves both the valves and the great arteries; therefore, surgical decision making is more complicated. Approximately 30% of adults undergoing aortic valve replacement will also need aortic root surgery (7). Because of the risk of further root dilation, many surgeons consider reinforcing or replace the ascending aorta at the time of valve surgery (91). The dimension of the aortic root felt to require surgical attention has varied over time, and in many cases, this threshold value for intervention is institution- and surgeon-specific. The current guidelines suggest that a cutoff of 5.0 cm be used for intervention or 4.5 cm if the surgery is otherwise being performed for valve indications (50). Although not incorporated into current guidelines, aortic size relative to body size may be a better method to define the high-risk group requiring surgery (92). In addition, the guidelines suggest that changes in root size more than 0.5 cm/year are an indication for root replacement. Average annual changes in ascending aorta in patients with BAV vary between 0.2 to 1.2 mm/year (73,82,122–124). Because of limitations with the current data, some have questioned the basis for these recommendations and have suggested that thresholds for intervention should be reconsidered (89).

In regard to valve surgery, there is controversy regarding the use of the Ross procedure and the use of valve repairs in this population. Abnormalities of the media are seen in both the aorta and the pulmonary artery in BAV disease (17,18,22). Intrinsic abnormalities in the wall of the pulmonary artery (neoaorta) may contribute to progressive neoaortic root dilation and/or aortic regurgitation when the pulmonary root is placed in the systemic position (125). Because of this potential late complication, some do not advocate the use of the Ross operation in patients with BAV disease. Despite good mid-term results with valve-sparing operations and the well-described progression of disease, some experts believe that leaving behind the abnormal BAV is ill-advised. Therefore, the optimal surgical approach for patients with BAV remains to be defined.

Pregnancy

During pregnancy there are changes in hemodynamics as well as changes in the aortic media, and therefore, women with BAV and significant aortic stenosis and/or dilated aortic roots are at risk for complications during pregnancy. Recent studies from our center and others suggest that the risk of adverse pregnancy events in women with severe aortic stenosis is less than previously described. Even though this group of women continue to represent a high-risk group for maternal and fetal morbidity, their overall mortality risk is likely <1% based on recent studies (126–128). In rare instances, women will develop progressive symptoms during pregnancy and require either valvuloplasty or valve surgery. Both interventions can be performed during pregnancy, but are associated with both maternal and fetal risks and should be performed only when necessary. Although the mechanisms that predispose some women to deteriorate during pregnancy are not completely understood, in a preliminary study, we reported that women with moderate and severe aortic stenosis who deteriorated in the antepartum period failed to increase left ventricle twist (129). Although pregnancy can be successfully completed in most instances, aortic surgery may be required early after pregnancy in some women with severe aortic stenosis (127,130). Pregnancy itself seems to accelerate the need for surgery postpartum in women with moderate or severe aortic stenosis, perhaps by affecting the ability of the left ventricle to adapt to the fixed outflow obstruction (130). It is therefore important that women be counseled about both the risk of pregnancy and the potential for late complications. Additionally, guidelines suggest that women with BAV and significant aortopathy (ascending aorta diameter >4.5 cm) "should be counseled against the high risk of pregnancy" (48). What this counseling would entail and the evidence underlying this recommendation is not clear as the risk of pregnancy in a woman with BAV and a dilated root has not been systematically examined.

Exercise

Because BAV can affect children and young adults, exercise guidelines are often important for this group of patients. However, there are little data available to support recommendations regarding exercise in subjects with BAV. In children with congenital severe aortic stenosis, for instance, sudden death can occur during exercise (131–133). The Task Force on Exercise in Patients with Heart Disease recommends that athletes with severe aortic stenosis or severe aortic incompetence with left ventricular dilation (left ventricular dimensions >65 mm) should not participate in competitive athletics. Athletes with or without aortic valve disease who have dilated aortic roots (>45 mm) are advised to only participate in low-intensity competitive sports. No restrictions exist for those with BAV with no significant valve dysfunction or aortic root/ascending aorta dilation (<40 mm) (134,135).

Future Directions

While recent cohort studies have helped to improve our understanding of the complication rate in adults with BAV, continued cohort studies remain important and ideally should begin in childhood. Understanding the disease from childhood to adulthood will help to define late survival accurately, identify high-risk groups earlier, improve timing of interventions, and accurately study outcomes after intervention. In addition to the traditional clinical and echocardiographic predictors of adverse outcomes discussed in this review, other prognostic markers of disease will likely become important such as serum markers, new cardiac imaging measures, and genetic markers. Apart from treating endocarditis, no medical therapy has proven beneficial, but randomized clinical trials are currently underway with the aim of improving outcomes by modifying valve and aortic root progression. Furthermore, with advances in our understanding of the process of valve degeneration and aortic root dilation, new potential therapeutic targets will be identified.

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