Bicuspid Aortic Valve and Associated Aortopathy: An Update

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Bicuspid aortic valve (BAV) is the most common form of congenital heart disease and most such patients develop cardiovascular complications over time. Recent studies have shed light on one of the most common of these complications, BAV-associated aortopathy. Two distinct BAV phenotypes have been identified, which may have different causes of their associated aortopathy. Increasing evidence suggests that the BAV stenosis phenotype is predominantly secondary to hemodynamic perturbances in transvalvular flow and is associated with a more benign long-term prognosis once the stenotic BAV is replaced. In contrast, the root phenotype—which is associated with aortic insufficiency—appears to have a genetic origin and may be associated with a higher risk of adverse aortic complications, irrespective of the extent of valvular disease. Such observations may have implications for patient decision making. Future studies should be performed so as to better define phenotypes and risk factors for BAV-associated aortopathy.

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EPIDEMIOLOGY AND NATURAL HISTORY OF BICUSPID AORTIC VALVE

Bicuspid aortic valve (BAV) disease is known to be the most common congenital anomaly of the human heart.1,2 Taking into account all complications associated with BAV disease, it accounts for more morbidity and mortality than that of all the other congenital cardiac lesions combined.3 A broad spectrum of complications associated with BAV has been described, including aortic valve stenosis (ie, the most common form of symptomatic BAV disease), aortic valve insufficiency, infective endocarditis, and ascending aortic complications.

There is adequate evidence that BAV is a heritable disorder with an autosomal dominant inheritance pattern and reduced penetrance.4 The prevalence of BAV historically quoted in the literature has been between 1% and 2% with an obvious male preponderance. However, these estimates are predominantly derived from necropsy studies from an earlier era.5,6 As emphasized by the authors of these early studies, the incidence of BAV determined by necropsy reports is unreliable because this anomaly may be easily overlooked.3

The development of echocardiography screening has a significant potential to increase our understanding of the prevalence of BAV in the general population. However, there are only limited population-based echocardiographic data on the prevalence of BAV in the pediatric and adult population.7–9 These echocardiographic surveys quote a BAV frequency of 0.5% in unselected healthy populations, which is significantly lower than previously expected. However, the sensitivity of transthoracic echocardiography to identify BAV has been reported in the range of only 60%.10 Therefore, at least one-third of BAV cases may remain undetected by means of transthoracic echocardiographic screening. Moreover, as BAV is a heritable disorder, some familial and endemic clustering may be encountered with a potential of accumulation of patients with BAV in certain geographic areas.11

Therefore, the true incidence of BAV in the general population may be underestimated. An underestimation of the true BAV incidence may have clinical consequences because the reported increased risk of aortic complications in these patients is based on the assumption that BAV prevalence is in the range of 1%-2% in the general population. If the true prevalence of BAV is higher, then the increased aortic complication risk may be exaggerated.
MORPHOLOGY OF BAV—WHAT IS IMPORTANT FOR FUNCTIONAL ANALYSIS?

There are several morphologic aspects that predispose to specific functioning patterns of bicuspid valves. One structural feature that influences transvalvular flow characteristics is the cusp fusion pattern. The 2 most common patterns of cusp fusion in BAV disease are fusion of the left and right coronary cusps, which occurs in 70%-85% of cases, and fusion of the right and noncoronary cusp, which occurs in 15%-30% of patients with BAV (Fig. 1). There is sufficient evidence in the literature demonstrating an association between BAV cusp fusion pattern and specifically oriented transvalvular systolic flow.13,14 Moreover, “cusp opening angle” (ie, degree of fused cusp alignment to the aortic outflow axis in systole) has been described recently by Della Corte et al15 to demonstrate the effect of fused cusp motility on transvalvular systolic flow detection. These investigators were also able to demonstrate a prognostic correlation of this parameter with yearly rate of aortic growth.

Another structural parameter that is important in the functional analysis of BAV is the angulation between the left ventricular outflow tract and the aortic root, as described previously by den Reijer et al.16 A significant correlation has been demonstrated between this angle, the degree of eccentricity of the systolic transvalvular flow, and the severity of the proximal aortic dilatation in a pediatric BAV population (ie, the larger the angle of misdirected flow with the aortic outflow axis, the larger the proximal aortic diameter).16

We recently examined transvalvular flow patterns, as determined by magnetic resonance imaging (MRI), in a prospective study on patients with BAV undergoing aortic valve replacement (AVR) surgery. We found variations in transvalvular flow patterns even in patients with the same cusp fusion pattern.17 We hypothesized that the exact geometric orientation of residual aortic valve orifice in patients with BAV stenosis may be responsible for these variations in transvalvular flow patterns.

This overview is aimed to illustrate the complex interaction between morphologic characteristics of BAV and functional alterations in blood flow, which is a crucial step in the understanding of pathogenesis of bicuspid aortopathy.

RHEOLOGICAL CHARACTERISTICS OF CLINICALLY “NORMAL” BAV: EVIDENCE FROM RECENT STUDIES

The asymmetric and dome-shaped opening of clinically “normal” aortic valves in patients with BAV has been demonstrated experimentally by Robicsek et al18 in their pioneering in vitro study. The resultant perturbations in transvalvular flow through the clinically “normal”—but morphologically stenotic—BAV orifice have been shown to be eccentric and directed toward the proximal aortic wall rather than toward the aortic lumen as in patients with normal tricuspid aortic valves (TAV). The effect of transvalvular flow eccentricity on the diameter of the proximal aorta (ie, degree of aortopathy) has been demonstrated in the pediatric BAV population.16

Barker et al19 evaluated wall shear stress along the lumen circumference of the ascending aorta in patients with BAV using phase-contrast MRI. The spatial distribution and magnitude of systolic wall shear stress in patients with BAV was shown to be significantly different from that in patients with TAV.19 In addition, the values of turbulent kinetic energy and shear stress were significantly higher in BAV than TAV models using finite element analysis20 and particle image velocimetry.21

The most recent contributions in this field14,22 compared flow and wall shear stress patterns in individuals with clinically “normal” bicuspid and TAV, using sophisticated 4-dimensional cardiovascular MRI. Similar to the findings of previous studies, BAV aortas were exposed to significantly higher

Figure 1. Cusp fusion patterns in BAV disease. (Adapted with permission from Sabet et al.12)
transvalvular flow-induced wall shear forces than TAV aortas were. These flow abnormalities may have a major effect on the development of BAV-associated aortopathy in patients with clinically “normal” BAV.

**BAV-ASSOCIATED AORTOPATHY: ALWAYS THE SAME DISEASE?**

Most of the literature on BAV disease considered proximal aortic involvement as a homogeneous clinical entity, which may lead one to conclude that more aggressive surgical treatment is justified. The controversy regarding optimal treatment of BAV-associated aortopathy was primarily triggered by inconsistency of published follow-up data on long-term outcomes after AVR in patients with BAV. Such a high variability in the prevalence of late aortic events (ie, 5%-30% over a mean of 13 years) may be explained by substantial differences in the patient population between studies (ie, heterogeneous characteristics of the included patients). The concept of heterogeneity in BAV disease became accepted in the last few years, which was followed by identification of separate anatomical-clinical forms—so-called BAV phenotypes.

**BAV Stenosis and Associated Aortopathy**

Pure or predominant calcific stenosis is the most common dysfunctional state of BAV (ie, 85% of surgically treated cases). The common association between BAV stenosis and asymmetric dilatation of the tubular aorta, starting from the sinotubular junction and predominantly involving the convexity of the vessel, has been identified as “BAD MATE” syndrome by Cotrufo et al and Della Corte et al (Fig. 2). This association has been proposed to be of pathogenetic origin and a result of an eccentric transvalvular flow jet through the stenotic BAV. The high-velocity turbulent jet propagates toward the greater curvature of the tubular ascending aorta, thus leading to its subsequent wall thinning and enlargement (ie, previously so-called poststenotic dilatation). Hemodynamic factors (ie, flow-induced vascular remodeling) have been proposed to play a major role in the development of such an aortopathy in patients with BAV stenosis. Until recently, this hemodynamic hypothesis has been mostly based on indirect observational data.

If abnormal transvalvular flow is the major determinant of coexistent aortopathy in patients with severe BAV stenosis, isolated AVR surgery should be sufficient in patients with mild to moderate concomitant ascending aortic dilatation. To test this hypothesis, we retrospectively examined a relatively large group of consecutive patients (n = 153) who underwent isolated AVR surgery for BAV stenosis with concomitant mild to moderate proximal aortic dilatation (ie, 40-50 mm) over a prolonged period of follow-up (mean = 11.5 years). Our analysis demonstrated a considerably low risk of adverse aortic events during follow-up, with a freedom from
adverse aortic events of 93% at 15 years.26 No documented aortic dissection or rupture occurred in this patient group, supporting the hypothesis that aortopathy in patients with BAV stenosis is predominantly a secondary hemodynamic effect.

To further test this hypothesis, we recently examined the long-term prognosis of moderate ascending aortic dilation after isolated AVR in patients with BAV vs that in patients with TAV stenosis.27 We observed a low risk of adverse aortic events during follow-up in both groups, with 15-year freedom from adverse aortic event rates of 93% vs 82% in the BAV vs TAV groups (P = 0.2).27

We also hypothesized that a significant correlation may be anticipated between rheological characteristics of transvalvular blood flow and microstructural changes in the proximal aortic wall in patients with BAV stenosis and associated aortopathy.17 Using preoperative MRI examinations and intraoperative aortic tissue samples, we were able to demonstrate a strong correlation between the systolic pattern of transvalvular flow jet and asymmetric proximal aortic wall changes in patients undergoing AVR for BAV stenosis. The histologic sum score was significantly higher in the jet sample (ie, area of maximal flow-induced stress in the proximal aorta as determined by preoperative MRI) vs control sample (ie, opposite aortic wall) in these patients.17

In summary, there is a growing body of evidence that BAV-associated aortopathy in patients with BAV stenosis represents a predominantly hemodynamic-induced phenomenon. Concomitant mild to moderate dilatation of the ascending aorta in these patients is not associated with an increased risk of adverse aortic events up to 15 years after isolated AVR.

Such observations may have important implications for clinical decision making in patients presenting with BAV-associated aortopathy. However, we do not suggest that ascending aorta replacement is contraindicated in patients with BAV stenosis and mild to moderate dilation of the ascending aorta. Concomitant replacement of the supracoronary aorta is a safe procedure that can be performed with low additional surgical risk, and it may be indicated in specific situations (eg, in patients with a thin aortic wall so as to prevent catastrophic bleeding at the end of the operation; in patients with a family history of adverse aortic events; and in patients with poorly controlled hypertension). However, it is possible to conclude from our data that very aggressive approaches to the aorta in patients with BAV stenosis (eg, prophylactic replacement of the aorta in patients without other indications for cardiac surgery and replacement of the aortic root, ascending aorta, and proximal aortic arch in patients requiring AVR surgery) are not justified in the absence of a markedly dilated aorta.

**BAV Root Phenotype**

A relatively small cohort of patients with BAV (approximately 10%) present with the second common phenotype, that is, predominant aortic dilatation at the level of the aortic annulus and the sinuses of Valsalva with varying degrees of accompanying aortic valve insufficiency (Fig. 3). This anatomical-clinical form of BAV disease has been described in the literature as “root phenotype.”

Root phenotype occurs primarily in the young BAV population, and male sex has a strong predisposition for the condition. There are some data in the literature that support the predominantly genetic origin of BAV root phenotype. A subgroup of young male patients with BAV who present with a varying degree of aortic valve insufficiency and dilatation of the aortic root, which occur independent of age and body size, has been identified by Nistri et al.28 Biner et al29 were able to demonstrate the congenital pattern of aortopathy in the first-degree relatives of patients with BAV who presented with aortic root dilatation. We reported on a patient with familial BAV disease and root dilatation phenotype, in whom the genetic origin was demonstrated to be a TGFBR2 gene mutation.30

The BAV root phenotype seems to have a different prognosis for aortic complications when compared with that of the BAV stenosis phenotype. We recently demonstrated a considerably higher prevalence of adverse aortic events during follow-up in a BAV cohort with aortic insufficiency.31 The freedom from aortic complications 15 years postoperatively was 78 ± 9% in patients with BAV root phenotype compared with 93 ± 3% in patients with BAV stenosis (P = 0.02).31

The aforementioned data suggest that BAV root phenotype may be a genetic, connective tissue disorder—like form of aortic disease that is independent of transvalvular flow perturbations. One could therefore recommend a more aggressive surgical approach to the aorta in this subgroup of patients with BAV. In addition, a distinction should be made between patients with root phenotype and patients with BAV stenosis in future studies of BAV-associated aortopathy.

**Biomolecular Studies on BAV Aortopathy**

One of the traditional arguments for a genetic origin of BAV-associated aortopathy has been data
from multiple biomolecular series demonstrating more severe microstructural lesions in the proximal aortic wall of patients with BAV when compared with that of matched TAV controls. Unfortu-

nately, most of these studies share 2 inherent limitations, which may have led to a misinterpreta-

tion of the results. The first limitation is the lumping of patients with BAV stenosis and patients with BAV root phenotype together, which is probably inappropriate for the reasons addressed earlier. Recently, some investigators have found more severe biomole-

cular lesions in patients with BAV insufficiency as compared with those in patients with BAV stenosis, further supporting the concept that these are 2 separate clinical entities. Another recent study, which included a high proportion of patients with BAV insufficiency (ie, 60% of the total study cohort), showed a high prevalence of moderate or severe histologic alterations in the aortic media even in the absence of clinically relevant proximal aortic dilata-

tion. In their multivariate analysis, these authors demonstrated a significant association between aortic media alterations and diameter of the aortic annulus, which is in turn an indicator of aortic root disease (ie, BAV root phenotype). The second major limitation of previous biomole-

cular studies is the inability to differentiate between primary congenital changes in the aortic wall architecture and secondary hemodynamically induced vascular lesions. Indeed, one may question whether this differentiation is possible at all. As previously mentioned by Robicsek, a study demonstrating the

Figure 3. Transthoracic echocardiography (A) and intraoperative findings (B) in a patient with BAV root phenotype. (Color version of figure is available online at http://www.semthorcardiovascsurg.com.)
primary nature of biomolecular changes by examining the aortic wall in the newborns would be required to definitely answer this question.

**INTERACTION OF MORPHOLOGY, FUNCTION, AND DISEASE PROCESS: FUTURE DIRECTIONS IN BAV RESEARCH**

Despite the fact that progress has been made in understanding BAV disease and its associated aortopathy in the last decade, major questions remain to be answered. Although we are aware of 2 distinct phenotypes of BAV disease, we are unable to assign every single patient with BAV to one of these entities. Other questions to be answered include the following: (1) Why does the aorta never dilate in 20%-30% of patients with BAV? (2) What is the cutoff value of aortic diameter that may be left untreated at the time of cardiac surgery in patients with BAV stenosis vs patients with BAV insufficiency vs patients with functionally normal BAV? (3) What will be the role of transcatheter valve technology in patients with BAV disease and associated aortopathy? (4) What are the diagnostic tools that will help us to distinguish the more aggressive from the more benign forms of BAV-associated aortopathy? Future research in BAV disease should focus on the ability to integrate information on the morphologic features and functional characteristics of the aortic valve and proximal thoracic aorta, preferably obtained by means of noninvasive imaging. Such information may allow us to correlate specific morphologic variants of BAV with functional alterations so as to better define individual BAV phenotypes and future risk patterns. Noninvasive image-based assessment of aortic wall qualities may be required to better understand the development and progression of aortopathy. Such information may eventually replace the nonspecific size-based criteria that are currently used for aortic surgery. Moreover, further genetic studies are required so as to better define the congenital basis of separate BAV phenotypes.

**SUMMARY**

BAV is a common congenital disorder and a significant proportion of such patients develop cardiovascular complications over time. Associated aortopathy is an important—but still poorly understood—lesion that is frequently found in patients with BAV. Two distinct clinical-pathologic BAV phenotypes can be identified. Patients presenting with BAV stenosis seem to have a more benign form of associated aortopathy, and aggressive management of the condition in such patients may not be justified. By contrast, more aggressive management of concomitant aortic dilation may be required in patients presenting with root phenotype BAV disease. Future studies should focus on better characterization of BAV subgroups, preferably based on noninvasive imaging or genetic testing, and the effects of these phenotypes on outcomes and patient management.

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