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Review

Is aortopathy in bicuspid aortic valve disease a congenital defect or a result of abnormal hemodynamics? A critical reappraisal of a one-sided argument

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Summary

Although there is adequate evidence that bicuspid aortic valve (BAV) is an inheritable disorder, there is a great controversy regarding the pathogenesis of dilatation of the proximal aorta. The hemodynamic theory was the first explanation for BAV aortopathy. The genetic theory, however, has become increasingly popular over the last decade and can now be viewed as the clearly dominant one. The widespread belief that BAV disease is a congenital disorder of vascular connective tissue has led to more aggressive treatment recommendations of the proximal aorta in such patients, approaching aortic management recommendations for patients with Marfan syndrome. There is emerging evidence that the 'clinically normal' BAV is associated with abnormal flow patterns and asymmetrically increased wall stress in the proximal aorta. Recent *in vitro* and *in vivo* studies on BAV function provide a unique hemodynamic insight into the different phenotypes of BAV disease and asymmetry of corresponding aortopathy even in the presence of a 'clinically normal' BAV. On the other hand, there is a subgroup of young male patients with BAV and a root dilatation phenotype, who may present the predominantly genetic form of BAV disease. In the face of these important findings, we feel that a critical review of this clinical problem is timely and appropriate, as the prevailing BAV–aortopathy theory undoubtedly affects the surgical approach to this common clinical entity. Thorough analysis of the recent literature shows a growing amount of evidence supporting the hemodynamic theory of aortopathy in patients with BAV disease. Data from recent studies requires a reevaluation of our overwhelming support of the genetic theory, and obliges us to acknowledge that hemodynamics plays an important role in the development of this disease process. Given the marked heterogeneity of BAV disease, further studies are required in order to more precisely determine which theory is the 'correct' one for explaining the obviously different types of BAV-associated aortopathy.

Keywords: Valves; Bicuspid aortic valve; Aorta; Congenital heart defects; Aortic surgery

1. Introduction

The bicuspid aortic valve (BAV) is the most common congenital abnormality of the human heart, affecting approximately 1–2% of the general population [1]. It is estimated that a bicuspid morphology will lead to structural aortic valve problems (stenosis or regurgitation) in all patients who live long enough to manifest them [2]. The BAV disease accounts for more morbidity and mortality than all other congenital heart diseases combined [3]. Mutations in the NOTCH1 gene [4] have been shown to be associated with the development of BAV.

In persons with BAV, the dimensions of the proximal aorta (especially the tubular ascending aorta) are significantly larger than those in persons with tricuspid aortic valve, even in the absence of significant valvular hemodynamic disturbance [5,6]. This has been empirically linked to an increased risk of acute aortic complications in BAV patients. Even though there is adequate evidence that BAV is an inheritable disorder (i.e., autosomal dominant disease with incomplete penetrance), there is a great controversy regarding the pathogenesis of dilatation of the proximal aorta. The two main theories explaining the phenomenon of aortopathy in BAV disease are: (1) the genetic theory,

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Table 1. Follow-up studies on BAV patients after aortic valve replacement.

Authors	Sample size	Study period	Follow-up (years)	Dissection/rupture	Aortic reoperations	Sudden deaths	Cumulative aortic events
Russo et al. [7]	50	1975–1985	19.5 ± 3.9	5 (10.0%)	3 (6.0%)	7 (14.0%)	15 (30.0%)
Borger et al. [13]	201	1979–1993	10.3 ± 3.8	1 (0.5%)	18[a] (9.0%)	3 (1.5%)	22 (11.0%)
Goland et al. [14]	252	1971–2000	8.9 ± 6.3	0 (0%)	1 (0.4%)	11 (5.6%)	12 (4.8%)

[a] 11/18 patients underwent simultaneous aortic valve re-replacement for structural deterioration of bioprosthesis.

whereby the presence of aortic wall fragility is a consequence of a common developmental defect involving the aortic valve and the aortic wall; (2) the hemodynamic theory, whereby the abnormal hemodynamic stress on the aortic wall induced by eccentric turbulent flow through the bicuspid valve leads to subsequent aortopathy.

Although the hemodynamic theory was the first explanation for BAV aortopathy, the genetic theory has become increasingly popular over the last decade and can now be viewed as the clearly dominant one. An ever-increasing amount of clinical and basic science research has focused on BAV aortopathy in the cardiac surgery and cardiology literature. The widespread belief that BAV disease is a congenital disorder of vascular connective tissue has led to more aggressive treatment recommendations of the proximal aorta in such patients, approaching aortic management recommendations for patients with Marfan syndrome [7,8]. However, an aggressive surgical treatment strategy of aortopathy in BAV disease has been questioned by some [9].

In the face of recent important *in vitro* and *in vivo* findings on BAV function [10–12], we found it necessary to once again address the issue of pathogenesis of BAV-associated aortopathy. We feel that a critical review of this clinical problem is timely and appropriate, as the prevailing BAV–aortopathy theory undoubtedly affects the surgical approach to this common clinical entity.

A systematic PubMed database search for English-language articles was performed using the subject headings 'BAV aortopathy', 'BAV and ascending aorta', 'BAV and aortic aneurysm', and 'BAV and aortic complications'. Publications were also identified from references of retrieved articles. This search yielded 196 publications, all of which were individually revised to determine the appropriateness. A total of 49 articles were found to be methodologically sound and appropriate for this review, after excluding the duplicated data, case reports, limited-number case series (i.e., which included less than 15 individuals), and follow-up studies with the limited surveillance period (i.e., mean follow-up time of less than 5 years).

2. Fate of the proximal aorta in BAV patients after isolated aortic valve replacement

According to the genetic BAV–aortopathy theory, enlargement of the proximal aorta would progress after isolated aortic valve replacement (AVR) surgery and lead to major vascular complications (i.e., aortic dissection or rupture) in a significant proportion of such patients. Such a situation is generally present in patients with Marfan syndrome and other congenital connective tissue disorders. The first question is, therefore, do we really know what happens to the proximal aorta during long-term follow-up after isolated AVR in BAV patients?

Given the high prevalence of BAV disease in the general population, there is a notable paucity of data on long-term outcomes after isolated AVR in such patients. We performed a thorough review of the literature and were able to identify only three methodologically sound follow-up studies on this topic [7,13,14]. The corresponding results and conclusions are very controversial, ranging from a quite benign long-term course (one reoperation for aortic aneurysm in a subgroup of 252 BAV patients followed for 8.9 ± 6.3 years) in the publication by Goland et al. [14] to a markedly unfavorable postoperative course (eight late aortic events and seven sudden deaths in the subgroup of 50 BAV patients followed for 19.5 ± 3.9 years) in the study by Russo and co-workers [7]. However, the latter study consisted of a small cohort of BAV patients with quite unusual characteristics: not a single patient had a dilation of the proximal aorta at the time of surgery and no patient had a history of arterial hypertension preoperatively. The cumulative analysis of results from these three studies shows that about 5–30% of BAV patients may experience late aortic events 10–20 years postoperatively after isolated AVR (Table 1). However, the incidence of documented aortic dissection or rupture was considerably low in these studies – only six events in 5288 cumulative patient-years. Although the precise rate of aortic complications in patients with Marfan syndrome is currently unknown, the estimated rate from a panel of experts is certainly much higher than that observed in our review of the BAV literature [15]. A low incidence of acute aortic events in BAV disease has also been reported by other authors [16,17]. The recent community-based study by Michelena and co-workers documented an excellent survival and no aortic dissection in a 20-year follow-up period in BAV patients without a significant aortic valve dysfunction [18]. Moreover, such a high variability in the incidence of late aortic events (i.e., 5–30% over mean of 13 years) may indicate significant differences in patient characteristics between studies.

The above information leads to an important second question – are there any predictors of late aortic events in BAV patients after isolated AVR? Unfortunately, this question has also not been adequately evaluated in the literature. Intuitively, larger dimensions of the ascending aorta at the time of aortic valve surgery (i.e., $\geq$45 mm) might be associated with the increased rate of late aortic events, as advocated by Borger et al. [13]. However, this in turn raises another question: does a mildly or moderately dilated ascending aorta in BAV disease behave differently from the ascending aorta of comparable dimensions in tricuspid aortic valve (TAV) patient after AVR? To the best of our knowledge, such a study has not yet been performed. Andrus and co-workers [19] analyzed the natural course of ascending aortic aneurysms after AVR in their follow-up study. However, only

half of the patients had a baseline ascending aorta diameter over 3.5 cm and only 13% (24/187 patients) had a congenital aortic valve lesion in this study. No clinical or valvular characteristics that predicted progressive ascending aorta dilatation could be identified in the aforementioned study. Davies and co-workers reported recently on the nature course of ascending aortic aneurysms in the setting of a nonreplaced BAV in comparison with TAV [20]. All adverse aortic events (i.e., rupture, dissection, and death) occurred at similar rates and at similar aortic diameters in both groups (i.e., BAV vs TAV) in this study. Moreover, the authors were able to clearly demonstrate the strong relationship between adverse aortic events and presence of aortic valve stenosis in the BAV subgroup [20].

We can conclude from the above information that the available data are not sufficient to elucidate the natural history of the proximal aorta after AVR in BAV patients. The incidence of late aortic events in the above-cited studies seems to be considerably lower than it would be expected for connective tissue disorders (e.g., Marfan syndrome).

3. BAV disease versus Marfan syndrome

One of the major arguments of the proponents of the genetic BAV–aortopathy theory has been the frequent histological finding of cystic medial degeneration in the wall of ascending aorta in BAV patients, similar to that observed in Marfan aortas [21]. However, similar medial changes have been also demonstrated in aortic dilatation and/or dissection regardless of etiology, indicating the nonspecific character of cystic medial degeneration [9,22]. Moreover, recent bio-molecular investigations have shown some major differences in the pattern of extracellular matrix proteins expression in BAV versus Marfan aortas [23]. Unlike the Marfan aortas, the tissue remodeling response (i.e., expression of fibronectin, tenascin, and type I and III collagens) was found to be asymmetrically spread in the convexity versus the concavity of BAV aortas [23]. This asymmetric pattern in the extracellular matrix protein expression in BAV aortas has been hypothesized to be the result of aortic wall stress-induced vascular remodeling [23,24], lending more credence to the hemodynamic theory of BAV-associated aortopathy.

The second purported similarity between BAV disease and Marfan syndrome has been the observed involvement of the pulmonary artery in the dilatation process [25]. As the pulmonary artery has the same embryological origin as the aorta, similar histological changes and dilatation of pulmonary artery in BAV disease would be a strong piece of evidence supporting the genetic origin of BAV–aortopathy. However, some more recent investigations [26] and an in-depth biomolecular analysis by Schmid and co-workers [27] have convincingly demonstrated that the main pulmonary artery is not pathologically involved in BAV disease. Moreover, aneurysm of the pulmonary artery in BAV disease is extremely rare [9,28], in contradistinction to Marfan syndrome.

Furthermore, an echocardiographic analysis by Beroukhim and co-workers showed a different anatomic pattern of aortic dilatation in children with BAV versus Marfan syndrome [29]. The BAV children had significantly greater aortic dimensions at multiple levels of the ascending aorta, while Marfan children had a more focal dilatation at the sinuses of Valsalva [29]. The authors stressed the risk of studying these two groups of patients together.

In conclusion, there are several major clinical and histological differences between BAV and Marfan patients, leading one to conclude that the supposed similarities between these two groups should not be used as an argument to support the genetic theory of BAV–aortopathy.

4. Functioning of the 'clinically normal' BAV

There is emerging evidence that the 'clinically normal' BAV (i.e., without transvalvular pressure gradient or significant insufficiency) is associated with abnormal flow patterns and asymmetrically increased wall stress in the proximal aorta [10–12,30,31]. The pioneering contribution by Robicsek and co-workers showed experimentally that the 'clinically normal' BAV is morphologically stenotic and produces eccentric turbulent transvalvular flow which results in asymmetrical wall stress distribution in the ascending aorta [10]. This has been supported most recently by *in vivo* analysis of transvalvular blood flow in BAV patients using sophisticated four-dimensional magnetic resonance imaging [11,12]. Hope and co-workers demonstrated a nested helical systolic flow in the ascending aorta in patients with BAV, including those without ascending aortic aneurysm or aortic valve stenosis [12]. Moreover, the authors were able to convincingly demonstrate two different nested helical flow patterns which are unique for the two most common cusp fusion types in patients with BAV [12]. The most common fusion pattern of the right- and left coronary cusps generated a right-anterior eccentric flow jet, which in turn may result in the larger aortic root dimensions [32] that are commonly seen in BAV patients. A left-posterior eccentric flow jet, which was observed in patients with the less common right-noncoronary cusp fusion, might explain the increased aortic arch dimensions in this subgroup of BAV patients [33]. These rheological studies provide a unique hemodynamic insight into the different phenotypes of BAV disease and asymmetry of corresponding aortopathy even in the presence of a 'clinically normal' BAV, and will be discussed in more detail in the following paragraphs.

5. Asymmetric pattern of aortopathy in BAV disease

Enlargement of the tubular ascending aorta in patients with BAV disease has a typical asymmetric configuration at the convexity of the vessel, as shown in the retrospective analysis of aortic angiograms by Bauer et al. [34]. The asymmetric ascending aorta involvement is familiar to all clinicians who routinely treat BAV patients, and has been confirmed by a series of consecutive bio-molecular investigations by Cotrufo and co-workers [35]. These authors were able to convincingly show in several studies an asymmetric spatial pattern of extracellular matrix protein expression and smooth muscle cell changes in the convexity versus the concavity of the dilated ascending aorta in BAV patients [23,24,35,36]. Moreover, this asymmetric pattern of extracellular matrix changes has been demonstrated for non-dilated ascending aortas in BAV patients [24].

The known frequency of right and left coronary cusp fusion type of BAV [37], plus the aforementioned rheological study findings [12] and *in vitro* data of eccentric wall stress distribution [10,30], lend support to a hemodynamic explanation for the observed asymmetry of BAV–aortopathy (i.e., flow-induced vascular remodeling) [38]. Isolated genetic defect, as supposed by the genetic theory of BAV–aortopathy, would be less likely to result in such localized findings.

6. Phenotypes in BAV disease

The heterogeneous nature of BAV disease has been recognized by many researchers and attempts have been made to stratify the most common anatomic-clinical forms. The clinically observed linkage between the specific bicuspid valve morphology and the associated lesions of proximal aorta has led to several phenotypic classifications which incorporate both valve and proximal aortic anatomy [32,35,37,40]. Discounting minor differences among these classification systems, there are many common features of the identified BAV phenotypes. The most common BAV fusion pattern of the right and left coronary cusps has been linked to aortic root enlargement [32,39,40] and asymmetric pattern of dilatation of the tubular ascending aorta [34]. Fusion of the right and noncoronary cusps has been associated with isolated ascending aorta dilatation (without involvement of aortic root), frequently extending to the transverse aortic arch [32,33,40]. Cotrufo and co-workers identified 'BAD-MATE' syndrome in order to describe the common association between BAV stenosis and asymmetric dilatation of the tubular ascending aorta [35].

These associations between different BAV morphologies and specific dilatation patterns of proximal aorta further support the hemodynamic theory of BAV–aortopathy. Different aortic cusp fusion patterns have been proven to result in specific orientation of eccentric flow jets [12], which in turn may lead to a differential distribution of aortic wall shear stress and subsequent flow-induced vascular remodeling [32]. These pathogenetic insights should be considered when one advocates the novel treatment guidelines of BAV–aortopathy. Some efforts have been made to cluster the BAV patients according to different patterns of proximal aortic dilatation and to propose the 'individualized' degree of aortic replacement for these subgroups (e.g., aortic arch replacement in 70% BAV patients undergoing surgery) [33,41]. However, such treatment recommendations cannot be drawn from purely observational studies, which included only limited number of highly selective BAV patients and did not respect the hemodynamic background of different BAV phenotypes.

7. Root dilatation phenotype

There is a relatively small subset of BAV patients (10–15%) who present with the predominant dilatation at the level of sinuses of Valsalva at an early age. This phenotype is observed mostly in young male patients, is associated with aortic valve annular dilatation, and a varying degree of aortic insufficiency [6]. An immunohistochemical study, which analyzed the expression and distribution of structural proteins in the aortic extracellular matrix in BAV patients, showed major differences in the transcription pattern of type I collagen between BAV patients with valve stenosis and pure valve insufficiency [36]. The authors of this study hypothesized that the root phenotype may be a genetic form of BAV disease and a completely different disease as compared with the BAV stenosis and asymmetric mid-ascending aortic dilatation [35]. A subgroup of young male BAV patients with the predominant dilatation of aortic root which occurred independently of age, body size, and valve function has been also identified in the echocardiographic study by Nistri and co-workers [42]. Another echocardiographic study by Biner and co-workers focused on the aortopathy in first-degree relatives (FDRs) of BAV patients [43]. Unfortunately, this study included only a small proportion of FDRs of BAV patients (i.e., 48 FDRs of 54 BAV patients) and compared them with a highly select control group (i.e., 45 healthy individuals without structural heart disease, included during a study period of 4 years). Irrespective of those methodological flaws, this study has demonstrated a high prevalence of mild aortic root dilation associated with abnormal elastic properties of aorta in FDRs of BAV patients with root phenotype. Notably, the aforementioned study included BAV patients with the predominant dilatation at the level of aortic annulus and sinuses of Valsalva (i.e., root dilatation phenotype). Therefore, the results of this study may not be generalized to the whole BAV population (i.e., with the predominant dilatation at the level of tubular ascending aorta). Similar findings have also been reported by Loscalzo and co-workers in a small number of highly selected families with a high prevalence of BAV and ascending aortic aneurysms [44].

Given the marked heterogeneity of BAV disease, the root dilatation phenotype may illustrate the predominantly genetic form of BAV disease, which is less influenced by the hemodynamic factors. However, there are no genetic/biomolecular studies and detailed surgical reports that focused on this type of BAV disease.

8. Hemodynamic answers to the genetic argument

Four important lines of evidence have been reported in the literature as a strong support for the genetic origin of BAV–aortopathy [45]. Considering recent advances in the understanding of BAV disease, some updated comments on these lines of evidence may be appropriate. The first argument has been the greater aortic size observed in patients with bicuspid versus tricuspid aortic valves, even after matching for hemodynamic severity of valvular lesions, as first reported by Keane and co-authors [46]. Although this observation has been confirmed subsequently by various studies, none of these studies considered the jet eccentricity that occurs through a stenotic BAV, which results in more severe flow alterations in the ascending aorta than in stenotic tricuspid aortic valves with similar gradients and valve areas, as convincingly demonstrated by recent investigations [12,47].

The second argument in favor of a genetic theory has been proposed to be the enlargement of the proximal aorta in BAV patients (including children) without aortic valve stenosis or regurgitation, compared with age-matched normal controls (i.e., aortic dilatation out of proportion to coexistent valvular lesion). However, this statement ignores the fact that a 'normally' functioning BAV is morphologically stenotic [10] and that the flow through it is highly eccentric, causing abnormal helical flow patterns in the proximal aorta [11,12]. This has been convincingly demonstrated in the very recent contribution by Conti and co-workers, using a sophisticated dynamic three-dimensional (3D) finite element model of the aortic root with a BAV [30]. This qualitatively altered flow, which affects the BAV individual from a very early stage of life, does not meet the standard criteria for aortic stenosis by common echocardiographic methods of grading and can only be characterized with sophisticated 4D flow magnetic resonance imaging [11,12]. Moreover, a significant correlation has been recently demonstrated between the degree of eccentricity of the systolic transvalvular flow and the severity of the proximal aortic dilatation in the pediatric BAV population (i.e. the larger the angle of misdirected flow with the aortic axis, the larger the aortic diameter) [31]. These abnormal flow patterns act over long periods of time and may lead to asymmetric stress-induced aortic wall lesions [23,24,30,36] with subsequent dilatation of specific aortic segments (i.e., flow-induced vascular remodeling), even in the absence of echocardiographically significant valvular lesions [38].

The third argument that supports the genetic origin of BAV—aortopathy has been the evidence of progressive enlargement of the proximal aorta after isolated AVR. However, this argument has not been adequately supported by the literature. As previously discussed, the available data are not sufficient to elucidate the natural course of proximal aorta dilation after AVR in BAV patients. Moreover, there is no existing evidence to show that the dilated proximal aorta in BAV disease behaves differently from the aorta of comparable dimensions in TAV patient after AVR [19].

The fourth argument for a genetic BAV—aortopathy theory has been proposed as the demonstration of similar histological and biomolecular changes in BAV and Marfan aortas. However, the asymmetric spatial distribution of histological and biomolecular changes in BAV aortas [23,24,36], as opposed to the circumferentially uniform involvement in the Marfan syndrome, advocates the primary role of hemodynamics in the development of reactive aortic wall changes. Moreover, as indicated by Dr Robicsek, a study demonstrating the primary nature of biomolecular and histological changes by examining the aortic wall of newborns with BAV has never been conducted [48].

In summary, there is a growing amount of evidence supporting the hemodynamic theory of aortopathy in patients with BAV disease. Data from recent studies require a reevaluation of our overwhelming support of the genetic theory and oblige us to acknowledge that hemodynamics also plays an important role in the development of this disease process. Such observations are not simply theoretical in nature, since they significantly affect our approach to the ascending aorta in patients presenting with BAV disease. Given the marked heterogeneity of BAV disease, further studies are required to more precisely determine which theory is the 'correct' one for explaining the obviously different types of BAV-associated aortopathy. From a clinical standpoint, there is an urgent need for diagnostic tools to reliably distinguish the more from the less 'malignant' phenotypes of BAV disease. The combination of protein assays (i.e., metalloproteinase 2 plasma levels) and magnetic resonance imaging tests (i.e., quantitative measurement of the angle of misdirected blood flow) has been recently envisioned as a future diagnostic tool for clinical risk stratification of BAV patients [31]. Prospective multicenter studies will be required to prove the predictive value of this concept.

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