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The genetic, molecular, and hemodynamic basis of bicuspid aortic valve aortopathy: A contemporary narrative review

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ABSTRACT

Bicuspid aortic valve (BAV) is the most common congenital heart defect. Along with the expeditious advancements in genetics, molecular science, and imaging, the body of literature surrounding BAV has grown immensely in recent years. The purpose of this review is to categorize and summarize articles published regarding bicuspid aortic valve aortopathy in the last five years. The increased availability of genomic testing has allowed the study of inherited factors contributing to BAV, with associations between variations in several genes and the development of aortopathy. It has also been found that epigenetics and microRNAs play a critical role. Molecularly, the arrangement of the extracellular matrix and its various components are related to the strength of the aortic wall. Compromises in the extracellular matrix have been shown to limit the ability of the smooth muscle cells and fibroblasts to maintain the integrity of the aortic wall. Advancements in cardiac imaging, notably magnetic resonance imaging, have allowed for intense study of the hemodynamics of various cardiac lesions. Recent articles have proposed that early aortic valve insufficiency rather than stenosis leads to aortic dilation. After reviewing recent publications regarding BAV and the development of aortopathy, the authors acknowledge that there is much still unknown. Further research in the fields addressed in this review will allow for improvements in diagnostics and treatments for affected individuals.

1. Bicuspid aortic valve aortopathy

Bicuspid aortic valve (BAV) is the most common congenital heart defect [1]. The prevalence is estimated to be as high as 1–2% in the general population and is more common in males, with a male-female ratio of 3:1 [1]. Patients with BAV have an increased risk of aortic intervention, with a 25-year risk of 25% aortic valve surgery and a 53% risk of valve replacement [1]. A well-described complication of BAV is the risk of aortopathy, characterized as progressive dilation of the ascending aorta, with increased prevalence with advancing age [1].

BAV is most frequently diagnosed in adulthood alongside aortic valve dysfunction and dilation of the ascending aorta [2]. Though most cases of BAV are sporadic, evidence supports familial clustering and an underlying genetic abnormality in some cases [1]. Further, research supports the heritability of BAV, as high as 89% with a 9% prevalence in first-degree relatives [1]. For this reason, routine screening in first-degree relatives is recommended to screen for BAV and other complications [1].

An autosomal dominant pattern of inheritance with variable expressivity and decreased presence is postulated to cause BAV [1]. Further, the association with Turner syndrome supports an X-linked component [1]. Other genetic syndromes associated with BAV include DiGeorge Syndrome, Loeys-Dietz Syndrome, Shone's Complex, and Marfan Syndrome [1].

This review aims to organize and summarize the rapidly developing body of evidence on the genetic, molecular, and hemodynamic basis of bicuspid aortic valve aortopathy published in the last five years.

2. The genetic basis of bicuspid aortic valve aortopathy

Though most cases of BAV and associated aortopathy are non-syndromic, at least one-third of patients have variants associated with familial ascending aortic aortopathy, including *ACTA2, MYH11, MYLK, FBN1, and TGFB2* [2]. An evaluation of individuals from a large family with an autosomal dominant inheritance of thoracic aortic aneurysms and variable BAV revealed a variation in the *MAT2A* gene, which encodes methionine adenosyltransferase II alpha (MAT IIα), an enzyme that functions in methylation metabolism [1]. Further research is

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required to evaluate the mechanism by which decreased MAT IIα activity results in aortic disease [1].

A genome-wide study of single nucleotide polymorphisms identified 47 recurrent copy number variations in patients with thoracic aortic disease, with increased prevalence in patients with BAV relative to controls [1]. An evaluation of 95 patients with BAV and thoracic aortic aneurysm identified copy number variation in *TBX2*0 that may be associated with the development of BAV aortopathy [3].

Substantial evidence describes highly penetrant variation in *NOTCH1, AXIN1, TFGBR2, FBN1, SMAD2, NSO3, ACTA2,* and *TGFB2* in bicuspid aortic valve aortopathy [2]. Of these, *FBN1* has demonstrated variants associated with aortic dissection in BAV and is likely a contributory component given its structural and signaling roles in TGF-β [2].

Genetic analysis identified rare, pathogenic variants among 63 patients following aortic valve replacement with root dilation in 30% of patients, most commonly in *NOTCH1,* with less common variants in *XIN1, NOS3, ELN FBN1,* and *FN1* [4]. Another evaluation of a small sample of 12 patients with BAV found that *GAPDH, UBC,* and *ACTB* would be best suited for gene expression studies on the basis of their stability in aortic tissue and presence in individuals affected by BAV aortopathy [5].

Recent data evaluating DNA in the developing hearts of experimental models and human congenital heart disease have demonstrated the presence of epigenetic variations in affected hearts [1]. It has been suggested that epigenetic control may be related to disrupted aortic flow secondary to BAV [1]. Aortic wall stress has been associated with increased expression of *TGFB1*, *MMP* types 1, 2, and 3, and *TIMP1* [2].

The smooth muscle cells of the ascending aorta arise from neural crest cells, whereas those of the descending aorta arise from the paraxial mesoderm [6]. When pluripotent stem cells from patients with BAV were differentiated into smooth muscle cells derived from neural crest cells, the contraction was impaired relative to normal controls and to paraxial mesoderm derived cells [6]. Further, neural crest-derived cells demonstrated increased mTOR signaling, which improved contractile function when inhibited by rapamycin [6].

Induction of *NOTCH1* has demonstrated impaired differentiation into smooth muscle and endothelial cells in pluripotent human stem cells [7]. In these cells, the expression of neural crest stem cell markers was also significantly lower [7]. Additionally, these cells demonstrated smaller cellular size and decreased expression of smooth muscle-specific contractile proteins [7]. It is hypothesized that these manifestations may contribute to the development of aortic disease in patients with BAV [7]. This has further been elucidated in subsequent studies with *NOTCH1* evidencing a role of signaling on cellular differentiation and apoptosis [8].

In individuals with Turner Syndrome and BAV, deleterious variations in *TIMP3* have been associated with an increased risk of aortic disease [9]. This gene encodes tissue inhibitors of matrix metalloproteinases that are postulated to protect the structural integrity of the aorta and aortic valve [9].

Additionally, epigenetic changes have been associated with BAV aortopathy, including differential methylation of non-cytosine wahine and cytosine phosphate guanine sites [10]. It is also proposed that MicroRNAs (miRNAs) may play a role in thoracic aortic aneurysms in patients with BAV [11]. Analysis of miRNAs in affected patients reveals a relationship to the Hippo signaling pathway, ErbB signaling, TGF-β, and local adhesion based on differential expression of 489 previously identified miRNAs and five new variants [11].

Another evaluation postulates that a unique miRNA, miR-145, is associated with *NOTCH1* variants, with lower expression in patients with BAV aortopathy with known *NOTCH1* variation [12]. Yet another study evaluating miRNAs associated with aortopathy demonstrated an inverse correlation between circulating miRNA and aortic diameter in BAV aortopathy [13]. This relationship was strongest for miR-17, miR-20a and miR-106a [13].

Similarly, higher circulating levels of miR-17 and miR-106a were strongly correlated with decreased aortic root diameter in BAV aortopathy among 63 patients undergoing valve replacement with or without aortic intervention [14]. Through recent research, it has been shown that genetic and epigenetic variations play a role in the development of aortopathy in individuals with BAV. The influence of genetic and epigenetic factors are critical to the molecular composition of the aorta and the following category analyzed in this review.

3. The molecular basis of bicuspid aortic valve aortopathy

Transduction of aortic wall stress is proposed to occur via the glycocalyx layer on the luminal surface, basal integrins, primary cilia, and platelet endothelial adhesion molecule-1 [2]. Additional factors include regulation of extracellular matrix remodeling, the transition from epithelium to mesenchyme, and nitric oxide metabolism [15]. Polycystin-1 and polycystin-2 form a mechanosensitive cation channel of primary cilia, which interact with filament-A bound actin to act as a mechanosensor [2].

In murine models of genetic aortic aneurysm, a compromise in extracellular matrix regulation is correlated with the inability of smooth muscle cells and fibroblasts to maintain circumferential stiffness [2]. These cells secrete TGF-β1, platelet-derived growth factor, and angiotensin-2 as self- and local-acting elements sensitive to hemodynamic changes [2]. TGF-β1 is a critical downstream signaling molecule of Fbn-1, a protein long known to be associated with Marfan syndrome when abnormal [2]. TGF- β1, along with platelet-derived growth factor ad angiotensin-2 are intimately involved in the cell-cell signaling pathway that influences the phenotype, contractile vs. proliferative, of a smooth muscle cell [2].

Emerging research aims to identify biomarkers associated with the identification of circulating biomarkers. Evidence suggests that the ratio of serum TGF-β1 to endoglin (T/E) is associated with BAV aortopathy. In comparison to healthy controls with tricuspid aortic valves, an increased T/E ratio has been found to be unique to BAV aortopathy [16]. Further, a ratio of greater than 9 was associated with higher matrix metalloproteinase-2 (MMP-2) and lower superoxide dismutase 3 [16]. Notably, the T/E ratio correlates with aortic diameter growth rate in patients without dilated aortas, suggesting a prognostic relationship [16]. Following Forte and colleagues' publication in 2017, there has been an increased interest in studying the use of the T/E ratio as an additional clinical data point to aid in follow-up and timing of surgical intervention. However, the authors are not aware of an additional study, which examines the T/E ratio in BAV aortopathy using a larger sample size.

It has also been suggested that nicotinamide phosphoribosyltransferase and Sod may predict the development of BAV aortopathy [10]. In addition, circulating sphingomyelin levels are associated with the progression of aortic dilation [10]. The molecular composition undoubtedly plays a role in how the aortic wall responds to abnormal hemodynamics resulting from BAV, a factor better understood by imaging advancements.

4. The hemodynamic basis of bicuspid aortic valve aortopathy

There is substantial evidence describing abnormal flow and shear stress in the ascending aorta due to BAV [2]. Aortic wall stress leads to alternations in the extracellular matrix and medial elastin fiber generation [2]. Evidence is conflicting on the influence of cusp fusion pattern on the development of aortopathy, warranting further research on this topic [2,10].

On the contrary, in an extensive study of 2122 children with BAV, among which 50% had ascending aortic dilation, right and noncoronary cusp fusion, an increased degree of stenosis and insufficiency, as well as older age were associated with dilation [17]. Interestingly, a history of coarctation was associated with less dilation, and even among patients

without stenosis or insufficiency, 37% had dilation [17].

Another study of adults with BAV undergoing computed tomography evaluation revealed an increased incidence of moderate-to-severe aortic stenosis in right- or left-noncoronary fusion (66.2% versus 46.2% in right-left fusion) [18]. Moderate-to-severe regurgitation was more common in right-left fusion than in right- or left-noncoronary fusion (32.3% versus 6.8%) [18]. A separate evaluation suggests that left-right fusion is the phenotype most associated with dilation of the aortic root and ascending aorta [19].

An evaluation of patients with both BAV and tricuspid valves requiring valve replacement underwent preoperative magnetic resonance imaging (MRI), revealing that regions of maximal jet impact did not affect the pathology score in the adventitia and middle and outer media of the aorta [20]. However, the inner media demonstrated loss of actin expression in both populations with enlarged intimal thickness without loss of elastic lamellae or vascular smooth muscle [20]. Another recent evaluation evaluating wall shear stress using 4D MRI revealed higher aortic shear stress in patients with BAV than among normal controls [21]. Elevated shear stress in the ascending aorta correlated with peak systolic velocity [21].

Recent studies postulate that individuals with primary valvular insufficiency rather than those with stenosis are at increased risk for aortic disease [22,23]. Further, root dilation was more common among those with insufficiency alongside large aortic annulus diameter [23].

5. Discussion

Though the amount of new information on the basis of BAV aortopathy is immense, it remains unclear how the genetic, molecular, and hemodynamic mechanisms may contribute to a unified hypothesis of its etiology [24]. Despite the unknown etiology, better understanding in each of these fields may translate to improvements in the monitoring and treatment of BAV and the development of aortopathy.

Early diagnosis, through improved genetic screening, would prove to be critical in syndromes that have a high incidence of BAV. Particularly in Turner and Marfan syndromes, where there are recommended surveillance and therapies outside of BAV. Aortopathy in Marfan syndrome is well described. Recent evidence suggests that patients with Marfan and BAV relative to those with tricuspid valves, are likely to have increased aortic root diameters and Z-score, and are likely to require aortic root surgery at younger ages [25]. However, the rate of aortic root dilation appears to be similar between patients with Marfan and non-syndromic BAV [26]. Early identification of initial biomarkers serves to assist in the identification of at-risk patients and improve understanding of the natural history of the evolution of BAV aortopathy [27].

Molecularly, the identification of factors may assist in the development of targeted therapies. Such therapies may aid in slowing the progression of BAV aortopathy, postponing or eliminating the need for surgical interventions. Targeted therapies may also be helpful in the immediate postoperative period to protect against further damage, increasing favorable outcomes and decreasing the rate of re-intervention.

Novel imaging modalities may improve understanding of hemodynamic factors and individualized approaches to resection [28]. This includes the use of four-dimensional-flow magnetic resonance imaging studies to assess metrics associated with flow derangement based on abnormal shear stress and wall pathology [29]. Improved understanding of hemodynamic factors may also aid in the development of artificial valves to mitigate flow patterns that may contribute to aortic dilation for the benefit of all patients with aortic valvular disease.

Despite emerging evidence, BAV aortopathy continues to be poorly understood [28]. Due to the prevalence of BAV, improved clinical guidelines and screening recommendations may broaden research and available data related to the genetic, molecular, and hemodynamic factors dictating the development of aortopathy in BAV [28]. As genetic screening becomes more accessible, using it to identify those that would benefit most from more resource-demanding measures, such as hemodynamic imaging and/or targeted therapies becomes more realistic.

With BAV being the most common congenital heart defect, it spans across all demographics, including but not limited to race, gender, economic status, and location of residence. The authors firmly believe that all screening recommendations, interventions, and therapies to emerge from this body of research should be equally accessible to all those affected by BAV and the potential development of aortopathy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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