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EDITORIAL

Etiology of bicuspid aortic valve disease: Focus on hemodynamics

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Abstract

The bicuspid aortic valve (BAV) is the most common form of inheritable cardiac defect. Although this abnormality may still achieve normal valvular function, it is often associated with secondary valvular and aortic complications such as calcific aortic valve disease and aortic dilation. The clinical significance and economic burden of BAV disease justify the need for improved clinical guidelines and more robust therapeutic modalities, which address the root-cause of those pathologies. Unfortunately, the etiology of BAV valvulopathy and aortopathy is still a debated issue. While the BAV anatomy and its secondary complications have been linked historically to a common genetic root, recent advances in medical imaging have demonstrated the existence of altered hemodynamics near BAV leaflets prone to calcification and BAV aortic regions vulnerable to dilation. The abnormal mechanical stresses imposed by the BAV on its leaflets and on the aortic wall could be transduced into cell-mediated processes, leading ultimately to valvular calcification and aortic medial degeneration. Despite increasing evidence for this hemodynamic etiology, the demonstration of the involvement of mechanical abnormalities in the pathogenesis of BAV disease requires the investigation of causality between the blood flow environment imposed on the leaflets and the aortic wall and the local biology, which has been lacking to date. This editorial discusses the different hypothetical etiologies of BAV disease with a particular focus on the most recent advances in cardiovascular imaging, flow characterization techniques and tissue culture methodologies that have provided new evidence in support of the hemodynamic theory.

Key words: Aortopathy; Valvulopathy; Hemodynamics; Bicuspid aortic valve; Shear stress

Core tip: The bicuspid aortic valve (BAV) is associated with secondary aortopathy and valvulopathy. However, the root cause of those complications remains controversial. While the genetic etiology has been the most popular historically, advances in cardiovascular imaging, flow characterization and tissue culture methodologies have provided new evidence in support of a hemodynamic origin. The assessment of the respective role of genetic and hemodynamic cues in BAV pathogenesis is critical to the development of improved diagnosis tools and patient-specific modalities. This editorial discusses the different possible etiologies of BAV disease with a particular focus on the most recent evidence for the hemodynamic pathway.

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INTRODUCTION

Despite a limited prevalence of 1%-2% in the general

population[1-3], the bicuspid aortic valve (BAV) is the most common inheritable valvular defect. As compared to a normal tricuspid aortic valve (TAV), which consists of three leaflets, the BAV forms with only two as a result of cusp fusion during development. The BAV exists in different morphologic phenotypes[4-6]. The most prevalent type- I morphology features two cusps of unequal size and a fibrous raphe at the location of congenital fusion[7-9]. While 71% of type- I BAVs result from the fusion between the right- and left-coronary leaflets (LR subtype), 15% feature right- and non-coronary cusp fusion (RN subtype) and 3% present with non- and left-coronary cusp fusion (NL subtype)[7]. The BAV has emerged as the most common indication for surgical valvular replacement and is often complicated by secondary valvular and aortic wall abnormalities such as calcific aortic valve disease (CAVD) and aortic dilation, respectively[3,10-17]. The current management of BAV disease presents significant challenges related to the nontrivial early identification of BAV patients, the difficult detection of the onset of aortic and valvular complications and the time-sensitivity of surgical intervention[18]. The development of improved clinical guidelines and more robust therapeutic modalities addressing the root-cause of BAV disease requires the knowledge of the etiology of those pathologies, which is still under debate. This editorial discusses recent clinical and bioengineering developments in support of the hemodynamic theory of BAV disease, future research needs and their potential impact on clinical management.

BICUSPID AORTIC VALVE DISEASE

CAVD

Formerly considered a passive age-related disease promoted by cardiovascular risk factors and genetic predispositions, CAVD is now recognized as an active disease process involving inflammatory, extracellular matrix remodeling and osteogenic mediators as well as phenotypic changes in the valve interstitial cell population[19-22]. The later stage is characterized by formation of calcium nodules preferentially on the fibrosa (*i.e.*, leaflet aortic surface)[23]. The stenosis caused by the stiffening of the leaflet tissue imposes a pressure overload on the left ventricle, which may result in hypertrophy and ultimately lead to heart failure[24]. While those disease features are common to both TAVs and BAVs, the valve anatomy is a strong predictor of the prevalence and progression of the disease. In the TAV population, CAVD affects about 25% of individuals above 65 years of age and the progression of the disease is relatively slow (20-30 years before severe valvular stenosis can be detected)[20,25-27]. In contrast, it is estimated that 40%-53% of BAV patients develop some form of CAVD and that it may take as little as 10-12 years for the disease to result in severe valvular stenosis[16,17].

Aortic dilation

Aortic dilation is another common complication in BAV patients[10,14,28-31]. This condition, which characterizes the gradual thinning of the aortic wall and the enlargement of the aortic lumen above 4.0 cm in diameter[32], is a precursor event to dissection and ultimate rupture. The dilation of the thoracic ascending aorta downstream of a BAV is marked by structural wall abnormalities including aortic medial degradation, smooth muscle cell apoptosis and depletion, elastic fiber degeneration and abnormal extracellular remodeling[31], which localize primarily to the convexity of the aortic wall[33,34]. The particular BAV morphotype has also been shown to affect the pattern of dilation. The LR type-I BAV subtype is associated with a larger annulus and sinus than the RN phenotype[35]. While aortic dilation generally spares TAV patients and only occurs in 12%-22% of those with hypertension[36,37], it affects between 35%-68% of BAV patients[16,17,31,38-41]. In addition, while TAV ascending aortas typically experience a dilation rate of 0.07-0.2 mm/year, BAV patients experience much more rapid progression of dilation at rates of 0.2-1.9 mm/year[42,43]. As a result, acute aortic dissection occurs 5 to 10 times more frequently and at an earlier age in BAV patients than in TAV patients[3,10,44-46].

HYPOTHETICAL ETIOLOGIES AND KNOWLEDGE GAP

While the genetic root of the BAV malformation has been clearly demonstrated, the etiology of BAV disease is still a matter of debate[47-49]. The most accepted genetic theory hypothesizes that the abnormal valve structure, the vulnerability of BAV leaflets to calcification and the BAV aorta to dilation originate from a common congenital defect. Supporting evidence for this etiology stems from the apparent heritability of the BAV defect[50,51] and the association between certain gene mutations (*e.g.*, *GATA5*, *NOTCH1*, *ACTA2*), leaflet calcification and aortic dilation[52-55].

The less popular hemodynamic theory considers the mechanical stresses produced by the abnormal valve anatomy as the driving factor of secondary valvulopathy and aortopathy. Evidence for this mechano-etiology is supported by the apparent correlation between the eccentric BAV orifice jet[56-59], the presentation of aortic dilation in wall regions subjected to wall shear stress overload[33,34] and the preferential formation of calcific nodules on the fused BAV leaflet, which experiences a higher degree of wall shear stress abnormality relative to the non-fused leaflet[3-5,60]. Despite those observations, the validation of the hemodynamic etiology of BAV disease requires demonstration of causality, which to date has been lacking.

EVIDENCE FOR A HEMODYNAMIC PATHWAY

The mechanistic elucidation of the role played by hemodynamics in BAV disease requires the implementation of integrative approaches that not only describe the genetics of valvular morphogenesis and the impact of the BAV anatomy on valvular function but also investigate the adaptive and pathological responses of valvular and aortic cells to the native BAV flow environment. The emergence of state-of-the-art flow measurement and modeling tools combined with advanced tissue conditioning systems have

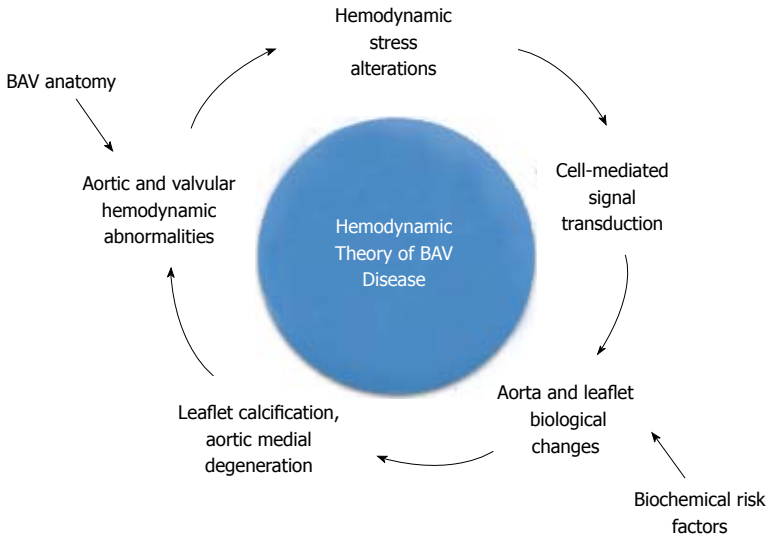

Figure 1 Hemodynamic theory of bicuspid aortic valve disease. The hemodynamic theory of bicuspid aortic valve (BAV) disease can be illustrated as an irreversible feedback loop in which the BAV anatomy would subject the valve leaflets and the ascending aortic wall to local stress overloads. Those stress abnormalities could be sensed by specific endothelial receptors and then transduced into different biological responses that would lead ultimately to the formation of calcific lesions on the leaflets or to the progressive degeneration of the aortic media.

provided a unique opportunity to examine *ex vivo* the role played by BAV hemodynamics, in the absence of underlying genetic defects and concurrent risk factors.

The implementation of advanced clinical and engineering tools toward the quantification of BAV flow has provided new insights into the hemodynamic complexity of this valvular defect and detailed maps of the wall shear stress abnormalities experienced by BAV leaflets and the BAV ascending aorta. *In vitro* particle-image velocimetry measurements in porcine valve models demonstrated the existence of an elliptical valve orifice, an eccentric jet skewed toward the non-coronary leaflet and an intrinsic degree of stenosis in type- I BAVs[61-63]. Pulsatile fluid-structure interaction simulations in valve and ascending aorta models[64,65], phase-contrast magnetic resonance imaging[59,66] and cardiovascular magnetic resonance[67,68] isolated dramatic differences in the frequency and magnitude of the wall shear stress generated on the leaflets and ascending aorta downstream of a TAV and a type-I BAV. Those modalities identified the fused BAV leaflet and the convex region of the BAV ascending aorta as those experiencing the highest degree of wall shear stress abnormality as compared to their TAV counterparts.

The concurrent development of sophisticated tissue culture systems capable of subjecting native BAV leaflets[69] or aortas[70] to their native local hemodynamic stress environment has enabled the rigorous investigation of the isolated effects of BAV flow on valvular calcification and aortic dilation. Those mechanobiological studies demonstrated for the first time: (1) the ability of the wall shear stress overload present on the convexity of LR type-I BAV ascending aortas to promote locally aortic medial degradation *via* matrix metalloproteinase-dependent pathways[65,71]; and (2) the particular susceptibility of the wall shear stress generated on the fused LR type- I BAV leaflet to trigger early calcification events such as endothelial activation, paracrine signaling, extracellular matrix degradation and bone matrix synthesis[72,73].

Collectively, those observations support a hemodynamic etiology by which the abnormal mechanical stresses experienced by BAV leaflets and BAV ascending aortas could trigger molecular pathways leading to the progressive calcification of the leaflets and the weakening of the aortic wall. Specifically, the hemodynamic theory postulates that the abnormal BAV anatomy subjects the valve leaflets and the ascending aortic wall to local stress overloads, which can be sensed by specific receptors in the tissue endothelium and then transduced into different pathological responses that would lead ultimately to the formation of calcific nodules on the leaflets or the progressive degeneration of the aortic media (Figure 1). The amplification of the degree of hemodynamic abnormality caused by the gradual stiffening of the leaflets and dilation of the proximal aorta may result in turn in the amplification of the pathological cascade and the acceleration of the disease process.

POTENTIAL CLINICAL IMPACTS

Whether and how hemodynamic cues contribute to BAV disease are important research questions that need to be addressed thoroughly in order to design improved diagnostic tools and more effective practice guidelines. As recognized by the Heart, Lung and Blood Institute (National Institutes of Health), the current state of the science on BAV disease does not permit to support particular pharmacological targets[74]. The effectiveness of the pharmacological approach depends on the ability to identify target molecules involved in the early stage of BAV disease before calcification and aortic medial degradation attain a point of no return. Therefore, the elucidation of the role played by hemodynamics in BAV valvulopathy and aortopathy may become instrumental to the future development of targeted cellular therapies as it has the potential to identify candidate mechano-sensitive molecules that may play a significant role in the initiation of BAV disease.

The current practice guidelines for the management of BAV complications[75] have been developed based on the prevailing theory of their etiology, which, historically, has been the genetic theory[47,48,53]. The limited understanding of the pathogenesis of BAV calcification and aortic dilation combined with the lack of pharmacological targets has driven the development of aggressive surgical procedures

aimed at recovering valvular function[76,77] and eliminating the weakened ascending aortic wall[78,79]. While such strategies may be appropriate to address a congenital disease, it may not be as effective should the formation of valvular calcific lesions or the structural degeneration of the aortic wall be the result of adaptive mechanisms to the abnormal BAV flow. In this context, the involvement of flow-mediated signaling pathways in BAV aortopathy and valvulopathy should not be ignored as they may guide the development of new therapeutic modalities aimed at normalizing BAV flow or inhibiting pharmacologically the valvular and aortic pathological cascades at an early age.

Lastly, current diagnosis techniques for BAV calcification and aortic dilation rely on criteria that can only be assessed at an advanced stage of the disease. The exploration of improved techniques enabling early detection in young patients requires the fundamental knowledge of the disease mechanisms. More importantly, the modeling of those mechanisms in individual patients could provide predictive capabilities that will transform clinical decision-making and personalized care. Therefore, the demonstration of cause-and-effects relationships between BAV hemodynamics, valvular calcification and aortic wall degeneration may lay the foundations for computer-based predictive models of BAV disease by integrating the mathematical formulation of flow-sensitive valvular and vascular biological pathways in patient-specific flow models. Such models will help predict disease onset and progression and guide the choice of the optimal treatment strategy.

FUTURE DIRECTIONS

The novel therapeutic perspectives discussed above suggest several recommendations for future research. The increasing need for understanding the pathogenesis of BAV disease motivates the investigation of potential links between BAV morphotype, genotype and hemodynamics, and the detailed description of the key features that stimulate BAV calcification and aortic dilation.

In addition, new emphasis should be put toward the elucidation of the basic biology of BAV disease from early events to long-term mechanisms. Those efforts would involve the characterization of the signaling pathways of BAV calcification and aortic dilation, as well as the multi-scale description of the synergistic effects between valvular calcification, aortic medial degeneration, micro-scale mechanotransduction and macro-scale hemodynamics.

The current evidence in support of the hemodynamic theory has been provided by short-term *ex vivo* studies and small-scale clinical investigations. The development of improved laboratory methodologies enabling prolonged tissue exposure to BAV hemodynamics while maintaining tissue sterility and integrity may shed some light on how the acute adaptive mechanisms reported thus far evolve in the long-term. Clinical investigations on large BAV patient populations will also permit to determine the validity of the hemodynamic and genetic theories in a more statistically significant way.

CONCLUSION

In summary, evidence for the causative effects of BAV hemodynamics on secondary valvulopathy and aortopathy is emerging. While those complications may still be promoted by some genetic predispositions, it is likely that their pathogenesis is also driven by synergies between the local mechanical stress abnormalities and the local biology of the leaflets and ascending aortic wall. Long-term *ex vivo* studies and large-scale clinical investigations are needed to assess the respective contribution of the genetic and hemodynamic pathways and to determine the full spectrum of mechano-sensitive processes triggered by BAV hemodynamics. The new knowledge gained from those efforts may enable the development of improved diagnosis tools and therapeutic modalities capable of addressing the root cause of BAV disease.

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