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Utilizing wall shear stress as a clinical biomarker for bicuspid valve associated aortopathy

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Abstract

Purpose of Review: Bicuspid aortic valve (BAV) results from fusion of two adjacent aortic valve cusps, and is associated with dilatation of the aorta, known as BAV-associated aortopathy, or bicuspid aortopathy. Bicuspid aortopathy is progressive, increasing the risk of life-threatening clinical events, such as aortic dissection. Regular monitoring and timely intervention with prophylactic surgical resection of the proximal aorta is recommended.

Recent Findings: Aortopathy is heterogeneous among patients. Studies have shown that different flow patterns lead to specific phenotypes of aortopathy. Although not uniform, BAV morphology affects flow patterns. Recent work has demonstrated the role of wall shear stress (WSS) in driving aortopathy, and it is suggested that individualized WSS “heat maps” can be used for clinically monitoring patients with BAV. WSS has the potential to be an imaging biomarker for directing resection timing, surgical strategies, and post-surgical follow-up care.

Summary: Finding and validating noninvasive hemodynamic biomarkers of aortic risk to assist in the management of BAV patients is of clinical importance. Herein, we will review the latest findings pertaining to the utility of WSS as a specific biomarker of risk for BAV patients with aortopathy.

Keywords

Bicuspid valve associated aortopathy; wall shear stress; imaging and clinical biomarker

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1. Introduction

Bicuspid aortic valve (BAV) is the most common congenital malformation of the human heart with a prevalence of 1–2% of the general population (1). BAV is characterized by the fusion of two adjacent aortic valve cusps, and is associated with dilatation of the aorta, known as bicuspid valve-associated aortopathy or bicuspid aortopathy. Unlike the majority of congenital cardiac pathologies, BAV is most frequently diagnosed in adulthood, with the onset of aortic valvular dysfunction, ascending aortic dilation, or endocarditis (2–5). Between 50% and 75% of BAV patients undergo aortic valve replacement during their lifetime (3). Similarly, more than 25% of patients with BAV undergo aortic surgery, often concurrent with aortic valve replacement, with most aortic surgery performed for dilation of the aortic root or ascending aorta, and rarely for aortic dissection (3). Recent advances in cardiac magnetic resonance imaging have shown that valve hemodynamics affect the progression of bicuspid aortopathy (6–8). Blood flow along a vessel will suffer a fluid spatial deformation known as shear rate. Since no flow occurs through the vessel wall, the speed of the blood flow at the vessel boundary is zero. Wall shear stress (WSS) expresses the tangential force per unit surface area acting on the endothelial cells in the fluid direction (Fig. 1). Some groups have postulated using WSS as a potential biomarker for bicuspid aortopathy (9–11). WSS could have important clinical implications for the timing and nature of surgery. Herein, we review the latest findings on bicuspid aortopathy as it relates to the utility of WSS and leveraging imaging modalities in the management of these patients.

2. BAV and Aortopathy

2 A. Classification BAV

The most widely used classification for BAV is that described by Sievers (12). Sievers Type I is further subclassified into fusion of the right-left coronary cusps (R/L), right-non-coronary cusps (R/N), and left-non-coronary cusps (L/N). The former two cusp fusion patterns represent the two most common BAV morphologies, accounting for approximately 75% and 20% of clinical cases, respectively (12). Sievers Type I L/N and patients without a raphe, or Sievers type 0, are uncommon. These specific fusion morphologies are excluded in most case series due to their low prevalence. Embryologic studies have demonstrated R/L and R/N cusp fusion patterns occur at different embryonic stages via distinct mechanisms and thus should be considered unique in their etiologies (13). The same factors which lead to different valve morphologies are also involved in driving distinct patterns of bicuspid aortopathy (13). Sievers and colleagues recently observed that stenosis is associated with more localized aortic dilatation, perhaps more related to flow disturbance, whereas insufficient BAVs were more often found in younger patients perhaps due to a genetic cause. (14). The R/N morphology has a higher frequency of myxomatous valve disease (15, 16).

2 B. Aortic Tissue Characteristics and mechanism

The aorta is composed of three layers: intima, media, and adventitia. The intimal layer is occupied by a layer of endothelial cells that sit directly on the internal elastic lamina. The media consists of concentric layers of smooth muscle cells (SMCs) and their extracellular matrix (ECM). The key mechanical function of the aortic media is providing elastic recoil

for pulsatile aortic pressure, which is enabled by its organized composition of SMCs and ECM. The adventitial layer is mainly composed of myofibroblasts which produce collagen. This layer is able to tolerate stresses above physiological pressures (17).

Smooth muscle cells are the major cell type within the aortic wall. They are not terminally differentiated, but possess the ability to express proteins involved in contraction and ECM synthesis during development and in response to mechanical and chemical stimuli. This plasticity facilitates transition along a continuum of fibroblast-like, to proliferative and ECM-producing phenotype, or a quiescent contractile phenotype. The latter population of SMCs produce less ECM proteins but express contractile proteins including smooth muscle alpha-actin and myosin heavy chains (18). SMCs are attached to Fibrin-1, collagen type VI, and to elastic fibers, with basal lamina bonds linking them to one another and providing a structure for laminar organization (19).

The extracellular matrix is mainly comprised of elastin. Other components of the ECM include collagen types I, III, IV, V, and VI; fibronectin; Fibrin-1; fibulin-4; proteoglycans of chondroitin, dermatan, and heparin, along with other proteins. These are all interspersed with SMCs and form lamellar plates within the vessels (20). Although the number of lamellae seems to remain constant after birth, there are more of them in larger vessels that are exposed to greater wall tension (20, 21).

Aortic aneurysm in a patient without a bicuspid aortic valve is characterized by extensive elastin degeneration with fibrosis and cystic degeneration of the media. There are concomitant inflammatory changes at the histologic level, in addition to adventitial and intimal thickening (22, 23). Patients with BAV, however, have distinct differences in their aortopathy from tricuspid aortic valve (TAV) aortopathy. In BAV patients, the ascending aorta shows non-inflammatory loss of SMCs, with multifocal apoptosis and medial degeneration (22). However, the fiber architecture is similar to that of the normal aorta (24). It has been shown that bicuspid aortopathy shares similarities with Marfan aortopathy: BAV aortic tissues have lower fibrillin content and greater TGF- β 1 levels which is due to the disease (21, 25, 26).

The aorta is histologically and macroscopically normal in BAV patients who do not have an aortic aneurysm. However, phenotypic variation is observed among patients with BAV undergoing non-aortic surgery. Histologic diversity is also seen throughout different segments of the ascending aorta within the same patient for those with aortic aneurysm. The adventitia and intima are both thickened (21, 23). The greater curvature of the aorta is more commonly dilated in patients with BAV, a change often attributed to greater shear stress from asymmetric flow across the valve. This portion has been reported to exhibit greater elastic fiber fragmentation, reduced collagen types I and III expression, and SMC apoptosis (27, 28). Matrix metalloproteases (MMP) are also differentially expressed across different aortic sites in BAV, with higher levels of MMP-2 and tissue inhibitor of metalloprotease (TIMP)-3 observed in the concavity of the ascending aorta (29). When comparing convex and concave portions of dilated aortas of BAV patients, similar trends are noted in microRNA expression of these proteins (21, 30). These findings strongly support the hypothesis that bicuspid aortopathy is influenced by active cellular processes.

Hemodynamics also play a role in the development of bicuspid aortopathy, however a direct and consistent link between regional histologic findings and hemodynamic stress has been lacking (31). Studies have failed to explain the mechanism for phenotypic differences between the dilated aortic root and the dilated tubular aorta (32).

2 C. Dilation patterns

Different dilation patterns for bicuspid aortopathy have been observed in some studies. The R/L cusp fusion morphology has been associated with increased diameters of the sinuses of Valsalva (15, 28, 33–35). The R/N cusp fusion phenotype is linked with smaller dimension of the aortic root and larger aortic arch diameters (15, 28, 34, 35). However, other studies have found no significant relationship between aortic dimensions and bicuspid valve morphology (36, 37). Nevertheless, literature has not been able to consistently show a valve-specific aortopathy pattern in BAV patients (38). Some studies have demonstrated an increased risk of aortic dilation in patients with R/L cusp fusion (35, 39), whereas other groups observed the same trend in patients with R/N cusp fusion morphology (40), and some have found no relationship between ascending aortic dilatation rates and BAV phenotype (33, 41). This inconsistency may be secondary to varied study designs prevalent in this literature. Most of these studies have included different age groups in their statistical analysis, which may explain their contrasting results, as it is accepted that bicuspid aortopathy progresses in an age-dependent fashion (16, 42). There is a paucity of data on unicuspid aortic valve-related proximal aortopathy.

3. Evidence from valvular and aortic flow

3 A. Flow patterns

Although there is evidence for genetics playing a role in the development of bicuspid aortopathy, it is well-accepted that abnormal flow patterns, secondary to a bicuspid valve, are a key contributor to aortopathy. Increased helical flow and changes in the aortic WSS are associated with dilatation of the proximal aorta (43–47). Echocardiography and phase contrast magnetic resonance imaging (PC-MRI) have shown the presence of stress overloads in BAV aortic wall regions prone to dilation (48), their association with extracellular matrix dysfunction (45), and their association with the BAV morphology (43, 49). Chandra *et al* demonstrated the existence of contrasted abnormalities in WSS directionality and magnitude on type-I BAV leaflets. This was shown in spatially resolved fluid-structure interaction simulations in intact valve-aorta geometries (50). Other studies have highlighted stress overloads in ascending aorta of BAV patients (46). More recent work has shown the influence of different bicuspid cusp fusion patterns in directing flow abnormalities in the aorta (51). Four dimensional flow MRI allows visualization and quantification of the blood flow in the aorta in a 3D image. Using 4D flow MRI, it was determined that R/L cusp fusion leads to an anterior blood flow distribution, whereas, R/N fusion results in a predominantly posterior outflow jet at the sinotubular junction that shifts to anterior or right-anterior in mid and distal ascending aorta (9, 38). These flow pattern findings were also observed using conventional phase contrast MRI (52). Another study showed fused R/L-cusp resulted in exaggerated right-handed helical flow, with eccentric outflow asymmetry toward the posterior-right wall (10). However a more comprehensive classification should be considered

for BAV associated pathology (i.e. valve stenosis, valve insufficiency or mixed valve disease). A comparison of flow patterns between a healthy control and patients with aortic stenosis is illustrated in Figure 2.

3 B. Valve jet assessment

Bicuspid aortic valve results in differential flow pattern which is associated with a particular valve jet flow stream. In a study that used 4D flow MRI, it was shown that the type of bicuspid valve determines the pattern of dilatation of the ascending aorta through the direction of the systolic transaortic jet and subsequent differential pressures on the various regions of the ascending aortic walls (8). Supported by 4D flow MRI, it has been shown that the inherent restricted leaflet opening of a bicuspid aortic valve, even when functioning normally, results in an asymmetrical, off center flow jet. Upon impact with the ascending aorta, this jet leads to marked helical flow (53). Leveraging the spatial and temporal resolution of 4D flow MRI, it is possible to determine specific flow patterns, while accurately assessing jet streams.

4. Aortic wall interaction

4 A. Flow displacement

Flow displacement is defined as the distance of flow jet deviation from the center of the aortic lumen indexed to ascending aortic diameter (54). Secondary to a bicuspid valve, blood flow patterns vary based on valve jet streams. A recent study using 4D flow MRI showed significantly increased flow displacement in BAV patients (53). In another small, longitudinal cohort study of BAV patients, flow displacement was correlated with aortic growth (55). It has been shown that flow distribution results in an increase in WSS in the anterior aortic wall of patients with R/L BAV. However, in patients with R/N BAV, there is an increase in the in-plane rotational flow and WSS in the mid and distal ascending aorta (9). An example of R/L and R/N WSS features is illustrated in Figure 3. Similar studies have corroborated these findings for valve-dependent flow displacement (56). These specific changes could explain different aortic dilatation phenotypes in the BAV population. Some groups have suggested that flow displacement was the most pronounced response to differences in bicuspid aortopathy phenotype, and added that this factor could offer a new means of quantifying hemodynamic abnormalities in aortic heart disease (8).

4 B. Wall shear stress and personalized heat maps

Wall shear stress (WSS) is defined as the force per unit area exerted by a moving fluid in the direction of the local tangent of the luminal surface. It has been suggested that WSS can be used as an important biomarker for aortic dilatation (44, 57). Specific WSS patterns could potentially explain the development of a certain phenotype in BAV patients (9). Studies have shown the presence of increased and asymmetric WSS related to ascending aortic flow jet patterns, which were influenced by the BAV fusion pattern (44). In order to detect if the regional expression of 3D WSS in the aorta of BAV patients was outside of that expected for healthy, normal physiology, WSS heat maps have been generated in recent studies (Fig. 4). The latter represent locations where patients exhibit abnormal WSS characteristics (6, 48). Other work has demonstrated regions of increased WSS were associated with greater medial

elastin degradation compared to adjacent areas with normal WSS. These regions also had an increase in transforming growth factor β -1, matrix metalloproteinase (MMP)-1, MMP-2, MMP-3, and tissue inhibitor of metalloproteinase-1, indicating ECM dysregulation in regions of high WSS (7, 58).

To investigate whether WSS triggers aortopathy, a recent study used 4D flow MRI to quantitatively compare the *in vivo* fluid dynamics in the thoracic aorta of two groups of subjects: five young patients with normo-functional BAV and with no aortic dilation and ten age-matched healthy volunteers. Their results suggested that WSS alterations may precede the onset of aortopathy and may contribute to its triggering, but WSS-driven anatomical remodeling is a very slow process (59). All of these studies have analyzed the magnitude and oscillatory characteristics of the total or stream-wise WSS in BAV patients. Current work is focused on the assessment of the circumferential WSS component. A recent study demonstrates the significance of this component and the existence of substantial WSS directional abnormalities in BAV ascending aorta. WSS magnitude and directionality index abnormality distributions in a BAV ascending aorta follow the phenotype-dependent occurrence of dilation in BAV aortas, suggesting the predictive potential of this metric for BAV aortopathy (60).

5. Clinical Value of WSS

The medical and surgical management of patients with BAV has been an important clinical query. Guidelines have alternated between conservative and aggressive recommendations for this patient population. Surgical strategies are mainly driven by surgeon and institution preferences, with higher volume centre preferring more aggressive approaches. To help standardize practices, a new set of guidelines was established specifically for the management of BAV patients (61).

There are still gaps in our understanding of the pathophysiology of bicuspid aortopathy. The relative contribution of genetic factors and hemodynamic stresses to aortopathy remain undetermined. Currently, the greatest unmet need and most critical area for improved knowledge is the identification of adequate criteria for risk stratification. Novel imaging modalities such as 4D flow MRI and WSS provide valuable insights into valve-mediated hemodynamics and progression of BAV aortopathy. The benefit of these tools is their safe and noninvasive nature. As our understanding of the mechanisms underlying bicuspid aortopathy improves, the utility of other prognostic criteria, such as molecular biomarkers, becomes more feasible. To achieve better outcomes, it is important to leverage the advantage conferred by 4D flow MRI and WSS, as clinicians and surgeons are able to better appreciate disease progression in BAV patients. Indeed, such an appreciation has important implications for the appropriate surveillance, management, and follow-up of these patients.

6. Conclusion

Managing bicuspid aortopathy remains a challenge. By elucidating the impact of differential flow patterns in the development of aortopathy we have been able to answer some key questions. As we have incorporated new technologies, our understanding of the disease has

improved greatly, but there are many unresolved issues. The ultimate goal is the delivery of optimal, customized care to BAV patients. Using novel imaging modalities and personalized risk stratification criteria in the form of WSS and heat maps we are able to take a step towards that final goal.

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7.

Key Points

1. Bicuspid aortopathy can have important clinical implications.
2. The pattern of aortopathy is highly variable among patients with a bicuspid aortic valve.
3. Wall shear stress has potential to be used as a noninvasive biomarker in risk prediction for bicuspid aortopathy.

Figure 1. Shear stress rate and wall shear stress.

The white dashed lines represent the location where the sample velocity profile was obtained. From these flow profiles the shear stress rate, or blood flow spatial deformation, which is illustrated by the gold lines, can be estimated. The intersection of the gold lines represents the distance from the vessel wall where the blood flow speed is equal to that on the fluid. Since no flow occurs through the vessel wall, the speed of the blood flow at the vessel boundary is zero. The near wall region, in orange, is the boundary layer where the wall shear stress (WSS) forces occur. WSS expresses the force per unit area exerted in the fluid direction on the local vessel tangent (τ_w). On the top, a healthy control (37-year-old man) illustrates the normal flow in the proximal ascending aorta. On the bottom, a 55-year-old man with bicuspid aortic valve illustrates the altered WSS produced by a right-left cusp fusion.

Figure 2. Flow patterns in the thoracic aorta.

From left to right, four cases are presented: normal valve, tricuspid valve with severe aortic stenosis (AS), bicuspid valve with right-left (RL) fusion and mild AS, and bicuspid valve with right-noncoronary (RN) fusion and mild AS. The top row illustrates the streamlines at peak systole for all cases and the bottom row the corresponding maximum intensity projections assessing the maximum velocities across the cardiac cycle.

Figure 3. Typical wall shear stress features of bicuspid valve and influence in the aortopathy. Aortic valve cusp fusion patterns influence wall shear stress features. Panel A and B show right-left cusp fusions on which flow jet is directed towards the right anterior wall of the ascending aorta promoting dilation of the proximal aorta. Panel C shows right-noncoronary cusp fusion on which flow jet is directed towards the posterior wall of the aorta promoting dilation in the distal aorta within the proximal arch.

Figure 4. Personalized wall shear stress heat map.

A patient with bicuspid aortic valve (BAV), man, 55-year-old, was scanned with standard cardiac magnetic resonance imaging including 4D flow. Panel A shows velocity streamlines at peak systole. Acquired velocities in the aorta are isolated and compared with a velocity and wall shear stress (WSS) normative atlases considering age-matching as illustrated in panel B. Panel C shows the personalized WSS heat map for indicating regions with abnormal WSS.