Perspective

The surgical implications of bicuspid aortopathy

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Introduction

It should not be a surprise that there is great interest today in bicuspid aortic valve (BAV) and, in particular, its associated aortopathy; perhaps it is more surprising that so little seems to be known about this most common type of congenital cardiac anomaly. Affecting between 0.5-2% of the general population, and men three times more often than women (1,2), BAV is frequently the underlying etiology of aortic valve dysfunction in the form of calcific aortic stenosis or aortic regurgitation and is often associated with other congenital and acquired cardiac anomalies.

Beyond the valve itself, there is growing appreciation of the potential for mortality imposed by the associated proximal ascending aortic aneurysm which predisposes the aorta to dissection. Necropsy studies have long suggested an up to nine-fold increased risk of aortic dissection in patients with BAV compared to patients with tricuspid valves based simply on numerical over-representation of the former (3). Given technical progress and improving results of aortic surgical interventions (4), recent years have witnessed adoption of a distinctly more aggressive posture among both surgeons and cardiologists towards replacement of even modestly dilated aorta in the presence of BAV. The question remains whether the momentum of this shift in opinion has led us to overshoot the mark.

Pathogenesis of BAV-aortopathy

Aortic dilatation in the setting of BAV represents a particularly interesting combination of known potential pathogenetic mechanism, and lends itself to significant ongoing debate. Genetic causes of such disease - Marfan syndrome being the archetype - and hemodynamic causes with post-stenotic dilatation recognized in other vascular beds for well over a century, are both present in this circumstance.

There is substantial evidence for a primary aortopathy independent of hemodynamic stresses playing at least some role. It has long been recognized that, on average, the aortic valve annulus, sinuses, and ascending aortic dimensions are larger among those with BAV even at an early age and is independent of valve function (5,6). Progressive dilatation even after successful aortic valve replacement has also been documented. Others would argue, however, that flow patterns through the abnormal valve or prosthesis exacerbate strain on the tissues of an inherently weak aortic wall, leading to tissue failure and aneurysm formation.

Some of the controversy must be attributable to the phenotypic heterogeneity of this condition. A bicuspid aortic valve is the result of abnormal fusion or failed division of any two aortic cusps during aortic valvulogenesis resulting in three distinct bicuspid valve morphologies. The underlying mechanisms of disordered leaflet formation are not clearly understood, however, and the fact that resultant bicuspid valves are not created in equal numbers suggests that a number of independent factors may be involved. Most commonly, there is a common left-right coronary cusp leading to an anteriorly-posteriorly orientation. Fusion of the right- and non-coronary cusp occurs four times less frequently and left-non fusion occurs somewhat infrequently (7).

Interestingly, valve morphology appears to be associated with variable aortic phenotypes. This association may be understood in part as both the aortic valve tissue and the proximal aortic wall arise from neural crest cells (8). Accordingly a defect in this tissue may link the abnormal aortic valve to the inherent aortopathy. Anterior-posterior cusp arrangement is more frequently associated with male gender, normal aortic shape, and increased diameter at the sinuses of Valsalva, whereas left-right orientation of the

cusps has been associated with greater degrees of ascending aorta dilatation, increased dimensions at the aortic arch and higher prevalence of myxomatous mitral valve disease (7). The variability of the aortic characteristics seen with alternate valve morphologies suggests that multiple genetic and developmental factors affecting neural crest are responsible for creating bicuspid aortic valves and the ensuing aortic pathology.

While the genetic elements that contribute to BAV are not fully known, familial clustering has been reported by numerous investigators and is well accepted (9-11). The prevalence of BAV in families where more than one member is known to have BAV has been reported to be as high as 24% (12), suggesting that at least some forms of BAV are heritable. Despite the high reported presence in this series, BAV is a trait which does not appear to follow simple Mendelian genetics. Rather, it appears that the bicuspid phenotype results from multiple genetic factors with variable degrees of penetrance. Thus far, while no gene has been identified as the "bicuspid aortic valve" gene, a few have been implicated. Some data suggest that mutations in cell signaling and transcriptional regulator NOTCH-1 may play a role in non-familial forms of BAV (13). Likewise, mutations in smooth muscle α-actin (ACTA-2) have been associated with thoracic aortic aneurysms and dissections. Population studies of patients with thoracic aneurysms and mutations of ACTA-2 have shown an increased prevalence of BAV, suggesting a role for this gene as well (14). Finally, animal research has demonstrated that disruptions in the expression of fibroblast growth factor 8 are associated with abnormalities of the great vessels BAV (15). This finding has yet to be validated in human examples of BAV. Although no single gene has been definitively linked to BAV, there certainly appear to be genetic factors in play which support current American College of Cardiology/American Heart Association guidelines recommending aortic screening for first degree relatives of patients with BAV (16).

As we look at genetic causes of aortopathy, comparison of tissues from patients with BAV to tissues collected from patients with other heritable forms of thoracic aortic aneurysms further support the theory of an underlying development defect as the cause of aortopathy. Since ascending aorta and aortic root dilation is a predominate feature of Marfans syndrome, the two disease processes have been studied side by side. Histologically, both conditions reveal "cystic medial necrosis" with loss of smooth muscle cells and elastin fragmentation (17). *In vitro* culture studies of aortic smooth muscle cells derived from both Marfan and BAV patients exhibit similar alterations in intracellular protein trafficking of fibrillin, fibronectin, and tenascin. Smooth muscle cells of both disorders demonstrate normal amounts of protein production with increased intracellular accumulation and reduced extracellular release of these extracellular matrix proteins. Vascular tissues collected from patients with BAV have confirmed the presence of decreased extracellular levels of fibrillin-1 (18), an extracellular matrix protein which has been shown to play an important role in the matrix sequestration of transforming growth factor-β (TGF-β). Deficiencies of fibrillin-1 have been associated with dysregulation of TGF-β activation and signaling, leading to apoptosis (19). In addition, fibrillin-1 deficiency triggers the production of extracellular matrix proteins responsible for vascular matrix remodeling and aneurysm formation (18). These matrix metalloproteinases (MMPs) have been shown to be responsible for extracellular matrix degradation in aneurysmal tissue (20). Increased levels of MMPs present in BAV tissues may be responsible for the decreased elastin and collagen content found in BAV aneurysms, accounting for greater rates of aneurysm formation and structural failure in these patients (21).

Similarities in fibrillin pathways and the presence of cystic medial necrosis in both Marfan's and BAV invite comparisons between the two disease processes, and reinforce the position of those who emphasize the role of an inherent genetic abnormality and its potential implications for early surgical intervention. Even so, known mutations of the gene encoding fibrillin have been identified in Marfan's and not in BAV and the finding of cystic medial necrosis is not unique to these disease processes and in fact may be found in aneurysms and dissections originating from other sources, begging the question whether it represents cause or consequence (22).

What then is the role of the MMPs? Patterns of expression and levels of activity of MMPs may provide insights into the etiology of aortic tissue weakness. Increased levels of MMP expression have been shown to promote proteolysis and vascular remodeling of the aorta (23). Levels of MMP-2 and MMP-9 are known to be increased in aortic aneurysms and are even higher in aneurysms presenting with dissection (23). When compared with aneurismal aortic tissue excised from patients with tricuspid aortic valves, aortic tissue in patients with BAV showed higher MMP-2 and MMP-9 expression (24,25). Further studies exploring the differences of MMP activity within the BAV population found that global activity levels of MMPs were increased while levels of tissue inhibitors of metalloproteinases

(TIMPS) were decreased in all types of BAV (26). Despite this, each distinct valve morphology was found to have a characteristic profile of MMP activity, lending support to the notion that certain valve morphologies may predict aggressive forms of aortopathy. Interestingly, simultaneous detection of MMPs and their inhibitors at four distinct aortic sites revealed that MMPs are variably expressed within the same patient (27). MMP-2 levels were higher in concave aortic sites than in convex aortic sites, while in contrast, MMP-8 and 9 levels were higher in the convex sites.

What then can be said about MMPs? It appears that MMPs are increased in aneurismal tissues and may be further increased in the aortas of patients with BAV who are already known to have increased aortic diameters at baseline. The ability to define characteristic patterns of expression depending upon valve morphology supports the idea that a genetic factor underlies the expression of these proteins while the geographic variability identified within the aortic wall lends support to the notion that regional differences in wall stress lead to local alterations in aortic tissues. Ultimately we do not know if changes in MMPs are due to inborn errors or are the result of local forces. Understanding the stimulus for MMP activity may allow us to identify modifiable factors related to aneurysm formation.

The regional tissue properties are not limited to MMP activity alone in providing additional support for a hemodynamic mechanism underlying BAV aortopathy. In contrast to the homogeneous distribution of cystic medial necrosis found in Marfan's, there is more cystic medial necrosis at the greater curvature of the aorta in BAV relative to the lesser curvature. Similarly, Marfan aortas have uniform decreases in Type I collagen whereas Type I and III collagens are more severely decreased on the greater curve of the aorta in patients with BAV (28). Finally, apoptosis is also increased at the greater curvature in patients with BAV (29) and has been shown to occur before overt aortic dilation in BAV.

The clinical expression of these histological abnormalities is wall strength and tissue integrity. Non-invasive studies designed to look at the tissue properties of the aortic wall have shown the aortic wall of patients with BAV to be less elastic than controls (30). This stiffness was independent of aortic diameter, again suggesting an inherent abnormality that may precede and in fact predispose to tissue failure expressed first as dilatation and subsequently as dissection. Aortic tissue samples collected from aneurysms of patients with and without BAV, however, demonstrated the mechanical strength of aneurismal tissues from both types of patients to be equivalent. Tensile strength testing showed no difference but did reveal an age related declined in both patient sets.

Even here we can find evidence of a hemodynamic component. Importantly, even the "functionally normal" BAV exhibits eccentric and turbulent flow past the valve as well as abnormal flow patterns in the ascending aorta with increased levels of wall stress compared to tricuspid valves (31). The bicuspid valve opens in an eccentric pattern (32) yielding greater flow acceleration across a relatively stenotic orifice (33). Four-dimensional flow magnetic resonance imaging has revealed abnormal helical systolic flow in the ascending aorta of patients with BAV, including those without aneurysm or aortic stenosis (34). In addition, restricted motion of the fused aortic valve cusp is frequently present and tends to redirect blood flow along the right anterolateral aortic wall. Cusp opening angle has been shown correlate with and predict aortic diameters and growth rates (35). The direction of the blood flow is determined by the orientation of the aortic cusps and the motion of the aortic valve leaflets, which may be a significant determinant of aortic wall stress. These characteristics provide a potential basis for explaining why valves with right and non coronary fusion tend to have greater degrees of aortic dilation than those with left-right fusion. In addition to sheer stress caused by altered blood flow through the bicuspid valve, it has been demonstrated that aortic wall stress is increased in patients with BAV when compared to normal valves for aortas of any size (36). Unifying the effects, MMP-2 activity has been shown to be up-regulated by increased wall tension (37). Therefore, abnormally accelerated and deflected flow through the aortic valve may be responsible for the increased aortic wall stress identified in these patients and lead to flow induced elevations of MMPs, vascular remodeling and aortic aneurysm. Perhaps these forces along with a genetic predisposition are responsible for the asymmetric expression of MMPs in BAV aneurysms.

Natural history of aortopathy

Laboratory investigations are intriguing, however, as the most relevant data impacting on our clinical decision-making regarding intervention on the aorta should be the actual clinical behavior observed in carefully performed studies of the natural history of the condition. Unfortunately the majority of such studies begin with highly selected subsets of the BAV population. Necropsy studies

have been interpreted as demonstrating an increased risk of dissection among patients with BAV with such patients over-represented in frequency the general population by a factor of 5-9 (3,38). This finding appears independently of functional valve pathology (39). Unfortunately, these studies do not tell us if the patient had an associated aortic aneurysm or not, an entity that increases the risk of dissection regardless of the morphology of the valve. As 30-50% of patients with BAV will have significant aortic enlargement, it is not possible to tell if valve morphology itself is an independent risk factor based on inherent abnormality of the aorta. Furthermore, a study of those who have experienced a complication will shed little light about the quantitative risk of those complications occurring among the population at large, as to calculate risk one needs both the numerator and the denominator. Still, the consequences of aortic catastrophe are sobering, particularly when one recognizes that BAV is responsible for more deaths than all congenital cardiac defects combined (40).

A somewhat more inclusive view of the natural history of the aorta comes from Yale investigators who followed patients with BAV presenting with either aortic aneurysm or dissection (41). The patients with BAV were more likely to present at younger ages and importantly - despite increased growth rates - more likely to demonstrate rupture or dissection at the same size as in patients without BAV. A more representative study comes from Olmsted County (42). The cohort included 416 patients with known BAV who were followed for a mean 16 years. Among this population, 2 aortic dissections occurred, yielding an age adjusted relative risk of 8.4, but an absolute incidence of only 3.1/10,000 patient years. Of 384 patients without baseline aneurysms, 49 developed aneurysms, however there were no dissections in patients with baseline aortic diameter less than 45 mm.

The fate of the aorta following isolated aortic valve replacement for BAV is also still a matter of debate. While the aorta of patients with BAV who have undergone AVR has been shown to dilate at the same rate as those without AVR (43), it is more challenging to define the risk of dissection. The majority of studies have focused on a composite endpoint of "aortic events", including aortic surgery as well as dissection, which are indeed higher after AVR for BAV, however they are subject to biases related to changing referral patterns as well as migrating indications for intervention (43-47). More recent studies suggest little increased risk of aortic dissection if the aorta is not aneurysmal at the time of AVR (48). Importantly, in a study from Toronto demonstrating 15-year freedom from ascending aorta-related complications to be only 86%, 81%, and 43% in patients with aortic diameters less than 4.0 cm, 4.0 to 4.4 cm, and 4.5 to 4.9 cm, respectively (45), many of the interventions were driven by the need for re-replacement of degenerated bioprosthetic valves. In a much larger study, McKellar found 15-year freedom from aortic events, including aortic dissection, enlargement or replacement, to be 89% for all patients but was lower for patients with documented aortic enlargement at time of AVR (46). Interestingly, the rate of aortic complications may be associated with the status of the aortic valve at the time of surgery as patients presenting with aortic regurgitation had significantly lower 10-year freedom from aortic events (88% *vs.* 95%), as shown in a study from Girdauskas and coworkers (47). Overall, the rate of aortic complications following isolated AVR for BAV has been found to be low but not negligible. The increased incremental risk of additional surgery, therefore, must be balanced by the low risk of late aortic complications following surgery and may be influenced by the BAV phenotype at the time of surgery.

Surgical implications of aortopathy

What elevates the phenomenon of BAV-associated aortopathy from an interesting experiment of nature in the pathogenesis of aortic aneurismal disease to a matter of pressing clinical importance, are the practical decisions that must be made relative to surgical intervention. While decisions are made before the patient is brought to surgery with regard to diagnostic imaging and frequency of follow-up, it is the specter of surgical intervention that forces us to take a public stand regardless of the imperfect nature of the data. Remarkably, only a decade ago, there seemed little interest in these questions. Perhaps the recent surge in interest is, in part, due to the progress made in the surgical management of the thoracic aorta. Still, regardless of how low the surgical mortality and morbidity fall, they will never reach zero and there will always be some price to pay for intervention, which will be higher should the procedure be more extensive.

Current guidelines for aortic replacement in patients with BAV are more aggressive than those in patients with tricuspid valves, despite the controversial nature of the data. Current guidelines state that asymptomatic patients with BAV should undergo surgery when the aortic diameter reaches 5.0 cm. Among those in whom the aortic valve is the primary indication for operation, replacement is recommended at 4.5 cm (16). Every practicing surgeon,

however, knows that clinically the decisions are more complex than simply following these guidelines. Does the root need to be replaced in this elderly patient with only mild sinus enlargement? Should the patient be subjected to the additional bypass time associated with hypothermic circulatory arrest or impose additional complexity for selective antegrade perfusion in order to replace the proximal arch? Should the 5.0 cm ascending aorta be replaced in an 80-year old with impaired renal function and a functionally normal valve? Should the presence of a 4.5 cm aorta prohibit an elective pregnancy? Despite the guidelines, these are common topics of discussion among clinicians.

In part the nuance of surgical management is demanded by the remarkable phenotypic heterogeneity we observe in the operating room. Surgeons will recognize three pathologic phenotypes of aortic dilatation in addition to the normal aorta. Frequently there is discrete enlargement of the ascending aorta with preservation of the sinotubular ridge. Occasionally the sinuses alone are enlarged, but more often there is generalized enlargement of the entire ascending aorta and sinuses, with effacement of the sinotubular junction and displacement of the coronary arteries. Advanced imaging studies have suggested that, collectively, almost two-thirds will have some root involvement (49). In addition to this phenotypic variability, the proximal arch is dilated to some degree in almost 75% of patients, extending into the mid-arch in up to one-third of patients (49).

It is worth remembering that the technical surgical options range from a supracoronary tube graft to full root replacement, either valve-sparing or composite with a mechanical or tissue prosthesis. Reduction aortoplasty is seldom indicated in the current era. Few studies directly comparing these interventions are available, but perioperative outcomes would appear similar whether the root is replaced or not (50,51). Inspired by concerns of progressive sinus enlargement after supracoronary tube graft as is seen in Marfan syndrome, there have been recommendations to perform root replacement in all patients with BAV. However, the long term risk of reoperation for sinus enlargement in long-term studies appears rare (52). Accordingly we are not reluctant to leave non-dilated sinuses behind, particularly as the patient's age advances. Despite ample reports in the literature supporting low risk associated with root replacement in experienced centers (53), coronary complications do occur and are more likely if the coronary ostia are not displaced. It is important to acknowledge the perils of making clinical decisions based on risks published in the literature, as publication bias is inescapable with only the best results reported. In the setting of repair of a regurgitant BAV, we are more inclined to leave the root alone in the interest of simplifying a subsequent valve replacement should that be necessary; although we acknowledge a school of thought that valve-sparing root replacement may stabilize the repair.

Regardless of management of the root, the distal extent of repair should be tailored to the anatomy as well. An aggressive approach may be argued based on the common embryonic origin of the ascending aorta and proximal arch, contemporary surgical series indicating that arch replacement may be undertaken with low mortality and morbidity (53), and long-term follow-up data indicating that the frequency of progressive enlargement of the unreplaced arch must be extremely uncommon (54). Accordingly, we avoid arch replacement when there is a "neck" of normal diameter aorta proximal to the innominate artery, or if the diameter at the innominate is 4.0 cm or less. Between 4.0 and 5.0 cm we are influenced by the age and comorbid conditions of the patient.

Future directions and considerations

The aortopathy associated with BAV is a clinical entity that we are only beginning to understand. Given advances in imaging modalities as well as genetic analysis, it would appear an ideal condition in which truly tailored medical and surgical care should be possible. Identification of the various molecular, cellular and genetic mechanisms responsible for aneurysm formation may help to distinguish patients who possesses malignant forms of aortopathy from those who will experience a more benign clinical course. This information will allow us to adopt aggressive surgical postures for the former while sparing the latter from unnecessary operative risk. This is an ideal opportunity for truly individualized surgical care.

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