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Year in Review: Bicuspid Aortopathy

Paul W.M. Fedak, MD PhD[1,2], **Alex J. Barker, PhD**[3], and **Subodh Verma, MD PhD**[4]

[1]Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Canada

[2]Division of Surgery-Cardiac Surgery, Bluhm Cardiovascular Institute, Northwestern University, Chicago, USA

[3]Department of Radiology, Northwestern University, Chicago, USA

[4]Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Canada

Abstract

Purpose of Review—To review and outline the key research contribution to BAV aortopathy over the past 18 months.

Recent Findings—Investigators have further defined the current gaps in knowledge and the scope of the clinical problem of BAV aortopathy. Support for aggressive resection strategies is waning as evidence mounts to suggest that BAV is not similar to genetic connective tissue disorders with respect to aortic risks. The role of cusp fusion patterns and valve-mediated hemodynamics on disease progression is a major area of discovery Molecular and cellular mechanisms remain elusive and contradictory.

Summary—BAV aortopathy is a major public health problem that remains poorly understood. New insights on valve-mediated hemodynamics using novel imaging modalities may lead to more individualized resection strategies and improved clinical guidelines.

Keywords

bicuspid aortic valve; aortopathy; hemodynamics; precision medicine

Introduction

Bicuspid aortic valve is the most common presentation of congenital heart disease (1–2% of the general population) and is frequently associated with pathology of the aorta. Dilatation of any or all segments of the proximal aorta, known as *bicuspid aortopathy*, is present in ~50% of individuals with congenital BAV(1) and ascending aortic aneurysms occur at a frequency of 1 in 100 BAV patients per year. Importantly, bicuspid aortopathy is often

Corresponding Author: Paul W.M. Fedak, MD PhD FRCSC FAHA, Associate Professor, Department of Cardiac Science, University of Calgary, Libin Cardiovascular Institute of Alberta, C880, 1403-29 Street NW, Calgary, Alberta, Canada, T2N 2T9, Fax: (403) 270-3715, Phone: (403) 944-5931, paul.fedak@gmail.com.

Conflicts of Interest

None.

progressive and its presence increases the risk of catastrophic clinical events such as aortic rupture and dissection, both associated with high mortality and morbidity.

Over the past 18 months, substantial research activity has focused on bicuspid aortopathy. For excellent general contemporary overviews of BAV aortopathy written by experts in the field, the reader is referred to publications by Michelena and co-workers(2) in addition to Verma with Siu(1). Recent original publications can be defined into specific themes. First, a series of publications have been focused on clinical guidelines and the development of more personalized and precise approaches to treat bicuspid aortopathy. Second, imaging modalities have been leveraged to gain further insights into risk prediction, clinical outcomes, and disease progression. Third, novel contributions have been published that further the debate on the underlying influences of hemodynamic and genetic factors on BAV aortopathy. Fourth, basic science studies have explored cellular and molecular targets and pathways in the pathophysiology of BAV aortopathy. The purpose of this review is to highlight selected high impact publications from the last 18 months with additional perspectives and commentary.

Clinical Guidelines and the Evolving Approaches to Bicuspid Aortopathy

BAV aortopathy is a major public health problem that remains poorly understood. It is concerning that the number of aortic surgeries in this population is increasing but there is limited scientific evidence for the timing and extent of these prophylactic interventions. The burden of surgery for BAV patients in the USA exceeds 1 billion dollars per year and the frequency of aortic interventions has doubled over the past decade(3). Measures of aortic geometry such as maximal aortic diameter and growth rate are most often used to guide patient management and trigger prophylactic surgical repair of the aorta(4). Based on such contemporary resection guidelines, prophylactic replacement of the ascending aorta is performed in approximately 25% of BAV patients (within 25-years from time of diagnosis) (5). More recently it has been postulated that physician bias and historical local practice within institutions often dictate decision-making regarding surgical interventions for patients with BAV(5–10).

To better understand these issues, surgeons' perspectives and approaches to bicuspid aortopathy were recently evaluated. A large survey of 100 cardiac surgeons revealed that operative approaches and management of BAV aortopathy are highly variable and not always consistent with current guidelines(10). Perspectives and attitudes on the etiology (inherited aortopathy versus acquired from hemodynamic stress) rather than validated scientific and clinical evidence appeared to influence the surgical treatment of BAV aortopathy. In support of these findings, Hardikar and Marwick published an excellent overview and analysis of the evolution of the clinical guidelines for BAV aortopathy(11). The analysis highlights that from 1998 to 2014 ten different international guidelines have been proposed for the surgical management of BAV aortopathy (Figure 1). Recommended thresholds for intervention began at a conservative cutoff level of 5.5cm in 1998(12), reached an aggressive approach of 4.0 to 4.5cm in 2010(13), and returned to a conservative 5.5cm cutoff level in 2014(14, 15). During this time, no conclusive or objective proof was published to support either an aggressive or conservative strategy for prophylactic aortic

resection in BAV aortopathy(11). Based on these wavering guidelines and the increasing number of prophylactic aortic resections in BAV patients it is possible that thousands of unnecessary resections are being performed. It is reassuring to know that in expert surgical programs, as studied by Rinewalt and colleagues, the additional risk of concomitant aortic resection in BAV patients at the time of valve surgery is minimal(16).

The wavering guidelines may reflect shifting perspectives in the etiology of bicuspid aortopathy. Aggressive approaches to aortic resection (early and wide resection) were based on the assumption that BAV aortopathy is inherited and the entire aorta is fragile and at continued risk of dilatation and rupture. More conservative approaches to resection consider that not all patients are at high risk of aortic complications and that hemodynamic and other risk factors may be at play. Over the past 18 months, original research publications and expert perspective contributions have shown a growing appreciation for the individual variability in the progression of the disease and the possible influence of hemodynamic determinants of the disease(17–29). Experts in this area have assembled into working groups, such as the International BAV Consortium (BAVCon), to define specific gaps in knowledge and develop collaborative research platforms to address these key issues(9, 30). Della Corte and members of the BAVCon provide an excellent overview of the key most critical knowledge gaps and research perspectives that relate to surgical treatment of BAV aortopathy(9). Many experts agree that there is a critical need to develop individualized risk assessments beyond size and growth criteria to offer more precise and individualized strategies for surgical resection of the aorta in BAV patients.

Over the past 18 months a number of key studies have provided further insights that may influence clinical strategies and patient management. Itagaki and co-workers examined the natural history of aortopathy after aortic valve replacement (AVR) in a retrospective comparison of over 13,000 patients(31). The study very clearly showed that the risk of aortic complications in long-term follow-up for BAV patients was much closer to control patients than those with Marfan syndrome. The authors of the study appropriately suggest that BAV patients should not be treated with aggressive approaches like those with Marfan syndrome and perhaps other inherited aortopathies. Recent clinical data from other groups also support the findings of Itagaki and co-workers(32, 33). Similarly, Sundt reviewed the strength of clinical evidence for aortic risks and provides a compelling and critical analysis that supports a more conservative approach to the BAV aorta(7). In large grouped series of BAV patients the risk of aortic events does not appear to be high, although selected patients may be at substantial risk.

The pressing challenge facing clinicians today is a lack of prognostic models to guide the timing and extent of surgical repair. BAV patients are offered aortic resection primarily based on maximal aortic dimension and the rate of aortic expansion; however, it is well recognized that measures of aortic size alone are insufficient to guide treatment strategies(6–8, 34–36). Substantial efforts are thus being made to improve risk prediction for aortic complications, with a focus on precision medicine(37–41). The literature suggests a precision approach, which attempts to account for individual variability in genes, environment, and lifestyle, is required to fully assess risk for BAV aortopathy. Based on recent data for BAV, this would likely include recognition of each individual patient’s

underlying genetics and valve-specific hemodynamics based on the pattern of cusp fusion and function (degree of aortic stenosis or regurgitation). In support, Della Corte and his team explored the use of current aortopathy classifications with valve fusion patterns in the determination of risk for aortic growth(42). The authors determined that valve fusion patterns could influence the risk of aortic disease progression. Such studies will aid in the development and validation of factors beyond simple aortic size metrics that may be incorporated into individual resection decisions. Sievers and co-investigators have gone a step further by proposing and implementing an individualized, multifactorial approach to aortic resection in BAV patients, focusing on the BAV phenotype and degree of aortic stenosis (AS) and aortic regurgitation (AR)(43). This study is particularly interesting as it shows the possibilities of using more than simple aortic size criteria for aortic resection decisions can be feasible with excellent outcomes. Further validation of the factors used to influence the decisions to intervene remains to be studied but the approach follows the principles of precision medicine and could serve as a platform for further individualized resection strategies.

Emerging Role for Novel Imaging of Aortic Hemodynamic Biomarkers

Many experts in the area of BAV aortopathy agree that the discovery and implementation of novel aortic risk markers will be critical for the development of consistent guidelines for optimal management of BAV patients with aortic dilatation(2, 29). Aortic hemodynamics are emerging as an important biomarker toward this goal. Past research on the hemodynamic hypothesis for BAV-related aortopathy has primarily focused on on the degree of AS or AR(5, 44, 45). These traditional hemodynamic metrics alone do not reflect the burden on the aortic wall due to the malformed valve. It is increasingly recognized that nontraditional parameters of valve-related changes in aortic hemodynamics (i.e. unrelated to AS or AR) may act as possible mediators of BAV aortopathy(2, 17, 18, 24, 28, 46–48). These findings suggest that the development of BAV aortopathy is not primarily driven by a genetic predisposition (as in Marfan’s syndrome). Supporting this hypothesis are recent studies that have shown that altered aortic flow and valve morphology in BAV patients are associated with the expression of the aortopathy phenotype(49, 50).

Although stimuli for BAV aortopathy are likely multifactorial, results from recent studies provide strong evidence that this stimulus, known as wall shear stress (WSS), may change local matrix homeostasis and, in turn, ascending aortic structure(51–57). Indeed, WSS is known to impact cell function and has been implicated in the development of aortopathy(58–60). Proof-of-concept data was recently obtained using a novel *ex vivo* tissue model. Atkins and co-workers modeled regional WSS from a TAV as compared to a BAV on the ascending aorta in an ex vivo procine tissue model(48). The impact of BAV-mediated WSS was determined on aortic wall remodeling. The investigators found cellular, molecular (increased MMP-2 activity), and structural changes that are characertistic of human BAV aortopathy. As highlighted by the investgators, the study indictates that altered WSS from a BAV can focally mediate aortic medial degradation. These unique experimental findings provide compelling support for an important role of hemodynamics in mediating BAV aortopathy.

Recent advances in MRI have permitted unobstructed in-vivo assessment of time-resolved 3D blood velocity, using a volumetric technique referred to as 4D flow MRI. 4D flow MRI provides the unique ability to quantify complex 3D blood flow patterns in-vivo and has facilitated new insights and discovery with respect to complex cardiovascular hemodynamics(50, 61–65). Multi-dimensional 4D flow MRI data (3 spatial dimensions describing 3D velocity over time) enables aortic blood flow visualization, quantification of regional flow and velocity,(66–69), and WSS quantification(51, 52, 54, 56, 57, 70). Recent MRI studies provide strong evidence that valve-mediated local flow dynamics(61) and regional differences in wall shear stress (WSS)(50) are associated with changes in regional aortic wall histology and proteolytic events(71), which are known to drive adverse aortic remodeling. Early studies employed non-invasive MRI techniques (2D PC-MRI) to demonstrate BAV-mediated changes in flow and WSS(70). Subsequent 4D flow MRI studies have conclusively documented that aortic WSS is increased in BAV subjects independent of stenosis severity when compared to age- and aortic size-matched controls[61] (Figure 2). Moreover, we have shown that regional variation of WSS within the aorta is dependent on aortic valve fusion phenotype[50, 61] and is associated with aortic diameter(72). A recent study with 30 BAV patients and 30 age-appropriate trileaflet aortic valve (TAV) controls by our group provided evidence that altered aortic hemodynamics may be a pathophysiologic mechanism by which right and left-coronary leaflet (RL-BAV) or right and non-coronary leaflet valve (RN-BAV) fusion influences the expression of aortopathy(50). Similar to the findings of Atkins and Sucosky in the porcine model, we recently discovered that aortic hemodynamic alterations are related to medial wall degeneration[71]. In a recent study that included both in-vivo 4D flow MRI and aortic tissue resection in 20 BAV patients, we found that elastin content and structure was severely disrupted in regions of high WSS with a shift in the expression of specific MMPs and TGF-beta (Figure 3). Girdauskas and colleagues found a similar correlation between systolic transvalvular flow patterns and proximal aortic wall changes in the setting of bicuspid aortic valve stenosis(47). With more extensive investigation it is conceivable that quantitative metrics of valve-mediated hemodynamics could be used to guide more precise and individualized surgical resection strategies beyond contemporary empirical size thresholds.

Cellular and Molecular Mechanisms of BAV Aortopathy

The critical molecular and cellular pathways mediating BAV aortopathy remain elusive. Research over the past 18 months in this domain has provided more new questions rather than specific answers. The critical role of MMP-2 as a key molecular mediator was supported by a recent meta-analysis. Wang and colleagues further showed MMP-2 as a circulating biomarker of aortic dilatation in BAV patients(73). Phillippi with Gleason and Vorp at University of Pittsburgh further characterized the medial matrix remodeling of the BAV aorta and found unique patterns as compared to TAV patients(74). Grewal and co-workers compared the histopathology of BAV, TAV, and Marfan aortic tissue and found both similarities and differences between all three groups with respect to parameters of matrix remodeling and vascular smooth muscle markers(75). The complexity of the histopathology remains high and it is not clear what molecular pathways are unique to the BAV aorta. The complexity is further confounded by the findings of Heng and colleagues. In this recent

study, tissue pathology was compared between TAV and BAV patients at matched aortic diameters(76). At odds with conventional wisdom, more severe histologic abnormalities were found in trileaflet aortic valve aorta as compared with BAV, especially when stratified by diameter. The authors suggest that the data do not support a more aggressive approach to surgical intervention for dilatation associated with BAV and the lack of correlation between aortic diameter and histologic abnormality in the setting of BAV highlights the inadequacy of diameter alone as a criterion for aortic resection. Further insights may be provided by biomechanical functional testing of tissue samples in addition to histopathology. Forsell and co-workers recently documented increased collagen-related stiffness in the aortic tissue of BAV patients as compared to TAV controls(77). Aortic stiffness is associated with progressive aortic dilatation and aneurysm formation which is characteristic of BAV aortopathy(34). Indeed, a recent study of abdominal aortic aneurysms found that segmental stiffening of the aorta preceded aneurysm growth and introduced the concept that stiffening may act as an early mechanism triggering elastin breakdown and aneurysm growth(78). Nonetheless, the evidence regarding cellular and molecular mechanisms for BAV aortopathy remain complex and contradictory, with a need for larger cohort, well-controlled studies.

Conclusions

Important contributions to research and perspectives on BAV aortopathy have been made in the past 18 months. Investigators have focused on defining the current gaps in knowledge and the scope of the clinical problem of BAV aortopathy. The role of cusp fusion patterns and valve-mediated hemodynamics on disease progression is a major area of discovery and new insights using novel imaging modalities may lead to more individualized resection strategies and improved resection guidelines. Support for aggressive resection strategies is waning as evidence mounts to suggest that BAV is not similar to Marfan syndrome with respect to aortic risks. Molecular and cellular mechanisms remain elusive and contradictory and deserve continued investigation.

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Key Points

- Substantial research efforts over the past 18 months have focused on defining individual risk factors for disease progression
- The risks associated with BAV aortopathy may be less than previously assumed warranting more conservative and selective approaches to prophylactic aortic resection
- New imaging modalities have been leveraged to obtain novel data that supports valve-mediated hemodynamics as a critical mediator of disease progression
- There remain substantial gaps in knowledge with respect to BAV aortopathy, particularly with respect to pathophysiology and molecular mechanisms of disease progression
- Expert perspectives highlight a critical need to develop individualized risk assessments beyond size and growth criteria to offer more precise and individualized strategies for surgical resection of the aorta in BAV patients

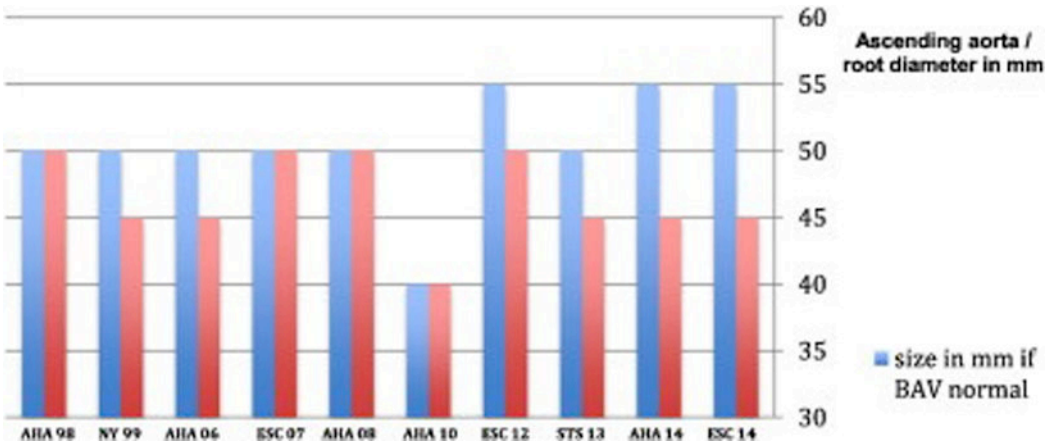

Figure 1. Recommendations for aortic surgery in patients with BAV aortopathy

From 1998 to 2014, 10 different international guidelines have focused on the aortopathy related to bicuspid aortic valves. Different criteria are used if the patient is undergoing surgery for aortic valve disease (red) or there are no surgical indications for the aortic valve (blue). With permission (pending) from reference #11.

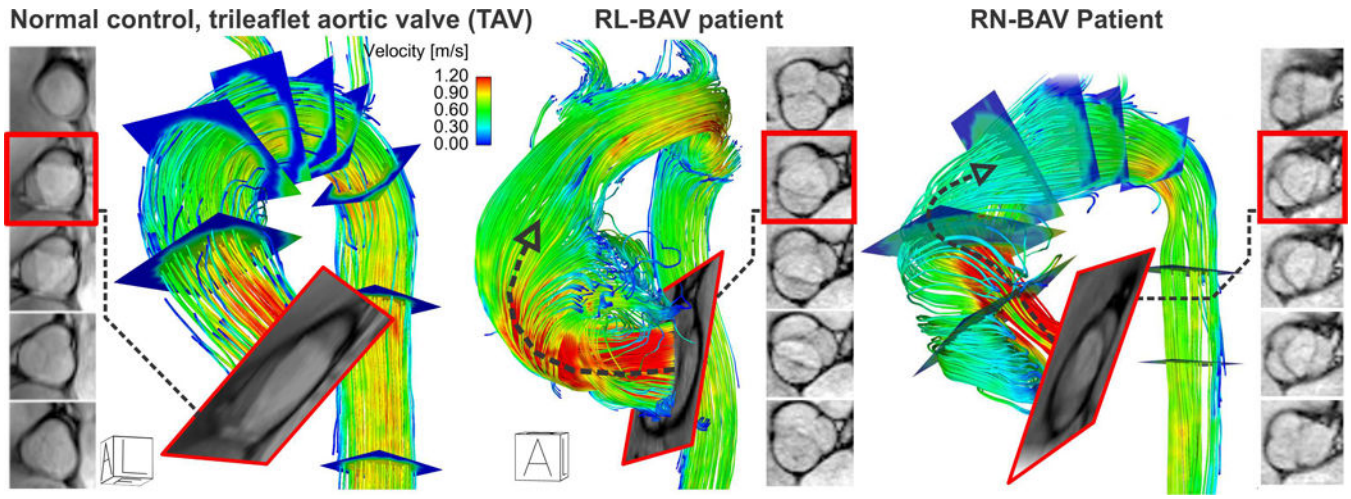

Figure 2. 4D flow MRI of BAV-mediated hemodynamics

Images show control and BAV patient with a right-left (RL) and right-noncoronary (RN) fusion pattern. Note that the RL-BAV resulted in a marked eccentric aortic outflow jet (but not higher velocity, arrow) impinging on the aortic wall compared to TAV. We have found that the BAV phenotype (RL vs right-noncoronary [RN]) strongly impacts aortic outflow and thus aortic regions exposed to elevated WSS(50, 61).

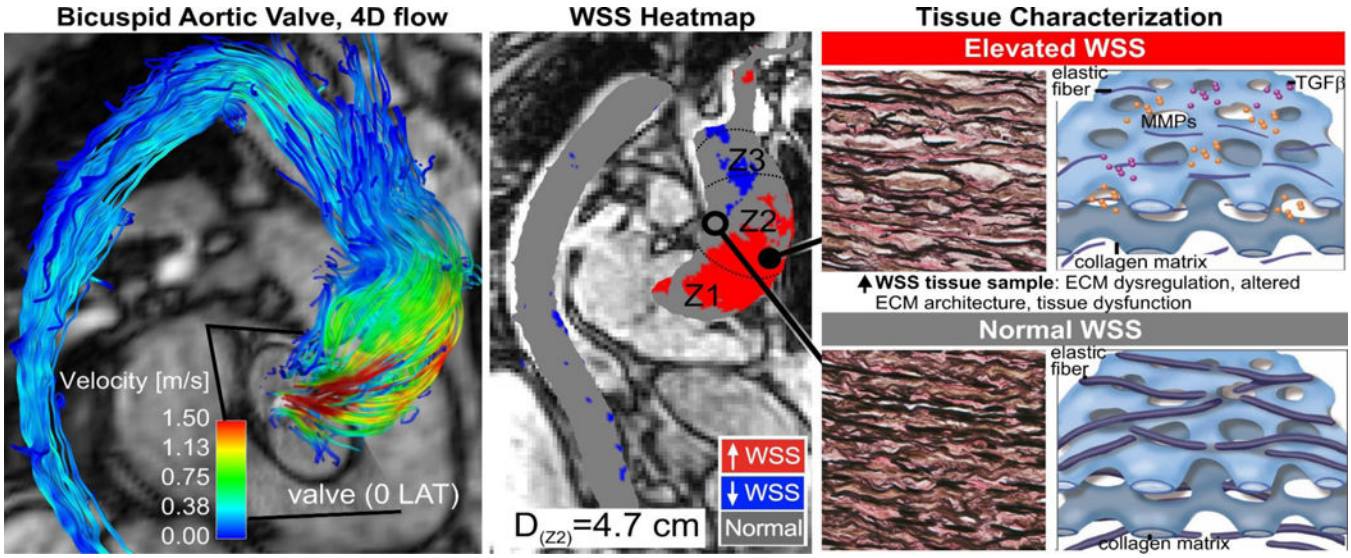

Figure 3. Correlation of WSS with tissue histopathology

Eccentric transvalvular BAV flow (left) exposes aortic wall regions exposed to elevated WSS (middle, red region) which exhibit abnormal tissue metrics of aortopathy (right)(71).