Editorial

Importance of bicuspid aortic valve phenotype on aortopathy

Evaldas Girdauskas[1], John A. Elefteriades[2]

[1]Department of Cardiothoracic Surgery, University Hospital Augsburg, Augsburg, Germany; [2]Aortic Institute at Yale-New Haven, Yale Medicine Department of Surgery, New Haven, CT, USA

Correspondence to: Prof. Dr. Evaldas Girdauskas. Department of Cardiothoracic Surgery, Augsburg University Hospital, Stenglinstrasse 2, 86156 Augsburg, Germany. Email: Evaldas.Girdauskas@uk-augsburg.de.

Submitted Jan 03, 2022. Accepted for publication Jun 07, 2022.
doi: 10.21037/acs-2022-bav-16
View this article at: https://dx.doi.org/10.21037/acs-2022-bav-16

Introduction

The heterogeneity of aortopathy associated with bicuspid aortic valve (BAV) remains a diagnostic and therapeutic challenge, despite several decades of exponential clinical and experimental research in this field. The interaction of congenital and hemodynamic factors plays a competing role in the aortopathy progression and hinders thereby the clinical prediction modelling. Nonetheless, several phenotypic features of BAV are associated with specific aortopathy patterns and may, therefore, guide our clinical decisions. This editorial article briefly summarizes the published associations between BAV phenotype and the concomitant aortopathy.

BAV cusp fusion pattern and aortopathy

Several observational studies described an empirical association between BAV cusp fusion pattern and the associated aortopathy. The most common pattern of the right and left coronary cusp fusion in BAV (i.e., BAV R/L) was linked to a more proximal type of aortopathy (i.e., dilatation of the sinus of Valsalva and of the proximal ascending aorta) as compared to the right coronary–non-coronary morphotype of BAV (i.e., BAV R/N) (1). On the contrary, BAV R/N was associated with a more distal form of aortopathy, limited to the distal ascending aorta and the proximal aortic arch, without involving the aortic root (1). These differences in the aortopathy shape might result from distinct transvalvular flow patterns in the different BAV cusp fusion patterns. Such transvalvular flow differences in distinct cusp fusion patterns were convincingly demonstrated by sophisticated 4D-flow cardiac magnetic resonance imaging (cMRI). This data supports the hemodynamic origin of BAV-associated aortopathy (2). Another evidence of hemodynamic impact has been the reported relationship between increased regional wall shear stress by 4D cMRI and regional aortic tissue remodeling (i.e., extracellular matrix dysregulation and elastic fiber degeneration) (3). These findings implicate BAV-related hemodynamics as a contributing factor in the development of aortopathy.

However, there is some discordant data regarding BAV phenotype and the concomitant aortopathy. Of note, symmetric BAV valves (i.e., Sievers type 0) have been shown to result in an almost central, laminar transvalvular flow pattern, without relevant rheological disturbances. However, type 0 BAV's are frequently associated with a root-type aortopathy, which cannot be explained by deleterious transvalvular hemodynamics. Furthermore, quite a few very asymmetric type I BAV's with a resultant eccentric, deleterious transvalvular flow have a completely normal proximal aorta and never develop clinically relevant aortopathy (4). Such clinical observations reveal obvious limitations of the hemodynamic/rheologic theory and turn our attention toward congenital factors.

In line with the congenital hypothesis, previous experimental work provided valid data showing that R/N BAVs and R/L BAVs may have different etiologies and result from distinct morphogenetic defects during embryogenesis (5). Furthermore, BAV morphotype, i.e., R/N BAV *vs.* R/L BAV, seems to be an important determinant of the elastic properties and dimensions of the aorta (6). Moreover, R/L BAVs have a more severe degree of aortic wall degeneration than R/N BAVs and are significantly more frequently associated with coarctation of the aorta. These data suggest that the congenital factors that determine the formation of

R/N and R/L BAV may also be involved in the occurrence and the progression of BAV-associated aortopathy.

Type of BAV dysfunction and aortopathy

Another important observation regarding BAV phenotype and the associated aortopathy is the reported correlation between type of BAV dysfunction and the phenotype of aortopathy. Della Corte and co-authors were the first to describe the ascending phenotype and the root phenotype that are associated with different baseline patient characteristics, specific histological changes in the aortic wall and grossly distinct natural history/clinical outcome (7). Patients with ascending phenotype present mostly in older age with a typical BAV stenosis and dilatation of the mid-ascending aorta, without relevant root involvement; they have a benign clinical course after an isolated aortic valve replacement (8). The extent of mid-ascending dilatation is proportional to the severity of aortic valve stenosis, which implicates the predominantly hemodynamic origin of ascending phenotype (7). On the other hand, root-phenotype represents a completely different form of BAV-associated aortopathy. Root phenotype is predominantly found in young men and occurs in combination with Marfan-like characteristics, indicating a congenital connective tissue disorder. Root phenotype presents as an isolated, predominantly aortic root dilatation with concomitant aortic regurgitation or a normally functioning aortic valve (7). Of note, such BAV patients have a much higher risk of late aortic events after an isolated aortic valve surgery, indicating the predominance of congenital aortic wall disease. Indeed, a wide spectrum of genetic abnormalities was found in the cohort of BAV patients presenting with a root phenotype (9). Aortic regurgitation in BAV patients with a root-phenotype seems a secondary phenomenon rather than an independent pathogenetic entity in the scenario of the progressive root dilatation. Our hypothesis that aortic regurgitation in BAV is associated with a more malignant form of aortopathy is supported by a meta-analysis demonstrating a 10-fold higher risk of type A aortic dissection after an isolated aortic valve replacement in patients with aortic regurgitation *vs.* aortic stenosis (10).

Conclusions

In summary, the available literature provides some evidence that distinct BAV phenotypes may be associated with specific forms of bicuspid aortopathy. However, there is still no robust evidence of causality between BAV phenotype and the concomitant aortopathy. Hemodynamic disturbances caused by eccentric transvalvular flow patterns in BAV play a role and may partially explain the development of aortopathy. However, other forms of BAV aortopathy (e.g., root phenotype) seem to progress independent of any hemodynamic disturbances; highlighting the relevance of congenital factors as well. Thus, the concomitant BAV phenotype may represent only a silent bystander in complex congenital aortic root disease.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Girdauskas E, Elefteriades JA. Importance of bicuspid aortic valve phenotype on aortopathy. Ann Cardiothorac Surg 2022;11(4):470-472. doi: 10.21037/acs-2022-bav-16

