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SPECIAL EDITION

Controversies in Surgery for Thoracic Aorta

Bicuspid aortic valve related aortopathy

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Abstract Bicuspid aortic valve related aortopathy is known to significantly increase the risk for catastrophic aortic events and, therefore, represents a considerable health burden. Albeit of ongoing research in this field including genetic, molecular, hemodynamic and morphologic aspects, bicuspid aortic valve related aortopathy still represents an imperfectly understood disorder. This lack in knowledge results in a lack of consistency considering different therapeutic approaches. Recent studies have provided new insights into the etiology and clinical impacts of bicuspid aortic valve related aortopathy in different clinical settings, leading to a growing body of opinion towards a more individualized surgical approach than currently provided by the guidelines. Especially valvular hemodynamics—stenosis and regurgitation—seem to have significant impact on the development of bicuspid aortic valve related aortopathy. In this context, there is evidence that regurgitation of bicuspid aortic valves is the more fatal pathomechanism. Furthermore, "age" represents an aspect that should be taken into account when deciding whether to replace the aorta or not, because the diameter depends mainly on a patients age. The same diameter of the aorta in a 70-year old and a 20-year old patient has to be interpreted differently and should, therefore, result in different therapeutic strategies.

Keywords Bicuspid aortic valve related aortopathy · Individualized approach

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Introduction

With a prevalence of 1–2% in the general population, the bicuspid aortic valve (BAV) represents the most frequent congenital cardiovascular malformation [1]. This anatomical variation leads to an increased risk for severe cardiovascular events, which are not only due to valvular dysfunction itself but further caused by concomitant dilatation of any or all segments of the proximal aorta occurring in roughly 40–60% of BAV patients. The so-called "BAV aortopathy" is associated with a 6- to 9-fold increased risk of aortic complications such as rupture and dissection compared to the general population [2–4], thus representing a striking risk factor for these catastrophic clinical events involving high mortality and morbidity.

Aiming to conceive and to deal with this concerning health burden, BAV aortopathy has been an omnipresent issue in cardiovascular research over the past years. Many investigators scrutinized BAV aortopathy considering its multifactorial pathophysiology, concentrating on hemodynamics, molecular as well as cellular pathways and genetics, its mechanisms of disease progression and the different therapeutic approaches during BAV surgery. Nevertheless, despite ever-new insights into the intricacy of BAV aortopathy, crucial questions of this eclectic disease remain unanswered and scientific findings of debatable interpretation.

Morphology of bicuspid aortic valve related aortopathy

As BAV aortopathy remains an imperfectly understood disorder with a heterogeneous nature, efforts in the past have been made to classify morphologic types to facilitate

risk stratification and standardize surgical approaches in BAV aortopathy. The technical surgical options range from a supracoronary tube graft through full root replacement—either valve sparing or composite with a heart valve prosthesis—to partial or full replacement of the arch with concomitant deep hypothermia and circulatory arrest. Since perioperative morbidity and mortality are related to the extent of the procedure, it is crucial to keep the surgical approach to "as much as necessary and as little as possible".

To reach this goal, several classifications including the anatomy of the proximal aorta with or without relation to the BAV phenotype have emerged [5–9]. Fazel and coworkers [5] defined four clusters of BAV aortopathy according to the dilated regions of the proximal aorta. Cluster I includes patients with dilation of the aortic root, Cluster II dilation of the tubular ascending aorta (AAo), Cluster III dilation of the tubular AAo and transverse arch and Cluster IV combined dilation of the aortic root, the tubular AAo and the transverse arch. A significant relation between cusp fusion pattern of the BAV and the different clusters was not detected. Another classification was derived by Della Corte et al. [6] including the four phenotypes (1) normal aorta, (2) small aorta, (3) "mild-ascending phenotype" consisting of a dilation of the tubular AAo and (4) "root phenotype" consisting of a dilated aortic root. In addition to the Fazel classification, Della Corte and colleagues also investigated in this study the role of valve failure in BAV patients and found a significant proportional relation in the degree of stenosis and ascending aortic diameter in the "mild-ascending phenotype", whereas "root phenotype" was often associated with regurgitation and independent of stenosis [6]. The association of BAV phenotype, aortic configuration and hemodynamics was further investigated by Sievers and coworkers [9] confirming the findings of Della Corte et al. and further reporting a correlation with BAV phenotypes [10] (Fig. 1). The authors demonstrated a significant association of stenotic BAV type 0 and type 1 LR with localized AAO dilation (Fazel Cluster II [5]), whereas regurgitant BAV type 1 LR and type 2/unicuspid were associated with more extended aortopathy involving the aortic root (Fazel Cluster I and Cluster IV [5]) (Fig. 2).

Though efforts have been made in the past to investigate further the different phenotypes of BAV aortopathy and to define distinct patterns, up to now no uniform classification scheme is ascertained. Nevertheless, the already acquired knowledge can guide clinical practice and might be helpful in making precise distinctions of surgical techniques in individual patients.

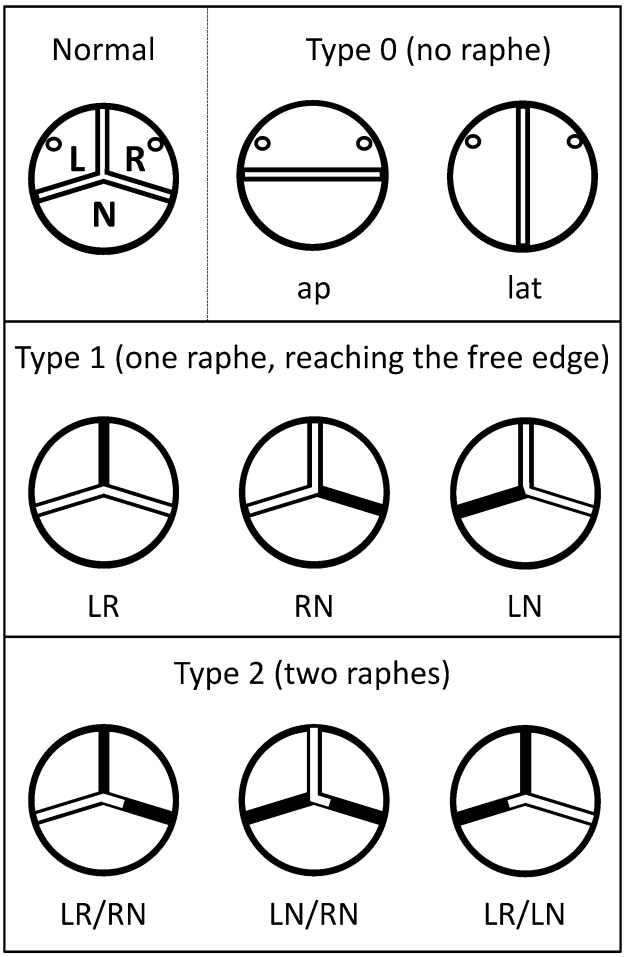

Fig. 1 Morphologic classification of bicuspid aortic valve phenotypes according to Sievers et al. [10]

Genetic basis and biomarkers of BAV aortopathy

BAV has a high heritability of approximately 0.89. A family-based genome-wide analysis found that BAV was linked to chromosomal regions 5q, 13q, and 18q with an autosomal dominant inheritance, reduced penetrance, and non-Mendelian pattern [11, 12]. Although the ascending aorta and semilunar valves share common embryological origins including the second heart field and cardiac neural crest cells, the etiology of aortopathy in patients with BAV remains unknown at present. Few studies have identified genes responsible for the genetic predisposition, e.g., mutations were detected in the transmembrane receptor *NOTCH1* (gene mapped to a locus on chromosome 9q) in familiar, sporadic cases, and in aortopathy of BAV [13–15]. Several genes and loci are known to be associated with familial thoracic aortic aneurysms and dissections (e.g., transforming growth factor beta (*TGFβ*) receptor type I and receptor type II, smooth muscle-specific myosin

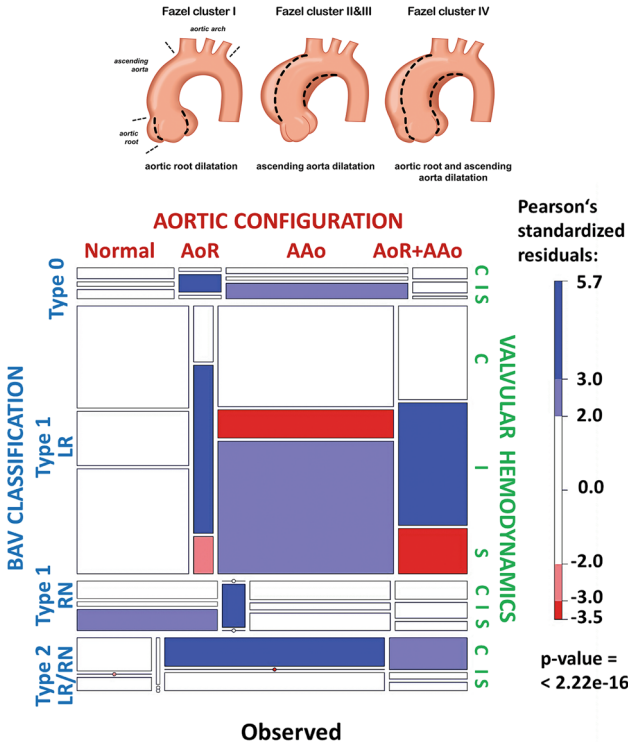

Fig. 2 Mosaic plot of the distribution of bicuspid aortic valve type, aortic configuration and valvular hemodynamics of a patient population. e.g. Type 1 LR and insufficiency is frequently associated with Fazel type IV (aortic root and ascending aorta dilatation, loss of sinotubular junction waist). Reprinted from Sievers et al. [9] with permission of Oxford University Press

heavy chain, myosin light chain kinase, and smooth muscle-specific alpha-actin (*ACTA2*). The *ACTA2* gene is thought to be responsible for approximately 10–14% of the inherited ascending thoracic aortic aneurysms and dissections [16, 17]. Other genes originating from the identification of knockout mouse models, e.g., *eNOS/apolipoprotein E* double-knockout detected a higher incidence of aortopathy and increased BAV occurrence in mice. Nevertheless, in BAV, molecular biological investigations have indicated an altered expression pattern of matrix metalloproteinases and their inhibitors. Furthermore, how the programmed cell death proceeds in the vascular smooth muscle cell of the aorta was also demonstrated. In a study by Grewal et al. [18], showed, that the smooth muscle cell of BAV leads to significant differences in the structure and maturation of the smooth muscle cells. Qualitative changes in collagen content in advanced glycation end products (AGEs) showed elevated levels of circulating soluble receptor for AGE in dilatation associated with BAV [19]. The collagen in BAV patients is highly AGE-modified in comparison with the control group [20]. The validation of circulating differentially expressed proteins will increase our understanding of the molecular mechanisms underlying BAV aortopathy and thus support the future development of clinical parameters, biomarkers, and monitoring patients at high risk to avoid dissections.

Does it all come down to hemodynamics?

Aortic hemodynamics is an emerging issue in research in BAV aortopathy. The hemodynamic hypothesis portraying the development of BAV aortopathy due to altered flow characteristics in the proximal aorta has been proposed as an alternative to the genetic hypothesis. And indeed, several studies have reported that the different phenotypes of BAV [10] (Fig. 2) and the type of valve dysfunction—stenosis versus regurgitation—result in distinct hemodynamics in the proximal aorta and strongly influence the risk for severe aortic events [2, 4, 6, 9, 21–34]. This stimulus, also known as wall shear stress (WSS), is supposed to affect local matrix homeostasis and subsequently the phenotype of BAV aortopathy [35–38]. This is a typical example of mechanotransduction trying to adapt to the altered force impact on the wall [39] (Fig. 3). Investigations of Atkins and colleagues validated this suggestion in a controlled ex vivo setting comparing regional WSS in BAV compared to tricuspid aortic valves (TAV) in a porcine tissue model [40]. The authors reported structural, molecular and cellular alterations, which can focally induce aortic medial degeneration, as seen in human BAV aortopathy. Considering WSS in vivo, advances in resonance magnetic imaging (MRI) enable nowadays the visualization and quantification of aortic blood flow and WSS [31, 36, 41–43]. Using 4D flow MRI, it was possible to prove that WSS in BAV is increased compared to TAV in an age and aortic size matched cohort [30]. Moreover, regional differences in aortic WSS were detected [29, 30], which lead to changes in regional aortic histology and proteolytic events [34], are associated with different morphologies of BAV aortopathy [33] and are dependent on the BAV phenotype [29, 30] (Fig. 4).

The role of BAV cusp fusion patterns in the expression of BAV aortopathy and its different phenotypes was issue of various studies, revealing a correlation of these two parameters [2, 9, 28, 29, 40, 44]. Sievers and colleagues highlighted in a recent study this dependence of aortic configuration, BAV phenotype and valvular hemodynamics. However, these authors state in accordance with the findings of Fazel et al. and Schäfers et al. that it is deficient to predict the morphology of BAV aortopathy only in relation to the BAV phenotype and vice versa [5, 7, 9], but the coincident consideration of valvular hemodynamics leads to significant patterns [9].

Thus, there is evidence that the mode of BAV dysfunction—stenosis versus regurgitation—and the resulting changes in aortic flow patterns influence the development

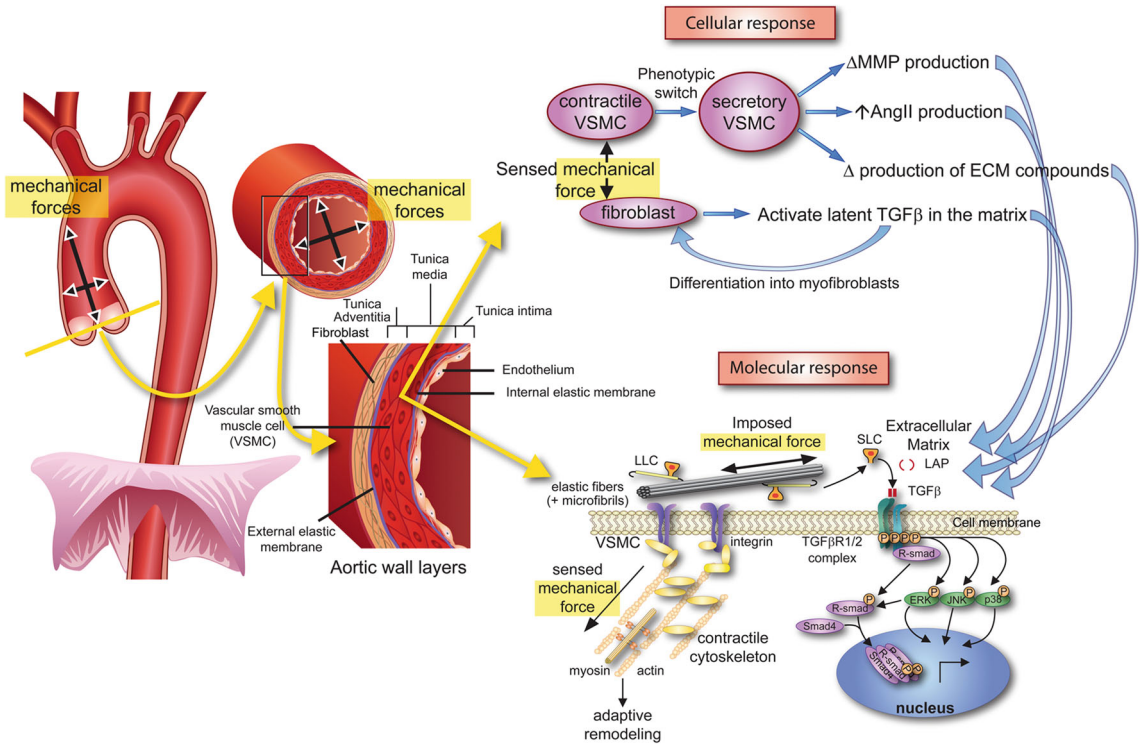

Fig. 3 Concept of mechanobiology underlying homeostasis in the thoracic aorta. Alterations, either due to higher imposed forces (hypertension) or due to (genetic) alterations in the various components required for proper sensing and/or transduction of the signal, may lead to aneurysms/dissections. Reprinted from De Backer [39] with permission of Oxford University Press

of BAV aortopathy, the involved regions of the proximal aorta and the risk for aortic dissection or rupture [9, 25, 26, 45–47]. Regarding BAV stenosis in comparison to regurgitation, recent studies strengthened the suspicion of BAV regurgitation resembling the more influential type of BAV dysfunction. Wang et al. found BAV regurgitation after isolated aortic valve replacement (AVR) to be significantly related to aortic events accompanied by faster aortic dilation compared to BAV stenosis or tricuspid aortic valve regurgitation [26]. Girdauskas et al. underlined and amplified these findings in a meta-analysis. In addition to a 10-fold increased risk for aortic dissection in patients undergoing AVR for regurgitant BAVs compared to a stenotic vitium, these authors provide a trend toward smaller aortic diameters in patients with regurgitant BAVs at the time of AVR leading to the suggestion that aortic dissection in patients with BAV regurgitation occurs at lower diameters [27]. Histological findings confirm the deteriorating character of BAV regurgitation, depicting more hazardous histological changes in the aortic wall compared to BAV stenosis [46]. In line with all these aspects, recent studies by Girdauskas and coworkers demonstrated that patients with BAV and TAV stenosis accompanied by mild to moderate AAo dilation are at comparably low risk for aortic events up to 15 years after isolated AVR and exhibit similar behavior of the proximal aorta [24, 48–50]. Therefore, a less aggressive policy considering replacement of the proximal aorta in patients with BAV stenosis seems to be justified.

Though these scientific achievements and gain in knowledge indicating the decisive role of hemodynamics in the development of BAV aortopathy, there is also evidence refuting the thesis of hemodynamics representing the sole precondition leading to aortic events. If BAV aortopathy was a disease only caused by altered hemodynamics, the replacement of the malfunctioning BAV would subsequently not only cure the valvular disease but also prevent further dilation of the proximal aorta. Whereas this thesis is suggested to be partially true in stenotic BAVs [49], potentially representing the more flow-related type of BAV dysfunction, it is elusive regarding regurgitant BAV. The more extended BAV aortopathy involving the aortic root is associated with regurgitant BAV and remarkably, aortic dilation and the risk of aortic events does not stagnate after AVR but further progress [26, 27]. Additionally, Sievers et al. [9] reported that extensive aortic dilation including the aortic root also occurred in a considerable amount of patients with only trace regurgitant BAV, indicating that hemodynamic stress is unlikely to explain this kind of BAV aortopathy, probably being more induced by a genetic pathway. Instead of considering hemodynamics and genetics as separate principles in the development of

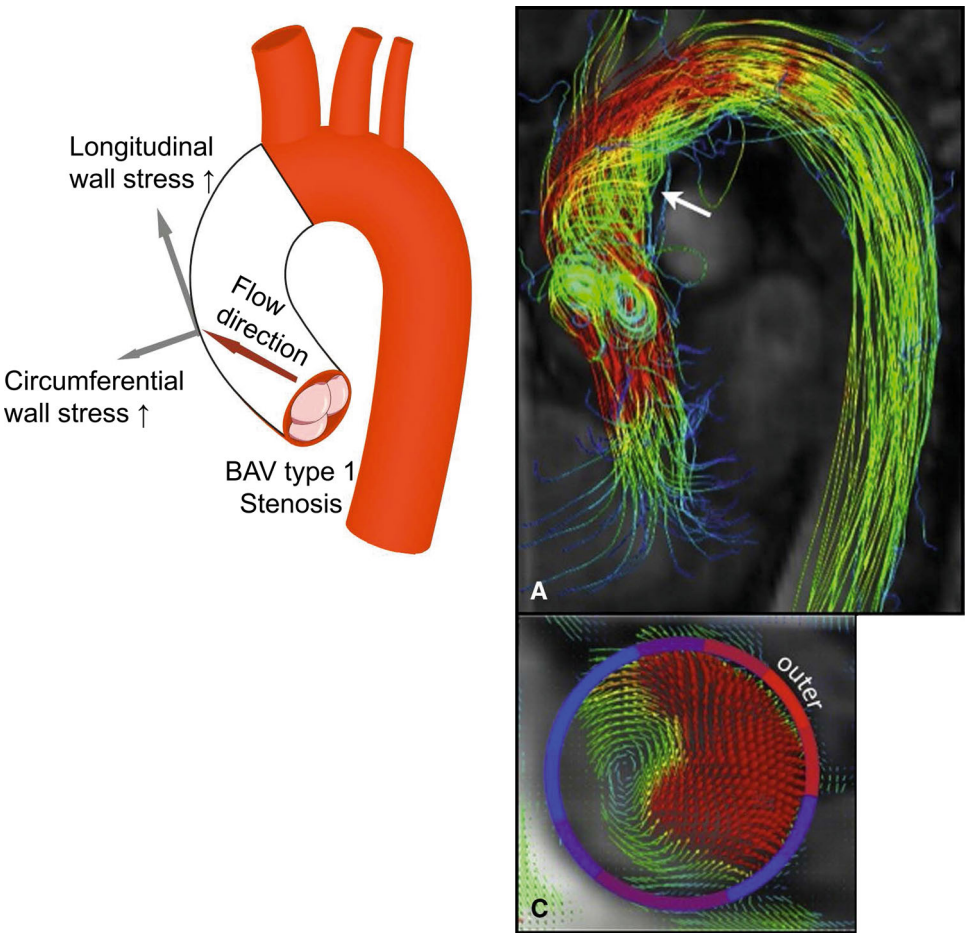

Fig. 4 Bicuspid aortic valve related flow abnormalities increase aortic wall stress. Reprinted from Publication Stephens et al. [83] with permission from Elsevier

BAV aortopathy, the manifold phenotype of this disease seems to result rather from individually different impacts of both factors and their individual interaction [2].

Surgical implications: size is not everything

Surgical decision making in BAV aortopathy still remains controversy without broad consistency, because the decision making process is far more complex than simply following an absolute diameter. This complexity affects daily clinical practice considerably and is emphasized by investigations of Verma et al. [51] reporting a sharp distinction in diagnosis and surgical approaches in BAV aortopathy based on significant differences in the attitude of surgeons towards the disease. Although the majority of the 100 surveyed surgeons was well-informed about current surgical guidelines, a considerable number performed aortic intervention in disagreement with these guidelines. The underlying causes were mainly personal attitude on the etiology (genetics versus hemodynamics) and consideration of different parameters other than AAo diameter. Nonetheless, current guidelines focus on the AAo diameter and recommend a threshold for surgical intervention in BAV aortopathy of >55 mm and in patients undergoing AVR of >45 mm [52, 53], but these cutoff levels have been fluctuating in the past. Hardikar and Marwick analyzed the evolution of the guidelines for BAV aortopathy [54], waving from a conservative threshold diameter of >55 mm in 1998 to an aggressive cutoff level of 40–45 mm in 2010 and returning to >55 mm in 2014. Remarkably, no conclusive data were published to support either an aggressive or more conservative approach for prophylactic aortic surgery in BAV aortopathy. This underlines the still continuing knowledge gaps leading to a lack of consistency and the foundation of surgical approaches to BAV aortopathy. Furthermore, when regarding AAo diameter as risk factor for aortic dissection or rupture, "diameter" and "diameter" is not supposed to be the same as it correlates with various factors. More as body surface area (BSA) and gender, age and the lifelong growth of the AAo diameter mainly influence the proximal aorta and, therefore, need to be taken into account when determining cutoff levels for aortic surgery in BAV patients [55]. Physiologically, the AAo is considered outgrown after adolescence in relation to the BSA.

Nevertheless, the diameter still increases with age and AAo tissue degeneration, faster in the early adulthood than in older age and with broad variably in individual patients [56–59]. For example, an AAo diameter of 40 mm at 25 years age is more pathological than at 75 years age [60]. Therefore, a more individualized approach based on a *z*-score—including BSA and age in addition to the diameter—seems to be advantageous [61]. Another problem rising from "diameter" as sole predictor for severe aortic events is highlighted by Pape et al., who reported that 40% of patients with aortic dissection had diameters <50 mm and 50% of patients with aortic dissection and normal aortic diameters (<40 mm) had no known risk factors (hypertension, Marfan, BAV) [62]. Additionally, a significant shortcoming is represented by the timing of the measurement of aortic diameters. Studies mostly include only AAo diameters post-dissection, which is known to be roughly 13 mm larger compared to pre-dissection [63]. But the pre-dissection diameter is the real diameter at risk.

Furthermore, the focus on ascending aortic diameter as solitary parameter for surgical intervention is delusive as wall tension of the aorta is the major determinant for the risk of aortic dissection or rupture. It is safe knowledge, that dissection occurs when wall stress exceeds the tensile strength of the material. Different factors have to be taken into account provided approximately by the law of Laplace.

$$\text{Wall tension} = \frac{\text{Diameter} \times \text{pressure}}{\text{Wall thickness/quality}}.$$

According to this formula, hypertension as second factor should be thoroughly kept in mind. The decisive role of severe hypertension as catalyst for aortic dissection and rupture of silent aneurysms has been highlighted by investigations of Elefteriades and colleagues, reporting a cluster of healthy young weight lifters suffering from these catastrophic aortic events [64, 65]. Further evaluation revealed an extreme elevation of blood pressures up to or even higher 300 mmHg during severe weight lifting in a healthy cohort [66, 67]. Additionally, a questionnaire revealed in a majority of the surveyed patients extreme exertion or severe emotional upset preliminary to acute aortic dissection, presumably leading to transient severe hypertension [68]. But though blood pressure can play a crucial role in the fate of the AAo, the options to keep it under control are limited. In contrast to the AAo diameter, that is measurable and in some way constant, blood pressure varies instantaneously, considerably and unpredictably. The supervening of an acute, severe hypertensive event to an already enlarged aorta with deteriorating mechanical properties is often the last straw leading to aortic dissection or rupture.

The third factor influencing aortic wall tension is the wall characteristic itself. Recent research in this field has provided more knowledge about histological anomalies, but the precise structural or qualitative determinants of the aortic wall in BAV aortopathy, however, remain elusive. When an experienced surgeon performs aortotomy, he may provide some information of the aortic wall quality, such as fragility or thinning of the tissue. A recent study showed that patients suffering from acute aortic dissection had significantly smaller aortic wall thickness, attributing to a thinner aortic media [69]. Histologically, there is evidence that the aorta in patients with BAV is biomechanically different from patients with TAV [70], but the complexity of this issue was further strengthened by investigations reporting more severe histological abnormalities in TAV compared to BAV aortas [71]. The extracellular matrix (ECM), which regulates cellular events and maintains the integrity of a vascular wall [72], seems to play a critical role, especially matrix metalloproteinases (MMPs) and their specific tissue inhibitors (TIMPs) [73]. A recent study of Wu et al. [74] also reported that micro-ribonucleic acid-17 (miR-17) is involved in BAV aortopathy as it controls TIMPs and interestingly, there were differences in miR-17 in less and more severely dilated regions in the same BAV aortas. This concept of regional heterogeneity of the ECM is additionally supported by various research groups [74–77]. But also intracellular factors like differences in the neural crest-derived smooth muscle cells of the AAo, show significant patterns in BAV aortopathy [78]. Furthermore, BAV aortopathy is presumed to cohere with connective tissue weakness. Roberts and colleagues found a significant loss of aortic medial elastic fibers in AAo tissue of BAV patients [46]. This connective tissue weakness, however, might not only influence the AAo and BAV itself but a larger part of the cardiovascular system. An entity described as WAMBIRE complex (weak aorto-mitral bicuspid relation) represents the coincidence of aortic and mitral regurgitation as well as dilation of the proximal aorta and was observed in patient with BAV type 1 LR [10, 79]. These WAMBIRE phenotype is supported by investigations of Lad et al., who reported on 29 BAV patients needing concomitant mitral surgery and presenting with aortic annular dilation. Further investigations by Charitos et al. [80] provided evidence that patients with BAV suffer more often from elongated anterior mitral leaflet compared to patients with TAV.

Bringing together these manifold aspects of surgical considerations in BAV aortopathy, "size" or diameter as sole parameter considered in the decision process whether to replace the aorta in patients with BAV is insufficient. The clinical heterogeneity of BAV aortopathy necessitates an individualized approach in every patient considering patient's specific characteristics. The feasibility and excellent outcome of such an individualized approach is underlined by Sievers and colleagues, who realized a

multifactorial approach to aortic resection in BAV aortopathy with regard to the mode of BAV failure (stenosis and regurgitation) and BAV phenotype [81]. We agree with Fedak and Verma that "the current guidelines for aortic resection in patients with BAV aortopathy are too simple" [82] to cover the diversity of this burdensome disease.

Compliance with ethical standards

Conflict of interest Hans-Hinrich Sievers receive royalties from B. Braun Melsungen (Germany) for Sinus prosthesis.

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