Towards an individualized approach to bicuspid aortopathy: different valve types have unique determinants of aortic dilatation†

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Abstract

OBJECTIVES: Bicuspid aortic valve (BAV)-related aortopathy is increasingly recognized to be a heterogeneous disease entity, although the surgical approach, from indications to techniques, is still standard rather than individualized. We aimed to define the determinants of aortic dilatation in BAV patients stratified according to the valve morphotype.

METHODS: A consecutive echocardiographic series of 622 BAV patients was analysed. Among demographic (age, sex), anthropometric (height, weight, body surface area, body mass index), clinical (associated diseases) and echocardiographic variables (valve function, ventricular parameters), the determinants of aortic root and ascending tract diameter were assessed by multivariate regression models, as well as the predictors of aortic dilatation (size index \(> 2.1 \text{ cm/m}^2\)) both in the overall population and separately in groups of different valve morphotypes (RL, right–left fusion; RN, right–non-coronary fusion).

RESULTS: Independent determinants of aortic root diameter (at sinuses) were age \((P < 0.001)\), significant aortic regurgitation \((P < 0.001)\), sex (female protective, \(P < 0.001)\) and valve morphotype (RN protective, \(P < 0.001)\). Independent determinants of ascending aortic diameter (tubular tract) were age \((P < 0.001)\), RN morphotype \((P < 0.001)\), body mass index \((P = 0.005)\) and chronic obstructive pulmonary disease \((P < 0.001)\). In univariate analysis, the RL morphotype was associated with dilatation (ASI > 2.1 cm/m²) at sinuses in 41% cases vs 22% for RN (\(P < 0.001\)), and the RN morphotype was associated with dilatation at the tubular tract in 68 vs 56% for RL (\(P = 0.007\)). The presence of root dilatation was predicted by age and absence of significant stenosis in the RL morphotype subgroup, and by severe regurgitation in the RN subgroup. In the RL-type subgroup, non-regurgitant aortic valve and chronic lung disease predicted dilatation at the ascending level, and in the RN-type subgroup, age and obesity.

CONCLUSIONS: The two most common BAV morphotypes are associated with aortic dilatation at two different tracts (RL at the root; RN at the tubular ascending tract) independently of valve function. Moreover, the determinants of aortic dilatation were at least in part different between the two morphotypes: this may provide stratification criteria for individualized methods of follow-up and treatment.

Keywords: Bicuspid aortic valve • Aorta • Aortic dilatation • Aortic diameters • Echocardiography • Determinants

INTRODUCTION

Under the single descriptor of ‘bicuspid aortic valve’ (BAV), a number of different morphological variants of the most common cardiac malformation are included. BAVs can anatomically vary in terms of which leaflets are fused together, whether a raphe is present or not, whether an indentation is found at the seam site between the margins of the conjoined leaflets, where the commissures are respectively located and to what extent the interleaflet triangle subtended by the raphe is obliterated [1, 2]. Whether this anatomical heterogeneity can be linked to the peculiar variability in the clinical manifestations of the associated valvar and aortic morbidity has been recently discussed by many authors, though with discordant results [3, 4].

An important recent survey among Canadian cardiac surgeons has revealed the existence of remarkable gaps between most up-to-date knowledge, guidelines and clinical practice with BAV aortopathy [5]. Of note, only 15% of the respondents got the notion that the pattern of valve leaflet fusion is associated with a unique pattern of aortic dilatation [5]. Nevertheless, the first attempts to investigate such association in the clinical setting date back at least 10 years [6].

The interest in possible correlations between valve type and risk or features of the associated aortopathy is fed by the outlook of improving the current level of individualization of clinical and surgical management in BAV patients [7]. The fact that some BAV patients can present severe forms of the aortopathy, with early onset in life [8], higher risk of acute complications such as aortic dissection [9],

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clear familiarity for aortopathy or subtle aortic alterations in non-BAV relatives [10], has led to greater general aggressiveness towards all forms of BAV-related aortopathy. However, this posture has been authoritatively criticized as being not based on a reasonable level of clinical evidence [11, 12], as the majority of BAV patients show a much less severe natural course [12]; the debate will only be definitively placated when our ability to stratify BAV patients will improve, so that indications will be less subjective and more individualized. Therefore, among the most important tasks at hand for the research in this field is to define and validate tools and criteria for risk stratification, in order to more rationally guide surgical management. In this perspective, we aimed to define the determinants of aortic dilatation in a large echocardiographic series of BAV patients stratified for the valve morphotype.

MATERIALS AND METHODS

Patients

The BAV database of our outpatient and perioperative echocardiography service includes all transthoracic and transoesophageal echocardiographic examinations performed in patients with BAV (either diagnosed by echocardiography itself or later on at surgical inspection of the leaflets, sinuses and inter-leaflet triangles [2]) along with their clinical data. For the present study, patients with rare valve morphologies (left-non-coronary leaflet fusion, unicuspid or quadricuspid aortic valve), associated significant congenital or acquired cardiac diseases (e.g. >mild dysfunction of another valve, cardiomyopathies, endocarditis, untreated or recurrent coarctation), aortic dissection, systemic syndromes (Marfan, Loeys-Dietz, Ehler-Danlos, Turner etc.) or previous cardiac surgery (except for successful coarctation repair) were excluded. From the remaining 692 BAV patients, all those with undoubted description of the valve morphology in terms of the leaflet fusion pattern (n = 622) were selected. The study was approved by the local Institutional Review Board.

Variables

Three experienced operators performed all echocardiographic examinations. Bicuspidity of the aortic valve was defined by systolic fish-mouth appearance of the orifice in parasternal short-axis views [13]. Valve morphotype, i.e. the pattern of leaflet fusion, was categorized as RL (fusion between right and left coronary leaflets), RN (between right and non-coronary leaflets) and LN (left and non-coronary). Aortic stenosis severity was graded by the integration of Doppler methods, continuity equation and planimetry; aortic regurgitation degree was defined by composite evaluation of proximal jet width, abdominal aortic Doppler and left ventricular end-diastolic dimension [14]. Several valve function variables were defined, as previously described [14] (see Supplementary material).

The aorta was measured at least twice (inner-edge method) by bidimensional imaging in parasternal long-axis views, at the root (maximal dilatation of the sinuses of Valsalva), sinotubular junction (STJ) and ascending aorta (at the right pulmonary artery level). When needed, aortic measurements were repeated ‘offline’ to get full consistency of methods throughout the present study. Aortic dilatation was defined according to the widely adopted criterion of an aortic size index (ASI) >2.1 cm/m² [5, 15, 16]. The complete list of variables considered in the analysis is shown in the Supplementary material.

Statistical analysis

Continuous variables, after assessment of normal distribution, were summarized as mean ± SD and compared between two and more groups, respectively, through an unpaired t-test and ANOVA (the latter with Bonferroni post hoc correction). Categorical variables were presented as a count (percentage) and compared by a χ² test (with Fisher’s exact test, whenever the expected cell count in a contingency table was <5). Correlation analyses between pairs of linear variables were performed by Pearson’s test. Multivariable linear regressions were performed with the stepwise method (stepping criteria: F probability <0.05 for entry, >0.1 for removal), to find the determinants of aortic diameter at the root and tubular ascending tract separately, both in the overall population and in subgroups of valve morphotype (RL and RN), and to rule out the effect of a possible referral bias, in subgroups of valve function (normal, stenosis/regurgitation). Binary logistic regression multivariable models with forward stepping (same criteria as above) were developed to identify independent predictors of dilatation of the root and of the tubular tract separately. Both in linear and in logistic regression models, those variables (from the list in the Supplementary material) showing significant association with the response variable in univariate analysis were included as covariates. Analysis was performed through the SPSS statistical software (ver16.0); the significance level was set at P (two-tailed) <0.05 for all tests.

RESULTS

Morphotype-related differences in study population characteristics

The mean age in the overall study population was 48 ± 16 years. The male/female ratio was 2.9: 1. In 225 patients (36%) the valve was normally functioning, in 221 (35%) it was predominantly stenotic and in 176 (28%) it was regurgitant. As far as valve morphotype is concerned, 433 patients had an RL type (69.6%) and 189 an RN type (30.4%). The RN morphotype was associated with slightly older age, greater prevalence of female sex, aortic valve stenosis and prolapsing/myxomatous mitral valve, thicker inter-ventricular septum, smaller aortic diameter at sinuses and STJ (Table 1). RL morphotype patients presented with dilatation (ASI >2.1 cm²/m²) at sinuses in 41% cases vs 22% for RN (P < 0.001), whereas RN morphotype patients had dilatation at the tubular tract in 68 vs 56% for RL (P = 0.007); after stratifying by valve function, the difference in root dilatation prevalence was significant in the normal function (P = 0.039) and stenosis (P = 0.001) strata, and the difference in the ascending dilatation prevalence reached significance in the stenosis (P = 0.046) and regurgitation (P = 0.02) strata (Fig. 1).

Determinants of the aortic diameters

The root diameter was significantly greater in male subjects (37 ± 6 vs 33 ± 5 mm, P < 0.001), in patients with the RL valve type (Table 1), with chronic obstructive pulmonary disease (COPD) (39 ± 7 vs 36 ± 6 mm, P = 0.002) and with hypertension (38 ± 6 vs 36 ± 6 mm, P = 0.001), and it was significantly smaller when the predominant valve dysfunction was due to stenosis (34 ± 5 vs 37 ± 6 mm normo-functional, vs 38 ± 6 mm regurgitant, P < 0.001) and in patients with a myxomatous mitral valve (35 ± 5 vs 37 ± 6 mm,
shows the increase in the mean ascending diameter with increase to determine root diameter also in veri
for valve function.

|Table 1: Comparison between BAV patients with RL and RN valve morphotypes (column percentages presented) |
|---|---|---|
|RL (n = 433) | RN (n = 189) | P |
| **Age (years)** | 47 ± 17 | 50 ± 16 | 0.046 |
| **Sex (male)** | 100 (23%) | 61 (32%) | 0.022 |
| **Body surface area (m²)** | 1.85 ± 0.2 | 1.83 ± 0.2 | 0.26 |
| **Valve function** | | | |
| Normal (mild dysfunction) | 189 (44%) | 36 (19%) | <0.0001 |
| Predominant stenosis (≥moderate) | 130 (30%) | 91 (48%) | |
| Predominant regurgitation (≥moderate) | 114 (26%) | 62 (33%) | |
| **Severe BAV stenosis** | 82 (19%) | 64 (34%) | <0.0001 |
| **Severe BAV regurgitation** | 66 (15%) | 28 (15%) | 0.90 |
| **Ejection fraction (%)** | 59 ± 6 | 58 ± 7 | 0.10 |
| **LVEdD (mm)** | 54 ± 8 | 54 ± 7 | 0.92 |
| **IVSTD (mm)** | 11 ± 2 | 12 ± 2 | 0.01 |
| **COPD (31 %)** | 77 (18%) | 37 (20%) | 0.42 |
| **Hypertension** | 72 (17%) | 37 (20%) | 0.88 |
| **BMI** | 1.85 ± 0.2 | 1.83 ± 0.2 | 0.26 |
| **Age (years)** | 47 ± 17 | 50 ± 16 | 0.016 |

aData needed to calculate the size index were missing in 40 patients.

The tubular ascending tract diameter also was greater in male 

In a previous study by the present authors [14], the phenotypic heterogeneity of the aortopathy associated with BAV was underscored: that was the first time in the literature that the segmental nature of BAV aortopathy was systematized, moreover suggesting that dilata
tions of different tracts of the ascending aorta may have distinctive determining factors. Such evidence has since contributed to shed some light on previous inconsistencies and uncertainties of clinical and surgical relevance. As an example, a widespread belief that 
aortic valve replacement (AVR) would not arrest or favourably affect the postoperative progression of an initial dilatation of the aorta 
had been derived from small studies with no phenotypic stratifica
tion [17]. Nevertheless, more recently, it has been demonstrated that patients with root phenotype aortopathy (usually associated with significant aortic valve regurgitation) do have an increased risk of aortic events in their post-AVR follow-up, but the more frequent ascending phenotype, associated with stenosis, is characterized by a nearly null rate of complications related to progression of the aortopathy [9]. The above-mentioned study by the present group [14], however, omitted valve morphology among the variables tested for possible association with risk and features of BAV-related aortic dilatation. The present analysis established in a larger BAV patient population that the valve morphology is a relevant information that can improve the phenotypic definition of the disease. Previous smaller studies either found similar association of RL type with root dilatation and RN type with ascending dilatation [18, 19], like the

**Predictors of aortic dilatation**

Univariate significant associations with aortic dilatation at the sinuses and at the tubular tract are shown in Tables 2 and 3, respectively.

When logistic regression models were developed to determine predicted dilatation at the root level (R² = 0.45), then age (OR: 1.04; 95% CI: 1.02, 1.06; P < 0.001), RL morphotype (OR: 4; 95% CI: 2.3, 6.6; P < 0.001) and predominant aortic regurgitation (OR: 2.7; 95% CI: 1.6, 4.8; P < 0.001) emerged.

In the RL-type subgroup, only the predictor was age (OR: 1.03; 95% CI: 1.01, 1.05; P = 0.002), whereas moderate or greater stenosis was a protective factor (OR: 0.36; 95% CI: 0.16–0.81; P = 0.013). In the RN-type subgroup, only severe regurgitation independently predicted root dilatation (OR: 4.9; 95% CI: 1.2–19.2; P = 0.023).

In logistic regression models predicting dilatation (ASI > 2.1 cm²/m²) at the level of the tubular ascending aorta (R² = 0.50), the predictors were age (OR: 1.03; 95% CI: 1.01, 1.05; P < 0.001), RL morphotype (OR: 2.59; 95% CI: 1.5, 4.4; P < 0.001), degree of stenosis (OR: 2.43; 95% CI: 1.28, 5.84; P = 0.024) and COPD (OR: 3.62; 95% CI: 1.29–10.1; P = 0.014).

In the RL-type subgroup, non-regurgitant predominant valve functional status, i.e. normal or stenotic function of the valve (OR: 5.9; 95% CI: 2, 16.7; P = 0.01), and severe stenosis (OR: 2.7; 95% CI: 1.5, 4.4; P < 0.001) were negative predictors. All predictors (except those related to valve function) were confirmed to determine root diameter also in verification models stratified for valve function.

The tubular ascending tract diameter also was greater in male subjects (42 ± 8 vs 40 ± 9 mm, P = 0.035), in patients with the RN type of BAV (Table 1), with COPD (47 ± 8 vs 41 ± 9 mm, P < 0.001), with hypertension (45 ± 9 vs 41 ± 8 mm, P = 0.001) and with obesity (44 ± 8 vs 42 ± 9 mm, P = 0.006). The most significant correlations with the ascending diameter were found for age (r = 0.37, P < 0.001) and BMI (r = 0.24, P < 0.001). Figure 2 shows the increase in the mean ascending diameter with increase in age class. Multivariate determinants (R² = 0.32) of ascending diameter included: age (coefficient: 0.015; 95% CI: 0.010, 0.019;
present one, or failed to observe significant relations [6, 20, 21]. In the present series, no significant difference between RL and RN was observed in terms of aortic dilatation at any site (bottom row in Table 1), underscoring that the morphotype may affect the preferential site of the dilatation, more than the risk of aortopathy.

Are all bicuspid aortic valves equal?

The type of leaflet fusion in BAV is believed to be most probably genetically determined: abnormalities in different molecular pathways, causing defective development of the valve in distinct embryogenetic phases (endocardial cushion formation and outflow tract septation for the RN and RL types, respectively) have been suggested in experimental studies on animal models [22], inferring that disparate genetic defects may subord the two valve types. Intriguingly, a recent family-based study found that the two main morphotypes (RL and RN) could be inherited interchangeably in families with more than 1 case of BAV, an evidence arguing against the above inferences from morpho-embryogenetic studies [23]. Thus, whether the two morphotypes share a common genetic substrate or not is still unclear, and the present finding that the two valve types are associated with distinct patterns of aortic dilatation could be either of genetic origin or haemodynamic in nature. As a matter of fact, in recent 4D flow magnetic resonance imaging (MRI) studies, different local flow abnormalities have been shown to be associated with the different leaflet fusion patterns [24]; in particular, unlike at the ascending tract, where average systolic wall shear stress with RL and RN BAVs reached similar magnitudes, higher shear stress values were computed with RL-type BAV at the more proximal tract of the aorta [24]. This is consistent with the finding in the present study of dilatation at the root being almost twice more frequent with the RL fusion pattern compared with the other valve type. Of note, the RN morphotype here proved to be a protective factor for dilatation at the root level, using quite a strict dimensional cut-off for definition of dilatation (indexed diameter >2.1 cm/m²). The greater rotational flow and consistently higher in-plane shear stress in cross sections at the tubular level observed in RN BAVs [24] are similarly concordant with the present finding of higher prevalence of ascending tract dilatation compared with RL BAVs. These evidences altogether call for systematic stratification of BAV patients according to valve morphotype in any type of investigation, from pathobiology to clinical studies. Rather than trying to establish whether the aortopathy has a genetic origin or a haemodynamic driving factor, a question that is probably nonsense in the clinical setting, as both factors are most likely to coexist [25], the research on

Figure 1: Prevalence of aortic dilatation in RL and RN patients stratified for valve function: (A) at the root level; (B) at the tubular ascending level. Asterisks indicate RN subgroups showing significant (P < 0.05) differences in dilatation prevalence compared with the respective RL subgroups. Note that, in all three strata, the RN-BAV patient subsets showed greater prevalence of ascending tract dilatation and lower prevalence of root tract dilatation compared with the RL-BAV counterparts.
BAV should focus on gaining the ability to discern case-by-case the prognostically most severe forms (Marfan-like) from the more frequent slow-progressing disease [9, 12, 25]. For this purpose similarly important, may be to stratify the BAV aortopathy population according to the phenotype of aortic dilatation [14]. Russo et al. [4] found in a morphological study that histopathological changes in the aneurysmal ascending aorta were more severe with RL-BAVs compared with RN-BAVs. However, the authors stated that the wall samples were taken from the level of maximal dilatation, without specifying which proportion of the RL patients had a dilatation of the root tract as opposed to the ascending tract [14, 18–21], thus, it could not be discerned whether the more severe wall changes were linked to the valve type or were inherent to the aortic phenotype [14].

Towards improved risk stratification

In previous studies, dilatation of the mid-ascending aorta was associated with BAV stenosis, which was conversely a protective factor for dilatation of the root [14, 19]; this was confirmed in the present analysis in a larger cohort. Valve function was significantly different between the two patient groups, with stenosis being the most frequent status for RN valves followed by regurgitation, whereas normal function was the most frequent for RL valves, followed by stenosis (Table 1). However, the association between valve morphotypes and respective preferential locations of aortic dilatation proved to at least part independent of the functional status (Fig. 1), as confirmed by multivariable analysis. Also the differences between the RN and RL morphotype patients in terms of mean diameter changes with increasing age suggested a different behaviour of the underlying degenerative process. The increase in aortic diameter with age was steeper at the ascending level with age was steeper at the ascending level with the mean root diameter measurement

### Table 2: Univariate correlates of aortic dilatation at the root level (column percentages presented)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>With dilatation at sinuses (n = 204)*</th>
<th>Without dilatation at sinuses (n = 378)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 18</td>
<td>54 ± 15</td>
<td>45 ± 16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>18–29</td>
<td>48 (24%)</td>
<td>102 (27%)</td>
<td>0.42</td>
</tr>
<tr>
<td>30–39</td>
<td>26 ± 4</td>
<td>27 ± 4</td>
<td>0.04</td>
</tr>
<tr>
<td>40–49</td>
<td>166 (81%)</td>
<td>243 (64%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>50–59</td>
<td>38 (19%)</td>
<td>135 (36%)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 60</td>
<td>83 (41%)</td>
<td>128 (34%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Predominant stenosis</td>
<td>53 (26%)</td>
<td>158 (42%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Predominant regurgitation</td>
<td>68 (33%)</td>
<td>92 (24%)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Data needed for size index calculation were missing in 40 patients. COPD: chronic obstructive pulmonary disease; IVSTd: interventricular septum diastolic thickness; LVEDd: left ventricular end-diastolic diameter.

was more homogeneous throughout age classes in RN-BAV patients, and, furthermore, showed an inverted trend when compared with the RL group, with a minor increase between ages 18 and 40 and a relatively greater increment thereafter (Fig. 2).

In the RL subgroup, an ascending indexed dimension exceeding 2.1 cm/m² was not predicted by age, and aortic regurgitation was a protective factor because of the significantly greater prevalence of dilatation in the subsets of RL-BAV patients with normal valve function or stenosis (Fig. 1). Some RL-BAV patients can indeed present with varying degrees of ascending tract dilatation even with a normally functioning valve and at an early age, suggesting the existence of genetically determined forms of aortopathy in this group [13]. Conversely, in the RN-BAV patient subgroup age did predict ascending dilatation: this finding, along with the evidence of a predilection of the ectasia for ascending tubular tract location in the RN-BAV group with usual sparing of the root tract (the typical morphology of ‘post-stenotic dilatation’) might suggest a greater prevalence of haemodynamically determined aortopathy forms within the RN-BAV population compared with RL-BAV.

All the above insights could be of clinical relevance, as the frequency of imaging controls, the need for familial screening, possible medical therapy, aggressiveness in surgical indications and extension...
of aortic resection at the time of operation might be decided taking the patient's valve morphotype into account along with other clinical-anatomical factors. Surely, further stratification is possible within each morphotype, especially in the more common RL type: in this group, the relations between age, valve function, other clinical features and location of aortic dilatation were more heterogeneous than in the RN-BAV group. We have recently observed that a novel MRI parameter (i.e. 'cusp opening angle') aimed at assessing the degree of sub-clinical functional derangement of valve function (i.e. restriction of the systolic opening excursion of the fused leaflet) can predict the growth rate of the aorta at the ascending tract in patients with RL BAV type with normal echocardiographic function and diameter [25]. Also 4D flow MRI promises to prove useful in further stratifying BAV patients on the basis of local flow disturbances [24] these functional imaging parameters could be considered in determining whether the degree of aortic dilatation observed in the individual BAV patients could be sufficiently explained by the unique sub-clinical biomechanical alterations occurring in their aorta, or whether a genetic predisposition may play a major role. When such novel metrics will be validated as prognostic markers and hopefully also genetic predictors of aortopathy will be available, multiple aspects of our management approach to the BAV patient are expected to importantly change.

**Limitations of the study**

This was not a population-based study; therefore, it suffered from the common limitations of retrospective, outpatient-based studies performed at secondary and tertiary referral centres. In particular, as in previous studies [6], this could affect the observed relations between valve function and aortic dilatation prevalence, as aortic surgery patients or those in follow-up for aortic dilatation follow distinct channels of enrolment compared with patients presenting with symptoms of valve dysfunction. However, we confirmed the main results of the analysis (i.e. the significant independent associations between valve morphotypes and aortic dilatation prevalence at either location) separately in two patient subgroups, one referred for symptoms, the other for known dilatation/accidental finding (data not shown).

The limited $R^2$ values of our multivariate analyses demonstrate that, as however expected, the variability in the phenomenon, i.e. dilatation of either tract of the aorta, is not fully explained by the determinants emerging from the models. Several other anatomical features of BAV can vary and possibly be associated with the variability of risk and features of the aortopathy, e.g. we did not distinguish between valves with and without raphe. However, other studies that have included this categorization did not find it to be associated with any significant difference in the pattern of aortic dilatation [19, 20]. Also, several other non-anatomical factors (e.g. refined haemodynamic parameters) could not be included in the analysis due to its retrospective nature, which might have improved the predictive power of our multivariable analysis.

Finally, given its cross-sectional nature, investigating the impact of the valve morphotype on the progression of the aortic disease was beyond the aim of this study.

**CONCLUSIONS**

The main result of the present analysis on a large BAV patient population undergoing echocardiography was the evidence of an independent association between the valve morphotype (pattern of leaflet fusion) and the preferential dilatation of one segment of the ascending aorta (root or tubular tract). Consistently, the two valve types have been recently demonstrated to imply different flow patterns in the ascending aorta and spatially different stress patterns on the aortic wall [24]. However, it could also be hypothesized that inherent genetically determined differences exist in the susceptibility of the ascending aortic wall to the biomechanical cues at different segments, so that both factors act in concert to drive the degenerative process underlying dilatation. In addition, the evidence that dilatation is independently predicted by clinical factors, at least in part, distinct between the two BAV types calls for an effort to stratify patients according to the valve morphotype in research studies on BAV disease as well as in the decision-making process in everyday clinical and surgical approach to the associated aortopathy.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available at EJCTS online.
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