Bicuspid aortic valve leaflet morphology in relation to aortic root morphology: a study of 300 patients undergoing open-heart surgery

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Abstract

Objective: There is an ongoing discussion regarding the mechanism of aortic dilatation in bicuspid aortic valve (BAV) disease, that is, is this a hemodynamic effect or related to an inborn weakness of the aortic wall? This study evaluated the possibility of BAV morphology being related to ascending aorta morphology as such a correlation would strengthen the idea that hemodynamic alterations cause the dilatation of the aorta.

Methods: The morphology of the ascending aorta of 300 patients admitted for aortic valve and/or ascending aorta disease was evaluated by echocardiography and related to the surgeon’s inspection of the aortic valve.

Results: A tricuspid aortic valve (TAV), BAV, or unicuspid aortic valve (UAV) was present in 130, 160, and 10 patients, respectively. Ascending aortic aneurysm was more common in patients with BAV compared with TAV (36% and 12%, respectively; \( p < 0.001 \)), while ectasia of the aorta was similarly common (8% in both groups). Aortic stenosis or regurgitation was equally distributed in TAV and BAV patients with normal aortas (\( p = 0.82 \)). When the aorta was dilated, aortic stenosis was predominantly associated with BAV (BAV 56%, TAV 4%; \( p < 0.001 \)), while aortic regurgitation was more common in TAV (TAV 81%, BAV 29%; \( p < 0.001 \)). In BAV patients, fusion of the right- and left coronary cusp was predominant (74%) followed by right- and non-crownery cusp fusion (14%) and true BAV (fusion of the right- and left coronary cusp without remnant raphe; 11%) (\( p < 0.001 \)). The relative distribution of ascending aortic aneurysm or ectasia was similar in all morphologically different BAV (\( p = 0.95 \)).

Conclusions: In our study population, >50% of the patients admitted for surgery had a bicuspid aortic valve. Aortic aneurysm was more common in BAV than in TAV patients. Aortic stenosis and aortic regurgitation were equally common in TAV and BAV with normal aortic dimensions, while aortic regurgitation was predominant in TAV with dilated aortas and aortic stenosis in BAV with dilated aortas. Dilatation of the aorta was similarly distributed regardless of BAV leaflet morphology. These findings support the idea of an intrinsic mechanisms underlying dilatation of the aorta in BAV patients.

Keywords: Bicuspid aortic valve; Aneurysm; Ectasia; Aortic stenosis; Aortic regurgitation

1. Introduction

Bicuspid aortic valve (BAV) is a commonly present cardiac malformation appearing in 1–2% of the population. BAV has a high incidence of valvular lesions such as aortic regurgitation and aortic stenosis as well as numerous associated cardiovascular aberrations, including coarctation and hypoplasia of the aorta, ventricular septum defect, and changes in coronary artery anatomy [1].

A common phenomenon observed in patients with BAV is dilatation of the aorta, and BAV patients have an increased risk of aortic aneurysm and dissection. This increased risk is probably not associated with the valve itself, since aortic valve replacement does not protect from later aortic dilatation or dissection [2,3].

Although there is an abundance of evidence suggesting a genetic component in BAV [1], to what extent the changes in the ascending aorta are related to inherent genetic mechanisms associated with the BAV, or represent a mechanical phenomenon due to the structural changes in the valve causing altered hemodynamics, remains unclear [2,4–6].

Suggesting a predominant hemodynamic effect is (1) dissection in BAV is strongly associated with hypertension and atherosclerosis, (2) aortic valve disease in tricuspid aortic valve (TAV) patients can be accompanied by aortic dilatation, and (3) morphological changes in the aortic wall (medial...
Patients with aortic valve and ascending aortic disease (operated on between February 2007 and December 2009) in Sweden. In this study, we have evaluated 300 operated patients for other concomitant valve surgery. If no correlation can be found between different morphologically distinct BAV patterns and the morphology of the aortic root, this would strengthen the idea of an inherent tissue weakness as the primary cause of the aortic dilatation observed in BAV patients. Furthermore, detection of an association between a distinct BAV leaflet morphology and changes in the aortic root would be important in choosing the appropriate surgical technique (i.e., more liberal replacement of the ascending aorta) at the time of surgery.

2. Materials and methods

2.1. Patient population

The Advanced Study of Aortic Pathology (ASAP) is a prospective, single-center, observational cohort study of patients with aortic valve and ascending aortic disease undergoing elective open-heart surgery at the Cardiothoracic Surgery Unit, Karolinska University Hospital in Stockholm, Sweden.

Inclusion criteria are patients aged 18 or above with aortic valve disease (i.e., aortic stenosis; AS or regurgitation; AR) and/or ascending aorta dilatation (aneurysm; A or ectasia; E) of the ascending aorta including the aortic root) but devoid of coronary artery disease (defined as lacking significant stenosis on coronary angiogram) and primarily not planned for other concomitant valve surgery.

In this study, we have evaluated 300 operated patients (operated on between February 2007 and December 2009) in terms of aortic valve morphology in relation to aortic root morphology. Patient demographics are given in Table 1.

2.2. Indications for surgery

According to the indications for surgery, the patients were classified into five groups: aortic valve stenosis (AS, 145 patients); ascending aortic aneurysm and AS (AAA + AS, 44 patients); aortic valve regurgitation (AR, 53 patients); ascending aortic aneurysm and AR (AAA + AR, 42 patients); and ascending aortic aneurysm (AAA, 16 patients).

Additional diagnoses were patent foramen ovale (11 patients), severe mitral regurgitation (three patients), tricuspid regurgitation (one patient), ischemic heart disease (one patient), and subaortic stenosis (two patients). One patient had Marfan’s disease (tricuspid aortic valve and aortic aneurysm).

2.3. Surgical procedure

All patients were operated on through a midline sternotomy using cardiopulmonary bypass with a centrifugal pump (BP 80, Biomedicus Biomed, Houston, TX, USA) and a membrane oxygenator (Affinity, Medtronic Inc., Minneapolis, MN, USA) primed with Ringers solution. Cardiac arrest was achieved with cardioplegia solution mixed 1:4 with blood and delivered at a temperature of 4 °C.

In the isolated aortic valve replacement group, a biological valve prosthesis was used in 137 out of 192 patients and a mechanical valve in 55 patients. A tubular graft prosthesis was used in 40 patients, either for isolated ascending aorta replacement with (n = 8) or without aortic valve repair (n = 15), or for replacement of the aortic root in a valve sparing David procedure with (n = 6) or without (n = 11) additional repair of the aortic valve. A tubular graft was further used in combination with a separate mechanical (n = 7) or biological (n = 17) prosthesis. Aortic root bioprosthetic replacement (Medtronic Freestyle®, Medtronic Inc., Minneapolis, MN, USA), alone (five patients) or in combination with tubular (n = 15) graft, was used in 20 patients. Aortic root replacement with a mechanical composite graft (St. Jude Medical® Valved graft — St. Jude Medical, Inc., St. Paul, MN, USA) was used in 15 cases and isolated aortic valve repair was performed in nine patients.

Other concomitant surgical procedures included cryoblation therapy for atrial fibrillation (20 cases), patent foramen ovale closure (11 patients), mitral valve repair (three patients), tricuspid valve repair (one patient), coronary artery bypass graft (one patient), and subaortic septal myectomy (two patients).

2.4. Echocardiographic evaluation

Transthoracic echocardiography (TTE) was performed preoperatively using a Philips iE33 ultrasound scanner (Philips Medical Systems, Bothell, WA, USA). Valve pathology (peak and mean valve gradients, aortic valve area, and degree of regurgitation), cardiac dimensions (left ventricular end-systolic and end-diastolic diameters), and left ventricular function were assessed. Standards outlined by the American Society of Echocardiography (ASE) [14–16] were applied for two-dimensional echocardiography and Doppler measurements. The Bernoulli equation was used to calculate the AS peak and mean transvalvular gradients and aortic valve area was calculated according to the continuity equation. Classification of AR into grades 0–4 (0 = none; 1 = mild; 2 = moderate; 3 = moderate to severe; 4 = severe) was made by means of the AR color flow jet area, vena contracta, pressure half-time, jet density, and diastolic flow reversal in the ascending aorta. Severe AS was defined as a peak
gradient of >50 mmHg and/or a mean gradient of >40 mmHg and/or an aortic valve area <1.0 cm² regardless of AR grade. Patients with combined AS and AR were classified as AS since the AR in these cases is primarily a consequence of the AS and this is also the rationale for the deviation from current recommendations in setting the cut-off value of peak gradient as above and not to >64 mmHg which would correspond to an aortic jet velocity of >4.0 m s⁻¹. Of the 300 patients, seven were not preoperatively assessed by TTE due to logistic reasons and were therefore not included in the analyses (five patients had previously been diagnosed with AS and two patients with AR grade 3/4).

Prior to surgery, transesophageal echocardiography (TEE) was performed on all patients on the operating table under general anesthesia, as previously described [17]. Of the 160 patients with BAV, one patient was not examined by TEE intra-operatively due to logistic reasons. The TEE evaluation was used to assess the aortic root morphology and the ascending aorta; the measurements were performed according to standards outlined by the ASE. A Siemens Sequoia c 512 ultrasound scanner (Siemens medical Systems, Mountain View, CA, USA) equipped with a 7-MHz multiplane transducer was used and image quality was optimized by adjustment of gain, depth, and sector width. The radial artery was used for invasive measurement of blood pressure simultaneous to the acquisition of the TEE images. Electrocardiogram (ECG) was recorded and displayed on the ultrasound images.

2.5. Definitions

2.5.1. Aortic root morphology

All TEE examinations of the aorta were analyzed by one experienced echocardiographer. Measurements were obtained from the left ventricular outflow tract (LVOT) at systole, while dimensions of the aortic annulus, sinus of Valsalva (SV), sinotubular junction (STJ), ascending aorta 40 mm above the annulus (AA 40), ascending aorta at maximal observed diameter (AA max), and the aortic root height (the distance from the annulus to the STJ) were measured in diastole.

Three distinct aortic morphological patterns were observed [13] (Fig. 1): normal aorta (N): SV > STJ and maximal diameter of the aorta ≤ 40 mm (BAV) or ≤ 45 mm (TAV); aneurysm of the aorta (A): SV > STJ and maximal diameter of the aorta > 40 mm (BAV) or > 45 mm (TAV) regardless of position, that is, aortic root or ascending aorta; ectasia of the aorta (E): SV ≤ STJ and always associated with dilatation of the aorta.

2.5.2. Aortic valve morphology

The morphology of the aortic valve was evaluated by inspection of the valve during surgery. Based on appearance, the valve was classified according to number of cusps and commissures. Three cusps and three commissures denote a ‘tricuspid’ valve; two cusps and two commissures denote a ‘bicuspid’ valve (if a remnant commissural raphe was present) or ‘true bicuspid’ valve (if no raphe was present; Fig. 2); a single cusp and a single commissure denote a ‘unicuspid’ valve.
2.6. Statistical analysis

The chi-square test was used to analyze a selection of data from Table 1. The data for Table 3 and 4 were analyzed using two-way analysis of variance (ANOVA), with two-between-group factors and the interaction between the factors using the Statistica 9.0, StatSoft® (Inc. Tulsa, OK, USA) software. The factors in Table 3 are ‘cusps’ with two levels (TAV and BAV) and ‘ascending aorta’ with three levels (normal aorta, aneurysm, and ectasia). The factors in Table 4 are ‘ascending aorta’ with three levels (normal aorta, aneurysm, and ectasia) and ‘cusp morphology’ with three levels (RL, RN, and LN). In case of a significant interaction, simple main effects tests were examined, that is, effects of one factor holding the other factor fixed, otherwise contrasts between the levels of the main factors were performed. First, we performed the simple effects test of each factor within each level of the other effects. These tests are based on the linearly independent comparisons among the estimated marginal means. A multiple procedure consists of two steps. In the first step, the omnibus null hypothesis was tested with an \( F \)-test. If the \( F \)-test was not significant, no more tests were performed. If the omnibus null hypothesis was rejected by the \( F \)-test, each of the pairwise contrasts was tested at the \( \alpha \)-level of significance. Fisher’s procedure controls the familywise error rate at \( \alpha \) when the complete null hypothesis is true. \( p < 0.05 \) was considered statistically significant.

2.7. Ethical approval

The study was approved by the local Ethical Committee of the Karolinska Institutet and oral and written consent was obtained from all patients.

### 3. Results

All patients have been followed up prospectively for 1 year (of the 293 1-year survivors) with outpatient clinic visits \( (n = 289) \) or by telephone contact \( (n = 4) \). Thirty-day and 1-year mortalities were 1.7% (5/300) and 2.3% (7/300), respectively. Postoperative complications included reoperations due to bleeding 4.7% (14/300), mediastinitis 1.7% (5/300), and valve dysfunction 1% (3/300).

#### 3.1. Aortic valve morphology

Of the 300 patients operated on, 53% had a BAV, 43% a TAV, and 3% a UAV. BAV and UAV were more frequently associated with aneurysm (36% and 30%, respectively) than TAV (12%), while ectasia was equally common regardless of valve morphology (TAV 8%, BAV 8%, and UAV 10%). Thus, ascending aortic aneurysm was more common in patients with BAV (36%) compared with TAV (12%) \( (p < 0.001) \), while ectasia of the aorta was equally common (8%) in both groups (Table 2).
At the time of surgery, BAV and UAV patients were younger than TAV patients \( (p < 0.0001) \). Neither TAV nor BAV morphology influenced the relative gender distribution (Table 1).

Aortic stenosis or regurgitation was equally distributed in TAV and BAV patients with normal aortas \( (p = 0.82) \). When the aorta was dilated, aortic stenosis was predominantly associated with BAV patients while aortic regurgitation was more common in TAV patients \( (AS: BAV 56\%, TAV 4\%); AR: TAV 81\%, BAV 29\% \ (p < 0.001 in both instances) \) (Table 2).

Intra-operative open eye inspection of the valves revealed three distinct patterns of BAV with 74% RL cusp fusion and 14% RN cusp fusion and 11% true bicuspid valves. This morphological distribution was similar in all BAV patient groups regardless of normal aorta, aneurysmatic aorta, or ectasia of the aorta (normal aorta: RL 75\%, RN 13\%, true BAV 11\%; aneurysm: RL 75\%, RN 16\%, true BAV 9\%; ectasia: RL 69\%, RN 15\%, true BAV 15\%). Conversely the distribution of aorta morphology was also similar in all types of BAV configuration (RL: 57% normal aorta, 36% aneurysm, 8% ectasia; RN 52% normal aorta, 39% aneurysm, 9% ectasia; true BAV 59% normal, 29% aneurysm, 12% ectasia). Thus, in BAV patients, fusion of the right- and left coronary cusps was predominant (74%) followed by right- and non-coronary cusp fusion (14%) and true BAV (11\%) \( (p < 0.001) \), and no patient was found to have an LN fusion. Moreover, BAV morphology did not influence the distribution of aorta morphology \( (p = 0.95) \) (Table 4).

### 3.2. Aortic root morphology

BAV patients consistently demonstrated larger annular and LVOT dimensions compared with TAV patients regardless of aortic morphology \( (p < 0.001) \) (Table 3). Within the BAV group, there were minor but statistically significant differences in aortic dimensions based on RL, RN, or true BAV morphology. Thus, the maximal aortic diameter was larger in the BAV RL or RN configuration compared with true BAV when the aorta was ectatic (RL: AA max \( p = 0.003 \); AA 40 \( p = 0.004 \) and RN: AA max \( p = 0.003 \); AA 40 \( p = 0.01)\). The aortic root height was lesser in BAV RL \( (p = 0.001) \) and RN \( (p = 0.01) \) configuration in comparison with true BAV in both non-dilated and aneurysmatic aorta. Thus, the maximal aortic diameter was larger in the BAV RL or RN configuration compared with true BAV when the aorta was aneurysmatic \( (p = 0.02) \) (Table 4). No other significant morphological differences between the groups could be detected.

### 4. Discussion

In this study on patients accepted for open-heart surgery due to aortic valve disease and/or dilatation of the aorta, a BAV was present in more than 50% of the patients and dilatation of the aorta was three times more common in BAV patients compared with TAV patients \( (p < 0.001) \).

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*Table 3. Aortic valve morphology in relation to aortic morphology.*

<table>
<thead>
<tr>
<th>Aorta</th>
<th>TAV</th>
<th>BAV</th>
<th>UAV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Aneurysm</td>
<td>Ectasia</td>
</tr>
<tr>
<td>N</td>
<td>103</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>AA max</td>
<td>34 ± 5</td>
<td>50 ± 9</td>
<td>56 ± 9</td>
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<tr>
<td>AA 40</td>
<td>33 ± 5</td>
<td>45 ± 9</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>Root height</td>
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<td>21 ± 8</td>
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</tr>
<tr>
<td>STJ</td>
<td>27 ± 4</td>
<td>34 ± 4</td>
<td>NA</td>
</tr>
<tr>
<td>SV</td>
<td>33 ± 5</td>
<td>41 ± 7</td>
<td>45 ± 7</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>23 ± 3</td>
<td>23 ± 5</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>LVOT</td>
<td>23 ± 3</td>
<td>24 ± 4</td>
<td>25 ± 3</td>
</tr>
</tbody>
</table>

*Table 4. Bicuspid valve leaflet morphology in relation to aortic morphology.*

<table>
<thead>
<tr>
<th>BAV</th>
<th>Aorta</th>
<th>Normal</th>
<th>Aneurysm</th>
<th>Ectasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Leaflet fusion</td>
<td>RL</td>
<td>RN</td>
<td>TB</td>
</tr>
<tr>
<td>N</td>
<td>67</td>
<td>12</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>AA max</td>
<td>33 ± 4</td>
<td>35 ± 4</td>
<td>32 ± 6</td>
<td>46 ± 5</td>
</tr>
<tr>
<td>AA 40</td>
<td>32 ± 4</td>
<td>34 ± 4</td>
<td>32 ± 6</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>Root height</td>
<td>18 ± 4</td>
<td>17 ± 3</td>
<td>22 ± 6</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>STJ</td>
<td>27 ± 3</td>
<td>27 ± 4</td>
<td>27 ± 6</td>
<td>32 ± 5</td>
</tr>
<tr>
<td>SV</td>
<td>34 ± 4</td>
<td>32 ± 4</td>
<td>32 ± 6</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>24 ± 4</td>
<td>24 ± 3</td>
<td>23 ± 4</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>LVOT</td>
<td>25 ± 4</td>
<td>25 ± 3</td>
<td>24 ± 4</td>
<td>25 ± 3</td>
</tr>
</tbody>
</table>

*Patients assessed by TEE. Data is presented as mean ± SD and given in frequencies or millimetres. NA = not applicable, for further abbreviations see text.*

*Statistically significant differences for RL or RN versus true BAV within each group of aortic morphology (for p-values see text).
patients than in TAV patients. Only minor differences in aortic morphology could be demonstrated with regard to the different BAV phenotypes.

BAV is present in 1–2% of the population and predisposes to aortic valve disease and aortic dilatation and dissection. The recognition of a BAV is therefore important as the timing of surgical intervention and the surgical techniques applied may differ compared with patients having TAV. It is of importance to the surgeon to know not only what to expect intra-operatively but also what to expect in the future in patients with BAV subjected to heart surgery. The contribution of BAV leaflet anatomy to the associated aortic wall dilatation has attracted considerable interest, but is unclear and contradicting. It has further been speculated that certain BAV phenotypes could be associated with a higher risk of dissection and predispose to aortic root dilatation and aortic regurgitation [20], but this remains to be shown.

The relative distribution of morphologically distinct pattern in BAV (i.e., RL and RN) observed in our study is similar to earlier reports [18]. Thus, 70–80% of BAV patients have a fused right- and left coronary cusp, while right- and non-coronary cusp fusion is less prominent and found in 20–30% of BAV patients. Considerably less common is a true BAV, which constitutes only 10% of BAV patients and left- and non-coronary cusp fusion is virtually nonexistent. Previous studies have demonstrated changes in aortic elastic properties in BAV patients [19]. This was further evaluated by Schaefer et al. [20] who showed that the BAV RL phenotype had a larger dimension and an increased wall stiffness of the aortic root compared with the RN phenotype. It was therefore speculated that differences in shear forces and pressure distribution within the aortic root had a direct impact on aortic root morphology. These findings would support the idea of hemodynamics playing a major part in the pathogenesis of BAV-related aortic dilatation. However, based on a similar classification and similar measurements we could not confirm these findings in our study, which is in accord with findings of Cecconi et al. [21].

BAV patients consistently demonstrated larger annulus and LVOT dimensions than TAV patients regardless of the presence of aneurysm or ectasia. However, no relation between BAV leaflet morphology and the frequency of aneurysm or ectasia could be established in contrast to earlier reports where BAV RL or RN configuration has been reported to be more frequently associated with dilatation of the aorta [12, 13]. Our finding that regardless of BAV phenotype the likelihood of dilatation of the aorta is similar suggests that BAV leaflet morphology may not be used to predict present or future aortic dilatation which is in contrast to the conclusions of Thanassoulis et al. [22].

Although changes in the ascending aorta can be found in nondiseased BAV, our study indicates that this is also present in nondiseased TAV (4/130 TAV patients without valve disease had aortic aneurysms; 9/160 BAV patients without valve disease had aortic aneurysms). Aortic stenosis or regurgitation was equally distributed in TAV (71% and 25%, respectively) and BAV (70% and 25%, respectively) patients with normal aortas. However, when the aorta was dilated, aortic stenosis was predominantly associated with BAV patients (BAV 56%, TAV 4%), while aortic regurgitation was more common in TAV patients (TAV 81% and BAV 29%). Thus, the distribution of aortic stenosis in BAV patients with aortic aneurysm was higher compared with aortic regurgitation (33 and 15 of 160 BAV patients had AS or AR combined with aortic aneurysm, respectively), suggesting a relation between BAV disease (stenosis/regurgitation) and ascending aortic pathology which is in agreement with earlier reports [23, 24]. This was further strengthened by the finding that AS in TAV patients with ascending aortic aneurysm was extremely rare.

In view of the ongoing discussion on the relative contribution of morphological valve changes (and related hemodynamic alterations) to the pathological dilatation of the aortic root and ascending aorta in BAV patients, we have assessed the valve morphology in relation to aortic morphology in patients being admitted for surgery. Our results confirm that BAV is more often associated with aortic aneurysm than TAV and has a larger annular diameter while the aortic root and ascending aorta morphology are similar regardless of valve type and without any relation to BAV leaflet morphology. This suggests that aortic dilatation in BAV represents a frequent and distinct entity not related to the valve itself but primarily caused by intrinsic mechanisms of the aortic wall.
4.1. Study limitations

The measurements of the aorta in this study were obtained from TEE examinations on fully anesthetized patients, hence cardiac hemodynamics, blood pressure, and loading conditions may differ compared with those of awake patients. However, TEE allows for more extensive evaluations of the aortic root and ascending aorta in comparison with standard preoperative TTE. The diameter set for classification of aneurysm in BAV and TAV patients was different (>40 mm and >45 mm, respectively) based on surgical guidelines [25], which should be considered when interpreting the relative frequency of aneurysm. Moreover, in our study all patients were accepted for open-heart surgery and may therefore not represent a true reflection of valve and aortic morphology of the nondiseased general population.

Acknowledgment

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References