Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression

Alessandro Della Corte *, 1, Ciro Bancone, Cesare Quarto, Giovanni Dialetto, Franco E. Covino, Michelangelo Scardone, Giuseppe Caianiello, Maurizio Cotrufo

Department of Cardiothoracic and Respiratory Sciences, Second University of Naples, Department of Cardiovascular Surgery and Transplant, V Monaldi Hospital, via L Bianchi, 80131 Naples, Italy

Received 14 September 2006; received in revised form 27 November 2006; accepted 4 December 2006; Available online 22 January 2007

Abstract

Objective: This study aimed to describe the features and identify the predictors of ascending aorta dilatation in patients with congenital bicuspid aortic valve (BAV). Methods: In 280 adult patients with isolated BAV undergoing echocardiography, multivariate logistic regression models, including clinical and echocardiographic variables, were developed to predict dilatation (aortic ratio exceeding 1.1) at both ascending and root level. Factors predicting aneurysm with surgical indication were also investigated. Classification tree models were used to identify factors influencing the probability of having a small aorta, normal aortic dimensions, a dilated ascending aorta or a dilated root (aortic phenotypes). Results: Aortic dilation was present in 83.2% patients, prevailing at the mid-ascending tract in 83.7% of them. Surgical indication criteria were reached in 43.2% patients. A small aortic root was found in 16 patients (5.7%), thereafter excluded from multivariate models predicting dilatation. Age (maximal risk at 50—60 years: OR = 13.7; reference category: <30 years) and severe aortic stenosis (OR = 23.8) independently predicted mid-ascending dilatation (p < 0.001). Male gender (OR = 4.1, p = 0.001), age >60 (OR = 2.6, p = 0.022) and severe regurgitation (OR = 3.9, p = 0.011) were determinants of root involvement, while stenosis (≥moderate; OR = 0.3, p < 0.001) was a protective factor. Aortic stenosis (any degree, OR = 2.4) and hypertension (OR = 4.3) were the most significant predictors of mid-ascending aneurysm reaching surgical indication. Classification analysis showed that increasing age significantly increased the prevalence of ascending dilatation phenotype, stenosis increased the prevalence of small aorta phenotype, and male gender of root dilatation phenotype. Once excluding patients with small aortas from the analysis, a positive correlation was observed between degree of stenosis and mid-ascending size (p = 0.016). Conclusions: BAV patients constitute an importantly heterogeneous population in terms of risk and features of aortic disease. The most common condition is an ectasia of the mid-ascending tract, with unaffected or mildly involved root. If further confirmed, this could suggest that surgical approach may spare the root in most BAV patients. Mid-ascending dilatation is proportional to stenosis severity, suggesting a post-stenotic causative mechanism. Root dilatation is rarer, mostly observed in younger men, and unrelated to the presence and severity of stenosis. The two different aortic dilatation phenotypes (mid-ascending and root) may be subtended by different pathogeneses.

Keywords: Bicuspid aortic valve; Aortic dilatation; Aortic valve disease; Small aortic root; Risk factors

1. Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart malformation, with a reported prevalence of 1—2% and it constitutes an important risk factor for early development of aortic valve disease [1]. Also ascending aorta dilatations, aneurysms and dissections have been shown to be particularly associated with BAV, giving rise to the theory of an underlying common congenital defect of both valve and vessel structure [2]. Alternatively, aortic dilatation has been deemed a post-stenotic phenomenon, secondary to the hemodynamic derangement accompanying BAV disease [3, 4]. One of the most important evidences in favour of the ‘genetic’ hypothesis came from echocardiographic studies demonstrating absence of statistical relation between the severity of valve stenosis and the degree of aortic dilatation [5—7]. Yet, despite extensive investigation, no clear genetic substrate and no specific pathogenetic sequence has been identified for BAV-related aortic dilation, and the evidence that post-valvular flow alterations may be underestimated in BAV by common diagnostic methods [8, 9] has been interpreted as possibly supporting the ‘hemodynamic’ hypothesis, thus leaving the debate still open.
The prevalence of aortic dilatation with BAV has been estimated between 35% and nearly 80% [5–7,10], depending on the different study populations and settings but also on the criteria employed for definition of dilatation; however, only in two of those studies were the predictors of aortic dilatation investigated in large BAV populations [6,10]. Basing on their surgical experience, many Authors [5,11,12] have incidentally expressed their impression that BAV patients constitute a heterogeneous population, including several clinical phenotypes differing each from another for risk and features of aortic dilatation, but this aspect has not been systematically addressed so far.

To verify and systematize this heterogeneity in phenotype, the present study aimed to assess prevalence and predictors of the diverse conditions of the proximal aorta that can be encountered in association with BAV.

2. Materials and methods

2.1. Inclusion criteria

All trans-thoracic and trans-esophageal examinations performed at our Institution’s Echocardiography Unit between January 1998 and January 2006 were retrospectively reviewed and those evidencing a congenital BAV in an adult subject were considered for inclusion in this study. Criteria of exclusion were: previous cardiac surgery (except for aortic coarctation repair), concomitant dysfunction (>mild degree) of other heart valves, aortic acute or chronic dissection, Marfan’s syndrome, aortic valve and/or root endocarditis, sub- or supra-valvular aortic stenosis, other congenital heart defects (including untreated coarctation or previous coarctation repair with relevant residual gradients). Patients with bicuspid morphology resulting from rheumatic commissural fusion of valve leaflets were excluded as well. Thus, 280 patients entered the study.

2.2. Echocardiography

Echocardiography was always performed by one of the same two operators (GD, FEC). The morphology of the aortic valve was defined in the parasternal short-axis views [13]. The severity of aortic stenosis was graded by integration of Doppler methods, continuity equation and planimetry, and the degree of aortic regurgitation was defined by means of standard colour-Doppler criteria. It has been routine practice at our Institution to measure, in parasternal long-axis views, aortic diameters at the sinuses of Valsalva, the sino-tubular junction and the ascending aorta (at the right pulmonary artery level, or at the level of maximal diameter, if different) in every BAV. Measurements were averaged from three subsequent estimations in stable hemodynamic conditions, according to the leading-edge method. Serial echocardiograms were available only for relatively few patients; therefore no estimation of dilation progression was attempted: for each patient the most recent examination was considered.

2.3. Study variables

Demographic variables considered were: age, codified both as a continuous and as a categorical variable (age ranks: <30 years, 30–39, 40–49, 50–59 and ≥60 years); weight; height; body surface area (BSA); gender. As regards BAV function, included variables were: degree of dysfunction (absent, trivial/mild, moderate or severe); presence of significant (at least moderate) or any degree (at least mild) dysfunction; functional status (predominant or isolated stenosis, predominant regurgitation or normal function, defined as absent or trivial/mild dysfunction). For each patient the expected normal aortic diameter was calculated on the basis of BSA and age, using the regression formulas by Roman et al. [14]; then the aortic ratio (AR), i.e. measured diameter divided by expected diameter was computed, for the root and the mid-ascending level. Aortic dilatation was defined as an AR exceeding 1.1, corresponding on average to a diameter of 3.7 cm, 2 standard deviations (SDs) above the mean expected value of the study population. According to the current surgical practice [15], an AR >1.4 defined a severe dilation, or aneurysm, indicating surgery: this corresponded averagely to a 4.5 cm diameter [16]. Moreover, on the basis of ascending and root AR values, patients were assigned to one of four subgroups of ‘aortic phenotype’: (1) normal aorta; (2) small aorta (AR < 0.9, or diameter <2.9 cm, 2 SDs below the mean normal diameter predicted for the study population); (3) ‘mid-ascending’ phenotype, consisting of dilatation at the tubular ascending portion (with normal sinuses or markedly lower dimensions at the root level; usually tapering to normal diameter just proximal to the innominate artery); (4) dilated root (flask-like dilatation, isolated or prevailing at the sinusal portion) (Fig. 1). Other considered variables were: hypertension, obstructive arterial disease (peripheral, abdominal or supra-aortic; OAD), chronic obstructive pulmonary disease (COPD), other diseases (among which mild mitral regurgitation and previous aortic coarctation repair were relatively frequent, so they were codified as separate variables), ejection fraction, end-diastolic left ventricular diameter, interventricular septum thickness.

![Fig. 1. Definition of the aortic phenotype in parasternal long-axis view: (A) normal aorta phenotype; (B) small aorta phenotype; (C) mid-ascending (or tubular tract) dilatation phenotype; (D) root dilatation phenotype.](image)
2.4. Statistical analysis

The SPSS (SPSS, Chicago, IL) software, ver. 13.0, was employed for the analysis. Continuous variables were summarized as mean ± SD and comparisons between groups were made by means of Student’s t-test or ANOVA with Bonferroni post-hoc correction; categorical variables were expressed in percentages and inter-group differences analysed using chi-square statistics. Multivariate logistic regression models were developed to find independent predictors of aortic dilatation and aneurysm at mid-ascending and root level: all the variables listed in the previous paragraph were introduced as predicting factors. To describe the clinical profiles of the different phenotype subgroups, both binary logistic regression models and classification tree models were employed. Two growing methods were used to develop classification tree models: the ‘chi-square automatic interaction detection’ (CHAID), a method capable to identify the variables that split populations into subgroups as different as possible for the response variable, and for countercheck the ‘classification and regression tree’ (CRT), a method that tends to the maximal possible homogeneity within subgroups with respect to the response variable. Some categories of the predictors can be merged by the model when they are not significantly different with respect to the response variable. Factors introduced were the same as in the previous logistic regression models; the target variable was aortic phenotype as defined above.

3. Results

3.1. Study population

BAV patients were quite homogeneously distributed in the five age ranks: 22% were 18–29-year-old, 18% were 30–39, 19% were 40–49, 23% were 50–59, and 17% were 60–77. About one fourth of the subjects were female (69 patients, 24.6%). The BAV showed substantially normal function in 39 patients, whereas it was predominantly stenotic in 33%, regurgitant in 28%. Important differences were observed between male and female patients, as shown in Table 1.

3.2. Prevalence of aortic dilatation

An aortic dilatation of any degree was present in 233 (83.2%) patients. The prevalence of dilatation at mid-ascending level tended to increase throughout the five age ranks, being 56% below 30 years, 74% between 30 and 40, 85% at 40–50, 91% at 50–60 and 88% over 60, while the prevalence of dilatation at the root level had a non-linear trend (48, 69, 52, 57 and 67%, respectively). The criterion for surgical indication was reached in 121 patients (43.2% of the population; 51.9% of the 233 patients with aortic dilatation): in 89% of them the aneurysm showed mid-ascending dimensions greater than root dimensions. Sixteen patients (5.7%) had an aorta smaller than normal.

3.3. Univariate correlates of aortic dilatation

Patients with aortic dilatation at any level were significantly older than those without any dilatation (45.6 ± 14.4 years vs 35.4 ± 15.5; p < 0.001), however this difference was not significant when root dilatation patients were compared to those with normal root (p = 0.15). Univariate correlates of dilatation (AR > 1.1) are reported in Table 2: of note, with BAV stenosis, root involvement was significantly rarer. Significant univariate correlates of mid-ascending aneurysm (AR > 1.4) were: female sex (61 vs 45% in male, p = 0.026), presence of any degree of stenosis (55 vs 43%; p = 0.037) and hypertension (64 vs 47%, p = 0.043). Univariate correlates of root aneurysm (AR > 1.4) were: male

Table 1
Features of the BAV patient population and gender-related differences

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Male (n = 211)</th>
<th>Female (n = 69)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.9 ± 15</td>
<td>42.1 ± 14.8</td>
<td>49.5 ± 14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.84 ± 0.2</td>
<td>1.89 ± 0.2</td>
<td>1.68 ± 0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BAV function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>39%</td>
<td>41%</td>
<td>30%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stenosis</td>
<td>33%</td>
<td>26%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Regurgitation</td>
<td>29%</td>
<td>33%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Stenosis (any degree)</td>
<td>54%</td>
<td>46%</td>
<td>75%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regurgitation (any degree)</td>
<td>75%</td>
<td>81%</td>
<td>54%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14%</td>
<td>15%</td>
<td>13%</td>
<td>0.45</td>
</tr>
<tr>
<td>OAD</td>
<td>4.3%</td>
<td>5.2%</td>
<td>1.4%</td>
<td>0.16</td>
</tr>
<tr>
<td>COPD</td>
<td>6.1%</td>
<td>6.2%</td>
<td>5.8%</td>
<td>0.58</td>
</tr>
<tr>
<td>Mild mitral regurgitation</td>
<td>14%</td>
<td>12%</td>
<td>17%</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous coarctation repair</td>
<td>4.6%</td>
<td>5.2%</td>
<td>2.9%</td>
<td>0.34</td>
</tr>
<tr>
<td>Ascending diameter (cm)</td>
<td>4.3 ± 0.9</td>
<td>4.3 ± 0.9</td>
<td>4.2 ± 0.7</td>
<td>0.44</td>
</tr>
<tr>
<td>Root diameter (cm)</td>
<td>3.6 ± 0.6</td>
<td>3.8 ± 0.7</td>
<td>3.3 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascending AR</td>
<td>1.34 ± 0.3</td>
<td>1.33 ± 0.3</td>
<td>1.37 ± 0.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Root AR</td>
<td>1.16 ± 0.2</td>
<td>1.19 ± 0.2</td>
<td>1.07 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dilated mid-ascending</td>
<td>78.6%</td>
<td>77%</td>
<td>83%</td>
<td>0.22</td>
</tr>
<tr>
<td>Dilated root</td>
<td>57.9%</td>
<td>65%</td>
<td>36%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mid-ascending AR &gt; 1.4</td>
<td>41.1%</td>
<td>38%</td>
<td>51%</td>
<td>0.04</td>
</tr>
<tr>
<td>Root AR &gt; 1.4</td>
<td>10.4%</td>
<td>13%</td>
<td>1.4%</td>
<td>0.002</td>
</tr>
<tr>
<td>Small aorta (AR &lt; 0.9)</td>
<td>5.7%</td>
<td>4.3%</td>
<td>10%</td>
<td>0.07</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; OAD: obstructive arterial disease.
gender (16 vs 1.8%, \( p = 0.002 \)) and absence of stenosis (18 vs 7.3% with any degree of stenosis, \( p = 0.01 \)). COPD was associated with higher rates of aneurysm at both levels (94% at mid-ascending, \( p < 0.001 \); 35% at root tract, \( p = 0.01 \)).

### 3.4. Multivariate predictors of aortic dilatation

A first logistic regression model predicting aortic dilatation (AR > 1.1 at any level) yielded only age as predictor, all decades being significant risk factors except the first two. Then, other models were developed, excluding from the study sample the 16 patients with small aorta, who could have represented a confounding factor, and separately addressing the predictors of mid-ascending and root dilatation. Age (with maximal risk for the 6th decade of life) and a severe degree of stenosis independently predicted a dilated mid-ascending tract (Table 3). Male gender and severe regurgitation were stronger predictors of root dilatation than older age, while stenosis significantly predicted absence of root dilatation (Table 3). Aortic stenosis and hypertension emerged as significant predictors of mid-ascending aneurismal dilatation, COPD of root aneurysm.

### 3.5. Subgroups of aortic phenotype

The majority of patients (69.6%) could be assigned to the ‘mid-ascending’ phenotype. ‘Root’ phenotype accounted for 13.6% of the population. Mean age in the ‘normal’ subgroup (11% of the study population) was 30.8 ± 14 years, significantly younger than all other subgroups: 43.2 ± 15 in the ‘root’ group, 44.4 ± 14 in the ‘small’, 46.1 ± 14 in the ‘mid-ascending’ (\( p < 0.001 \)). In logistic regression models the ‘small aorta’ phenotype was predicted by severe stenosis (OR = 10; 95% CI = 3.2–31.4; \( p < 0.001 \)) and mild mitral regurgitation (OR = 6.3; 95% CI = 1.8–21.3; \( p = 0.003 \)), the
‘mid-ascending’ phenotype by age 50–60 (OR = 3.7; 95% CI = 1.6–8.5; \( p = 0.001 \)) and the ‘root’ phenotype by male sex (OR = 5.0; 95% CI = 1.1–22; \( p = 0.03 \)) and left ventricular dimensions (OR = 2.1; 95% CI = 1.1–4.3; \( p = 0.03 \)).

The classification tree algorithm (Fig. 2) confirmed the association between BAV stenosis and ‘small aorta’ phenotype (node 2). Age 22 was selected by the model (node 3) as the cut-off age for a significant decrease in the ‘normal’
phenotype: indeed, above 22 years the prevalence of ‘mid-ascending dilation’ type was significantly higher ($p < 0.001$), while the rate of ‘root dilation’ type remained almost the same as below 22 years. Eighty-four percent of all root dilatation patients were distributed between the terminal nodes 8 and 11 (young males with no or low degree of stenosis). The two different classification methods employed, i.e. CHAID and CRT, selected the same partitioning variables and produced similar terminal nodes.

3.6. BAV stenosis and aortic dilatation

Because BAV stenosis emerged as a predictor of mid-ascending dilatation (Table 3) but also as a factor associated to the ‘small aorta’ phenotype (Fig. 2), its relation with aortic size was investigated, once excluded patients with small aorta from the analysis, to avoid interference between these two associations. Then, Spearman’s rho test showed a statistically significant correlation between increasing stenosis severity and mid-ascending AR ($r = 0.15; p = 0.016$). The correlation coefficient increased when also the patients with aneurismal root were excluded ($n = 235; r = 0.34; p = 0.001$), and also ANOVA ($p = 0.004$) confirmed the association (Fig. 3). In fact patients with aneurismal root showed no correlation of aortic dimensions with stenosis degree ($p = 0.85$) nor with regurgitation degree ($p = 0.46$).

4. Discussion

In the present study, the predictors and features of aortic dilatations occurring in adults with congenital BAV were assessed. Differently from previous studies on this topic, root dilatation was distinguished from mid-ascending dilatation, and abnormal enlargement was defined on the basis of the aortic ratio value, thus allowing for the estimation of aortic disease prevalence at the two levels, regardless of age and body size differences [10,14], and avoiding to derive prevalence estimations from comparisons with unmatched control subjects [6]. Indeed, different dilatation prevalence rates were reported in the literature, ranging from 33%, when 4.3 cm was chosen as cut-off [10], to 60% when it was 3.7 cm [17], and from 44%, among young males <20 years of age [5], to 77% in patients >40 years [7]. In the present study a sensitive cut-off was chosen (AR > 1.1), yielding a prevalence of 79% for mid-ascending dilatation and of 58% for root dilatation in adults.

BAV-associated aortopathy is a complex phenomenon, and the current lack of some univocal interpretation of its causes and treatment can be ascribed also to the multiform nature of its clinical presentations [11,12].

4.1. Small aorta phenotype

This study was the first to focus on a particular form of aortic abnormality in BAV, observed by trend more in women than men, and more frequent with increasing stenosis severity, namely the small aorta. In a population including predominantly patients with senile degenerative tricuspid aortic valve stenosis, the prevalence of small aortic root was reported about 4% [18], slightly lower than in the present series (6%). These few patients represent an anomaly compared to the general trend, and their small aorta likely reflects a developmental disorder that is at the opposite end of the broad range of BAV-related aortic anomalies, compared with the more common tendency to dilatation: risk factor analyses for dilatation may be biased by those outliers. In the two previously published multivariate analyses [6,10], in whom the possible confounding effect of small aortas was disregarded, the only predictors of dilatation were age [6,10], body size [6] and root diameter [10]. These are indeed non-specific determinants of mid-ascending dimensions, also in the general population [19]. Besides, in those previous studies [6,10,20], no direct correlation was found between stenosis degree and mid-ascending aortic size. In the present series, the results obtained in the overall population agreed with those previous studies [6], nevertheless the exclusion of the 16 small aortas

---

Fig. 3. Association (ANOVA with Bonferroni correction) between BAV stenosis degree and aortic size: (A) in the overall population ($n = 280$); (B) after exclusion of cases of small aorta and cases of aneurismal root ($n = 235$). Error bars represent 1 SD above the mean value. $p < 0.01$ versus non-stenotic, mildly and moderately stenotic BAVs; $p < 0.01$ versus non-stenotic and mildly stenotic BAVs; $p = 0.019$ versus non-stenotic BAVs.
revealed that stenosis was a risk factor for mid-ascending enlargement and that, consistently, a significant positive correlation existed between stenosis grade and mid-ascending aortic size. It would be interesting to assess whether also in this setting dilatation occurs with progressive development of valve stenosis, and whether smaller aortas dilate at a lower progression rate, as expected, or not. This study was not able to investigate the hypothesis that small aortas could have been even smaller originally and their present size could result from superimposed relative dilatation occurred during life.

4.2. Mid-ascending dilatation phenotype

The most common anatomical form of dilatation was the ‘mid-ascending’ type, in accordance with previous studies on younger BAV patients showing that the most frequently involved tract and the site of maximal annual growth rate was the tubular ascending aorta [5,21]. In recent flow pattern studies, the abnormal opening mechanism of BAV (even in the absence of significant gradient) has been found to cause excessive post-valvular recirculation vortices: unlike in the tri-leaflet valve, those vortices were not confined into the sinuses of Valsalva, but extended into the mid-ascending tract, where the aortic wall stress was thereby locally increased [8]. After that evidence, the observation that aortic dilatation occurs also in the absence of ‘clinical’ valve dysfunction [5] could not exclude anymore a pathogenetic role of the hemodynamic disturbance. In a previous study from Della Corte et al. [22], including 552 BAV and tricuspid aortic valve patients, all with AR > 1.1, 94% of aortic dilatations associated with normally functioning BAVs showed the same anatomical configuration (dilation of the mid-ascending tract with normal root diameters) as 95% of dilatations associated with stenotic tricuspid aortic valves. The predominance of the mid-ascending phenotype in the present series is consistent with those abnormal wall stress patterns [4,8]. Moreover, in the setting of mid-ascending dilatation phenotype, aortic dimensions proved to be proportional to the degree of stenosis (Fig. 2), that was also the most significant risk factor in multivariate analysis. When aneurismal dilatation was considered (AR > 1.4), the risk factors emerging were interestingly those commonly known to predispose to degenerative aneurysms, i.e. hypertension, COPD, advanced age. This could indicate that different factors, some with an initiating role, some others with an aggravating one, could converge to common pathways in the determinism of aneurysms.

4.3. Root dilatation phenotype

The relatively rare ‘root’ phenotype was observed almost exclusively in men, often with some degree of regurgitation, and its prevalence was not significantly affected by increasing age and stenosis, unlike the ‘mid-ascending’ form of dilatation. One possible explanation to this evidence could be that some intrinsic aortic wall weakness may cause, in the specific subset of BAV patients with ‘root’ phenotype, a form of dilatation that occurs earlier in life and independent of hemodynamic factors. However, the hypothesis could also be considered that the lack of relation with aortic stenosis may reflect a role of other forms of flow disturbances not simply quantifiable by stenosis grade. From the surgical standpoint, in the present series patients needing root replacement according to the current guidelines [15] accounted for only 10% of the sample. Furthermore, in view of the above results, in patients with mid-ascending aneurysm without risk factors for root involvement — especially patients with hemodynamically relevant BAV stenosis — it would seem not justified to extend surgical resection also to the sinuses of Valsalva. Extrapolation of surgical guidelines is far beyond the aims and design of this study, however good freedom from recurrence has been reported for BAV-associated aneurysms following surgical procedures that leave the native root untreated, i.e. separate valve and graft replacement [12] and ascending reduction aortoplasty [23].

4.4. Limitations of the study

The referral patterns for echocardiography could have influenced prevalence rates, which may therefore diverge from those in BAV subjects from the general community. However, the activity of our echocardiography laboratory includes both in-hospital and outpatient examinations: the relatively high observed rate of normally functioning BAVs (39%, 108 patients) indicated that the referral bias was negligible. Furthermore, some possible technical bias should be briefly addressed. Overestimation of stenosis degree due to the pressure recovery phenomenon could have conditioned the observed association of small aortas with severe stenosis [24]. Nevertheless, overestimation due to pressure recovery is known to decrease with jet eccentricity, as it typically happens in BAV stenosis [25]. Moreover, for each degree of stenosis, non-hypertensive small aorta patients showed mean values of ventricular septum thickness, a measurement that may reflect the real functional severity of stenosis and is not influenced by root dimensions, comparable to those of non-hypertensive patients without small aorta (data not shown). Finally, without computed scan imaging, no analysis could be provided on the more distal portions of the aorta, in particular the transverse arch. However, a previous community-based study [20] showed no difference in aortic arch dimensions between BAV subjects and age- and sex-matched controls.

4.5. Conclusions

BAV patients constitute a heterogeneous population with respect to risk and features of aortic disease. Patient sample homogeneity should be considered a requirement when reporting on pathology series as well as clinical or surgical experiences with BAV-associated aortic dilatation. In the most common condition, i.e. enlargement of the mid-ascending tract, with unaffected or mildly involved root, the dilatation appears strictly related with presence and severity of BAV stenosis, suggesting a pathogenetical role of hemodynamics. The surgical consideration arising from these results, that most BAV patients may not need preventive surgical repair of their aortic roots but only of the ascending aorta, needs further confirmation in adequately designed clinical trials. On the other side, a minority of BAV patients, especially male without stenosis, appears to be at significant

risk of root involvement and should probably be followed-up more carefully and treated more radically.

References


[18] Fedak PWM, Verma S, David TE, Leask RL, Weisel RD, Butany J. Importance of aortic root involvement and should probably be followed-up more carefully and treated more radically.

Appendix A. Conference discussion

Dr D. C. Miller (Stanford, California, USA): Perhaps I missed it, but did you describe the distal extent of aortic dilatation, that is, how far into the arch the aorta was dilated? Having the transverse arch involved in our experience is another important distinguishing morphological feature of the aneurysm in many patients with a bicuspid aortic valve.

Dr Della Corte: No, the study dealt only with the proximal extent of dilatation. We assessed whether the dilatation was isolated to the mid-ascending tract or it involved the root.

Dr Miller: And your work is just an echo database, so you really cannot image the arch in everybody?

Dr Della Corte: No, we didn’t look at the arch in this study.

Dr Miller: I would hope that many people in this room already have appreciated that even if a bicuspid valve is functioning normally, the aneurysm typically does not end at the innominate takeoff, but actually extends to the left common carotid or left subclavian artery. As Hans Borst, for whom this session is named, told us long ago, you cannot ignore the aortic dilatation going into the arch even if the valve is functioning normally. This is a very exciting and interesting topic; someday, we hopefully will also know the molecular biology and genetics of this phenotype.

Let’s have Thoralf Sundt tell us in 10s what currently is known about the molecular genetics of this bicuspid valve aortopathy.

Dr T. Sundt (Rochester, Minnesota, USA): Well, I think the author’s group has done significant work on protein expression in the various parts of the aorta. Perhaps the speaker would like to comment about that.

Dr Della Corte: We have performed a pilot study, and we are currently continuing it, to assess the expression of some proteins formerly neglected by pathology studies on bicuspid aortic valve, proteins other than fibrillin, like tenasinc, laminin, collagen type 1 and 3.

And in particular we studied the differences in protein expression between the convex aspect of the mid-ascending aorta and the concave aspect. And we found that some proteins that are known to be related to flow-induced vascular remodeling processes are over expressed at the convexity of the ascending aorta, whereas, according to the flow patterns and the stress patterns anticipated by finite element models, wall stress is higher. While structural proteins, like collagen 1, were decreased at the convexity to a greater extent than at the concave aspect of the mid-ascending aorta. And this could also explain why dilatations associated with bicuspid aortic valve tend to expand anteriorly towards the right.

Dr Miller: By convexity do you mean the greater curvature?

Dr Della Corte: Yes, the greater curvature.

Dr Sundt: Could I ask what are the implications of your theory for the pathogenesis of the aneurysms and their genetic inheritance? For example, perhaps root aneurysms are due to a genetic cause, and supravalvular aneurysms are due to hemodynamics. Have you looked at the family histories of these patients?

Dr Della Corte: No, we didn’t, since this was a cross-sectional study on echocardiographic evaluations performed at our echocardiographic unit. Surely it would be interesting to look at the family history of that subset of patients with bicuspid aortic valve and root dilatation.

The main finding of this study I think was the distinction between two types of dilatation possibly associated with bicuspid aortic valve and that different clinical and demographic factors were associated with each one of those phenotypes.

Dr Miller: Just one more quick question your group might be able to answer.
Do you have any idea if the elevated tissue MMP-2 and MMP-9 matrix metalloprotease levels found by some investigators are just "passenger" molecules or are they truly causal?

Dr Della Corte: We have not yet studied MMP expression in the ascending aorta. We are going to include this in our next studies, along with other proteins and the same proteins that we already looked at in our previous studies. However, the pathogenetical meaning of MMP over expression could also be debated, since they also are known to be involved in the flow-induced vascular remodelling process and they could not be a sign of genetic disturbances.