CHAPTER

4

Is morphology and extent of the raphe associated with clinical outcome in patients with bicuspid aortic valves?

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4

ABSTRACT

Background: The clinical course of bicuspid aortic valve (BAV) disease is variable. Data on predictors of aortopathy and valve dysfunction are limited. This study sought to define a risk profile for BAV patients based on clinical patient characteristics.

Methods: Valve morphology and aortic dimensions of 255 BAV patients (179 men
(70.2%), 48±15 years) were evaluated retrospectively from the center's echocardiography database. Patient characteristics, clinical course and echocardiographic parameters including morphology were obtained.

Results: Type 1A BAV patients (n = 151, fusion right and left coronary cusps) showed significantly larger sinuses than type 2A BAV patients (n = 37, fusion right coronary and non-coronary cusps) (p= 0.001). Regurgitation was most apparent in type 1A BAVs with a complete raphe (p=0.017). All regurgitant valves showed larger sinuses (p=0.023) and patients with valve regurgitation had a larger LV mass (p<0.001). Male gender was associated with aortic valve regurgitation (p<0.001), larger aortic diameters and a larger LV mass (p=0.01). Patients with a history of aortic coarctation showed less valve regurgitation (p=0.048) and smaller diameters of the ascending aorta and arch (p<0.001). Patients with hypertension had faster dilation of the ascending aorta (p=0.049), statin use was associated with a smaller diameter of the ascending aorta (p=0.017).

Conclusions: This study provides a working model showing that males with a type 1A BAV with a complete raphe, hypertension and no statin use exhibit the highest risk of complications such as progressive aortic and valvular dysfunction necessitating intervention.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, with a clear male predominance and an estimated prevalence of 0.5-1% (1-3). BAV can occur in an isolated form or in association with other congenital malformations, such as coarctation of the aorta (CoA). The prevalence of BAV in CoA patients is reported to be as high as 40-50% (4).
Although some patients with isolated BAV remain asymptomatic throughout their lifetime, others develop severe cardiac complications from an early age onwards, such as aortic valve stenosis, aortic insufficiency and/or endocarditis. However, the first presentation can also be a clinically relevant aortic wall abnormality, including ascending aortic dilation (reported to occur in 45% of patients (5)), aneurysm formation or rupture of the ascending aorta. Identifying patients who are prone to develop complications is a major, clinically relevant, challenge.
It is now recognized that BAV should not be considered as one single entity, but that distinct morphological phenotypes are distinguishable based on the presence and number of raphe, as classified by Sievers et al. (6) Most BAVs consist of one free cusp and two cusps that are conjoined (or have failed to separate during embryonic development). The term 'raphe' defines the conjoined area of the two underdeveloped cusps turning into a malformed commissure between both cusps (6).
There is discussion in the literature about the relationship between BAV morphology and long term clinical outcome. Several studies reported that BAVs with fusion of the right coronary cusp and left coronary cusp (Type 1A in this study) are associated with more aortic dilation in adults, whereas BAVs with fusion of the right and non-coronary cusp (Type 2A in this study) are responsible for valve dysfunction at a younger age (7-12). The third phenotype resulting from fusion between the left and non-coronary cusp (Type 3A in this study) is rare compared to the other two types (8). Some studies reported that type 1A BAVs are more stenotic than type 2A and 3A, whereas other studies described that the latter types are more stenotic and type 1 BAVs are more regurgitant (13-15). When no raphe is present, the valve is called strictly bicuspid (subtype B in our study). The raphe position has been linked to the area of dilation, type 2A BAVs are for instance responsible for dilation of the aortic sinus, whereas type 1A BAVs are related to dilation of the ascending aorta (16,17). In contrast, other studies reported

valve regurgitation as the main cause of sinus dilation, whereas stenosis causes a much milder ascending aortic dilation and valve morphology is proposed to be of little influence (18-21). The extent of the raphe (i.e. the extent to which the cusps are conjoined) however, has not been taken into account in the mentioned studies.
The purpose of this study was to determine whether valve morphology is associated with the degree of aortopathy and valvular dysfunction. By also taking the extent of the raphe and individual patient characteristics into account, a tailored risk stratification was developed.

METHODS

Study population

Consecutive patients who had undergone transthoracic echo-cardiography between 2005 and 2010 and had been diagnosed with BAV disease were identified retrospectively from the Leiden University Medical Center (LUMC) echocardiography database. Clinical and echocardiographic data were collected and analyzed from the departmental Cardiology Information System (EPD-Vision®, LUMC) and the echocardiography database respectively. For this analysis of clinically acquired data, the Institutional Review Board waived the need of patient written informed consent. A total of 255 patients was selected, all had situs solitus of the atria and concordant AV and VA connections. Other patient characteristics recorded included date of birth, height, weight, body surface area (calculated using the Du Bois formula (22)), other congenital malformations, genetic syndromes, history of arrhythmias, ischemic procedures, cardiovascular risk factors, use of medication, known valve dysfunction, history of valve surgeries and age at time of surgery (Table 1).

Classification of valve morphology

As from a developmental point of view a morphological spectrum may exist in which the extent of the raphe can be regarded as a continuum, in the current study we chose to describe the major valve morphologies observed in BAV patients as 3 different types (Type 1A, 2A and 3A, based on valve cusp orientation), in which the extent of the raphe can vary (Fig. 1). In this study, fusion of the right and left coronary cusp is defined as type 1A BAV, fusion

Table 1 *Patient Characteristics*

Variable	***n (%)***
Gender	
- Male	179 (70.2)
- Female	76 (29.8)
Bicuspid aortic valve	
- Type 1A	151 (59.2)
- Type 2A	37 (14.5)
- Type 3A	1 (0.4)
- Strictly bicuspid (type B)	66 (25.9)
o Type 1B	42 (63.6)
o Type 2B	24 (36.4)
Extent of the raphe	
- Complete	111 (43.5)
- Incomplete	78 (30.6)
Valve surgery	66 (25.9)
- Mitral valve replacement	1 (0.39)
- Pulmonary valve stenosis	1 (0.39)
- Pulmonary valve regurgitation	1 (0.39)
Arrhythmias	64 (25.1)
- Atrial fibrillation	39 (15.3)
- Supraventricular tachycardia	19 (7.5)
- Ventricular tachycardia	14 (5.5)
- Pacemaker	6 (2.4)
- Implantable cardioverter defibrillator	15 (5.9)
o Secondary prevention	10 (66.7)
o Primary prevention	5 (33.3)
Medication	140 (54.9)
- Angiotensin converting enzyme inhibitors	91 (35.7)
- Statins	61 (23.9)
- Carbasalate calcium	45 (17.6)
- Oral anticoagulants	43 (16.9)
- Antiarrhythmic drugs	33 (12.9)
Risk Factors	117 (45.9)
- Hypertension	65 (25.5)
- Mitral valve repair	2 (0.78)
- Aortic valve replacement	50 (19.6)
- Aortic valve repair	10 (3.9)
- Bentall	22 (8.6)
- Tricuspid valve repair	1 (0.39)
- Pulmonary valve replacement	1 (0.39)
Congenital defects	51 (20.0)
- Aortic coarctation	39 (15.3)
- Atrial septal defect	1 (0.39)
- Ventricular septal defect	11 (4.3)
- Marfan	2 (0.78)
- Common truncus	1 (0.39)
- Patent ductus arteriosus	5 (2.0)
Valvular dysfunction	189 (74.1)
- Aortic valve stenosis	120 (47.1)
- Aortic valve regurgitation	120 (47.1)
- Mitral valve regurgitation	16 (6.3)
- Tricuspid valve regurgitation	8 (3.1)
Smoking	54 (21.2)
Diabetes	11 (4.3)
Cerebrovascular accident	14 (5.5)
Hypercholesterolemia	33 (12.9)
Peripheral arterial disease	7 (2.7)

of the right and non-coronary cusp as type 2A BAV and fusion of the left and non-coronary cusp as type 3A BAV. As at this time there is no consensus on whether or not a strictly bicuspid valve (i.e. a valve without a raphe) should truly be regarded as a separate group, strictly bicuspid valves were defined as a subgroup B to facilitate analysis of data (Fig. 1).

Echocardiography

Transthoracic echocardiography was performed using a GE Vivid7 or E9 (GE-Vingmed, Horten, Norway) ultrasound machine with standard views from the parasternal, subcostal, suprasternal and apical windows. The aortic valve was examined in the two dimensional parasternal short-axis view and classified as bicuspid when two cusps could be clearly identified and the

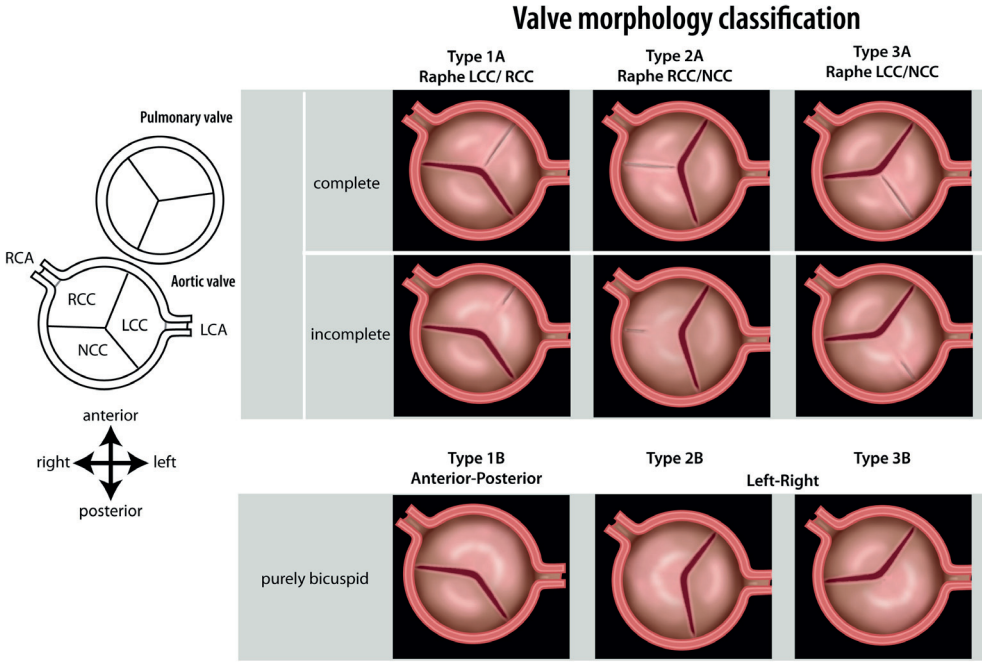

Figure 1. *Schematic overview of BAV morphologies.*
Drawings are oriented in echocardiographic, i.e. inferior, view of the aortic valve. Upper panel: The three major valve morphologies observed in BAV patients are described as three different types based on the valve cusp orientation: type 1,2 and 3. The extent of the raphe is indicated as analyzed in this study (<0.5, >0.5, complete). Lower panel: Strictly bicuspid valves (without a raphe) are defined as a subgroup B. BAV: bicuspid aortic valve

typical 'fish-mouth opening' of the valve was observed (Fig. 2). Diameters of the aortic root and ascending aorta were determined in the parasternal long axis view.

Echocardiographic analysis

All echocardiographs were evaluated by one experienced observer, using GE Medical Systems's EchoPac, Version 7 (110.0.0, GE-Vingmed, Horten, Norway). The aortic valve was evaluated in a cross-sectional view for the presence and extent of a raphe. For valves where a raphe could be distinguished (subgroup A), distinction was made between a complete raphe and an incomplete raphe. Cases where no raphe was detected (subgroup B) were defined as strictly bicuspid valves. Diameters of aortic sinus, ascending aorta and aortic arch were measured from leading edge to leading edge in end-diastole according to the European Association of Echocardiography recommendations (23). Aortic annular diameter was measured from inner edge to inner edge during systole. All measurements were made in mm, rounded to 2 significant figures. The ascending aorta was considered dilated at a diameter of >38mm. Subgroup analysis was performed in: 1) patients with pronounced dilation of the aortic wall, defined as an ascending aortic diameter >44 mm; 2) patients with a history of CoA; 3) patients who had undergone ascending aortic or aortic valve surgery. If a patient had undergone surgery of either the aortic valve or the ascending aorta, the last echocardiographic study before surgery was used to measure aortic diameters and to evaluate valve morphology.

Of 199/255 patients serial echocardiographic studies at least 6 months apart were available. Both the first and most recent studies were selected for quantitative evaluation of the dynamics of aortic dilation over time. To evaluate left ventricular hypertrophy, end-diastolic left ventricular mass was calculated by measuring the end diastolic outer and inner left ventricular wall thickness in the M-mode view using the Devereux formula (24).

Statistical Analysis

All collected data were registered in a Microsoft Office Access 2003 database. The database was exported into IBM SPSS Statistics Version 20 for computing variables and statistical analysis. Independent samples T-tests were used to compare means of numerical data in 2 categories. One-way ANOVA tests were used for comparing numerical data in more than 2 categories. Cross-

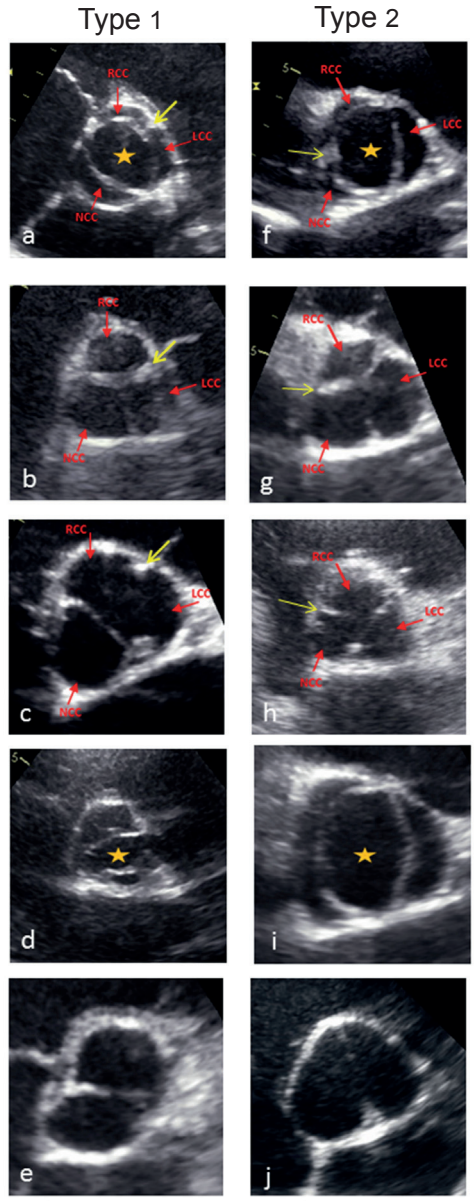

Figure 2. *Representative examples of different BAV types as seen from the short-axis parasternal view on echocardiography.*
The yellow arrow indicates the raphe. The orange star indicates the typical fish mouth opening of the valve. a: Type 1A in open position. b: Type 1A with complete raphe in closed position. c: Type 1A with incomplete raphe in closed position. d: Type 1B in open position. e: Type 1B in closed position. f: Type 2A in open position. g: Type 2A with complete raphe in closed position. h: Type 2A with incomplete raphe in closed position. i: Type 2B in open position. j: Type 2B in closed position.BAV: bicuspid aortic valve

tabulations were made for binary categorical data, on which chi-square goodness-of-fit-tests were performed to test for independence. For sets of independent numerical data linear regression analysis was used to evaluate trends. Similarly, trends for binary categories were evaluated with binary logistic regression to correct for possible confounding factors such as age and gender. To evaluate surgery-free survival for different patient groups, Kaplan-Meier survival curves were made whereby the age of a patient at the time of a surgical intervention of the aortic valve or ascending aorta was considered an uncensored 'event' and the age of an un-operated patient at the end of the study was considered censored data. All statistical analyses were two-tailed and considered significant if $p<0.05$.

RESULTS

Patient characteristics

A total of 255 patients with BAV (age 18-85 years, mean 48±15 years) were identified and analyzed. Of these, 179 were male (70.2%) and 76 female (29.8%). Patient characteristics and echocardiographic data are summarized in Table 1. The distribution of valve morphology is shown in figure 3.

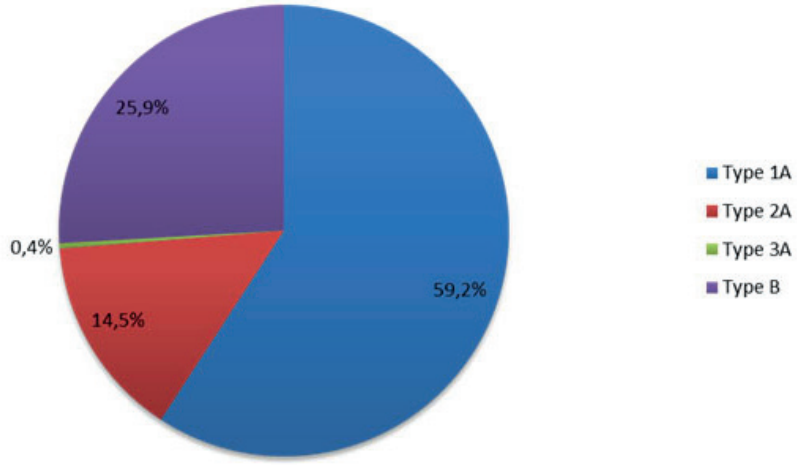

Figure 3. *Schematic overview of the distribution of valve morphologies in the study population.*

BAV morphology as related to valve function

120 patients were diagnosed with aortic stenosis, the same number of patients showed aortic regurgitation (Table 1). There were no significant differences in valve function between the different morphological subtypes. However, BAVs with a complete raphe had a significantly higher prevalence of valve dysfunction than BAVs with an incomplete raphe (82.9% vs. 66.7%, p=0.01, Table 2). When specifying this for type of valve dysfunction, this difference remained significant in patients with aortic regurgitation (56.8% vs. 42.3%, p= 0.05), whereas in patients with aortic stenosis there was no difference between patients with a complete or incomplete raphe (49.5% vs 43.6%, p=0.419, table 2). In type 1A BAVs with a complete raphe the difference in prevalence of aortic regurgitation was even more outspoken compared to the rest of the study population (57.6% vs. 41.8% p=0.017). Aortic valve regurgitation was a greater predisposing factor of valve surgery than aortic stenosis, as shown by the Kaplan-Meijer survival curves (Fig; 4a, b).

BAV function and left ventricular mass

In patients with valve regurgitation, left ventricular mass was larger compared to those without regurgitation (128g/m2 vs. 103g/m2, p<0.001). Both aortic valve regurgitation and a larger left ventricular mass were associated with male gender (53.6% in males vs. 31.6% in females, p= 0.001; 122.2 in males vs. 94.2 g/m2 in females, p<0.001 respectively). This remained significant even after correcting for body surface area (p=0.01). Surprisingly, aortic stenosis was not associated with either left ventricular mass, nor with gender.

BAV morphology as related to aortic diameters

All type 1A BAVs, compared to type 2A BAVs, showed a significantly larger

Table 2: *Valve morphology as related to dysfunction*

Valve dysfunction	**Complete raphe**	**Incomplete raphe**	***P* value**
Valve dysfunction (*n* = 144)	92 (82.9%)	52 (66.7%)	0.01
Aortic regurgitation (*n* = 96)	63 (56.8%)	33 (42.3%)	0.05
Aortic stenosis (*n* = 89)	55 (49.5%)	34 (43.6%)	Not significant

sinus (37.29 vs. 33.89mm, p=0.001, table 3a). Valves with a complete raphe had significantly larger aortic diameters at the level of the ascending aorta, as compared to valves with an incomplete raphe (p=0.041). At the level of the aortic sinus and aortic arch this difference was not significant (Table 3b). Type 1A BAVs and a complete raphe also showed a significant difference in sinus diameter (37.74 vs. 36.01 p=0.031) compared to the rest of the study population. Males had significantly larger absolute aortic diameters compared to females at all levels, but these gender differences became non-significant when corrected for body surface area.
Regurgitant valves showed a significantly larger sinus (37.5mm vs. 35.8mm, p= 0.023) compared to non-regurgitant BAVs. Stenotic valves on the other hand had a significantly smaller sinus (38.1mm vs. 39.9mm p<0.001) and annulus (20.93mm vs. 22.96mm, p<0.01) compared to the rest of the study population, but a larger aortic arch (30.2mm vs. 28.7mm, p=0.036).
When corrected for body surface area, age and gender, statin intake was associated with a significantly smaller diameter of the ascending aorta (p= 0.017) and with a significantly longer surgery free survival compared to no statin use, apparent on the Kaplan-Meijer survival curve for intervention-free lifespan and statin use (Fig. 4c). The latter finding corresponded with the mean age at the time of operation, BAV patients taking statins were almost 14 years older at the time of an intervention as compared to those who do not (56.0 vs. 42.2 years old, p<0.001) (Fig. 4c).

Table 3 *Valve morphology as related to aortic diameter*
a: Type 1A versus type 2A

Aortic diameter	Type 1A	Type 2A	P value
Sinus (mm)	37.29 ± 5.88	33.89 ± 4.84	0.001
Ascendens (mm)	37.34 ± 6.75	36.33 ± 7.03	Not significant
Arch (mm)	29.30 ± 5.45	30.94 ± 4.70	Not significant

b: In all types BAV with complete raphe versus all types BAV with incomplete raphe

Aortic diameter	Complete raphe	Incomplete raphe	P value
Ascendens (mm)	38.02 ± 6.53	35.91 ± 7.00	0.041
Sinus (mm)	36.91 ± 5.82	36.13 ± 5.81	Not significant
Arch (mm)	30.07 ± 5.16	29.21 ± 5.66	Not significant

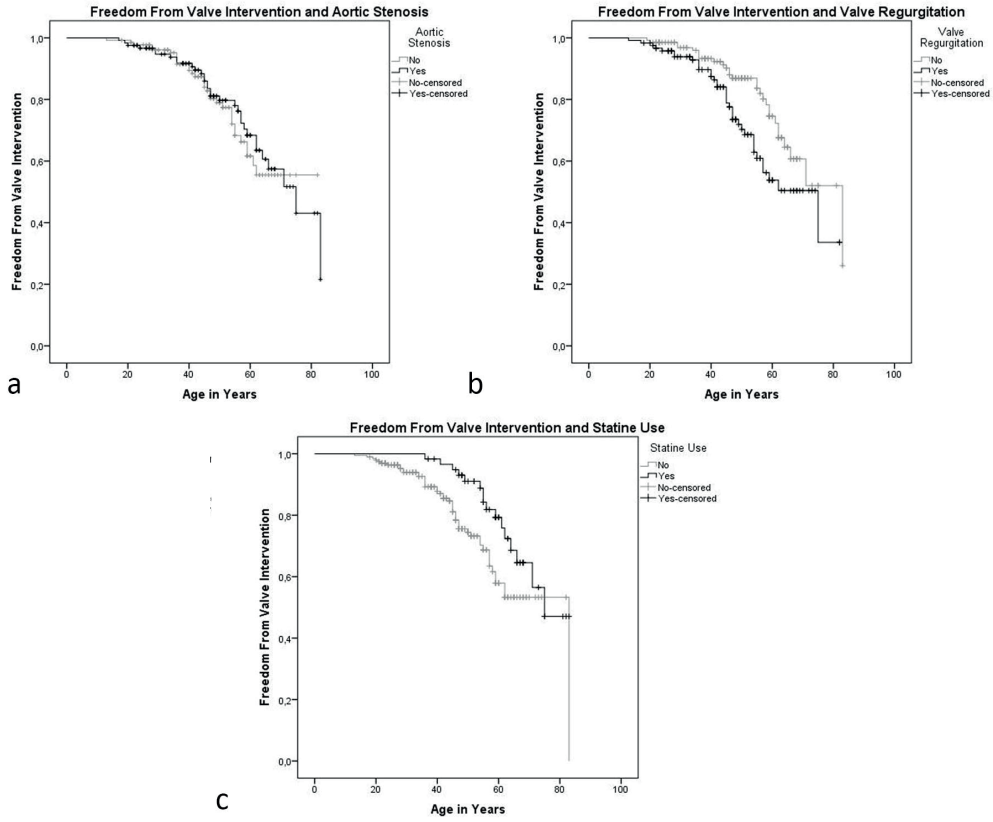

Figure 4. *Kaplan-Meijer curves of freedom from intervention with age in years* amongst a) patients with aortic stenosis versus patients without; b) patients with valve regurgitation versus patients without; c) patients with statin use versus patients without.

Aortic dimensions over time

The interval between the evaluated echoes ranged from 1 to 17 years with an average of 5.6 (SD 4.1) years follow-up. Dilation was most pronounced at the ascending aorta followed by the sinus, arch and annulus.

Increase in diameter of the ascending aorta, occurred more often in males than in females (46.9% vs. 28.9%, p= 0.008). Evaluation of the subgroup with dilation of the ascending aorta >44 mm, showed that these patients were on average 10 years older than patients with smaller degrees of dilation, indicating a progression of dilation with age. These patients also had more rapid aortic dilation per year at all locations, except for the aortic arch.

Patients with isolated aortic dilation received valve/aortic surgery 10 years later in life than patients with isolated valve disease who underwent surgery

(p<0.05), probably reflecting the fact that the latter group became symptomatic earlier in life. When studying the progression of dilation of the ascending aorta over time, hypertension was found as a predisposing factor; 14.6% of patients with hypertension showed dilation of more than 1.5 mm/year, compared to only 5.7% of patients without hypertension (p= 0.049 when corrected for age and gender).

BAV and Aortic coarctation

Patients with aortic coarctation constituted the largest group of patients with associated congenital cardiac malformations (n=39). Other congenital malformations included atrial or ventricular septal defect, and patent ductus arteriosus (numbers too small for sufficient power for analysis). Patients with a history of aortic coarctation were 9 years younger than those without (40.7 vs. 49.3 years old, p<0.001) and there was no statistical difference in gender (p=0.47).

Distribution of BAV morphology in patients with aortic coarctation was identical to the rest of the study population, the majority having a type 1A BAV (56.4% in patients with versus 59.7% in patients without aortic coarctation, p=0.321). However, in the majority (72.7%) of aortic coarctation patients and type 1A BAV an incomplete raphe was seen as compared to only 38.8% in the population without aortic coarctation. A complete raphe was found in only 27.3% of aortic coarctation patients, whereas 61.2% of the patients with type 1A BAV without aortic coarctation, had a complete raphe (Table 4).

Patients with aortic coarctation and type 1A BAV had significantly less valve regurgitation (13.6% vs. 55.8%, p<0.001) and significantly smaller diameters of the ascending aorta (33.7mm vs. 37.8mm, p<0.001) and aortic arch (25.8mm vs. 30.2mm, p<0.001) than patients with isolated BAV. Figure 5 shows a working model for the risk stratification of BAV patients, based on findings of this study.

DISCUSSION

Key findings of this study are 1) Patients with type 1A BAV and a complete raphe show more aortic regurgitation and root dilatation as compared to the rest of the study population 2) Patients with type 1A BAV have larger aortic sinuses than patients with type 2A BAV 3) aortic coarctation patients have

Table 4: *Characteristics of patients with type 1A BAVs with aortic coarctation versus without aortic coarctation*

Variable	Aortic coarctation	No aortic coarctation	P value
Type 1A BAV, n (%)	22 (56.4%)	129 (59.7%)	Not significant
Raphe			0.003
- Incomplete	16 (72.7%)	50 (38.8%)	
- Complete	6 (27.3%)	79 (61.2%)	
Ascendens (mm)	33.3 ± 6.06	37.8 ± 6.78	<0.001
Arch (mm)	25.5 ± 4.77	30.2 ± 4.98	<0.001
Valve regurgitation	3 (13.6%)	72 (55.8%)	< 0.001
Valve stenosis	10 (45.5%)	56 (43.4%	Not significant

smaller aortic root diameters and less valve regurgitation 4) Males have a higher prevalence of aortic regurgitation, larger aortic diameters 5) Use of statins is correlated with smaller aortic diameters and a delay in valve intervention.

Valve morphology and extent of the raphe as predictors of outcome.

The most important findings were related to the extent of the raphe. A complete raphe predisposed for larger aortic diameters and more valve regurgitation. However, the extent of the raphe could not explain the gender differences described above as the prevalence of complete raphe was the same in males and females. To our knowledge, the extent of a raphe in BAV disease has not been studied previously as a prognostic factor. The worse outcome observed in patients with a complete raphe is possibly due to the fact that BAVs with incomplete raphe have a more physiological, tricuspid-like opening and therefore function better. BAVs with complete raphe seem to have more uneven sized cusps and smaller openings which may predispose to valve dysfunction. With regard to the orientation of the raphe, type 2A BAVs showed a trend to more aortic valve stenosis and dilation of the ascending aorta over time than type 1A BAVs. The same is observed in patients with type B BAVs (no raphe), when comparing type 2B to type 1B, with about the same level of significance. This is supported by developmental findings of Fernandez et al, who state that the etiology underlying various BAV orientations is different (25). In this study eNOS knock-out mice developed only type 2 BAVs with abnormal development of cardiac valve cushions, suggesting that

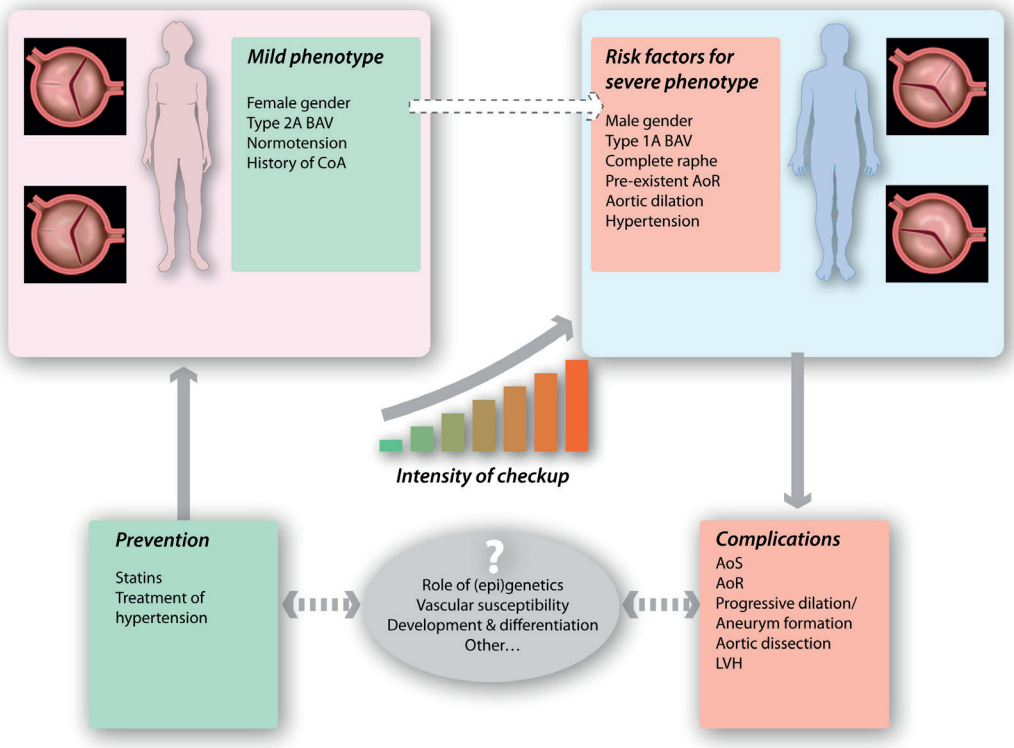

Figure 5. *Working model for risk stratification of BAV patients*. BAV: bicuspid aortic valve

the type 2 BAV may be a product of a developmental defect related to an exacerbated NO dependent epithelial-to-mesenchymal transformation. The Syrian hamster on the other hand develops only type 1 BAV, which seemed to be the product of an abnormal embryonic outflow tract septation and may therefore be related to alterations in neural crest cell behaviour (25).

Type 1A BAVs had a significantly larger sinus and these patients underwent 10% more operations as compared to type 2A BAVs. These data are in line with previous studies (6,7,10). Patients with type 1A BAVs and a complete raphe showed significantly more regurgitation and root dilation as compared to the rest of the study population. As freedom from valve and aortic intervention is an important criterion for a better prognosis in BAV disease, type 1A BAVs can be regarded as the valve orientation with the highest risk, which is in line with the above mentioned studies. This indicates that type 1A BAVs with a complete raphe are more susceptible for aortic dilation and should be monitored more closely for valve regurgitation and aortopathy.

Aortic valve regurgitation versus stenosis as predictors of outcome

Aortic valve regurgitation was a stronger predictor for adverse outcome than stenosis. Patients with regurgitant BAVs had larger sinus diameters, showed more left ventricular hypertrophy and underwent surgery earlier in life than patients without aortic regurgitation. In contrast, stenosis has little effect on the age at time of operation (Fig. 4). This corresponds to the data reported by Cotrufo et al. and by Della Corte et al., who found BAV regurgitation responsible for root dilation, whereas stenotic BAVs had an unaffected root (18,19). Hence, the type of valve dysfunction is an important tool for the clinician when monitoring BAV patients.

Exponential dilation and aneurysm formation of the ascending aorta

Dilation was most apparent in the ascending aorta, with a progressive growth per year seen with increasing diameters. This stresses the indication for careful follow up of patients with larger diameters, as they may show more rapid progression in the course of their disease. The age at the time of operation of patients with dilation of >44mm however, was 10 years older than other BAV patients. This may be explained by the fact that patients with isolated dilation can remain asymptomatic for many years, whereas patients with valve disease develop symptoms and are referred for a surgical intervention. Concomitant aortic surgery can be performed then, also in cases with a non-critical aortic diameter.

BAV patients with hypertension showed a higher incidence of rapid dilation of the ascending aorta than those without. This again stresses the detrimental effects of strain on the aortic wall caused by high blood pressure, predisposing for dilation and the necessity for careful regulation of blood pressure (26).

The use of statins was correlated with smaller aortic diameters and a delay in valve interventions. Based on these results the preventive use of statins could be considered in high risk patients with BAV. Statins are already known for limiting the progression of stenosis in BAV disease (27) as well as slowing aortic dilation in patients with BAV and stenosis (28). Further research is warranted to determine whether statins may also be used as preventive measure in patients with BAV without valve stenosis.

BAV and aortic coarctation

Subgroup analysis of the aortic coarctation group revealed that these patients are on average 9 years younger than the rest of the study population, which

may be explained by the fact that these patients usually show symptoms earlier and are often referred from the pediatric cardiologist as soon as they reach adulthood. The prevalence of BAV in aortic coarctation patients is an estimated 40-50%(4). The majority of patients in the current study had type 1A BAV, which corresponds to reports in literature (29). Aortic coarctation patients had smaller aortic root diameters and less valve regurgitation, which may be explained by the fact that less aortic coarctation patients had a BAV with complete raphe. The prevalence of stenosis was similar in the aortic coarctation group compared to the rest of the study population. This in contrast to earlier research which found an association between aortic coarctation and valve dysfunction (29).

Male gender and prognosis

Male patients with BAV had a higher prevalence of valve dysfunction, especially regurgitation. They also had larger absolute aortic diameters and more often increase in aortic diameter. More left ventricular hypertrophy was observed in male BAV patients as compared to females. These data indicate that male gender is a risk factor for a worse prognosis in patients with BAV, which is in line with previous studies (17,24). The larger degree of regurgitation may be a direct result of the larger aortic dimensions observed in male patients, although an opposite effect (regurgitation leading to dilation of the sinus and ascending aorta) may also be the case. The hypertrophy could be a result of chronic volume overload caused by aortic regurgitation, as reported previously (30). Why this is more pronounced in male patients, is not clear. Nistri and colleagues (31) have attributed aortic dilation, which was predominantly observed in young males, to a congenital weakness of the aorta, independent of valve dysfunction, age or body size. On the other hand, Della Corte and colleagues state that aortic dilation in young males should be attributed to varying degrees of regurgitation of the aortic valve (18). The current study indicates that this gender difference is not only seen in ‘young’ males, but remains significant at any age, indicating that males with BAV should be monitored more frequently than females throughout their lifetime.

STUDY LIMITATIONS

This was a retrospective analysis of clinically obtained patient data derived from a single center. A retrospective analysis is subjected to selection bias, as the investigator self-selects the cases. This bias was minimalized by including consecutive BAV patients who underwent an echocardiogram between 2005 and 2010.

CONCLUSIONS AND CLINICAL IMPLICATIONS

With regard to valve morphology in BAV patients, this study shows that the extent of the raphe is of clinical importance, as a complete raphe predisposes for more valve dysfunction and aortopathy.
This study provides a working model showing that males with a type 1A BAV with a complete raphe, hypertension and no statin use exhibit the highest risk of complications such as progressive aortic and valvular dysfunction necessitating intervention (Fig. 5).

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