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## **Clinical insights into a tertiary care center cohort of patients with bicuspid aortic valve**

Alexis Théron<sup>1,2</sup>,MD,PhD; Anissa Touil<sup>2</sup>,MD; Noémie Résseguier<sup>4</sup>,MD,PhD; Gwenaëlle Collod-Beroud<sup>1</sup>,PhD; Giulia Norscini<sup>3</sup>,MD; Anne-Sophie Simoni<sup>2</sup>,MD; Gaëlle Odelin<sup>1</sup>,DVM,PhD; Gilbert Habib, MD,PhD; Frédéric Collart<sup>2</sup>,MD,PhD; Stéphane Zaffran<sup>1,\*</sup>,PhD and Jean-François Avierinos<sup>1,3,\*</sup>,MD,PhD

<sup>1</sup>Aix Marseille Univ, INSERM, Marseille Medical Genetics, U1251, Marseille, France.

<sup>2</sup>Hôpital de la Timone, Département de Chirurgie Cardiaque, Marseille, France.

<sup>3</sup>AP-HM, Hôpital de la Timone, Département de Cardiologie, Marseille, France.

<sup>4</sup>EA 3279, Faculté de Médecine, 27 Bd Jean Moulin, Marseille, France.

### **\*Co-corresponding authors:**

Jean-François Avierinos  
[jfavierinos@ap-hm.fr](mailto:jfavierinos@ap-hm.fr)

Stéphane Zaffran  
[stephane.zaffran@univ-amu.fr](mailto:stephane.zaffran@univ-amu.fr)

**Short title:** BAV and valve dysfunction

## **Abstract**

Although bicuspid aortic valve (BAV) is one of the most common congenital heart diseases, clinical data associated with valve dysfunction are still limited. We evaluated clinical characteristics and echocardiography of French patients with BAV associated with leaking and stenosis degeneration. We initiated a prospective registry from 2014 to 2018 at a tertiary center. A total of 223 patients (168 males [75%], age  $53 \pm 17$  years) were enrolled. Among these patients 83% had left-right coronary cusps fusion, 80% Sievers type 1 BAV and 49% showed aortic dilatation. Twenty-four patients (11%) had normal valve function, 66 patients (31%) had aortic stenosis (AS), 91 patients (41%) had aortic regurgitation (AR) and 40 patients (17%) had AR and AS. BAV phenotype did not predict neither AS nor AR (all  $p > 0.1$ ). By multivariable analysis, age  $> 50$  ( $41.6 [10.3-248.2]$ ,  $p < 0.001$ ) and presence of raphe/fusion ( $12.8 [2.4-87.4]$ ,  $p < 0.001$ ) were significantly associated with AS, whereas male gender was associated with AR ( $5 [1.6-16.4]$ ,  $p = 0.005$ ). In addition, leaking degeneration was observed at a much younger age than stenosis ( $44 \pm 14$  years vs.  $66 \pm 10$  years,  $p < 0.01$ ) and among patients with valve dysfunction younger age was independently associated with AR ( $1.9 [1.85-1.94]$ ,  $p < 0.001$ ). In this study we confirmed high prevalence of valve dysfunction at first diagnosis of BAV in a referred population. The degenerative process differs according to type of dysfunction and is mainly dependent on age and gender.

**Keywords:** Heart disease, Bicuspid aortic valve, Aortic stenosis, Aortic regurgitation

## Introduction

Bicuspid aortic valve (BAV) is defined as a spectrum of altered aortic valves presenting with two functional cusps and less than three zones of parallel apposition without fusion.<sup>1</sup> It is the most frequent congenital heart disease (CHD) affecting 0.5 to 2% of the population with a strong male predominance.<sup>2</sup> BAV is associated with excess mortality in some cases<sup>3</sup> and accounts for more complications than all other CHDs combined,<sup>4,5 6</sup> related to increased risk of ascending aorta aneurysm, dissection and valve degeneration, the latter occurring 15 to 20 years earlier as compared to normal tricuspid aortic valve.<sup>7,8</sup> Aortic valve and/or ascending aorta replacements are the only therapeutic option,<sup>9,10</sup> with 25% incidence of this end-point at 20 years in patients without significant valvular dysfunction or aorta dilatation at first diagnosis.<sup>7</sup> Predictors of surgery include age>50 years and presence of valve degeneration at diagnosis, associated with a 4-fold increased risk of valve replacement at 20 years.<sup>7</sup> However, mechanisms underlying degeneration from normal to leaking or stenotic BAV remain poorly understood.<sup>2 11 12</sup>

The Bicuspid Aortic valve Project (BAP) is designed to collect clinical and genetic data on consecutive patients prospectively admitted with a definite diagnosis of BAV. We sought to describe the clinical and echocardiographic spectrum of consecutive BAV patients as they present in a tertiary care center and to determine factors associated with each type of valve degeneration.


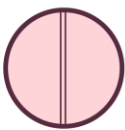
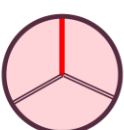
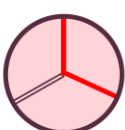
## Materials and Methods

### Study population

The BAP is a French single center prospective study including consecutive patients with non-syndromic BAV for clinical and genetic purpose. Patients were recruited between 2014 and 2018 in La Timone Hospital, Marseille, France. Patients were not included if they had connective tissue disease, previous aortic valve surgery and less than 18 years old. This study was performed in accordance with institutional guidelines. Written consent was obtained from all patients.

### BAV diagnosis

Definite diagnosis of BAV was based on visualization by ultrasound imaging in short axis view of two functional cusps in mid-systole; partial fusion between cusps was considered as BAV. Transesophageal echocardiography (TEE) was performed when diagnosis was uncertain after transthoracic echocardiography (TTE). Raphe was considered as definitely present when clearly visible by TTE or TEE. BAV phenotypes were specifically classified regarding both Siever's classification and embryologic classification<sup>1,6</sup> and all echocardiograms were performed by two experienced cardiologists (JFA,AT) to ensure homogeneous collection of data.

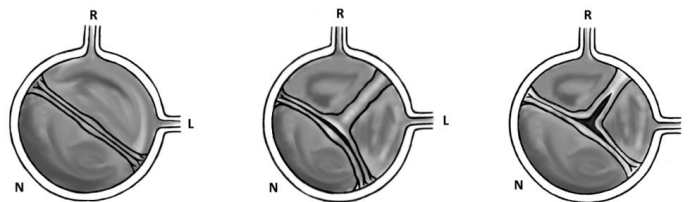
Commonly used terms		tricuspid	bicuspid		
scheme of morphological appearance					
functional characteristics	No of cusps	3	2	2	2
	No of raphe	0	0	1	2
morphological characteristics	size of cusps	equal	equal	non-equal	non-equal
	No of commissures	3	2	1 under- and 2 fully developed	2 under- and 1 fully developed

Schematic presentation of the developmental phenotypes of the aortic valve and typical characteristics according to Sievers *et al. J Thorac Cardiovasc Surg* 2007;133:1226-1233

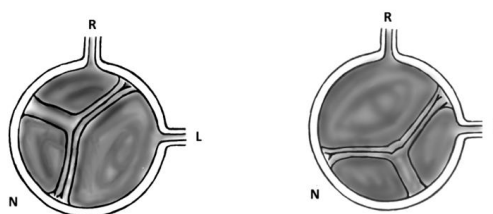
## BAV classification

Sievers classification is based on presence or absence of raphe (fusion) between fused cusps. Embryologic classification refers to type of embryologic cusp fusion -or non-separation- based on commissural axis orientation in short axis view. Typical BAV is defined by 11-17 or 10-16 o'clock positions of commissural axis, corresponding to left-right coronary cusps fusion (L-R BAV). Atypical BAV is defined by 13-19 or 12-18 o'clock positions of commissural axis, corresponding to non-coronary and right coronary cusps fusion (NC-R). The rare non-coronary-left coronary cusps fusion (NC-L) is also labeled atypical and defined by 14-20 o'clock position.

### Typical BAV



### Atypical BAV



Embryologic classification according to Michelena *et al. Circulation. 2014;129:2691-2704*

## **Baseline Clinical data**

Clinical data were prospectively collected at the time of inclusion as well as family history of cardiac surgery, aortic dissection and CHD. Surgical correction of valve dysfunction and associated aortic dilatation (BAV aortopathy) was indicated according to the European and US guidelines.<sup>10,9</sup>

## **Baseline Echocardiographic data**

Aortic regurgitation (AR) was graded through an integrative approach.<sup>9,10</sup> Mechanism of AR was separated into prolapse of the fused leaflet, cusps restriction or both. Aortic stenosis (AS) was considered as present when mean transvalvular gradient >10mmHg with a restriction of the aortic valve opening. Severe AS was defined by a mean gradient >40mmHg and an indexed AVA <0,6cm<sup>2</sup>/m<sup>2</sup>.<sup>9</sup> Normal valve function was defined by the absence of AR even mild and of AS with a mean trans-valvular gradient <10mmHg. Aortic dilatation was defined by an ascending aorta diameter ≥40mm and separated into “root phenotype”, “tubular phenotype” or “combined phenotype” according to the site of main dilatation. Baseline clinical and echo data were compared according to aortic valve function (AS vs normal valve function, AR vs normal valve function, AS versus AR).

## **Follow-up assessments**

Patients were monitored by their personal physicians during follow up. The primary endpoint was the indication for cardiac surgery at 6month follow-up.

## **Statistical analysis**

Statistical analyses were performed using R-software 3.0.3. Quantitative variables are expressed as mean±SD and categorical variables are presented as numbers and percentages. Comparisons between groups were performed using the Student's t test or the Mann-Whitney U test for quantitative variables, and using the chi-2 test or the Fisher's test for categorical variables. Univariate logistic regression analyses were performed to assess the association between potential determinants of valve dysfunction. Firth's correction was

applied by performing Firth's penalized-likelihood logistic regression to take into account the small number of patients without valve dysfunction.<sup>13</sup> Potential factor associated with valve dysfunction were considered as candidate for the multivariable analysis when their p-value was less than 0.20 according to the univariate analysis. A backward selection procedure was then applied to build a final regression model.



## Results

Baseline patient characteristics are shown in Table 1. Two hundred twenty-three patients were prospectively included in the cohort. Mean age was  $53\pm 17$  years, majority were asymptomatic and male (sex ratio = 3:1). Mean follow-up was  $242.3\pm 249.5$  days. None had history of aortic dissection or family history of unexplained sudden death in the youth. Among 17 patients with infective endocarditis (IE) at presentation, 12 (5% of all BAV patients) had isolated aortic valve endocarditis and 4 (24% of all IE) peri annular complications.

### Echocardiographic characteristics

BAV phenotype are shown in Table 2. According to Sievers classification, majority of patients (80%) had type 1 BAV, localized between left and right coronary cusps in 88% of them, 15% had type 0 and only 2% had type 2 BAV. According to embryologic classification, L-R BAV with or without raphe was observed in 83% of all BAV patients, NC-R BAV in 10% and NC-L BAV in 1% (Figure 1). Aortic dilatation was present at diagnosis in half BAV patients, evenly distributed between root and tubular phenotype.

Normal and pathological measurements are shown in Tables 1 and 2. Twenty-four patients (11% of all patients) had normal valve function and 199 patients (89%) presented with valvular dysfunction at the time of inclusion. Patients with normal valve function were predominantly male, younger than patients with AS or combined AS and AR ( $p<0.01$ ) but were of similar age than patients with isolated AR at diagnosis ( $p=0.4$ ) (Figure 2). Only four of those patients with normal valve function were older than 60 years old. They presented less frequently with raphe than patients with valve dysfunction (54% vs. 84%,  $p<0.01$ ). Majority had L-R BAV as patients with valve dysfunction (75% vs. 84%,  $p=0.58$ ). Prevalence of aortic dilatation (BAV aortopathy) was similar to that observed in patients with any type of valve dysfunction (50% vs. 49%,  $p=0.41$ ).

Sixty-eight patients (31% of all patients) had isolated AS, including 58 (26% of all BAV patients) with severe AS. Mean indexed aortic valve area was  $0.49\pm 0.24$   $\text{cm}^2/\text{m}^2$  and mean

trans-valvular gradient was  $56\pm 21$ mmHg. Patients with AS were significantly older than patients with normal function or with isolated AR. They were predominantly males, but proportion of women (39%) was higher than among AR patients (14%). Majority had raphe and L-R BAV as patients with AR. Prevalence of aortopathy was lower than among patients with isolated AR and of different phenotype, mostly tubular.

Ninety-one patients (41% of all patients) had isolated AR, including 50 (22% of all BAV patients) with severe AR. Mean effective regurgitant orifice area  $34\pm 15$ mm<sup>2</sup> and mean regurgitant volume was  $83\pm 39$ ml. As expected, LV diameters and volumes were higher than in AS patients. Mechanism of AR was pure leaflet prolapse in 40 patients (44% of all AR patients), restriction in 5 (6%), combined prolapse and restriction in 46 (50%). Among AR patients, male predominance was more prominent than among AS patients, mean age was 22 years younger, comorbidity was lower but endocarditis higher at diagnosis. Majority had raphe and L-R BAV. Prevalence of aortopathy was twice higher than among patients with AS, mostly of root phenotype.

Forty patients (17%) had combined significant AS and AR. They were predominantly male and clinical and echocardiographic pattern was in-between isolated AS and AR patients. Majority had raphe and L-R BAV. Aortopathy was mostly of tubular or combined phenotype.

### **Surgical event during follow-up**

Cardiac surgery was performed within 6 months of diagnosis in 145 patients (65%), including 141 aortic valve replacements, mainly with bio-prothesis (n=85) and 4 isolated ascending aorta tubular graft replacement. Mean age at cardiac surgery was  $56\pm 15$  years and 72 (49%) of operated patients were so before the age of sixty. Forty-two patients (42/145 = 29%) were NYHA 1 class and 80 patients (80/145=56%) were NYHA 2. Among NYHA 1 class patients, indication for surgery was driven by an ascending aorta dilatation (>55mm or 50mm in case of risk factors) in 12 patients (12/42=28.5%, aortic root dilatation (n=3), tubular aorta dilatation (n=9) ; 12 patients had severe asymptomatic AS with  $V_{max} > 5.5$ m/s (n=5) or

positive exercise test (n=7) ; 8 patients had severe asymptomatic AR with severe LV dilatation (mean LVES volume index =57mL/m<sup>2</sup>).

Indication for surgery was AR in 26 patients (18% of all aortic valve replacements, mean age= 44±17 years), AS in 92 patients (65%, mean age=62±13years) and ascending aorta dilatation in 27 patients (including 23 combined surgery).

### **Clinical factors associated with BAV dysfunction**

We compared normal with AS valve function. By univariate analysis (OR[95%CI]), age>50 years (18.6[6.2-64], p<0.001), presence of raphe (5.7[1.8-19.5], p=0.003), diabetes (8.8[1.1-1147.3], p=0.04) and dyslipidemia (3.8[1.2-15.5], p=0.02) were significantly associated with BAV stenosis whereas male gender (1.4[0.5-3.6], p=0.5) and orientation of commissures (1.5[0.3-14.8], p=0.7) were not. By multivariable analysis, age>50 years (41.6[10.3-248.2], p<0.001) and presence of a raphe (12.8[2.4-87.4], p<0.001) were significantly associated with AS.

We also compared normal with AR valve function. By univariate analysis, male gender (5.0[1.6-16.4],p=0.005), aortic annulus diameter(1.2[1.02-1.56],p=0.03) and presence of raphe (3.6[1.1-11.9],p=0.03) were significantly associated with BAV regurgitation whereas age (0.9[0.3-2.5],p=0.8) and orientation of commissures (1.9[0.4-19.0],p=0.5) were not. By multivariable analysis, only male gender (5[1.6-16.4],p=0.005) was significantly associated with AR.

Finally, we compared AR with AS valve function. By univariate analysis, male gender (3.6[1.7-8.7], p=0.001), younger age (10[5.2-20.0], p<0.001) and higher aortic annulus diameter (1.27[1.14-1.43], p=0.001) were significantly associated with AR whereas dyslipidaemia (3.3[1.6-7.1, p=0.002) was associated with AS. Multivariable analysis identified younger age (1.9[1.85-1.94], p<0.001) as independently associated with AR and dyslipidemia (3.3[1.22-8.22], p<0.001) with AS, while male gender was of borderline significance for predicting AR (1.15 [0.70-2.54],p=0.07).

## Discussion

The present study conducted on 223 consecutive patients diagnosed with BAV in routine clinical practice shows that in a tertiary care center 1) prevalence of severe AS and AR are similar, observed in a quarter of all patients at diagnosis, 2) AR is mainly due to leaflet prolapse and occurs at a much younger age than AS, 3) presence of raphe is associated with valve dysfunction mainly AS whereas embryologic phenotype is not.

BAV is the most common CHD and is associated with high rates of valve degeneration.<sup>7,8,14</sup> Development of ascending aorta aneurysm is observed in one fourth of patients 25 years after diagnosis of BAV with an excess risk of aortic dissection.<sup>8</sup> Subsequently BAV patients experience high rates of surgical aortic interventions at younger age than patients with tricuspid aortic valve.<sup>7,6,8,15</sup> However, data from populations referred to tertiary care centers at evolving clinical and echocardiographic stages unveil excess mortality in some subsets as compared to expected survival in an age- and sex-matched population due to higher prevalence of valvular dysfunction.<sup>3</sup> Our study is consistent with these data<sup>3</sup> reporting low prevalence of strictly normally functioning aortic valve at diagnosis of BAV, barely exceeding 10% of patients despite the young age of the study population. Almost none of them were older than 60, making valve degeneration an early process. Conversely, the vast majority of BAV patients presented with significant valvular dysfunction at diagnosis, associated with aortic dilatation in half of them, explaining the high incidence of surgery within 6 months of diagnosis reaching two thirds of patients at a mean age of 56 years-old, even younger when indication was driven by AR. In accordance with recent studies confirming that early surgery offers better outcome than conservative care in severe aortic valve disease, majority of patients were asymptomatic or with low symptoms at time of surgery.

Such high burden of morbidity and mortality imposes comprehensive assessment of determinants of clinical outcome and mechanisms of valve degeneration, critical for follow-up and management of patients with a first diagnosis of BAV. To date, identified risk factors of cardiac events, include presence of valve degeneration at first diagnosis of BAV, baseline

ascending aorta diameter<sup>>40mm</sup>,<sup>7</sup> female gender particularly with significant AR<sup>3</sup> and older age.<sup>3,7</sup> In turn, risk factors of outcome in patients with strictly normal BAV are poorly defined and BAV ability to maintain normal valve function or to become dysfunctional is not understood. BAV phenotype has been correlated to the type of dysfunction in one study, typical phenotype, defined by 11-17 or 10-16 o'clock positions of commissural axis, being associated with AR and atypical phenotype, defined by 13-19 or 12-18 o'clock positions of commissural axis, being associated with AS.<sup>16</sup> Our results do not confirm this association since embryologic phenotype was not associated with neither type of dysfunction, which is consistent with the overwhelming majority of L-R fusion in community and tertiary series<sup>3</sup>, making hazardous any attempt of risk stratification using this parameter. Proportions of typical and atypical phenotype were indeed almost identical in our series in both types of degeneration and close to those observed in normal BAV. Likewise, within each phenotype, normal valve function, leaking or stenotic degeneration were evenly distributed. Presence of raphe has been associated with higher prevalence of AS and AR and increased incidence of aortic surgery.<sup>17</sup> BAV differs from the tricuspid valve by number of cusps and sinus, by the elliptical shaped of the aortic ring and the restrictive and asymmetrical opening of aortic valve during systole.<sup>18,19</sup> MRI revealed eccentric systolic jet and abnormal downstream helical flow patterns through normal BAV resulting in greater flow acceleration and higher shear stress.<sup>12,20</sup> This phenomenon attributed to commissural fusion could lead to higher sensitivity to valve degeneration and calcification<sup>12</sup> and could be magnified by the increased stiffness of the fused leaflet due to the presence of raphe. Our data corroborated this hypothesis by showing an independent association between raphe and valve dysfunction mainly AS and a lower prevalence of raphe in normal BAV. However, raphe can be seen as the expression of an already ongoing degenerative process and could be acquired.<sup>21</sup> In addition, in our population more than half of normally functioning BAV presented with raphe and almost 20% of AR patients without, leaving unanswered the issue of valve dysfunction in many patients and imposing to identify determinants of degeneration independently of phenotype.

The most striking observation of our series was the major age difference at diagnosis of AR as compared to AS, patients with significant AR being more than 20 years younger than patients with significant AS. Interpretation of such age marked differences at initiation of leaking or stenotic process are unclear. Specific interactions between genetic pathways and environmental factors linked to aging could be argued. For instance, overexpression of *RUNX2* signal has been observed in mice models of calcified aortic valve.<sup>22</sup> This transcription factor is connected to NOTCH1, a single-pass transmembrane receptor expressed in valvular endothelial cells during development, which mutations have been reported in patients with BAV associated with valve calcification.<sup>2</sup> Conversely, dysregulation of genetic signals implicated in valvular interstitial matrix homeostasis has not been reported to date but could shift BAV towards myxomatous degeneration, leaflet prolapse and AR.

### **Limitations**

Any cohort of BAV patients is susceptible to diagnostic errors between tricuspid and bicuspid valve, with the risk of data contamination by non BAV patients. The prospective design of this study and the cautiousness taken in scanning with exclusion of all unclear diagnosis particularly among AS patients should reduce this bias. The fact that many patients with well-functioning BAV were not diagnosed and not captured in this tertiary cohort creates also a selection bias. A part of elective patients with BAV had been referred from another clinic and only those with valve dysfunction could have been referred to our tertiary care center. This could have falsely increase the prevalence of valve dysfunction in our population. Close follow-up of BAV patients from birth to occurrence of valve dysfunction would be the ideal way to disclose mechanisms of degeneration but is not conceivable. Therefore, cross sectional comparison of BAV patients according to valve function at first diagnosis of BAV is an imperfect but acceptable method.

Valvular degeneration is obviously a complex interplay of various factors including hemodynamic constraints due to the fused leaflets and genetic pathways dysregulation yet to

be determined, leading to maladaptive response of valvular ECM to the aortic flow environment.

## **Conclusion**

This study reported high prevalence of valve dysfunction at first diagnosis of BAV among patients referred to a tertiary care center. The leaking or stenotic degenerative process is poorly associated with clinical and phenotypic markers, dominated by age, gender and presents of raphe. BAV degeneration might be a complex phenomenon involving several contributors, among which genetic pathways dysregulation will deserve specific investigation.

## Figure legends

**Figure 1: Phenotypic patterns of bicuspid aortic valve according to embryologic and Sievers classification.** (A) Typical BAV with 10-16 o'clock position of commissural axis due to fusion of left and right coronary leaflets without raphe (Sievers Type 0 BAV). (B) Atypical BAV with 12-18 o'clock position of commissural axis due to fusion of non-coronary and right coronary leaflets with raphe (Sievers type 1 BAV). (C) Atypical BAV with 14-20 o'clock position of commissural axis due to fusion of non-coronary and left coronary leaflets with raphe (Sievers Type 1 BAV). Of note, non-coronary leaflet is identified as the cusp overlapping the interatrial septum. (D) BAV with aortopathy of tubular phenotype. LC, left coronary sinus; NC, non-coronary sinus; RC, right coronary sinus, \*; raphe; Commissural axis in red.

**Figure 2: Phenotypic patterns of bicuspid aortic valve according to valve dysfunction.** (A) Stenotic degeneration of typical BAV without raphe. (B) Leaking degeneration of typical BAV due to prolapse of the fused leaflet.



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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest

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