CLINICAL STUDY

Distribution Patterns of Valvular and Vascular Complications in Bicuspid Aortic Valve
A Hospital-Based Study of 3673 Adult Chinese Patients

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Summary
For its high occurrence and elevated risks for aortic valve dysfunction and vascular complications, bicuspid aortic valve (BAV) represents a great health challenge. However, the prevalence and clinical features of BAV in the Chinese population are inadequately illustrated.

From January 2011 to December 2015, 3,673 BAV patients with 69.1% male predominance were identified among 325,910 recipients of transthoracic echocardiography in our institution, demonstrating 58.4% overt aortic valve dysfunction, 52.5% ascending aortic dilatation, and 19.2% aortic root dilatation. The prevalence of pure aortic stenosis and mixed aortic valve dysfunction rose strikingly with age (both \( P < 0.0001 \)), while pure aortic regurgitation showed significant decrease with age (\( P < 0.0001 \)). Males showed elevated prevalence of pure aortic regurgitation (OR 3.16, 95% CI 2.55-3.91, \( P < 0.0001 \)) and mixed aortic valve dysfunction than females (OR 1.63, 95% CI 1.23-2.17, \( P = 0.0008 \)), but lower prevalence of pure aortic stenosis (OR 0.51, 95% CI 0.43-0.60, \( P < 0.0001 \)). Aortic root dilatation was associated with male gender (OR 5.02, 95% CI 3.74-6.74, \( P < 0.0001 \)), pure aortic regurgitation (OR 2.61, 95% CI 2.15-3.17, \( P < 0.0001 \)), and right-left (RL) cusp fusion type (OR 1.98, 95% CI 1.64-2.40, \( P < 0.0001 \)). Ascending aortic dilatation was associated with an elder age (OR 1.04, 95% CI 1.04-1.05, \( P < 0.0001 \)), pure aortic stenosis (OR 1.37, 95% CI 1.16-1.61 \( P = 0.0002 \)), and mixed aortic valve dysfunction (OR 2.51, 95% CI 1.89-3.33, \( P < 0.0001 \)).

Bicuspid aortic stenosis and ascending aortic dilatation demonstrate a similar pattern of age escalation, while aortic regurgitation is more prevalent in younger BAV patients. Aortic root dilatation intervenes closely with a unique phenotypic subgroup of male BAV patients with pure aortic regurgitation and RL fusion type.

Key words: Aortic valve dysfunction, Aortopathy

Bicuspid aortic valve (BAV), the most common congenital cardiac disorder, represents a multifaceted clinical challenge for its variable manifestations and complications including aortic valve dysfunction, aortic dilatation, aneurysm, and dissection.26 The staggering high prevalence, along with the unpredictability of its clinical presentation and outcome, have prompted collective efforts to identify pathophysiology of both valvular and vascular ailments of BAV, thus aiming for the optimization of clinical management for this enormous patient population.

The natural history of BAV has been illustrated on the basis of community studies, especially in the study by Michelen, et al. with their patients from Olmsted County, Minnesota.4,5 However, our knowledge on the prevalence, manifestation, and complication risks of BAV in the East Asia population is still limited. Nevertheless, several single-centered surveys, mainly from recipients of cardiovascular surgery, have implied the presence of unique clinical features in the Chinese BAV population.6,7 With the advent of transcatheter aortic valve replacement (TAVR) techniques during the past decade, BAV has gained growing interest among cardiologists. Therefore, it is important to have a better understanding of BAV in Chinese patients, including disease burden, distribution of valvular and vascular ailments, and risk factors for dire complications.

With the access to a large echocardiographic database from our institution, the present study intended to comprehensively investigate the prevalence and clinical features of BAV from a wide variety of clinical disciplines in a tertiary teaching hospital. The main objectives were three-
fold. Firstly, we intended to give an estimation of the burden of BAV disease on the basis of the total amount of echocardiographic examinations. Secondly, we tried to elaborate on the age-, gender-, and morphology-associated distribution of BAV valvular and vascular ailments. Thirdly, we attempted to find risk determinants associated with BAV aortopathy as aortic root dilation or ascending aortic dilatation.

Methods

Study population: This was a retrospective study at a 2000-bed tertiary teaching hospital with an average annual echocardiography department volume of 50,000 adult patients. From this database, we reviewed all transthoracic echocardiographic (TTE) reports of outpatient and hospitalized data from January 2011 to December 2015. TTE was indicated according to the American Society of Echocardiography recommendations in the following clinical scenarios: symptoms or conditions potentially related to suspected cardiovascular etiology; evaluation and routine surveillance of cardiovascular abnormalities including valvular heart disease, congenital heart disease, coronary artery disease, arrhythmias, hypertensive heart disease, heart failure, cardiomyopathy, cardiac mass, aortic disease, pulmonary artery hypertension, or pericardial disease; evaluation of perioperative risk for noncardiac surgery; and detection of cardiotoxicity of oncologic treatments.

Details of the screening process for BAV reports are depicted in Figure 1. Patients with suspected BAV diagnosis by TTE but who were not confirmed by transesophageal echocardiography or intraoperative observations were excluded. Reports of patients without preoperative examination or with redundant follow-up examinations were also screened out during the process. Therefore, only the first echocardiography report of each BAV patient was preserved for further analysis, which meant that a total of 3,673 BAV patients aged 15-91 years were found valid to form the study population, as identified from 325,910 TTE recipients during the referring period in our institute.

The present study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Zhongshan Hospital, Fudan University, Shanghai, China.

Data collection: All patients underwent TTE at rest in the left lateral decubitus position using commercially available machines followed by a uniform and standardized protocol based on the ACC/AHA practice guidelines and the American Society of Echocardiography recommendations. The diagnosis of BAV was confirmed according to Sievers’ classification in a short-axis view of the aortic valve with two functional cusps and less than three zones of parallel apposition between cusps. Aortic valve stenosis of moderate to high severity was defined as mean transaortic pressure gradient above 20 mmHg or valve area less than 1.5 cm² via the continuity equation. Aortic regurgitation was graded as moderate to severe when regurgitant color jet width was ≥ 25% of the left ventricular outflow tract diameter by color Doppler in the parasternal long-axis as well as in the apical long-axis and five-chamber view. If there existed combined moderate to severe aortic stenosis and regurgitation, the diagnosis was mixed aortic valve dysfunction. The diameters of the aortic annulus, aortic root (at the sinus of Valsalva) and ascending aorta (at the level of the bifurcation of the pulmonary artery) were measured perpendicular to the long-axis of the aorta, during systole, from leading edge to leading edge. The criteria of aortic dilatation were defined as diameter > 40 mm. All measurements were performed by experienced echocardiologists according to the standard methods.

Statistical analysis: Data were reported as mean ± standard deviation or medians (interquartile ranges) for continuous variables and as frequencies (percentages) for categorical variables. The Kolmogorov-Smirnov test was
The Mann-Whitney existing congenital heart disease. Statistical significance mitral valve regurgitation, infective endocarditis, and co-

gender, BA V fusion type, aortic valve dysfunction type, for entry into the logistic regression model included age, wise logistic regression analysis. Variables that competed risk factors for aortic dilatation were determined by step-
morphology with aortic valve dysfunction. Independent used to analyze the association of age, gender, and BA V

was adjusted using Bonferroni correction when multiple
test. The level of significance for pairwise comparisons

ues lower than five. Otherwise, we used the Fisher’s exact
ones tests when no cell had an expected value less than
ferences in percentages were evaluated using the chi-

Results

Study cohort: BAV was present in 3,673 individuals, comprising 1.1% of the adult patient population eligible for TTE examination in our institution (Table I). The frequencies of BAV morphology forms were as follows: right-left (RL) cusp fusion type (1941, 52.8%); right-non-
coronary cusp fusion type (1175, 32.0%); left-non-

Table I. Echocardiographic Characteristics of BAV Patients with Advancing Age Groups

|                  | 15–44 | 45–54 | Age (years) | 55–64 | 65–74 | 75+ | Total | P-value for trend |
|------------------|-------|-------|-------------|-------|-------|-----|-------|------------------|
| Patients, n      | 1063  | 770   | 1031        | 600   | 209   | 3673| —     |                  |
| Male, n (%)      | 756   | 533   | 713         | 405   | 131   | 2538| —     |                  |
| (71.1)           | (69.2)| (69.2)| (67.5)      | (62.7)| (69.1)|    |       |                  |
| RL fusion type, n (%) | 566  | 418   | 514         | 315   | 128   | 1941| —     |                  |
| (53.2)           | (54.3)| (49.9)| (52.5)      | (61.2)| (52.8)|    |       |                  |
| Pure moderate to severe aortic stenosis, n (%) | 132  | 149   | 341         | 257   | 99    | 978 | <0.0001|                  |
| (12.4)           | (19.4)| (33.1)| (42.8)      | (47.4)|       |     |       |                  |
| Pure moderate to severe aortic regurgitation, n (%) | 379  | 209   | 199         | 374   | 16    | 3797| <0.0001|                  |
| (35.7)           | (27.1)| (19.3)| (12.3)      | (7.7) |       |     |       |                  |
| Mixed aortic valve dysfunction, n (%) | 50   | 54    | 90          | 73    | 23    | 290 | <0.0001|                  |
| (4.7)            | (7.0)| (8.7) | (12.2)      | (11.0)| (7.9) |     |       |                  |

Comorbid conditions

Aortic root > 4.0 cm, n (%) | 181  | 147   | 216         | 120   | 40    | 704 | 0.081 |                  |
| (17.0)           | (19.1)| (21.0)| (20.0)      | (19.1)|       |     |       |                  |

Ascending aortic > 4.0 cm, n (%) | 316  | 434   | 652         | 392   | 136   | 1930| <0.0001|                  |
| (29.7)           | (56.4)| (63.2)| (65.3)      | (65.1)|       |     |       |                  |

Moderate to severe mitral valve regurgitation, n (%) | 35   | 33    | 73          | 61    | 28    | 230 | <0.0001|                  |
| (3.3)            | (4.3)| (7.1) | (10.2)      | (13.4)|       |     |       |                  |

Infective endocarditis | 47   | 26    | 32          | 10    | 3     | 118 | 0.001  |                  |
| (4.4)            | (3.4)| (3.1) | (1.7)       | (1.4) |       |     |       |                  |

Prevalence, n (%) | 1063/31982 | 770/55897 | 1031/93529 | 600/65222 | 209/39281 | 3673/325910 | — |                  |
| (1.5)           | (1.4)| (1.1) | (0.9)      | (0.5) |       |     |       |                  |

used to evaluate the normal distribution of continuous parameters. We tested trends across age groups with the Cochran-Armitage test. Differences among groups were assessed by one-way Analysis of Variance (Gaussian distribution) or Kruskal-Wallis H analysis (non-Gaussian distribution). If the parameter was significantly different between groups (P < 0.05), multiple comparisons were analyzed using the Student t-test (Gaussian distribution) or the Mann-Whitney U-test (non-Gaussian distribution). Differences in percentages were evaluated using the chi-
square tests when no cell had an expected value less than one and no more than 20% of the cells had expected values lower than five. Otherwise, we used the Fisher’s exact test. The level of significance for pairwise comparisons was adjusted using Bonferroni correction when multiple comparisons were performed. Logistic regression was used to analyze the association of age, gender, and BAV morphology with aortic valve dysfunction. Independent risk factors for aortic dilatation were determined by step-

wise logistic regression analysis. Variables that competed for entry into the logistic regression model included age, gender, BAV fusion type, aortic valve dysfunction type, mitral valve regurgitation, infective endocarditis, and coexisting congenital heart disease. Statistical significance was defined as 2-sided P < 0.05. Analysis was performed with SPSS 15.0 software (Chicago IL, USA).

With advancing age, there was a significant increase in the prevalence of pure aortic stenosis and mixed aortic valve dysfunction among all BAV patients along with decrease of pure aortic regurgitation (all P < 0.0001, Table I and Figure 3). As to comorbid conditions, the prevalence of ascending aortic dilatation and mitral valve regurgitation rose strikingly with age (both P < 0.0001), although the trend across age groups for aortic root dilatation was not found (P = 0.081, Table I and Figure 4).

Distribution of aortic valve dysfunction: Significant differences were found in the distribution of gender and BAV morphology among BAV patients with different type of aortic valve dysfunction (Table II and Figure 3). When gender and BAV morphology were adjusted, the odds ra-
Figure 2. Distribution of coexisting congenital heart diseases among BAV patients displayed by pie chart. The 10 patients in “Others” section consist of 4 tetralogy of Fallot, 4 persistent truncus arteriosus, 1 Shone’s syndrome, and 1 aortic arch interruption.

Figure 3. Prevalence of aortic valve dysfunction by age, gender, and bicuspid morphology displayed by line chart (A) and stacked bar plot (B). RL-BAV indicates bicuspid aortic valve with right-left cusp fusion type.

Figure 4. Prevalence of aortic root and ascending aortic dilatation by age, gender, and aortic valve dysfunction is displayed by line chart (A) and stacked bar plot (B).

tio for the association of aortic valve dysfunction with increasing age (per 10 years) was remarkable for pure aortic stenosis (OR 1.71, 95% CI 1.60-1.83, P < 0.0001), mixed aortic valve dysfunction (OR 1.33, 95% CI 1.21-1.47, P < 0.0001), and pure aortic regurgitation (OR 0.62, 95% CI 0.58-0.67, P < 0.0001). Males showed elevated prevalence of pure aortic regurgitation (29.7% versus 10.8%, OR 3.16, 95% CI 2.55-3.91, P < 0.0001) and mixed aortic valve dysfunction (8.8% versus 5.9%, OR 1.63, 95% CI 1.23-2.17, P = 0.0008), but lower prevalence of pure aortic stenosis (21.9% versus 37.3%, OR 0.51, 95% CI 0.43-0.60, P < 0.0001) than females after adjustment for age.
and BAV morphology. Adjusted for age and gender, BAV patients with RL fusion type were more prone to having pure aortic regurgitation (32.5% versus 14.2%, OR 2.81, 95% CI 2.61–3.02, P < 0.0001), but had fewer occurrences of pure aortic stenosis (20.6% versus 33.4%, OR 0.52, 95% CI 0.44–0.61, P < 0.0001) than those with non-RL fusion type. Mitral valve regurgitation was more prevalent in BAV patients with any kind of aortic valve dysfunction (all P < 0.0001). Infective endocarditis, on the other hand, was associated with pure aortic regurgitation (age-adjusted OR 7.42, 95% CI 4.94–11.16, P < 0.0001) and mixed aortic valve dysfunction (age-adjusted OR 2.65, 95% CI 1.59–4.43, P = 0.0002).

**Determinants of BAV aortopathy:** Compared to BAV patients without overt aortic valve dysfunction, those with pure aortic regurgitation and mixed aortic dysfunction demonstrated remarkably larger aortic annulus and aortic root (all P < 0.0001, Table II). Logistic regression analysis revealed that male gender (OR 5.02, 95% CI 3.74–6.74, P < 0.0001), pure aortic regurgitation (OR 2.61, 95% CI 2.15–3.17, P < 0.0001), and RL fusion type (OR 1.98, 95% CI 1.64–2.40, P < 0.0001) could serve as independent risk factors for aortic root dilatation. BAV patients with an elder age (OR 1.04, 95% CI 1.04–1.05, P < 0.0001), pure aortic stenosis (OR 1.37, 95% CI 1.16–1.61 P = 0.0002), and mixed aortic valve dysfunction (OR 2.51, 95% CI 1.89–3.33, P < 0.0001) were inclined to develop ascending aortic dilatation (Table III and Figure 4).

**Cardiac remodeling:** Cardiac chamber remodeling revealed consequences of pressure and volume overload among BAV patients with different types of aortic dysfunction. BAV patients with pure aortic stenosis demonstrated left ventricular hypertrophy without enlargement, whereas those with pure aortic regurgitation and mixed aortic dysfunction showed left ventricular enlargement and hypertrophy with impaired left ventricular systolic function (Table IV and Figure 5).

**Discussion**

The findings of this large cross-sectional study have shown a considerable disease burden of BAV as well as its associated aortic valve dysfunction and aortopathy in the Chinese population. The present study advocated divergent pathophysiology characterized by distinct age-, gender-, and morphology-associated distribution between BAV patients with aortic stenosis and regurgitation. We also provided convincing evidences indicating that two major phenotypes of BAV aortopathy, aortic root dilatation and ascending aortic dilatation, could be associated with different sets of risk determinants and thus have plausibly different underlying etiology.

The prevalence of BAV estimated in our echocardiography database was 1.1% with a male predominance of approximately two to one, which was comparable with the data from the Caucasian population.\(^{25,33}\) Despite the discrepancies between hospital-based and community-based data, it was important to be aware of the fact that over 50% of BAV patients in our institute demonstrated aortic valve dysfunction and ascending aortic dilatation requiring surgical or interventional attention. Therefore, BAV patients contributed to a remarkably larger propor-
Table IV. Cardiac Chamber Remodeling Associated with Aortic Valve Dysfunction among BAV Patients

|                  | No aortic valve dysfunction | Aortic stenosis | Aortic regurgitation | Mixed aortic valve dysfunction | P-value |
|------------------|-----------------------------|-----------------|----------------------|--------------------------------|---------|
|                  | n = 1375                    | n = 887         | n = 777              | n = 255                        |         |
| Left ventricular end-diastolic diameter (cm) | 4.8 (4.4–5.1)              | 4.7 (4.3–5.1)   | 5.9 (5.5–6.7)*       | 5.7 (5.2–6.2)*                 | < 0.0001|
| Left ventricular end-systolic diameter (cm) | 3.0 (2.7–3.2)              | 2.9 (2.7–3.3)   | 3.8 (3.4–4.6)*       | 3.7 (3.3–4.5)*                 | < 0.0001|
| Left ventricular mass (g)                   | 153.4 (127.8–184.7)        | 205.0 (158.8–253.7)* | 248.5 (194.5–322.7)* | 291.4 (233.7–365.4)*           | < 0.0001|
| Left ventricular ejection fraction           | 0.67 (0.63–0.70)           | 0.66 (0.61–0.70) | 0.62 (0.56–0.67)*    | 0.62 (0.51–0.67)*              | < 0.0001|
| Left atrial diameter (cm)                   | 3.6 (3.2–3.9)              | 3.9 (3.5–4.2)*   | 3.9 (3.5–4.3)*       | 4.2 (3.8–4.7)*                 | < 0.0001|

All continuous data are presented as median (interquartile range). *Individuals with mitral valve dysfunction and congenital heart diseases were excluded because of their impact on cardiac chamber remodeling. *Significant differences are compared with individuals without aortic valve dysfunction (P < 0.00125 after Bonferoni correction).

Figure 5. Comparisons of left ventricular end-diastolic diameter and left ventricular mass among different types of aortic valve dysfunction. Box plot indicates median (line), interquartile range (boxes), and minimum to maximum range (whiskers).

tion of TAVR recipients in several Chinese registries, which was also argued to be attributed to the relatively lower incidence of severe calcific aortic valve stenosis among patients with tricuspid aortic valves in China.14) Besides, we found that coexisting congenital heart disease was present in 4.3% of adult BAV patients, while Michelena, et al. in their study reported a much higher 15% in their community-based database that included pediatric patients.15) Aortic coarctation was reported to be the most frequent coexisting cardiac malformation for BAV and often warranted early intervention in response to the elevated risk for aortic dissection and premature death,13,14) which could explain why it was less frequent than ventricular septal defect, patent ductus arteriosus, and atrial septal defect in our adult BAV database. Although the actual disease burden of BAV could only be attained from community surveys, hospital-based comprehensive echocardiography studies could help to interpret the epidemiology picture and also provide essential information for the development of therapeutic strategies for the adult BAV population.

As illustrated in Figure 3 and Figure 4, distinct patterns of clinical features were identified between BAV patients with pure aortic stenosis and pure aortic regurgitation. The prevalence of pure aortic stenosis escalated with aging, which was similar to what occurred in the general population with tricuspid aortic valves and could indicate common pathophysiological processes as senescence or chronic inflammation.17,18) With the malformed aortic valve, more than 40% BAV patients over the age of 65 would eventually need aortic valve intervention for symptomatic aortic stenosis, which was advocated by Subramanian, et al. and Roberts, et al.19,20) in their cohort studies. On the other hand, patients with pure aortic regurgitation seemed to demonstrate preference for younger age, male gender, and RL fusion type, and were inclined to develop aortic root dilatation. As a potentially devastating complication, infective endocarditis remains a big challenge,21) especially among young regurgitant BAV patients. The occurrence of endocarditis was 3.2% in the present study, which was in agreement with a recent cross-sectional study by Li et al.22) Similar incidences could be found in follow-up studies by Michelena, et al. and Tzemos, et al. in 2008, while Roberts reported a much higher occurrence.
in his pilot BAV autopsy study in 1970.\textsuperscript{2,23,24} With growing awareness and improving surveillance, even before the onset of significant aortic valve dysfunction, we could expect better management of BAV valvular ailments and therefore fewer cases of infective endocarditis and overt cardiac remodeling.\textsuperscript{25,26}

Determinants of BAV aortopathy in the present study offered valuable insights regarding therapeutic options in BAV patients with aortic dilatation, especially during concomitant aortic valve surgery. The ongoing controversy of BAV aortopathy is reflected by the dichotomy between genetic and hemodynamic pathogenesis. This “fate versus flow” debate has led to the constantly changing consensus in practical guidelines for BAV aortopathy, swinging to and fro between aggressive and conservative surgical strategies. The past decade has witnessed the emergence and recognition of phenotypic heterogeneity in BAV aortopathy, which advocates the coexistence of both genetic and hemodynamic elements, albeit with variable weighing, from patient to patient.\textsuperscript{21,23} The present study demonstrated a similar 20% prevalence of aortic root dilatation across different age groups, but this prevalence was distinctly higher in males with pure aortic regurgitation. It perfectly corresponded to the signatures of the acknowledged clinical subgroup as “root phenotype,” who tended to suffer from adverse aortic events after isolated aortic valve procedures, implying stronger genetic background.\textsuperscript{20,30} Current guidelines have marked aortic regurgitation as a risk factor for BAV aortopathy and as an indicator for preemptive vessel intervention during valve procedure.\textsuperscript{31} We further recommended thorough familiar survey and genetic testing in BAV patients with root dilatation, especially those of male gender, RL fusion type, and pure aortic regurgitation. Ascending aortic dilatation, acknowledged as one of the hallmark features of BAV aortopathy, was more prevalent than root dilatation across age groups and rose above 50% among those older than 45 years. Recent histological and imaging researches have demonstrated elevated and eccentric aortic wall shear stress generated by a bicuspid valve, particularly in the cases of stenotic BAV.\textsuperscript{31,32} Prolonged exposure to the aberrant hemodynamic changes could be the reason why we found ascending aortic dilatation associated with both aging and aortic stenosis. Therefore, different therapeutic strategies should be carefully selected on the basis of distinct determinants associated with aortic root and ascending aortic dilatation, which represented two of the most important phenotypic subgroups of BAV aortopathy.

**Study limitations:** Several limitations should be noted concerning inherent referral bias related to the cross-sectional and single-centered nature of the present study. Providing a broad descriptive view of phenotypic heterogeneity of BAV from a hospital-derived echocardiography database, the present study could always benefit from community surveys and follow-up cohorts to better illustrate the natural history of BAV, as well as potential indicators for cardiovascular outcomes. Although transthoracic echocardiography is a well-adapted and rigid method for large-scale clinical survey, additional imaging techniques such as CTA could provide data on the entire aorta for better categorization of BAV aortopathy. Considering the hazard of exposure to contrast agents or ionizing radiation, these methods might be applied for subsequent studies on ascending aorta or aortic arch involvements, which could not be well apprehended by echocardiography.

**Conclusions**

The disease burden of BAV in the Chinese population is considerable, with male predominance and elevated risk for developing valvular and vascular complications. Bicuspid aortic stenosis and ascending aortic dilatation demonstrate a similar pattern of age escalation, while aortic regurgitation is more prevalent in younger BAV patients. Aortic root dilatation seems age insensitive and intervenes closely with a unique phenotypic subgroup of male BAV patients with pure aortic regurgitation and RL fusion type. Further efforts are encouraged to better define phenotypic subgroups of BAV on the basis of current understandings, thus aiming for the optimization of clinical management of BAV patients.

**Disclosure**

**Conflicts of interest:** none declared.

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