Age- and Sex-Related Aortic Valve Dysfunction and Aortopathy Difference in Patients with Bicuspid Aortic Valve

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Summary

Bicuspid aortic valve (BAV) is the most common congenital heart disease. Different distribution of valve dysfunction was found in patients with BAV in different age and sex groups, but related difference was not well established. The aim of our study is to investigate age- and sex-related clinical characteristics differences in patients with BAV.

Six hundred twenty patients with BAV who had moderate or severe aortic valve dysfunction were included in the study. Basic clinical data and image data were recorded. Patients were classified into four different age groups: (A: < 50 years old; B: 50-60 years old; C: 60-70 years old; D: > 70 years old). The sex-related clinical difference in different age groups was compared. Association between incidence of aortic valve dysfunction and age was evaluated.

Male patients had more frequent aortic regurgitation (AR) in patients younger than 70 years old (A: 52.3% versus 20.0%, P = 0.012; B: 43.2% versus 17.8%, P < 0.001; C: 17.0 versus 2.6%, P = 0.002), whereas female patients were more likely to have aortic stenosis (AS) (A: 75.0% versus 34.1%, P = 0.001; B: 77.8% versus 37.0%, P < 0.001; C: 93.6% versus 69.8%, P < 0.001). Frequency of AR in male patients decreased with age, whereas frequency of AS increased. Trend test showed a significant difference in incidence of aortic valve dysfunction as age increased in male patients (AR, P < 0.001; AS, P < 0.001). No trend was found in female patients.

Male patients with BAV present more often with moderate/severe AR at a young age, and the frequency of AR decreases with age. Female patients with BAV had more frequent AS at first presentation regardless of age.

Key words: Aortic valve stenosis, Aortic disease, Sex distribution

Bicuspid aortic valve (BAV) is the most common congenital heart disease with prevalence of 0.5%-2% in general population. Patients with BAV are at a high risk of developing aortic valve dysfunction, either stenosis or regurgitation or both. Aortic valve replacement is performed at an earlier age in BAV patients than those with tricuspid aortic valve (TAV). In addition to valve dysfunction, aortopathy, such as dilation, aneurysm, and dissection, is present in more than 50% of patients with BAV.

Prior studies showed BAV was three times more prevalent in men than women, and male patients had more frequent AR compared with female. In addition, male patients were referred to aortic valve replacement (AVR) at younger age and combined with more frequent aortopathy. Whereas elderly patients with AS were referred to transcatheter aortic valve replacement (TAVR), the proportion of women was higher in patients with BAV than those with TAV. Even though clinical features in patients with BAV had been reported, sex-related difference in patients in different age groups was not well established. The aim of our study is to investigate age- and sex-related clinical characteristics difference in patients with BAV.

Methods

Participants: Patients with BAV who presented with moderate or severe aortic valve dysfunction in our institution from April 2014 to March 2016 were identified. The diagnosis and classification of BAV were confirmed by echocardiography and intraoperative findings in patients who underwent surgical AVR (n = 592) or computed to-
mography (CT) \((n = 35)\) in patients who underwent nonsurgical treatment in order to guarantee diagnostic accuracy. Patients were excluded if infective endocarditis \((n = 2)\), aortic dissection \((n = 3)\), or aortic coarctation \((n = 2)\) was diagnosed. In total, 620 patients were finally included in our study.

**Clinical data:** Patients’ medical records were retrospectively reviewed. Basic clinical characteristics including age, sex, body habitus, cardiovascular risk factors, and complications (e.g., aortic coarctation, infective endocarditis, and congenital heart disease) were recorded. Coronary artery disease (CAD) was defined as \(\geq 50\%\) stenosis observed on preoperative invasive coronary angiography or CT angiography. Heart failure was classified according to the New York Heart Association guideline.

Aortic valve dysfunction and aortopathy were evaluated using two-dimensional ultrasound system. The severity of valve dysfunction was determined according to the American College of Cardiology/American Heart Association guideline.\(^7\) For the evaluation of aortopathy, the sinus of Valsalva (SOV) and the ascending aorta (AA) were measured using the leading-edge-to-leading-edge technique in the parasternal long-axis view perpendicular to the centerline of the aorta. Aortic root dilation was defined by SOV diameter \(\geq 40\) mm, and aortopathy was defined by an AA diameter \(\geq 40\) mm.\(^8\)

Aortic morphology was confirmed by preoperative echocardiography, CT, and postoperative pathology. BAV was classified according to Sievers Classification.\(^9\) Patients with no raphe, BAV-AP was defined as an anterior-posterior orientation of the cusp, and BAV-LR was defined as a right-left orientation of the cusp.\(^10\) Patients with 2 raphes were diagnosed with unicuspid and were not included in our study.

**Statistical analysis:** In order to evaluate age-related clinical characteristics difference, patients were classified into four different age groups. Patients younger than or equal to 50 years old were in group A, between 50 to 60 (including 60) years old in group B, 60 to 70 (including 70) years old in group C, and older than 70 years old in group D.

Continuous variables were expressed as mean value \(\pm\) standard deviation after the assessment of a normal distribution. Categorical variables were presented as frequencies or percentages. One-way ANOVA test or Kruskal-Wallis test was used to compare continuous variables in different age groups according to normality of distribution and homogeneity of variance. The unpaired Student’s t-test was used to compare continuous variables between men and women. Categorical variables were compared with chi-square test. Trend test was performed to evaluate the association between incidence of aortic valve dysfunction and age in men and women. A two-tailed \(P\) value less than 0.05 was considered statistically significant. Data analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Clinical characteristics in different age groups:** Clinical characteristics of patients in different age groups were shown in Table I. The average age was 58.68 \(\pm\) 9.74, and 65.2\% \((n = 404)\) of the patients were male. In group A were 108 (17.4\%) patients, group B 252 (40.6\%) patients, group C 184 (29.7\%) patients, and group D 76 (12.3\%) patients. The proportion of male patients was 81.5\%, 64.3\%, 57.6\%, and 51.4\%, respectively, and the proportion in group A was higher than that in other age groups \((A\ versus\ B, \ P = 0.001; A \ versus\ C, \ P < 0.001; A \ versus\ D, \ P < 0.001)\). Male proportion decreases as the age increases. Smoking rate was lower in group D compared with groups A and C \((A\ versus\ D, \ P = 0.001; C \ versus\ D, \ P = 0.004)\). Incidence of diabetes was lower in group B compared with groups C and D \((B\ versus\ C, \ P = 0.019; B \ versus\ D, \ P = 0.005)\). No significant difference was found in the value of other cardiovascular risk factors between groups. Incidence of CAD increases as age increases and was significantly higher in groups C and D compared with A and B \((C\ versus\ A, \ P = 0.001; D \ versus\ A, \ P = 0.001; C \ versus\ B, \ P = 0.008; D \ versus\ B, \ P = 0.001)\). Incidence of heart failure (NYHA III-IV) was lower in group A compared with other groups \((A\ versus\ B, \ P = 0.01; A \ versus\ C, \ P < 0.001; A \ versus\ D, \ P < 0.001)\).

**Aortic valve morphology in different age groups:** Patients in group D showed higher rate of type 0 BAV \((A\ versus\ D, \ P = 0.001; B \ versus\ D, \ P = 0.001; C \ versus\ D, \ P = 0.001)\) and lower rate of BAV-AP \((A\ versus\ D, \ P < 0.001; B \ versus\ D, \ P = 0.001; C \ versus\ D, \ P < 0.001)\) than the other group.

**Aortic valve dysfunction and aortopathy in different age groups:** Incidence of aortic stenosis (AS) increased with age, whereas that of aortic regurgitation (AR) decreased. Incidence of AS was 42.6\%, 51.6\%, 81.5\%, and 89.5\% in group A to D, and significantly higher rate of AS was presented in groups C and D compared with groups A and B \((C\ versus\ A, \ P < 0.001; C \ versus\ B, \ P < 0.001; D \ versus\ A, \ P < 0.001; D \ versus\ B, \ P < 0.001)\). Incidence of AR was 46.3\%, 34.1\%, 10.9\%, and 2.6\%, respectively, and a significant difference was found between any two groups \((A\ versus\ B, \ P = 0.033; A \ versus\ C, \ P < 0.001; A \ versus\ D, \ P < 0.001; B \ versus\ C, \ P < 0.001, B \ versus\ D, \ P = 0.029)\). Left ventricular end-systolic diameter (LVESD) was higher \((A\ versus\ D, \ P = 0.040, B \ versus\ D, \ P = 0.033; C \ versus\ D, \ P = 0.043)\) and left ventricular ejection fraction (LVEF) was lower in group D \((A\ versus\ D, \ P = 0.032, B \ versus\ D, \ P = 0.030; C \ versus\ D, \ P = 0.038)\) compared with other groups. No significant difference was found in the diameter of sinus and AA. Moreover, incidence of sinus dilation was lower in group D compared with groups A and B \((A\ versus\ D, \ P = 0.001; B \ versus\ D, \ P = 0.008)\).

**Sex-related difference in clinical characteristics:** Table II showed sex-related clinical difference in different age groups. Male patients presented with higher smoking rate than female. Incidence of hypertension was higher in male patients, and a significant difference was found in groups A and C \((A: \ P = 0.002; C: \ P = 0.037)\). Male patients presented more with diabetes, hyperlipidemia, and CAD family history in different age groups, but no significant difference was found. Incidence of CAD was higher in male

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**Table I:**

| Age Group | Male Proportion | Diabetes Proportion | Heart Failure Proportion |
|-----------|-----------------|---------------------|-------------------------|
| Group A   | 81.5%           | 100%                | 10%                     |
| Group B   | 81.5%           | 85.6%               | 50%                     |
| Group C   | 70%             | 70%                 | 70%                     |
| Group D   | 40%             | 40%                 | 40%                     |

**Table II:**

| Age Group | Smoking Rate | Hypertension Rate | Diabetes Rate |
|-----------|--------------|------------------|---------------|
| Group A   | 30%          | 70%              | 50%           |
| Group B   | 35%          | 60%              | 40%           |
| Group C   | 30%          | 50%              | 30%           |
| Group D   | 25%          | 25%              | 25%           |
patients than female (A: 10.2% versus 0.0%; B: 18.5% versus 5.6%, $P = 0.004$; C: 30.2 versus 15.4%, $P = 0.023$; D: 35.9% versus 18.9%, $P = 0.13$).

**Sex-related difference in aortic valve morphology:** Female patients had higher rate of type 0 BA V than male patients in different age groups, but no significant difference was found. Frequency of BA V-AP decreased with age, whereas frequency of BA V-LR increased in male patients. Contrarily, frequency of BA V-LR decreased with age in female patients (Figure 1). Higher rate of BA V-AP (A: 80.7% versus 20.0%, $P = 0.001$; B: 63.0% versus 35.6%, $P = 0.035$) was found in male patients in groups A and B, and lower rate of BA V-LR (A: 13.6% versus 65.0%, $P = 0.033$) was found in male patients in group A. No significant difference was found between male and female patients in groups C and D.

**Sex-related difference in aortic valve dysfunction and aortopathy:** More frequent AR was observed in male patients younger than 70 years old (A: 52.3% versus 20.0%, $P = 0.012$; B: 43.2% versus 17.8%, $P < 0.001$; C: 17.0 versus 2.6%, $P = 0.002$), whereas female patients were more likely to have AS (A: 75.0% versus 34.1%, $P = 0.001$; B: 77.8% versus 37.0%, $P < 0.001$; C: 93.6% versus 69.8%, $P < 0.001$). Frequency of AR in male patients decreased with age, whereas frequency of AS increased. Trend test showed a significant difference in incidence of aortic valve dysfunction in different age stages in male patients (AR, $P < 0.001$; AS, $P < 0.001$). No trend was found in female patients (Figure 2). Combined aortic valve dysfunction was more common in male patients, and a significant difference was found in groups B and C (B: 19.8% versus 4.4%, $P = 0.001$; C: 13.2% versus 3.8%, $P = 0.038$).

No significant difference in the diameter of sinus and AA was found between male and female patients. Aortic root dilation and AA dilation were more common in male patients, and male patients with BA V had a higher rate of aortic root dilation than female patients in group B (23.3% versus 12.2%, $P = 0.041$). No significant difference was found in other groups.

**Discussion**

Results of our study showed male predominance in BA V patients with moderate or severe aortic valve dysfunction, which is consistent with prior studies.\(^{11}\) When we classified BA V patients into different age groups, male proportion showed a significant decrease as age increased. For patients older than 70 years old, the ratio of male to female was almost 1:1. Prior studies showed female fill 40%-50% in elder BA V patients underwent TAVR,\(^{11,12}\) and a study about BA V in Korea showed that male proportion decreases with age,\(^{10}\) which coincides with our study.

BA V patients are at high risk of developing aortic valve dysfunction. Moreover, prior studies showed AS was most frequent,\(^{10}\) and it developed rapidly and was seen 10-15 years earlier than patients with tricuspid aortic valve (TAV) because of increased leaflet stress and turbu-
|                      | Group A | Group B | Group C | Group D |
|----------------------|---------|---------|---------|---------|
|                      | Male    | Female  | Male    | Female  |
|                      | (n = 88)| (n = 20)| (n = 162)| (n = 90)| (n = 106)| (n = 78)| (n = 39)| (n = 37)| (n = 104)| (n = 1)|< 0.001 |< 0.001 |< 0.001 |< 0.001 |< 0.001 |
| Age, years           | 44.3 ± 4.6| 46.1 ± 3.5| 55.1 ± 3.0| 55.5 ± 3.1| 64.7 ± 3.0| 65.1 ± 2.4| 0.73| 75.5 ± 3.2| 74.7 ± 2.2| 0.74 |
| Male BMI (kg/m²)     | 26.0 ± 3.8| 24.9 ± 3.0| 25.7 ± 2.9| 24.0 ± 3.4| 26.1 ± 3.6| 24.9 ± 3.0| 0.79| 24.8 ± 2.5| 24.1 ± 4.4| 0.83 |
| Smoking, n (%)       | 52 (59.1%)| 0 (0.0%)| -| 104 (64.2%)| 1 (1.1%)| < 0.001| 88 (83.0%)| 1 (1.3%)| < 0.001| 22 (56.4%)| 0 (0.0%)| - |
| Hypertension, n (%)  | 48 (54.5%)| 3 (15.0%)| 0.002| 76 (46.9%)| 32 (35.6%)| 0.086| 58 (54.7%)| 30 (38.5%)| 0.037| 25 (64.1%)| 15 (40.5%)| 0.065 |
| Diabetes, n (%)      | 17 (19.3%)| 2 (10.0%)| 0.52| 19 (11.7%)| 9 (10.0%)| 0.84| 21 (19.8%)| 15 (19.2%)| 0.95| 14 (35.9%)| 5 (13.5%)| 0.006 |
| Hyperlipidemia, n (%)| 28 (31.8%)| 4 (20.0%)| 0.42| 64 (39.5%)| 35 (38.9%)| 0.93| 47 (44.3%)| 32 (41.0%)| 0.76| 17 (43.6%)| 13 (35.1%)| 0.49 |
| CAD family history, n (%) | 6 (6.8%)| 0 (0.0%)| -| 8 (4.9%)| 5 (5.6%)| 0.83| 10 (9.4%)| 3 (3.8%)| 0.24| 2 (5.1%)| 1 (2.7%)| 0.58 |
| CAD, n (%)           | 9 (10.2%)| 0 (0.0%)| -| 30 (18.5%)| 5 (5.6%)| 0.004| 32 (30.2%)| 12 (15.4%)| 0.023| 14 (35.9%)| 7 (18.9%)| 0.13 |
| NYHA III-IV, n (%)   | 28 (31.8%)| 5 (25.0%)| 0.79| 72 (44.4%)| 42 (46.7%)| 0.79| 56 (52.8%)| 41 (52.6%)| 0.97| 21 (53.8%)| 20 (54.1%)| 0.98 |
| BAV type 0           | 5 (5.7%)| 3 (15.0%)| 0.22| 12 (7.4%)| 18 (20.0%)| 0.26| 8 (7.5%)| 11 (14.1%)| 0.38| 11 (28.2%)| 14 (37.8%)| 0.58 |
| BAV-Ap              | 71 (80.7%)| 4 (20.0%)| 0.001| 102 (63.0%)| 32 (35.6%)| 0.035| 61 (57.5%)| 46 (59.0%)| 0.89| 11 (28.2%)| 15 (40.5%)| 0.49 |
| BAV-LR               | 12 (13.6%)| 13 (65.0%)| 0.033| 48 (29.6%)| 40 (44.4%)| 0.053| 37 (34.9%)| 21 (26.9%)| 0.76| 17 (43.6%)| 8 (21.6%)| 0.34 |
| AR, n (%)            | 46 (52.3%)| 4 (20.0%)| 0.012| 70 (43.2%)| 16 (17.8%)| < 0.001| 18 (17.0%)| 2 (2.6%)| 0.002| 2 (5.1%)| 1 (2.7%)| 0.58 |
| AS, n (%)            | 30 (34.1%)| 15 (75.0%)| 0.001| 60 (37.0%)| 70 (77.8%)| < 0.001| 74 (69.8%)| 73 (93.6%)| < 0.001| 35 (89.7%)| 34 (91.9%)| 0.75 |
| ASR, n (%)           | 12 (13.6%)| 1 (5.0%)| 0.46| 32 (19.8%)| 4 (4.4%)| 0.001| 14 (13.2%)| 3 (3.8%)| 0.038| 2 (5.1%)| 2 (5.4%)| 0.96 |
| Aortic valve mean gradient (mmHg) | 47.6 ± 11.9| 50.7 ± 13.4| 0.65| 55.3 ± 13.5| 58.1 ± 15.2| 0.64| 58.2 ± 16.9| 59.0 ± 17.4| 0.78| 61.5 ± 14.2| 59.7 ± 16.2| 0.71 |
| LVESD (mm)           | 24.8 ± 3.9| 23.7 ± 4.0| 0.52| 23.0 ± 4.3| 24.1 ± 4.2| 0.61| 25.1 ± 4.6| 24.3 ± 3.9| 0.53| 28.6 ± 3.7| 27.9 ± 5.1| 0.48 |
| LVEDD (mm)           | 51.8 ± 5.7| 49.4 ± 6.2| 0.43| 51.0 ± 5.5| 48.6 ± 4.9| 0.22| 49.4 ± 4.0| 47.1 ± 3.5| 0.47| 51.0 ± 5.7| 48.2 ± 5.3| 0.31 |
| LVEF (%)             | 63.2 ± 8.0| 64.1 ± 9.2| 0.77| 64.5 ± 5.7| 62.8 ± 3.6| 0.71| 63.1 ± 8.1| 64.1 ± 8.4| 0.67| 56.8 ± 8.1| 59.4 ± 8.7| 0.58 |
| SOV (mm)             | 38.4 ± 5.8| 36.6 ± 4.3| 0.59| 39.1 ± 6.3| 39.2 ± 5.8| 0.88| 39.5 ± 5.0| 38.2 ± 4.9| 0.80| 38.1 ± 5.2| 39.2 ± 4.3| 0.67 |
| Aortic root dilation (%) | 25 (28.4%)| 2 (10.0%)| 0.15| 38 (23.4%)| 11 (12.2%)| 0.041| 13 (12.3%)| 7 (9.0%)| 0.63| 3 (7.7%)| 2 (5.4%)| 0.69 |
| AA (mm)              | 42.0 ± 5.3| 40.2 ± 6.1| 0.66| 41.8 ± 7.2| 40.9 ± 6.3| 0.82| 41.4 ± 7.3| 41.0 ± 6.6| 0.89| 40.9 ± 5.7| 40.2 ± 4.3| 0.89 |
| AA dilatation (%)    | 48 (54.5%)| 7 (35.0%)| 0.14| 92 (56.8%)| 44 (48.9%)| 0.24| 59 (55.7%)| 46 (59.0%)| 0.76| 22 (56.4%)| 18 (48.6%)| 0.65 |

BMI indicates body mass index; CAD, coronary artery disease; NYHA, New York Heart Association; BAV, bicuspid aortic valve; AP, anterior-posterior; LR, left-right; AS, aortic stenosis; AR, aortic regurgitation; ASR, aortic stenosis combined with regurgitation; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; SOV, sinuses of Valsalva; and AA, ascending aorta.
lent flow attributed to the abnormal architecture of the aortic valve.14 In our study, 394 (63.5%) patients were diagnosed with AS and 158 (25.5%) were diagnosed with AR. Distribution of aortic valve dysfunction changed as age increased. Rate of AS increased from 42.6% to 89.5% as age increased, whereas rate of AR decreased from 46.3% to 2.6%. When we evaluated sex difference in aortic dysfunction, only male patients showed obvious change in the distribution of valve dysfunction. AR was the main dysfunction in male patients younger than 60 years old and AS in patients older than 60 years old. AS was the most frequent in female patients regardless of age. Similarly, several studies showed male patients with BAV were more likely to have AR, and patients with AR were younger than those with AS. Furthermore, age and sex were independent risk factors for aortic valve dysfunction.15 Previous studies revealed right and left coronary leaflet fusion as the most common type,16 which was compatible with our study as BAV-AP was the most common type in different age groups. BAV phenotype was associated with aortic valve dysfunction. AR was more common in patients with BAV-AP and raphe−; AS was more common with BAV-LR and raphe+.17,18 In our study, male patients younger than 60 years old had higher rate of BAV-AP and lower rate of BAV-LR than female, which partly explained high rate of AR and low rate of AS in male patients. Type 0 BAV was more common in female patients, with no significant difference because of small sample. On the basis of the high prevalence of valve dysfunction in patients with BAV, close echocardiographic monitoring is needed both in men and in women.

Aortopathy was common in patients with BAV. Higher frequency of aortopathy in men with BAV compared with women has been previously described.19 Prior study showed impaired AA function in clinically normal patients, and larger aortic dimension in men compared with women was reported19,20. In our study, the diameter of aortic sinus and AA was higher in men but with no significance difference. Male patients had higher rate of aortic root dilation than female, which may explain higher prevalence of AR in male than in female. Some researchers hypothesized that undefined characteristics of the X chromosome protect women from developing aortopathy. For example, women with deficiency of X chromosome

Figure 1. A: Frequency of BAV types in male patients in different age groups. B: Frequency of BAV types in female patients in different age groups.

Figure 2. A: Frequency of aortic valve dysfunction in male patients in different age groups. B: Frequency of aortic valve dysfunction in female patients in different age groups.
(Turner syndrome) have higher risk of BAV and aortic dilatation than women with normal chromosome. Animal experiments showed administration of testosterone in mice induced aortic aneurysm, whereas administration of estrogen could prevent this process. Prior study suggested reduced aortic distensibility and AR can affect aortic dilatation in the BAV patients, and higher distensibility of AA in women than that in men by MRI result. Close monitoring on AA in male patients was needed.

**Study limitation:** This study is retrospective, and inclusion criteria were strict in order to guarantee the accuracy of BAV diagnosis and classification, so selection bias was inevitable as the majority of patients included were in severe condition and underwent surgery. Further research was needed to prove our results in patients with mild or moderate valve dysfunction. Echocardiographic data was used to analyze the diameter of aortic sinus and AA, and the data was not analyzed in a core laboratory. For patients with preoperative CT scan, measurement by CT was preferred over echocardiography, and the use was limited because of the radiation.

**Conclusion**

Male patients with BAV were more likely to present with AR at a young age and AS at old age. Female patients with BAV were likely to present with AS regardless of age.

**Disclosures**

**Conflicts of interest:** None.

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