The Heterogeneous Phenotype of Bicuspid Aortopathy Attribute to Different Dominant Pathogenesis

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Purpose: Our study aimed to investigate the potential pathogenetic theories of different phenotype prevalence in bicuspid aortopathy.

Methods: A total of 407 bicuspid aortic valve (BAV) patients with aortic dilation were retrospectively reviewed. Association was determined between aortic valve lesion types and aortic configurations to confirm the homogeneous BAV subsets, and then, dominance analysis was used to evaluate the relative importance of two components of aortic valve lesion (BAV phenotype and valvular dysfunction) that associated with aortic configurations in each subgroup.

Results: Dominance analysis showed that Type-1 LR was the dominant contributor (79.0% and 79.6%) associated with the higher prevalence of the dilation of aortic root (AoR) and ascending aorta (AAo) in BAV patients with Type-1 LR and aortic regurgitation (AR) or aortic stenosis (AS) + AR. However, AS was the main contributor (60.0%) associated with the raised incidence of the dilation of AAo and proximal aortic arch (PArc) in Type-0 LAT and AS.

Conclusions: Different dominant pathogenetic theory determined the phenotype of BAV aortopathy. In patients of Type-1 LR with AR, inherent disposition is mainly responsible for the higher frequency of AoR dilation. Valve-related hemodynamics determined greater prevalence of the dilation of AAo and PArc in patients of Type-0 LAT with AS.

Keywords: bicuspid aortic valve, dilation of proximal aorta, computed tomography angiography, dominance analysis

Introduction

Bicuspid aortic valve (BAV) is common congenital heart disease with an estimated prevalence of 1% to 2% in the general population, and the dilation of the aorta is a frequently observed phenomenon. Clinical heterogeneity of BAV-associated aortic dilation was found in previous studies, which implied that its pathogenesis was dominated by distinguishing way in the different phenotype of aortic configurations. Two main theories were...
widely accepted to explain the phenomenon of BAV aortopathy.\textsuperscript{3,5} The genetic theory led to more aggressive treatment recommendations of the proximal aorta in BAV patients with aortopathy, whereas the belief that bicuspid aortopathy is a secondary disorder of hemodynamic causes supported the policy of being less aggressive in these patients concerning aortic replacement.\textsuperscript{3–6} Hence, the different homogeneous subsets of BAV aortopathy individuals should be discretized to focus on and highlighted for a deeper understanding of pathogenesis.

Researchers have revealed the association between BAV phenotypes, patterns of valvular dysfunction and aortic configuration to investigate explanations for BAV aortopathy.\textsuperscript{7–9} The correlation indicated that BAV phenotypes and/or valve hemodynamics may predict aortic configuration and the homogeneous groups of BAV aortopathy could be discretized, implying the explanation of potential pathogenic theory of bicuspid aortopathy. However, the combination of BAV phenotype and pattern of valvular dysfunction was routinely used to investigate the association with aortic configuration.\textsuperscript{3} The contribution rate of these two components was not accurately evaluated in the association analysis procedure, and homogeneous subsets of BAV aortopathy could not be precisely identified, which is difficult to provide accurate evidence of pathogenesis for further researches.

Our study tried to analyze the relative importance of BAV phenotype and pattern of valvular dysfunction about aortic configuration after the determination of the association between the aortic valve lesion type (combining by BAV phenotype and patterns of valvular dysfunction) and aortic configuration. The contribution rate of BAV phenotype and valvular dysfunction in the correlation can be correctly discerned by dominance analysis.

**Materials and Methods**

**Data collection**

Our study was a retrospective study, and all of the data were collected through electronic medical records at our institution with ethical approval and analyzed anonymously. Informed consent was not available because no change was applied to the patients’ treatment. We retrospectively reviewed 523 patients with BAV who underwent both aortic computed tomography angiography (CTA) and transthoracic echocardiography between February 2011 and January 2016. All of these patients underwent aortic surgery (aortic root [AoR] and/or ascending aorta [AAo] and/or proximal aortic arch [PArc]) with or without surgery of the aortic valve.

In all, 83 patients were excluded who were diagnosed with connective tissue diseases, aortic coarctation, abdominal aortic aneurysm and aortic dissection. Additionally, we excluded 33 patients who had undergone previous cardiac surgery. As a result, a total of 407 patients were included in the study. Every patient’s age, sex, body habits, and medical history were recorded.

**Definition and diagnostic criteria**

**Classification of the BAV phenotypes**

BAV phenotypes were observed and recorded during surgery according to three criteria: number of Valsalva sinuses and leaflets, number of raphes, and spatial orientation of the raphes.\textsuperscript{10} The morphologies of BAV were classified into five types (Fig. 1). Type-0 presented with two aortic sinuses and two valve leaflets with no raphe, and anterior-posterior (AP) was defined as the ostium of left coronary and right coronary in one Valsalva sinus and lateral (LAT) in two Valsalva sinuses. Type-1 presented with three aortic sinuses and two valve leaflets with one raphe between two sinuses. The raphe positioned between the left (L) and right (R) coronary sinus was determined as LR, and it positioned between the right coronary sinus and noncoronary (N) sinus was determined as RN, in the same method, LN meant that the raphe positioned between the left coronary sinus and noncoronary sinus.

**Definition of aortic valve lesion types**

Valvular dysfunction in all patients was evaluated by a two-dimensional echocardiographic imaging system pre-operation. Valvular dysfunction was categorized as aortic stenosis (AS) due to leaflet calcification (no regurgitant grade >1, orifice area of 1 cm² or mean pressure gradient of transvalvular >50 mmHg), aortic regurgitation (AR) due to no stenotic coexistence (maximal transvalvular pressure gradient <20 mmHg, no calcification of the valve intraoperatively) or AS combined with AR (AS+AR).\textsuperscript{3} Aortic valves that functioned well were defined as normal function BAV. Aortic valve lesion types were defined by the two combinations of BAV phenotypes and types of valvular dysfunction.

**Determination of the clusters of aortic dilation**

Gated CTA was used to measure the diameter of three sections: (1) the aortic sinus (maximum value), (2) tubular portion of the AAo, (3) PArc. All of the CTA images were
different pathogenesis in bicuspid aortopathy

reviewed by applying three-dimensional reconstruction to analyze the aortic morphology and were finally assessed by two experienced radiologists independently.

Dilation was defined as a diameter $\geq 40$ mm at each measured level. Based on the measurements of the diameter and modifications of other studies, five clusters of aortic configurations were confirmed: AoR dilation: Valsalva sinus diameter $\geq 40$ mm and other levels $< 40$ mm; AAo dilation: the tubular portion of the AAo $\geq 40$ mm and other levels $< 40$ mm; AAo and PArc dilation: both the tubular portion of the AAo and transverse of the PArc $\geq 40$ mm and Valsalva sinus $< 40$ mm; AAo+AoR dilation: the Valsalva sinus and AAo diameters both $\geq 40$ mm and the transverse of the PArc $< 40$ mm; AoR+AAo+PArc dilation: the diameters of all three levels $\geq 40$ mm.

Statistical analysis

Continuous variables were presented as the mean $\pm$ standard deviation. Categorical variables were expressed as frequencies and percentages. One-way analysis of

Fig. 1 Schematic presentation of the classification of the BAV phenotypes. The phenotypes were classified according to three criteria: the number of Valsalva sinuses, the number of raphes, and the spatial orientation of raphes. (A) The patterns of the BAV phenotype: the solid line represents the edge of leaflets, and the dashed line represents the raphe between two leaflets. The gap shows the ostium of the coronary artery. (B) Images acquired from 3D reconstruction CTA (faint white arrows: the ostium of coronary artery). In the right panel, three types of BAV are shown. (C) Intraoperative view of the different BAV types (white arrows: raphes between two leaflets; black arrows: normal commissures). 3D: three-dimensional; BAV: bicuspid aortic valve; CTA: computed tomography angiography; AP: anterior–posterior; LAT: lateral; L: left coronary sinus; N: noncoronary sinus; R: right coronary sinus
Table 1  Patient characteristics

| BAV phenotypes | Type-0 AP (n = 13) | Type-0 LAT (n = 98) | Type-1 LR (n = 221) | Type-1 RN (n = 66) | Type-1 LN (n = 9) | Total (n = 407) | P values |
|----------------|--------------------|--------------------|--------------------|-------------------|------------------|----------------|----------|
| Age (years)    | 56.52 ± 9.55       | 55.74 ± 9.18       | 50.48 ± 10.68      | 51.49 ± 11.85     | 45.67 ± 17.45    | 52.00 ± 10.92 | <0.01   |
| Gender (male %)| 8 (61.5)           | 64 (65.3)          | 186 (84.2)         | 48 (72.7)         | 8 (88.9)         | 314 (77.1)    | 0.002   |
| Height (cm)    | 166.92 ± 6.38      | 167.52 ± 7.33      | 169.88 ± 7.28      | 167.76 ± 7.68     | 170.78 ± 8.53    | 168.89 ± 7.42 | 0.03    |
| Weight (kg)    | 70.31 ± 9.19       | 70.37 ± 10.86      | 72.26 ± 12.20      | 70.36 ± 11.85     | 75.39 ± 9.77     | 71.50 ± 11.70 | 0.46    |
| Hypertension (n %) | 5 (38.5)          | 28 (28.6)          | 76 (34.4)          | 23 (34.8)         | 2 (22.2)         | 134 (32.9)    | 0.77    |
| Aortic dimension |                  |                    |                    |                   |                  |                |         |
| AS             | 10 (76.9)          | 79 (80.6)          | 60 (27.1)          | 30 (45.5)         | 4 (44.5)         | 183 (45.0)    | <0.001  |
| AR             | 0 (0)              | 1 (1.0)            | 62 (28.1)          | 6 (9.1)           | 1 (11.1)         | 70 (17.2)     | <0.001  |
| AS+AR          | 2 (15.4)           | 9 (9.2)            | 85 (38.5)          | 26 (39.4)         | 3 (33.3)         | 125 (30.7)    | <0.001  |
| Aorta dilatation |                  |                    |                    |                   |                  |                |         |
| AoR (mm)       | 41.00 ± 5.03       | 42.95 ± 6.19       | 44.81 ± 7.66       | 43.34 ± 6.11      | 43.71 ± 6.75     | 43.57 ± 6.95  | <0.001  |
| AAo (mm)       | 53.16 ± 4.98       | 49.07 ± 2.93       | 50.98 ± 7.12       | 53.11 ± 5.30      | 49.38 ± 4.80     | 51.76 ± 6.33  | 0.005   |
| PArC (mm)      | 43.36 ± 5.00       | 39.85 ± 4.77       | 38.66 ± 5.13       | 42.36 ± 6.10      | 40.51 ± 6.46     | 40.47 ± 5.66  | <0.001  |

AAo: ascending aorta; AoR: aortic root; AR: aortic regurgitation; AS: aortic stenosis; BAV: bicuspid aortic valve; PArC: proximal aortic arch; for description of BAV types, see Fig. 1

variance were used to compare continuous variables based on the normality of distribution and homogeneity of variance. The chi-square test and Fisher’s exact test were used to compare frequencies among groups. Due to limited samples and based on disease morbidity, five main aortic valve lesion types (Type-1 LR+AS, Type-1 LR+AR, Type-1 LR+AS+AR, Type-1 RN+AS, Type-0 LAT+AS) were selected to analyze the association with the four main aortic configurations (excluding AoR). After the determination of the association, the significant distributions (Pearson’s standardized residuals $>2$, or $<2$) of patient clusters were selected.

In the logistic regression model, aortic configuration was viewed as the ending variable, and odds ratios (95% CI) for the associations of BAV phenotype and patterns of valvular dysfunction with aortic configuration in six identified groups were calculated using binary logistic regression analysis, which adjusted for age, gender and height in each individual model. Dominance analysis was adopted for the relative importance of two components of aortic valve lesions (BAV phenotype and pattern of valvular dysfunction) in logistic regression model to evaluate the relative importance of independent variables by calculating and comparing the average incremental contribution $\Delta R^2$ of a variable relative to all possible subset models, and the $\Delta R^2$ was calculated as the difference between the 2 pseudo $R^2$’s of logistic regression when the predictor is added to the model.12,13 All analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA). A mosaic plot was generated with R version 3.5.0 (R Development Core Team 2018; R: A Language and Environment for Statistical Computing. Vienna, Austria; 2018, available at http://www.R-project.org/). The P values were reported two-sided, and $P < 0.05$ was considered significant.

Results

Patient demographics are summarized in Table 1. Of the 407 patients in our study, 314 (77.1%) were males. The mean age of all patients was 52.00 ± 10.92 years, and the incidence of hypertension was 32.9% (134 of 407). At the time of surgery, BAV Type-1 (50.56 ± 11.19 years) patients were younger than Type-0 (55.83 ± 9.18 years) patients ($P < 0.001$), and patients with AR (45.93 ± 9.65 years) were younger than those with AS (54.02 ± 10.76 years). AS was the most common hemodynamic abnormality (45.0%), followed by AS+AR (30.7%). For the bicuspid aortopathy, AoR+AAo+PArC dilatation was the most common type in these patients (35.1%).

The association between the type of aortic valve lesion and aortic configuration

The cross-tabulation presented a clear significant difference between aortic valve lesion type and aortic configuration ($X^2 = 90.81$, 12 df, $P < 0.001$). The distribution of the null hypothesis is shown in Fig. 2 (left), and the frequency distribution of certain observed events is shown in Fig. 2 (right). Pearson’s standardized residuals of an observed value and the difference between the
observed value and estimated value of the quantity of interest were color-coded based on the frequency distribution of events. Pearson’s standardized residuals $>2$ or $<-2$ were considered statistically significant. More patients ($>2$ Pearson’s standardized residuals) who had Type-1 LR and AS with AAo dilation were observed. Patients with Type-1 LR and AR were much more likely ($>4$ Pearson’s standardized residuals) and tended to have AoR+AAo dilation, and there were fewer patients with AAo+PAr dilation. More patients ($>2$ Pearson’s standardized residuals) who had Type-1 LR and AS+AR with AoR+AAo dilation were observed. Besides, patients with Type-0 LAT and AS ($>2$ Pearson’s standardized residuals) were prevalent in the AAo+PAr dilation group, and there were significantly fewer patients with AoR+AAo dilation.

The contribution of BAV phenotype and pattern of valvular dysfunction in the overall participant logistic regression model

After adjustment for confounding factors in each model, BAV phenotype and patterns of aortic valve dysfunction were significantly associated with an increased prevalence of aortic configuration, and the detailed results are presented in Table 2. Dominance analysis showed the contribution rate of BAV phenotypes and patterns of valvular dysfunction (Table 3). The variance contribution of Type-1 LR was 51.2%, AS was 48.8% for higher prevalence of AAo dilation in BAV patients of Type-1 LR with AS. Type-1 LR occupied the main variance contribution (79.0% and 62.3%) for the elevated prevalence of AoR+AAo dilation and morbidity reduction of AAo+PAr dilation in BAV Type-1 LR and AR. The similar result (Type-1 LR, 79.6%) was also observed in patients having BAV Type-1 LR, AAo+AoR dilatation and AS+AR. On the contrary, in Type-0 LAT and AS, the variance contribution of Type-0 LAT was 40.0%, AS was 60.0% for the raised incidence of AAo+PAr dilation, Type-0 LAT was 23.2%, and AS was 76.8% for the lower prevalence of AoR+AAo dilation.

Discussion

Most of the studies have focused on the heterogeneity of bicuspid aortopathy, and many researchers have accentuated the variability of possible presentations and explored patient characteristics or leaflet fusion patterns or valvular dysfunction types that may help in anticipating the development of aortic dilation in BAV individuals. Association between valve phenotype and aortic configuration also has been analyzed to investigate possible pathogenetic clues, whereas divergent results between the studies were observed. Schäfer et al.8) showed in 2008 that Type-1 LR BAV associated with AoR dilation and Type-1 RN associated with mid-AAo dilation. However, Sievers et al.3) did not find similar results, and they revealed the weak association between BAV phenotypes and aortic configurations only for Type-0 BAV and AoR dilatation. In the study of Kang et al.7) 3 BAV phenotypes (Type-1 RN, Type-1 LN and Type-0 LAT) were
concluded as “BAV-RL” that results from the fusion of the right or left coronary cusps with a noncoronary cusp. They found that board dilation of AAo was the most frequent phenotype in BAV-RL patients. From the differences of the results in various epidemiological studies, clinical heterogeneity among BAV populations could be found. It implied that BAV individuals should be identified, according to the continuum of possible anatomic-clinical forms, and separated as homogeneous subsets to focus on in further researches.\(^\text{16}\)

In our study, the association analysis between the aortic valve lesion type (combining by BAV phenotype and patterns of valvular dysfunction) and aortic configuration identified the homogeneous subgroups of BAV patients who have the similar clinical characteristics. Dominance analysis that proceeded in six identified homogeneous subgroups, showed that the BAV phenotype and valvular dysfunction type have an almost equal contribution rate to the higher prevalence of AAo dilation in BAV patients of Type-1 LR with AS. In patients with Type-1 LR and AR or AS+AR, BAV phenotype was the main contributor to the higher prevalence of AoR+AAo dilation and the less frequently occurring of AAo+PAr dilation. AS was mainly responsible for the higher prevalence of AAo+PAr dilation and the lower prevalence of AoR+AAo dilation in patients with Type-0 LAT and AS.

Potential causality correlation has been demonstrated between valve-related hemodynamics or inherent disposition and bicuspid aortopathy. Post-stenotic aortic dilation, causing by high-speed flow disturbance downstream of a stenotic valve, is a common phenomenon that related to elevated wall shear stress of the AAo.\(^\text{6,17}\) Guzzardi et al.\(^\text{6}\) proved that regions of increased wall shear stress correspond with ascending aortic wall lesion of BAV patients, implicating valve-related hemodynamics involved in the development of aortopathy. However, AoR dilation may be an inherent form of BAV associated disease and a heterogeneous disease compared with tubular mid-ascending aortic dilatation, confirming the speculation of Cotrufo et al.\(^\text{16}\) Aortic annulus enlargement that responses to AoR stretch occur in AoR dilation, leading to AR.\(^\text{18}\) The heterogeneity of BAV aortopathy was elaborated by Norton et al.\(^\text{19}\) and they believed that AoR dilation and AR should be treated more aggressively during surgery.

Hence, the pattern of valvular dysfunction could represent the valve hemodynamics\(^\text{20}\) in the process of analysis, and then the implication of the BAV phenotype could be viewed as an inherent factor. Both inherent disposition

| Table 2 | Adjusted odds ratios of six identified subgroups for the associations of aortic valve lesion components with aortic configurations |
|---------|-------------------------------------------------------------------------------------------------------------------------|
| Aoo    | Aoo+PAr                                      | Aoo+PAr                                      | Aoo+PAr                                      | Aoo+PAr                                      | Aoo+PAr                                      | Aoo+PAr                                      |
| 2.53   | 2.48                                        | 2.76                                          | 2.89                                          | 2.76                                          | 2.62                                          |
| Type-1 LR | Type-1 LR                                 | Type-1 LAT                                   | Type-1 LAT                                   | Type-1 LAT                                   | Type-1 LAT                                   |
| AS     | AS                                          | AS+AR                                        | AS+AR                                        | AS+AR                                        | AS+AR                                        |
| 0.36   | 0.38                                        | 0.36                                          | 0.36                                          | 0.36                                          | 0.36                                          |
| 0.19   | 0.21                                        | 0.19                                          | 0.21                                          | 0.19                                          | 0.21                                          |
| 0.66   | 0.66                                        | 0.66                                          | 0.66                                          | 0.66                                          | 0.66                                          |
| 5.00   | 5.00                                        | 5.00                                          | 5.00                                          | 5.00                                          | 5.00                                          |
| 0.60   | 0.60                                        | 0.60                                          | 0.60                                          | 0.60                                          | 0.60                                          |
| 0.06   | 0.06                                        | 0.06                                          | 0.06                                          | 0.06                                          | 0.06                                          |
| 3.57   | 3.57                                        | 3.57                                          | 3.57                                          | 3.57                                          | 3.57                                          |
| 0.02   | 0.02                                        | 0.02                                          | 0.02                                          | 0.02                                          | 0.02                                          |
| 0.48   | 0.48                                        | 0.48                                          | 0.48                                          | 0.48                                          | 0.48                                          |

Values are odd ratios (95% confidence interval). All estimates are adjusted for age, gender and height. AAo: ascending aorta; AoR: aortic root; AR: aortic regurgitation; AS: aortic stenosis; PAr: proximal aortic arch; for description of BAV types, see Fig. 1.
and abnormal hemodynamics were proved as criminals in the development of BAV-associated aortic dilatation, the different specific phenotypes of aortic dilation may be dominated by one main factor, and others (even some unknown reasons) are accomplices.\(^{5,16,19}\) Our dominance analysis may imply that (1) inherent disposition was mainly responsible for the higher frequency of AoR+AAo dilation and lower prevalence of AAo+PAr in patients of Type-1 LR with AR or AS+AR; (2) in patients with Type-0 LAT and AS, valve-related hemodynamics may be the determinant for the bias prevalence of different types of aortic dilation (more AAo+PAr and less AoR+AAo), and (3) the higher prevalence of AAo dilation may be attributed to both of above two variables in patients with Type-1 LR and AS.

Our results could provide the potential indication of surgical strategy for surgeons. For Type-1 LR patients with AR, the higher prevalence of AoR dilation may imply that the aortopathy results from inherent disposition, and the more aggressive surgical treatment is recommended for the root dilation of these patients. However, the higher frequency of AAo dilation is responsible for valve-related hemodynamics in Type-0 LAT patients with AS, supporting the policy of being less aggressive surgical treatment in these patients concerning aortic replacement.

In our study, we also found the heterogeneity of BAV phenotype morbidity among Chinese, European, and American. The incidence of Type-0 LAT phenotype is rare (4.5%) in Sievers’ study\(^{10}\); however, the incidence is 24.1% in our cohorts and 9.3% in Schäfers’ study\(^{8}\). Besides, the incidence of Type-0 AP phenotype in Schäfers’ cohorts (20.2%) is significantly higher than our study (3.2%) and Sievers’ study\(^ {3} (2.4\%).

| Table 3 Dominance analysis for the relative importance of two components in the participants’ logistic regression model |
|---------------------------------------------------------------|
| Model | ΔR\(^2\) | Additional contribution ΔR\(^2\) |
| X\(_{\text{Type-1 LR}}\) | X\(_{\text{AS}}\) | 0.1259 | 0.0299 |
| X\(_{\text{AS}}\) | 0.1244 | 0.0314 | - |
| X\(_{\text{Type-1 LR+AS}}\) | 0.1558 | - | - |
| Variance contribution (%) | 51.2 | 48.8 | - |
| X\(_{\text{Type-1 LR+AS}}\) | X\(_{\text{AR}}\) | 0.1699 | 0.0267 |
| X\(_{\text{AR}}\) | 0.1525 | 0.0441 | - |
| X\(_{\text{Type-1 LR+AR}}\) | 0.1966 | - | - |
| Variance contribution (%) | 62.3 | 37.7 | - |
| X\(_{\text{Type-1 LR+AR}}\) | X\(_{\text{AS}}\) | 0.1416 | 0.0145 |
| X\(_{\text{AS}}\) | 0.1017 | 0.0544 | - |
| X\(_{\text{Type-1 LR+AR+AS}}\) | 0.1561 | - | - |
| Variance contribution (%) | 79.0 | 21.0 | - |
| X\(_{\text{Type-1 LR+AR+AS}}\) | X\(_{\text{AS+AR}}\) | 0.1416 | 0.0159 |
| X\(_{\text{AS+AR}}\) | 0.0953 | 0.0622 | - |
| X\(_{\text{Type-1 LR+AS+AR}}\) | 0.1575 | - | - |
| Variance contribution (%) | 79.6 | 20.4 | - |
| X\(_{\text{Type-1 LR+AS+AR}}\) | X\(_{\text{AS}}\) | 0.1568 | 0.0334 |
| X\(_{\text{AS}}\) | 0.1679 | 0.0223 | - |
| X\(_{\text{Type-0 LAT+AS}}\) | 0.1902 | - | - |
| Variance contribution (%) | 40.0 | 60.0 | - |
| X\(_{\text{Type-0 LAT+AS}}\) | X\(_{\text{AS}}\) | 0.1386 | 0.0724 |
| X\(_{\text{AS}}\) | 0.1891 | 0.0219 | - |
| X\(_{\text{Type-0 LAT+AS}}\) | 0.2110 | - | - |
| Variance contribution (%) | 23.2 | 76.8 | - |

Each model was adjusted for age, gender and height. AAo: ascending aorta; AoR: aortic root; AR: aortic regurgitation; AS: aortic stenosis; PAr: proximal aortic arch; for description of BAV types, see Fig. 1.
heterogeneity of BAV phenotype morbidity may affect the results of patients’ characteristics. However, we found it did not affect the results of the association analysis between valve phenotype, pattern of valvular dysfunction and aortic configuration in BAV patients. Our association analysis got a similar results with Sievers’ study, which showed that Type-1 LR BAV patients with AR associated with higher prevalence of AoR dilation and Type-0 or Type-1 LR patients with AS associated with higher prevalence of AAo dilation.

Our study confirmed the heterogeneity of bicuspid aortopathy and identified the homogeneous BAV subsets. It is essential for the more in-depth and comprehensive understanding of the phenomenon of BAV disease itself and aortic complications. The strict patient’s selection strategy, according to different study aims including appropriate homogeneous participants, could be benefit for improving result consistency of the further researches about BAV aortopathy.

Conclusion

Our study revealed specific associations between BAV phenotypes, patterns of valvular dysfunction and aortic configurations and identified the homogeneous BAV aortopathy subsets. The different phenotype prevalence of bicuspid aortopathy was affected by valve-related hemodynamics and inherent disposition, and dominated by different dominant pathogenetic theory. In patients of Type-1 LR with AR or AS+AR, inherent disposition mainly responsible for the higher frequency of AoR+AAo dilation and lower prevalence of AAo+PAr dilation, whereas valve hemodynamics was the primary determinant for the bias prevalence of higher AAo+PAr and lower AoR+ AAo dilation in patients of Type-0 LAT with AS. The higher prevalence of AAo dilation may be attributed to both of the above two mechanism in patients with Type-1 LR and AS.

Disclosure Statement

The authors declare that they have no conflict of interest.

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