Bicuspid aortic valve disease – the influence of valve morphotype on age at and types of surgical treatment

Michelle S. Lim a,b,⇑, David S. Celermajer a,b,c, Paul G. Bannon a,d

a The University of Sydney, Faculty of Medicine and Health, Camperdown, New South Wales, Australia
b Royal Prince Alfred Hospital, Department of Cardiology, Camperdown, New South Wales, Australia
c Heart Research Institute, Sydney, Australia
d Royal Prince Alfred Hospital, Department of Cardiothoracic Surgery, Camperdown, New South Wales, Australia

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Background: Patients with bicuspid aortic valve (BAV) with zero or two raphes have been under-represented in previous studies. Whether these patients have unique clinical courses remains unclear. We describe the indications for and types of surgery in patients with BAV, and describe differences between valve morphotypes.

Methods: Adults who had undergone aortic and/or aortic valve surgery for BAV disease at our centres were identified and classified according to the Sievers definitions.

Results: 317 patients were included (74.4% male, median age at surgery 62 years). Of these, 187 (59.0%) had aortic valve surgery, 7 (2.2%) aortic surgery, 120 (37.9%) combined valve and aortic surgery and 3 had a Ross procedure. Most patients had aortic stenosis (71.9%), followed by aortic regurgitation (16.7%). 30-day mortality was low (1.6%). The commonest valve morphology was type-1 (one raphe) in 89.6%; type-0 (no raphes) occurred in 7.9% and type-2 (two raphes) in 2.5%. Patients with type-2 valves were substantially younger at time of surgery than type-1 patients (median 36 vs 63 years, p = 0.008). A higher proportion of patients with type-0 valves required aortic surgery than those with type-1 (68.0% vs 37.3%, p = 0.007). There were no differences between groups for the indication for surgery, valvular abnormality or 30-day mortality.

Conclusions: The number of BAV raphes was independently and significantly associated with age at surgery and the need for aortic intervention. Patients with type 0 and type 2 valves are a small but important proportion of the BAV population, potentially requiring different clinical surveillance and management.

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1. Introduction
Bicuspid aortic valve (BAV) is the commonest congenital heart defect in adults, with an incidence of 1–2% in the general population [1]. BAV is associated with significant morbidity as patients are at risk of developing aortic valve dysfunction, often requiring surgical intervention [2]. BAV is also associated with aortic dilatation, irrespective of valve haemodynamic function [3], and patients have a higher rate of aortic complications including aneurysm and dissection, with a reported 25-year risk of aortic surgery after BAV diagnosis of 25% [4].

Dating back to the 1970s, various valve configurations (“valve morphotypes”) have been identified within BAV patient cohorts [5], however up until recently, BAV patients with varying valve morphologies have mostly been studied together as one group. Recently, there has been growing interest into the various BAV morphotypes, and how they differ with regards to clinical features and outcomes. As the most common valve configurations, BAVs with one raphe and right- and left-coronary cusp fusion, or right- and non-coronary cusp fusion have received the most attention, with studies revealing that these two morphotypes are associated with unique molecular [6], cellular [7] and haemodynamic profiles [8], and differing clinical patterns of disease [9]. “True” BAVs (those without a raphe) however, occur less frequently, and those with two raphes even less frequently still. Consequently, patients with these valve morphotypes have often been under-represented, and as such, the nature of any distinguishing features or differing clinical outcomes of valvular and aortic complications, for patients with these less common BAV types, remains poorly understood.

⇑ Corresponding author at: Royal Prince Alfred Hospital Missenden Road, Camperdown, NSW, Australia.
E-mail address: michelle.lim@sydney.edu.au (M.S. Lim).

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Therefore, in this study, we firstly describe the patient characteristics, clinical indications and operative details in a large cohort of adult patients with BAV undergoing aortic valve or aortic surgery; and secondly, we stratify and compare patients according to the presence and number of valve raphes, to investigate whether patterns of aortic valve or aortic surgery differ in patients with the less common BAV morphotypes.

2. Materials and methods

The study protocol was approved by the ethics committees at the two hospital sites. The need for written informed consent was waived by the Institutional Ethics Committee in accordance with NHMRC guidelines. All procedures in this study, were carried out in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.

Patients: Adult patients who had undergone aortic or aortic valve surgery for BAV related disease were recruited retrospectively from the Royal Prince Alfred Hospital and Strathfield Private Hospital’s Adult Congenital Heart Disease and Cardiothoracic Surgery databases. Only patients in whom the BAV morphotype was clearly identified on intra-operative inspection, or through pre- or intra-operative trans-thoracic or trans-oesophageal echocardiography were included. Patients were excluded if the patient underwent transcatheter aortic valve replacement (TAVR, n = 3), had Ehlers Danlos or Marfan’s syndrome (n = 3), had insufficient clinical information (n = 5), or associated complex congenital heart disease (n = 11) except for patent ductus arteriosus (PDA), unrepaird ventricular septal defect (VSD), atrial septal defect (ASD), left superior vena cava (SVC) and/or hypoplastic aortic isthmus.

Bicuspid aortic valve morphology: Valve morphology was ascertained from operative reports or if not specified in operative reports, from pre/intra-operative transthoracic or transoesophageal echo studies, and classified according to the number of raphes present and the orientation of the valve cusps, according to the classification system proposed by Sievers and Schmidtke [10] (Fig. 1). Patients were categorised according to the number of raphes present (ie. type 0, type 1 or type 2 BAV).

Study Variables and Definitions: Patient demographics and surgical data was collected from the databases, patient medical records, operation reports and echocardiography studies. If the exact date of surgery was not known, but the year of surgery was known, the patient was included and the age at surgery was calculated assuming the surgery was performed on the 30th June of that year. All de-identified data was recorded and stored in a secure password protected REDCap (“Research Electronic Data Capture”) database, provided by the Clinical Research Centre at Sydney Local Health District.

Surgical indications: Patients were firstly classified according to the primary indication for surgery; valvular dysfunction (aortic stenosis (AS), aortic regurgitation (AR), or mixed AS/AR), aortic disease, infective endocarditis (IE) or ischaemic heart disease (IHD). There was a proportion of patients in whom their primary indication for surgery was IHD, but due to concomitant aortic valve or aortic disease, underwent valve/aortic surgery as well. Generally, concomitant aortic intervention was performed if ascending aortic dimension exceeded 45 mm, and aortic valve intervention was performed if the valve was significantly calcified, was more than mildly stenosed, or was assessed as having haemodynamically significant aortic regurgitation. Patients in whom multiple indications were listed, but the primary indication was not flagged, were classified as “unknown” for indications. Patients were also secondarily classified according to the valve abnormality, irrespective of the primary surgical indication; AS, AR, mixed AS/AR or IE related valve dysfunction.

Operative details: Operation type, valve replacement type, and concomitant coronary artery bypass graft (CABG) surgery was recorded. Data on aortic surgery was also collected, and patients were classified as having aortic root replacement only (“proximal”), ascending and/or hemi-arch replacement only without aortic root replacement (“distal”), or both aortic root and ascending and/or hemi-arch replacement (“proximal-and-distal”).

Statistics: Continuous variables are reported as median and inter-quartile ranges, and categorical data are expressed as frequency and percentage. Comparison between BAV morphotype groups was performed using the Kruskal-Wallis test for continuous variables, and the Chi-Square or Fisher’s exact tests for categorical variables. Post-hoc analyses were carried out using Multiple Fischer’s exact tests with Bonferroni Correction method. A two-tailed value of p < 0.05 was considered statistically significant. All statistical analysis was performed using SPSS version 25.0.

3. Results

A total of 317 patients with clearly identified valve morphology were included for analysis (table 1): 74.4% were males and the median age at surgery was 62 years (interquartile range 50–69 years). The primary indication for surgery was aortic valve dysfunction in 68.1%, aortic disease in 18.3%, infective endocarditis in 3.2%, and ischaemic heart disease in 6.0% (primary indication for surgery was unknown in 3.8%). All patients who required surgery for aortic disease had aortic aneurysms, except one patient who required urgent surgery for aortic rupture. No patients underwent surgery for aortic dissection. When classified according to valve abnormality, 71.9% had AS, 16.7% AR, and 5.0% mixed aortic valve disease. 3.2% had infective endocarditis and the remainder normal valve function (2.5%) or valve function was not documented (0.6%).
The commonest operation type was isolated aortic valve replacement (AVR) (59.0%), followed by combined aortic valve and aortic surgery (37.9%). A small number of patients had valve sparing aortic surgery (2.2%) or a Ross procedure (0.9%), 40.1% of patients underwent aortic intervention, with or without concurrent aortic valve surgery. Of the patients requiring aortic surgery, 52.0% underwent both proximal and distal aortic replacement, and 16.5% proximal only. The majority of patients received tissue valve prostheses (69.7%), with mechanical the next most common (26.5%), 23.7% of patients had concomitant CABG. 30-day mortality was low (1.6%). There was no statistically significant difference in 30-day mortality between patients with and without aortic replacement surgery (2.4% vs 1.1%, p = 0.379).

### Differences between BAV morphotypes

The distribution of BAV morphotypes is provided in [Table 2](#). The commonest morphotype were valves with one raphe (type 1) (284, 89.6%) and each of the sub-types within that group: 1RL (209, 65.9%), 1RN (61, 19.2%), and 1LN (14, 4.4%). There were no differences in distribution of valve morphotypes when comparing males to females, with 1-RL valves remaining the commonest valve type in both groups (p = 0.625).

Comparison between patients with different BAV morphotypes is shown in [Table 1](#). There were no statistically significant between group differences in gender distribution, proportion of patients with previous valvuloplasty or valvotomy, or primary indication for surgery. In all three groups, the commonest primary indication for surgery was aortic valve dysfunction, followed by BAV related aortic disease. There was also no between group difference in the distribution of valve abnormalities at the time of surgery, with the majority of patients in each group undergoing surgery for aortic stenosis.

Age at surgery differed significantly between groups (p = 0.008), with patients with type 2 valves being substantially younger at the time of surgery than patients with type 1 valves (median 36 vs 63 years, p = 0.015). The need for aortic surgery also differed between valve morphotypes (p = 0.007), with a higher proportion of patients with type 0 valves undergoing aortic surgery than patients with type 1 valves (68% vs 37.3%, p = 0.008). Of those patients who required aortic surgery, there were no significant differences in the type of aortic surgery required. Patients with type 2 valves were more likely than type 1, to receive a mechanical valve replacement (62.5% vs 24.6%, p = 0.047) or undergo a Ross Procedure (12.5% vs 11.1%, p = 0.006), which likely reflects the younger median age at surgery. There were no significant differences between groups, in 30-day mortality.

### Discussion

In this study, we describe the surgical indications and operative characteristics of a large cohort of adults undergoing surgery for BAV associated disease, and explore differences between various

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**Table 1**

Patient and Surgical Details, and Comparison between bicuspid aortic valve Morphotypes.

|                          | Whole Cohort n = 317 | Type 0 n = 25 (7.9%) | Type 1 n = 284 (89.6%) | Type 2 n = 8 (2.5%) |
|--------------------------|----------------------|----------------------|------------------------|---------------------|
| Male                     | 236 (74.4%)          | 16 (64.0%)           | 213 (75.0%)            | 7 (87.5%)           |
| Age at surgery           | 62                   | 58                   | 63                     | 36                  |
| 28 – 51                  | (50 – 69)            | (48 – 65)            | (52 – 69)              | (28 – 51)           |
| Previous Valvotomy/valvuloplasty | 13 (4.1%)        | 0 (0%)               | 12 (4.3%)              | 1 (12.5%)           |
| Primary Indication for Surgery |                      |                      |                        |                     |
| Valvular dysfunction     | 216 (68.1%)          | 16 (64.0%)           | 196 (69.0%)            | 4 (50.0%)           |
| Aortic disease           | 60 (18.9%)           | 6 (24.0%)            | 51 (18.0%)             | 3 (37.5%)           |
| IE                       | 10 (3.2%)            | 3 (12.0%)            | 7 (2.5%)               | 0 (0.0%)            |
| IHD                      | 19 (6.0%)            | 0 (0.0%)             | 19 (6.7%)              | 0 (0.0%)            |
| Unknown                  | 12 (3.8%)            | 0                    | 11 (3.9%)              | 1 (12.5%)           |
| Valve Abnormality        |                      |                      |                        |                     |
| Normal function          | 8 (2.5%)             | 2 (8.0%)             | 6 (2.1%)               | 0 (0.0%)            |
| AS                       | 228 (71.9%)          | 15 (60.0%)           | 207 (72.9%)            | 6 (75.0%)           |
| AR                       | 53 (16.7%)           | 4 (16.0%)            | 48 (16.9%)             | 1 (12.5%)           |
| Mixed AS/AR              | 16 (5.0%)            | 1 (4.0%)             | 14 (4.9%)              | 1 (12.5%)           |
| IE                       | 10 (3.2%)            | 3 (12.0%)            | 7 (2.5%)               | 0 (0.0%)            |
| Valvular Dysfunction     | 2 (0.6%)             | 0                    | 2 (0.7%)               | 0                   |
| Operation Type           |                      |                      |                        |                     |
| AVR only                 | 187 (59.0%)          | 8 (32.0%)            | 176 (62.0%)            | 3 (37.5%)           |
| AVR plus Aorta           | 120 (37.9%)          | 16 (64.0%)           | 100 (35.2%)            | 4 (50.0%)           |
| Aorta only (no valve)    | 7 (2.2%)             | 1 (4.0%)             | 6 (2.1%)               | 0 (0.0%)            |
| Ross Procedure           | 3 (0.9%)             | 0 (0.0%)             | 2 (0.7%)               | 1 (12.5%)           |
| Need for aortic surgery  | 127 (40.1%)          | 17 (68%)             | 106 (37.3%)            | 4 (50.0%)           |
| Proximal vs distal aorta replacement | 21 (16.5%) | 1 (5.9%) | 19 (7.0%) | 1 (25.0%) |
| Proximal                 | 39 (30.7%)           | 6 (35.3%)            | 33 (31.1%)             | 0 (0.0%)            |
| Distal                   | 66 (52.0%)           | 10 (58.8%)           | 53 (50.0%)             | 3 (75.0%)           |
| Proximal and distal      | 1 (0.8%)             | 0                    | 1 (0.9%)               | 0                   |
| AVR type                 |                      |                      |                        |                     |
| Mechanical               | 84 (26.5%)           | 9 (36.0%)            | 70 (24.6%)             | 5 (62.5%)           |
| Tissue                   | 221 (69.7%)          | 15 (60.0%)           | 204 (71.8%)            | 2 (25.0%)           |
| Ross                     | 4 (1.3%)             | 0 (0.0%)             | 3 (1.1%)               | 1 (12.5%)           |
| Valve sparing            | 7 (2.2%)             | 1 (4.0%)             | 6 (2.1%)               | 0 (0.0%)            |
| Not Documented           | 1 (0.3%)             | 0                    | 1 (0.4%)               | 0                   |
| Concurrent CABG          | 75 (23.7%)           | 5 (20.0%)            | 69 (24.3%)             | 1 (12.5%)           |
| 30-day mortality         | 5 (1.6%)             | 0 (0.0%)             | 5 (1.8%)               | 0 (0.0%)            |

Continuous variables reported as median (interquartile range). Categorical variables reported as n (%).

* p < 0.5 type 0 vs type 1.
** p < 0.5 type 1 vs type 2.

AR = aortic regurgitation, AS = aortic stenosis, AVR = aortic valve replacement, CABG = coronary artery bypass graft, IE = infective endocarditis, IHD = ischaemic heart disease.
BAV morphologies. Most prior studies have focussed on the differences between the two most common subtypes of BAV (1RL and 1RN). Our study, however, is one of few to analyse the significance of the presence and number of raphes, including patients with type 0 and type 2 valves. We found that patients with type 2 BAV were significantly younger at the time of surgery, compared to type 1 BAV patients. Furthermore, more patients with type 0 BAV underwent aortic surgery than patients with type 1 BAV. These data therefore, suggest that patients with type 0 and type 2 valves, may have different clinical courses to patients with the more common type 1 valves, and may require differing surveillance and management strategies.

BAV is associated with clinically significant valvulopathy and/or aortopathy. Similar to previous studies, in our cohort, patients with BAV were more likely to be male and undergo surgery at a relatively younger age than those requiring surgery for tricuspid aortic valve disease. Valvular disease, and specifically AS, is the commonest indication for BAV-associated surgery. The number of patients requiring concomitant aortic surgery is relatively high in our cohort, with 40.1% of patients undergoing aortic intervention. The reported incidence of coexistent aortopathy requiring intervention in previous surgical BAV studies is broad. Sievers et al. (2014) demonstrated a similar proportion of patients with 33.5% of their 1362 patients undergoing aortoplasty or aortic replacement [11], however concomitant aortic disease has been reported as low as 11% [12], and as high as 45% [13] in other studies. This variability likely reflects differing surgical practices [14], and changing guideline recommendations over time [15]. No patients in our cohort underwent surgery for aortic dissection, re-iterating that the risk of aortic dissection is low in patients with BAV and severe valvular and/or aortic disease, although we acknowledge the possibility that patients with dissection could have died prior to undergoing operative intervention.

The presence and number of valve raphes influences patient age at time of surgery – patients with type 2 BAVs are significantly younger at the time of surgery than those with type 1. Whilst our study did not address mechanistic features of BAV disease, we postulate potential explanations for this finding. Firstly, the fundamental anatomic abnormality of type 2 valves, whereby two sites of cusp fusion leave only one functional commissure for forward flow, means that the valve naturally has a smaller orifice area and thus is inherently more dysfunctional, compared to the type 0 and 1 valves. This is supported by the findings of Merkx et al. (2017) who showed that in a paediatric population, by the mean age of 6 years, significantly more patients with type 2 BAVs already had any valve dysfunction, compared to the other BAV morphologies [16]. Secondly, abnormal mechanical stresses and distorted haemodynamics have been demonstrated in 1RL BAVs compared to tricuspid aortic valves [17], and may therefore also be a precipitant in progressive valvulopathy of type 2 valves.

Valve morphotype also influences patterns of disease – patients with type 0 valves are more likely to require aortic intervention. The literature surrounding the association between BAV morphology and aortopathy has primarily focussed on Sievers type 1 valve patients, and clear relationships have emerged when comparing 1RL to 1RN valves. 1RL valves are associated with predominant aortic root dilatation, whilst 1RN valves are more likely associated with ascending aortic or more distal aortic dilatation [18,19]. Patients with type 0 valves however, have often been neglected in BAV studies, likely due to the relative infrequency of this valve morphotype. Consequently, any relationship between the presence or absence of a raphae in BAV, and aortopathy remains unclear. Two groups have shown that associations exist; Shin et al. (2015) found that patients with a raphae (type 1 valves) had larger annulus dimensions, whilst patients without a raphae (type 0 valves) had bigger sino-tubular junction and ascending aorta indexed dimensions [20]. Conversely, Michalowska et al. (2014) found that patients with raphae (type 1 BAV) had larger aortic root, and mid- and distal-ascending aorta dimensions than type 0s [21]. Other groups however have shown no association; in Kong et al. (2017) large study of 2118 patients with BAV, whilst valves with raphae had a higher prevalence of valve dysfunction and were more likely to therefore require AVR, there was no difference in aortic sizes or aortopathy pattern [22]. When Sievers et al. (2016) considered valve haemodynamic in addition to valve morphology and aortopathy morphotype, exclusive associations were still not evident [23]. Unfortunately, differing classifications of valve morphotypes, and hence differing comparisons, makes synthesis of the body of research around the relevance and implications of the presence/absence of a raphae challenging.

Our results suggest that the presence or absence of raphae is an important feature, with clinical implications for aortopathy risk; with patients without any raphae more likely to have aortic disease requiring intervention. We theorise two possible explanations. Firstly, that type 0 BAVs without a raphae, might be a different disease entity compared to BAVs with raphae, that confer differing aortopathy risk. Secondly, differing haemodynamic patterns as a result of the differing geometries that occur in type 0 valves, including orifice shape, differing types of valvular dysfunction with differing rates of progression, and differing aortic geometries, may contribute to progressive aortic disease. Whilst type 0 valves have been neglected in the majority of 4D MRI flow studies, altered flow patterns and regional elevations in aortic wall shear have been demonstrated in the various type 1 valve morphotypes [24], and suggest that differing valve morphotypes cause differing flow disturbances, which may lead to aortic enlargement.

5. Study limitations

Our study has several limitations. This cohort of patients represents those with clinically significant bicuspid aortic valve disease requiring surgery, and therefore are only representative of a select group of BAV patients. Patients therefore with absent or less severe valvular or aortic disease are underrepresented. Due to these selection biases, our conclusions cannot necessarily be extrapolated to all BAV patients, nor to the natural history of BAV disease in general.

### Table 2

|          | Type 0 | Type 1 | Type 2 |
|----------|--------|--------|--------|
|          | 25 (7.9%) | 284 (89.6%) | 8 (2.5%) |
| 0AP      | 13 (4.1%) | 1RL 209 (65.9%) | 2RL/RN 8 (2.5%) |
| 0Lat     | 12 (3.8%) | 1RN 61 (19.2%) | 2RL/RN 8 (2.5%) |
|          |        | 1LN 14 (4.4%) |        |

0 Lat = type 0 lateral, 0 AP = type 0 anterior posterior, 1RL = type 1 with right and left coronary cusp fusion, 1RN = type 1 with right and non-coronary cusp fusion, 1LN = type 1 with left and non-coronary cusp fusion. 2RL/RN = type 2 with fusion between the right and left, and right and non-coronary cusps.

Results are reported as n (%).
In our study, whilst concomitant aortic intervention was generally undertaken in line with aortic dimension cut-offs recommended by international guidelines, quantitative data on aortic dimensions was not uniformly available. Nonetheless, in this large retrospective surgical cohort clear patterns have emerged, and future research including all-comers with BAV are needed to confirm these observations and clarify the generalisability of these findings to all BAV patients.

6. Conclusion

Whilst type 0 and type 2 valves occur less frequently than type 1, these patients make up an important proportion of the BAV population. Understanding differences in their clinical profiles is essential to informing risk stratification and in providing patient-specific care. This study adds to the currently limited body of evidence surrounding the significance of the presence and number of raphes in BAV disease. Patients undergoing surgery with type 0 and type 2 valves had significantly different patterns of disease and thus, the identification and differentiation of BAV with and without raphes may be important in the diagnosis and management of patients with BAV and their risk stratification for valve and aortic complications. Further research is required to clarify the genetic, biological, and haemodynamic differences between BAV with and without raphes, to assist in the management of this heterogeneous population of patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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