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Bicuspid aortic valve: different clinical profiles for subjects with versus without repaired aortic coarctation

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ABSTRACT

Objectives A small proportion of patients undergoing bicuspid aortic valve (BAV) intervention have had prior repair of aortic coarctation (CoA). We aimed to describe phenotypic differences between BAV patients, comparing those with versus those without previous coarctation repair.

Methods 556 adults with BAV who had undergone aortic valve and/or ascending aortic surgery were identified, and relevant clinical and operative details were retrospectively analysed.

Results Of the total cohort, 532 patients (95.7%) had isolated BAV ('BAV-only'), and 24 (4.3%) had had a previous successful CoA repair ('BAV-CoA'). The median age at surgery was significantly lower in BAV-CoA patients compared with BAV-only (median, IQR: 40 years, 26–57 vs 62 years, 51–69, p<0.001). Indications for surgery also differed, with BAV-CoA patients much more likely to undergo surgery for aortic regurgitation (BAV-CoA 38% vs BAV-only 13%, p<0.001); patients with isolated BAV were more likely to require surgery for aortic stenosis (BAV-only 75% vs BAV-CoA 50%, p<0.001). Two different BAV morphotypes were commoner in the BAV-CoA group; type 0 valves (24% vs 8%, p<0.05) and type 2 valves (12% vs 3%, p<0.05). The proportion of patients undergoing concomitant aortic surgery at the time of valve surgery were similar (BAV-only 38% vs BAV-CoA 42%, p=0.8).

Conclusion In adult patients undergoing aortic valve surgery for BAV disease, those with a prior history of repaired CoA underwent surgery at a very much younger age, and a higher proportion required intervention for aortic regurgitation.

Key questions

What is already known about this subject?

- The link between bicuspid aortic valve (BAV) and aortic coarctation (CoA) as frequently coexistent congenital abnormalities is well recognised.
- The nature of this association, however, is not well understood, with limited previous investigation yielding conflicting results.
- The clinical implications, therefore, for BAV patients who have also had repaired CoA are unclear.

What does this study add?

- In patients with BAV who require aortic valve surgery, those with prior repaired CoA (BAV-CoA) may have different clinical profiles, compared with those with BAV alone.
- Patients with repaired coarctation were over two decades younger at the time of requiring BAV-related surgery, compared with those with BAV-alone.
- The type of aortic valve dysfunction also differed: BAV-CoA patients were more likely to require intervention for aortic regurgitation, while those with BAV-only more frequently underwent surgery for aortic stenosis.
- Bicuspid valve morphotypes also varied between these groups, with type 0 and type 2 valves being significantly more common in BAV-CoA patients, while a significantly higher proportion of BAV-only patients had type 1 valves.

How might this impact on clinical practice?

- These observed differences in patients with BAV, with and without repaired CoA, raise the possibility of a more aggressive clinical phenotype in patients with coexistent BAV and CoA.
- Patients with both conditions may require counselling about differing prognosis, and alternative surveillance strategies might be employed in BAV-CoA patients, to detect important complications earlier in adult life.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital heart abnormality in adults, and it is well recognised that aortic coarctation (CoA) coexists in a small but significant proportion of these patients. Despite this established link, however, the impact of past CoA repair on the natural history of BAV disease is not well described. Before the advent of repair techniques, aortic dissection accounted for 19% of deaths in patients with coarctation, which was amplified when BAV was also present.[1] In the current era of effective CoA repair, however, few studies have specifically sought to investigate the impact of repaired CoA on BAV, and thus far, limited investigation of this important clinical question has led to conflicting results. We, therefore, aimed to identify any differences between patients with BAV alone, and those with BAV and coarctation, in order

to better understand what clinical bearing coexistent coarctation may have on BAV disease.

METHODS

Patient and public involvement

Patients and the public were not directly involved in the undertaking of this research.

Patient selection

Adult patients (age >17 years) who had undergone aortic valve surgery for a BAV, with or without concomitant aortic surgery, were retrospectively recruited from the Adult Congenital Heart Disease and Cardiothoracic Surgery databases, at Royal Prince Alfred and Strathfield Private Hospitals. Patients were categorised as having BAV without coarctation ('BAV-only') or BAV with previous CoA repair ('BAV-CoA'). We have separately reported the 30-day outcomes for 346 of the BAV-only patients.[2] This paper focusses on the differences in characteristics and outcomes between BAV patients with or without previously repaired coarctation.

We prospectively determined that we would exclude any patients if they had developed any clinically significant recurrence of CoA, however, no such patients were identified in our databases. Patients were also excluded if the presence of a bicuspid valve could not be confirmed (4), the patient underwent transcatheter aortic valve replacement (1), surgery was primarily performed for ischaemic heart disease with aortic valve intervention an incidental/secondary operation (31), the patient had aortic surgery only, without valve intervention (10), had Ehlers Danlos or Marfans syndrome (3), had insufficient clinical information (5), their CoA had not been repaired (2), or they had associated complex congenital heart disease (14) except for patent ductus arteriosus, unrepaired ventricular or atrial septal defects, left superior vena cava and/or hypoplastic aortic isthmus.

Study variables and definitions

Patient demographics and surgical data were collected from the databases, 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 30 June of that year. All deidentified data were 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.

BAV morphology: The presence of a BAV was confirmed in all patients from operative reports or preoperative transthoracic or transoesophageal echo studies. BAV morphology was 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[3] (figure 1). Morphological classification was not possible in 232 patients due to insufficient operative report descriptions or unclear or unavailable echo studies. A subanalysis of BAV morphotype was, therefore, performed in the 336 (60%) patients in whom classification was possible.

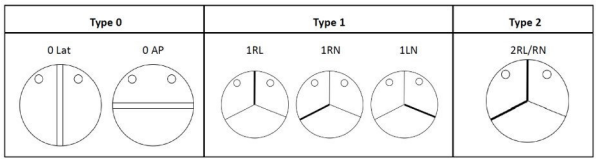

Figure 1 Classification of BAV morphotypes. Adapted from the classification system proposed by Sievers and Schmidtke.[3] Type 0 valves have no raphe: 0 lat=type 0 lateral, 0 AP=type 0 anterior posterior. Type 1 valves have one raphe: 1RL=type 1 with right and left coronary cusp fusion, 1RN=type 1 with right and non-coronary cusp fusion, 1LN=type 1 with left and non-coronary cusp fusion. Type 2 valve with 2 raphes: 2RL/RN=type 2 with fusion between the right and left, and right and non-coronary cusps. BAV, bicuspid aortic valve.

Surgical indications: Patients were first classified according to the primary indication for surgery; valvular dysfunction (either aortic stenosis (AS), aortic regurgitation (AR) or mixed AS/AR), aortic disease, or infective endocarditis. Patients in whom multiple indications were listed, but the primary indication was not flagged, were classified as 'unknown'. Patients were also secondarily classified according to the valve abnormality; normal, AS, AR, mixed AS/AR or infective endocarditis related valve dysfunction.

Operative details: Data were collected on operation type, valve replacement type and any concomitant coronary artery bypass graft surgery. Data on aortic surgery were also collected, and patients were classified as having no aortic surgery ('none'), aortic root replacement only ('proximal'), ascending and/or hemiarch replacement only without aortic root replacement ('distal'), or both aortic root and ascending and/or hemiarch replacement ('proximal and distal'). Choice of operation was at the discretion of the managing team (physician, surgeon and for valve type, patient preference was also considered). 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 AR.

Statistics

Continuous variables were non-parametric in distribution and so are reported as median and IQR, and categorical data are expressed as frequency and percentage. Comparison between groups was performed using the Mann-Whitney U test for continuous variables, and the χ^2 test or Fischer's exact tests for categorical variables. Post hoc analyses were carried out using multiple Fischer's exact tests with Bonferroni correction. A two-tailed level of $p<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS V.25.0.

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Table 1 Patient characteristics

	BAV only n=532 (95.7%)	BAV and repaired CoA n=24 (4.3%)	p-value
Age at surgery	62 (51–69)	40 (26–57)	<0.001
Male	389 (73%)	20 (83%)	
Previous valvuloplasty or valvotomy	22 (4.2%)	4 (16.7%)	<0.05
Age at surgery if no previous valvotomy/ valvuloplasty	63 (52–70)	43 (29–59)	<0.001
BAV morphology—data available in 336 (60%)			
Type 0	24 (7.5%)	4 (23.5%)	<0.05
0AP	12 (3.8%)	4 (23.5%)	<0.001
0Lat	12 (3.8%)	0	
Type 1	259 (81.2%)	9 (52.9%)	<0.05
1RL	190 (59.6%)	7 (41.2%)	
1RN	57 (17.9%)	1 (5.9%)	
1LN	12 (3.8%)	1 (5.9%)	
Type 2 (2RL/RN)	8 (2.5%)	2 (11.8%)	<0.05
Unicuspid	3 (0.9%)	0	
Cannot classify	25 (7.8%)	2 (11.8%)	

Continuous variables reported as median (IQR). Categorical variables reported as n (%).
AP, anterior posterior; BAV, bicuspid aortic valve; CoA, aortic coarctation; Lat, Lateral; 1 LN, type 1 with left and non-coronary cusp fusion; 1 RL, type 1 with right and left coronary cusp fusion; 1 RN, type 1 with right and non-coronary cusp fusion.

RESULTS

Patient characteristics

Patient characteristics are presented in table 1. Of the 556 recruited patients, 24 (4.3%) had a history of repaired CoA ('BAV-CoA'). BAV-CoA patients were significantly younger at the time of surgery than BAV-only patients (median, IQR: 40 years, 26–57 vs 62 years, 51–69, p<0.001). A higher proportion of patients with BAV-CoA had undergone previous balloon aortic valvuloplasty or surgical valvotomy (16.7% vs 4.2%, p=0.022). Even after excluding these patients, however, a significant difference in median age at surgery remained (BAV-CoA 43 years, 29–59 vs BAV-only 63 years, 52–70 p<0.001).

BAV morphology

Data on valve morphotype were available on 60% of patients (table 1). A significantly higher proportion of patients in the repaired coarctation group had type 0 valves compared with patients without (23.5% vs 7.5%, p=0.02), while BAV-only patients were more likely to have type 1 valves (81.2% vs 52.9%, p=0.005). A higher proportion of patients with repaired coarctation had type 2RL/RN valves (11.8% vs 2.5%, p=0.029).

Table 2 Indications for and types of surgery

	BAV only n=532 (95.7%)	BAV and repaired CoA n=24 (4.3%)	p-value
Primary indication for surgery			
Valve dysfunction	397 (74.6%)	16 (66.7%)	
Aortic disease	80 (15.0%)	6 (25.0%)	
IE	19 (3.6%)	2 (8.3%)	
Unknown	36 (6.8%)	0	
Valve haemodynamic			<0.001
Normal function	10 (1.9%)	0 (0.0%)	
AS	398 (74.8%)	12 (50.0%)	<0.05
AR	68 (12.8%)	9 (37.5%)	<0.001
IE	19 (3.6%)	2 (8.3%)	
Mixed AS/AR	25 (4.7%)	0	
Unknown	12 (2.3%)	1 (4.2%)	
Type of operation			
Need for aortic surgery	200 (37.6%)	10 (41.7%)	
Proximal versus distal aortic surgery			
None	332 (62.6%)	14 (58.3%)	
Proximal only	46 (8.7%)	6 (25.0%)	
Distal only	54 (10.2%)	1 (4.2%)	
Prox and distal	98 (18.5%)	3 (12.5%)	
Type of surgery			
AVR	324 (60.9%)	12 (50.0%)	
Ross	8 (1.5%)	2 (8.3%)	
AVR plus Aorta	200 (37.6%)	10 (41.7%)	
AVR type			<0.05
Mechanical	185 (34.8%)	13 (54.2%)	<0.05
Tissue	333 (62.7%)	9 (37.5%)	<0.05
Homograft	3 (0.6%)	0	
Ross	9 (1.7%)	2 (8.3%)	<0.05
Valve repair	1 (0.2%)	0	
Concurrent CABG	109 (20.5%)	2 (8.3%)	
30 day mortality	7 (1.3%)	0	

Categorical variables reported as n (%).
*p<0.001.
†p<0.05.
AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; BAV, bicuspid aortic valve; CABG, coronary artery bypass graft; CoA, aortic coarctation; IE, infective endocarditis.

Indications for and types of surgery

Indications for and types of surgery are presented in table 2. There were significant differences in valve abnormalities that led to the aortic valve being replaced; a significantly higher proportion of patients with BAV-CoA required valve surgery for AR (38% vs 13%, p=0.001), while a higher proportion of patients with BAV-only required surgery for AS (75% vs 50%, p=0.007) (figure 2). Due to the higher proportion of patients with BAV-CoA

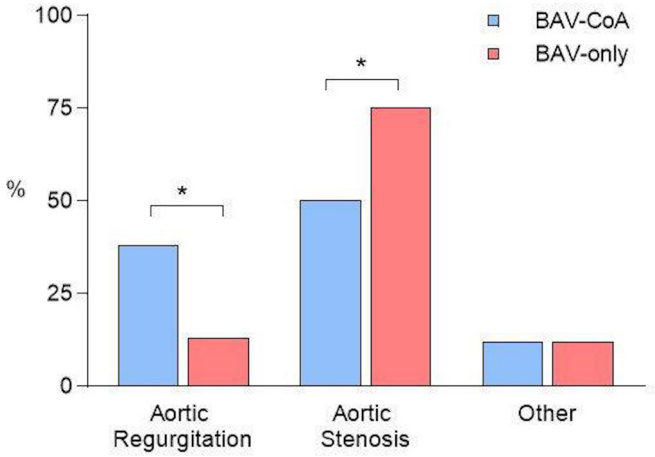

Figure 2 The indication for valve surgery significantly differs between patients with BAV-only and BAV-CoA. *P<0.001. BAV-CoA, patients with bicuspid aortic valve and prior repaired coarctation. BAV-only, patients with BAV only.

having had previous valvuloplasty/valvotomy, a sensitivity analysis was performed, which showed that these significant differences remained, even when patients who had had previous valvuloplasty/valvotomy were excluded from analysis.

While there were no differences in surgery types, valve replacement type differed, likely reflecting the younger age at surgery in the BAV-CoA cohort; a higher proportion of BAV-CoA patients had Ross procedures (8.3% vs 1.7%, p=0.022), and BAV-only patients were more likely to have tissue valve replacements (62.7% vs 37.5%, p=0.013). There was no significant difference in the proportion of patients undergoing concomitant ascending aorta surgery (BAV-only 38% vs BAV-CoA 42%, p=0.8). 30 day mortality was similar between groups (BAV-only 1.3% vs BAV-CoA 0%, p=1.0).

DISCUSSION

While the association between BAV and CoA is widely recognised, a history of prior CoA repair has traditionally had minimal impact on the clinical management of the bicuspid valve. The implications of the coexistence of the two conditions are not well appreciated. This study demonstrates for the first time, significant clinical differences between patients with isolated BAV requiring surgery, and those with BAV and prior repaired coarctation. Patients with BAV-CoA developed BAV-related complications requiring surgical intervention over two decades earlier than their BAV-only counterparts, and a significantly higher proportion required valve surgery for AR. These differences suggest that BAV patients with past CoA repair may have an accelerated clinical course, necessitating different surveillance strategies to detect the development of important BAV complications much earlier in life, and contributes to our understanding of the nature of the relationship between these two frequently associated conditions.

The impact of repaired coarctation on the valvular complications of BAV has not been extensively investigated. A small number of studies in children have found that children with BAV-CoA have less AS/AR than children with pure BAV[4] and less valve intervention.[5] While this indicates that repaired CoA does not appear to have deleterious effects on the BAV early in life, the consequences of any prolonged aberrations relating to the repaired CoA may not yet have manifested in this young cohort. No studies of adults have specifically studied the impact of CoA on BAV valve complications, however, one large study of 642 adults with BAV, of whom 25% had a history of CoA, found that a significantly higher proportion of adults with CoA did not experience valve and aortic complications,[6] suggesting that in fact patients with coarctation have a better prognosis. By contrast, a study of patients with aortic coarctation found BAV to be a predictor of developing AR in patients with CoA.[7]

The significance of CoA for the possible ascending aortic complications of BAV has been more widely studied. It appears that the presence of coarctation is not associated with aortic dilatation, as paediatric studies have found children with concomitant CoA actually have smaller aortic dimensions, and slower rates of aortic dilatation.[8 9] Once again in adulthood, however, the impact of CoA on BAV-related aortic complications is contentious. While some data suggest that BAV-CoA patients are more likely to develop aortic complications (predominantly driven by increased aneurysm risk,[10] although dissection risk also appears to be higher[10 11]), other data suggest there is no difference in aortic complications.[12 13] Despite the conflicting evidence, clinically there remains sufficient concern of the potential increase in risk, which is reflected in the lower threshold for aortic surgery for patients with BAV-CoA in the European guidelines.[14]

We propose a few possible explanations for our findings. It has been previously postulated that BAV and CoA are part of a spectrum of manifestations of a single disease process, with shared embryological,[15] histological and clinical features.[16 17] It is possible, therefore, that patients with both conditions have a unique aortic/valvular profile, both innately and acquired, compared with patients with only one or the other.

At a cellular level, a recent study of neonatal aortic tissue sampled proximal to a coarctation demonstrated significantly different proteomic and histological profiles when BAV was present, compared with TAV.[18] A unique phenotype may also be evident on a macroscopic level. In our cohort, patients with BAV-CoA had a higher frequency of prior valvuloplasty or valvotomy. This may suggest that BAV-CoA patients are born with more severe valve abnormalities, although the paediatric studies referred to earlier did not find this. Alternatively, there may be a preponderance for particular BAV morphotypes to cluster in patients with CoA. We found that while 1-RL BAVs were the most common valve morphotype in both BAV-only and BAV-CoA groups, a significantly higher proportion of BAV-CoA patients had type 0-AP valves.

Other series have previously shown that BAV-CoA is associated with 1-RL morphology,[4 8] however, synthesis of literature on BAV morphotype distribution is challenging, due to variable morphotype classification systems, with many not specifying the presence or absence of a raphe. One study that did compare the differences between BAV with and without raphe was Michałowska *et al*,[12] who found that CoA was more commonly associated with patients with BAV-without raphe, than BAV with raphe (44.4% vs 13.3%)—findings which are similar to our study findings.

In addition to histological and morphological differences between BAV-only and BAV-CoA patients, disturbed haemodynamic and loading conditions, may be an alternative or contributing cause. Abnormal aortic biomechanics in coarctation has been demonstrated, initially in animal models,[19] and then in humans, with evidence of reduced aortic elasticity and increased stiffness both before and after coarctation repair.[20] Additionally, systemic hypertension is a known complication of repaired coarctation, accounting for a significant proportion of the morbidity affecting these patients.[21] Hypertension is a well-recognised risk factor for the development of aortic valve disease, inclusive of both stenosis and regurgitation.[22] Altered aortic geometry may be an additional differing feature, as previous CoA repair is associated with a 'gothic' aortic arch.[23] Mechanobiological studies on the aortic valve have elucidated the intricate relationship between altered leaflet pressure, stretch and shear stresses and the cellular, proteomic and genomic profiles of aortic valves which may be involved in aortic valve dysfunction.[24] These abnormalities in aortic and aortic valve mechanics, therefore, may potentially contribute to the accelerated valvular dysfunction that we observed in the patients with BAV-CoA.

More complex haemodynamic perturbations may also be implicated. Regional disturbances in wall shear stress (WSS) in patients with BAV[25] have been implicated in the haemodynamic theory of BAV-aortopathy. Flow disturbances have also been demonstrated in patients with CoA,[26] with computational fluid dynamic methods showing how these are compounded when BAV is also present.[27] While we did not find a statistically significant difference in the proportion of patients who underwent concomitant ascending aortic surgery, the known role of aortic dilatation in AR raises speculation for a haemodynamic explanation for the higher proportion of patients with AR in the BAV-CoA group. Finally, differences in valve leaflet WSS has been demonstrated in BAVs compared with tricuspid aortic valves[28] and between BAV morphotypes.[29] Whether or not valve leaflet WSS is further disturbed by concomitant CoA has not been studied, but if present, may also potentially contribute to accelerated valve dysfunction, leading to surgery at a younger age in patients with BAV-CoA.

Study limitations and future directions

This study has limitations including its retrospective design. The BAV-CoA group was small compared with the BAV-only comparator, however, the 4.3% proportion is consistent with previous reports.[13 30] This study also includes only patients who have clinically significant BAV related complications requiring surgical intervention. The impact, therefore, of concomitant CoA on patients across the broad spectrum of (milder) BAV disease remains unknown. In this study, quantitative data on aortic dimensions were not collected. While at our two institutions, aortic intervention was undertaken according to international guideline recommendations, the lack of aortic dimension data in our study precludes us from making firm conclusions on the nature of BAV-related aortic disease in our cohort.

Future study of 'all-comers' with BAV including longitudinal follow-up will be important, to clarify the applicability of our findings to all patients with BAV. Further clinical, scientific and imaging research, investigating the phenotypic, biological and haemodynamic differences in patients with these co-occurring conditions, is needed to elucidate the mechanisms for our findings, and guide future management strategies.

CONCLUSION

In patients undergoing aortic valve replacement for BAV disease, those with a prior history of repaired coarctation had significantly different clinical profiles, requiring surgery over two decades earlier than their BAV-only counterparts and with a higher proportion undergoing surgery for AR. These findings suggest that the coexistence of BAV and CoA may lead to a more aggressive clinical phenotype, requiring that these patients undergo different surveillance strategies to detect the development of important BAV complications, earlier in adult life.

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Data availability statement Data are available on reasonable request.

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