Coronary artery dilation associated with bicuspid and unicuspid aortic valve disease in children: a series of 17 patients

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Abstract

Introduction: Coronary artery dilation associated with bicuspid/unicuspid aortic valves is described in adults with limited data in children. We aimed to describe the clinical course of children with bicuspid/unicuspid aortic valves and coronary dilation including coronary Z-score changes over time, association of coronary changes with aortic valve anatomy/function, and complications. *Materials and methods:* Institutional databases were searched for children ≤18 years with both bicuspid/unicuspid aortic valves and coronary dilation (1/2006-6/2021). Kawasaki disease and isolated supra-/subvalvar aortic stenosis were excluded. Statistics were descriptive with associations measured by Fisher's exact test and overlapping 83.7% confidence intervals. *Results:* Of 17 children, bicuspid/unicuspid aortic valve was diagnosed at birth in 14 (82%). Median age at coronary dilation diagnosis was 6.4 years (range: 0-17.0). Aortic stenosis was present in 14 (82%) [2 (14%) moderate, 8 (57%) severe]; 10 (59%) had aortic regurgitation; 8 (47%) had aortic dilation. The right coronary was dilated in 15 (88%), left main in 6 (35%), and left anterior descending in 1 (6%) with no relationship between leaflet fusion pattern or severity of aortic regurgitation/stenosis on coronary Z-score. Follow-up evaluations were available for 11 (mean 9.3 years, range 1.1–14.8) with coronary Z-scores increasing in 9/11 (82%). Aspirin was used in 10 (59%). There were no deaths or coronary artery thrombosis. *Discussion:* In children with bicuspid/unicuspid aortic valves and coronary dilation, the right coronary artery was most frequently involved. Coronary dilation was observed in early childhood and frequently progressed. Antiplatelet medication use was inconsistent, but no child died nor developed thrombosis.

Bicuspid and unicuspid aortic valves are common congenital abnormalities with an estimated incidence between 0.4 and 2.25%.[1,2] Bicuspid/unicuspid valves can be associated with multiple aortic pathologies including aortic stenosis, aortic regurgitation, and dilation of the aorta.[1-4] Coronary artery dilation associated with bicuspid/unicuspid aortic valves has been well documented in adults, but data in children are limited.[5-7] The prognostic significance of coronary artery dilation including the natural history and management in the setting of bicuspid/unicuspid aortic valves in children is unknown. However, evidence of prior myocardial infarction was observed in a retrospective angiographic study of adult patients with idiopathic coronary artery dilation,[8] and coronary artery ectasia and aneurysm are associated with exercise-induced ischaemia in the absence of significant coronary artery stenosis.[9] The paucity of knowledge regarding the natural history of coronary artery dilation in the setting of congenital aortic valve disease prevents clinicians from providing informed medical and surgical care. Our aims were to 1) determine the progression of coronary artery dilation in children with bicuspid/unicuspid aortic valves; 2) determine the relationship between coronary artery dilation progression and aortic valve anatomy and function; 3) describe the clinical management and outcomes of these patients.

Materials and methods

This retrospective observational cohort study was approved by the Institutional Review Board at Primary Children's Hospital and the University of Utah. A single-centre paediatric cardiology imaging database was searched for children ≤ 18 years old with a diagnosis of both 1) bicuspid or unicuspid aortic valve and 2) coronary artery dilation between 1/2006 and 6/2021. Patients were excluded if they had a history of Kawasaki disease or isolated supravalvar or subvalvar aortic stenosis. Echocardiogram reports and images were reviewed from the time of bicuspid/unicuspid aortic valve diagnosis through the most recent cardiology visit. Coronary artery dilation was defined as a Z-score ≥ 2.0 for the right, left main, or left anterior descending

coronary artery using the Boston Children's Hospital Z-score model.[10] The same model was applied when coronary artery imaging was adequate to measure dimensions from cardiac catheterisation, CT, and MRI. We used the current American Heart Association criteria to classify coronary artery Z-scores into four categories: dilation (2–2.49); small aneurysm (2.5–4.99); medium aneurysm (5–9.99); and large aneurysm (≥10).[11] The severity of aortic stenosis was defined using mean spectral Doppler gradients: mild < 20 mmHg, moderate 20–39 mmHg, and severe ≥ 40 mmHg.[12] Aortic regurgitation was classified into mild, moderate, or severe using the width and cross-sectional area of the proximal colour jet (parasternal long- and short-axis views) as well as the presence or absence of holodiastolic flow reversal in the abdominal aorta.[13] Cusp fusion was determined by the presence of a raphe between cusps.[14] Dilation of segments of the proximal aorta was defined by Z-scores of ≥ 2.0 using the last measurement prior to aortic valve surgery or at the latest follow-up echocardiogram if the child had not had surgery.[10] All imaging measurements were verified by the senior author. The electronic medical record was accessed for each patient, and surgical and catheterisation notes were reviewed for information regarding cardiac interventions and electrocardiograms.

Analysis

The primary outcome of interest was change in coronary artery Z-score over time. Continuous variables were described using mean and standard deviation or median and interquartile range for completeness. Categorical variables were described using frequency count and percentages. Given the small sample size, between-group comparisons were limited to a Fisher's exact test comparing aortic valve fusion patterns (unicuspid, right-left fusion, and right-non fusion) with affected coronary artery (right, left main, or both). For the same reason, the impact of degree of aortic stenosis and aortic regurgitation (none/mild vs. moderate/severe) on coronary artery Z-score was evaluated using overlapping confidence intervals. In this method, two groups are statistically non-significant (p value > 0.05) if their corresponding 83.7% CIs overlap.[15] This method is recommended to test hypotheses in situations for which standard tests do not exist to attain a desirable type I error rate.[16] Statistical significance was assessed at the 0.05 level. Statistical analyses were implemented using R v. 4.0.3.[17]

Results

A total of 1279 patients had an ICD code designating a bicuspid or unicuspid aortic valve during the study period. From the imaging database search, we identified 17 patients including 6 (35.3%) with unicuspid aortic valve and 11 (65%) with bicuspid aortic valve (Table 1). Of the 2 (12%) patients with genetic syndromes, 1 had Turner syndrome and 1 had 8p23 duplication. The family history was positive for a first-degree relative with bicuspid/unicuspid aortic valve in 2 (12%) children. The aortic valve anatomic abnormality was identified early (0–9 days) in most (14/17; 82%) patients, while the time of coronary artery dilation diagnosis varied widely (1 day–17 years) and tended to be made at a much older age (median 6.4 years; interquartile range 3.0–10.2). Coronary artery dilation was diagnosed by echocardiography in 16 (94%) children and incidentally by coronary angiogram during stenting of an aortic coarctation in one (6%) child. Mean follow-up for the cohort from the diagnosis of aortic valve disease was 11.2 ± 7.4 years

(range: 0.8 to 22 years). Eleven (64%) patients had multiple measurements after the initial diagnosis of coronary artery dilation with mean follow-up 9.3 ± 4.0 years (range: 1.1–14.8).

All 17 children had echocardiographic imaging of the coronary arteries during their follow-up. Of the 9 children with advanced imaging (4 CT, 2 MRI, 3 both), 2 had studies ordered specifically to evaluate coronary artery dilation. The coronary artery dimensions for all patients with advanced imaging were within 1 mm of the measurements obtained from the temporally closest echocardiogram (time range between echo and advanced imaging: 0 days–2.8 years, median 96 days). The severity of coronary artery dilation varied widely (Table 1) from 3 (17%) having only mild coronary artery dilation (Z-scores 2–2.49) to 5 children with maximal Z-scores exceeding the threshold of giant aneurysm. The right coronary artery was the most frequently involved (15/17, 88%) followed by the left main coronary artery in 6 (35%) children. Multivessel dilation occurred in 5 (29%) children with 4 having right and left main coronary artery dilation and 1 having left main and left anterior descending coronary artery dilation. Z-scores at the latest follow-up tended to be higher for the right coronary artery (median Z-score: 6.8; interquartile range: 3.9–9.4) vs. the left main coronary artery (median Z-score: 2.3; interquartile range: 0.5–3.4). Of the 11 children with multiple measurements, 9/11 (82%) demonstrated an increase in Z-scores (Fig 1). The left anterior descending and the left main coronary artery Z-scores decreased during follow-up for 3 children (left anterior descending for patient 6 and left main for patient 5, 6, and 7), but among these patients the right coronary artery remained dilated in patients 5 and 7. The remaining 6 children had only a single data point, so the trajectory of coronary artery growth could not be ascertained. Figure 2 demonstrates echocardiograms and CT imaging for patient 7.

Of the 11 children in the cohort with bicuspid aortic valves, right and left coronary cusps were fused in 7 (64%), and right and non-coronary cusps in 4 (36%). No patient had fusion of the left and non-coronary cusps. Of the 6 children with unicuspid aortic valves, 3 (50%) had combined right and left main coronary artery dilation, 2 (33%) had isolated right coronary artery dilation, and 1 (17%) had isolated left main coronary artery dilation. The cusp fusion pattern (right-left, right-non, and unicuspid) was not associated with the coronary artery (right, left main or both) that was dilated (P = 0.17).

Aortic stenosis was present in 14 (82%) patients, and the maximal degree of aortic stenosis during follow-up varied: 4 mild, 2 moderate, and 8 severe. There were 10 (59%) children with aortic regurgitation: 4 mild, 4 moderate, and 2 severe. The degree of aortic stenosis and regurgitation (none/mild vs. moderate/severe) did not correlate with coronary Z-score (Fig 3). Nearly half of the patients (8/17, 47%) had ascending aorta dilation, including 2 with dilation of the entire proximal aorta from the annulus to the transverse arch. Only 1 patient had isolated dilation of the sinotubular junction. Of the entire cohort, 6 patients (35%) underwent repair of coarctation of the aorta, with 1 of these children having persistent left ventricular dysfunction (patient 3) at the most recent echocardiogram.

Clinical management of coronary artery dilation was inconsistent among providers. Coronary artery dilation was first addressed in the clinical cardiology notes for 10 (59%) patients at the time of echocardiographic diagnosis while 3 had no documentation in the notes for 2 or more encounters, and 4 had no mention of the echocardiographic finding of coronary artery dilation at any time

Table 1. Patient characteristics.

Pt.	Sex	Age at BAV/UAV diagnosis (days)	Age at CA dilation diagnosis (years)	Valve anatomy	Cusp fusion	CA affected	Last CA Z-score	Mean AS gradient (mm Hg)	AR grade	Largest proximal aorta Z-score
1	M	1	1.5	UAV	–	RCA	6.84	50	Mild	2.48
2	M	1	9.2	BAV	R/N	RCA	3.65	57	Moderate	−1.65
3	F	1	8.4	BAV	R/N	RCA	11.73	17	Moderate	2.47
4	M	1	10.2	BAV	R/L	RCA	5.34	14	Trivial	1.24
5	M	3	12.8	BAV	R/L; partial R/N	**RCA**, LMCA	8.07	43	Severe	3.95
6	M	1	0	BAV	R/N	**LMCA**, LAD	3.71	38	Trivial	4.85
7	M	1	6.9	UAV	–	**RCA**, LMCA	9.83	40	Moderate	4.47
8	M	1	6.4	BAV	R/L	RCA	10.04	57	Trivial	0.34
9	F	1	3.9	UAV	–	RCA	9.94	33	Trivial	4.81
10	M	1	0	BAV	R/L	RCA	9.06	4	None	3.61
11	F	9	17	BAV	R/L	RCA	7.13	8	Mild	1.36
12	M	1	0.4	UAV	–	LMCA	2.45	53	Trivial	0.05
13	M	1	3	UAV	–	**RCA**, LMCA	4.22	48	Mild	1.21
14	M	1	11	UAV	–	**RCA**, LMCA	6.36	47	Moderate	4.58
15	M	365	11	BAV	R/L	RCA	2.4	5	None	2.28
16	F	1474	9	BAV	R/N	RCA	2.44	8	Mild	1.83
17	M	450	5	BAV	R/L	RCA	3.3	6	Severe	6.34

Table 1. Description of coronary artery and aortic valve anatomy. If multiple coronary arteries are involved, the measurement of the largest CA (bold) is provided. Aortic stenosis: greatest aortic valve mean gradient over study period is provided. Aortic insufficiency: Last measurement or last measurement prior to aortic valve repair/replacement. Abbreviations: BAV = bicuspid aortic valve; CA = coronary artery; CoA= coarctation of the aorta; d = day(s); F = female; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; M = male; Pt.=Patient; RCA = right coronary artery; R/L= fusion of right and left coronary cusps; R/N= fusion of right and non-coronary cusps; UAV = unicuspid aortic valve; y = year(s)
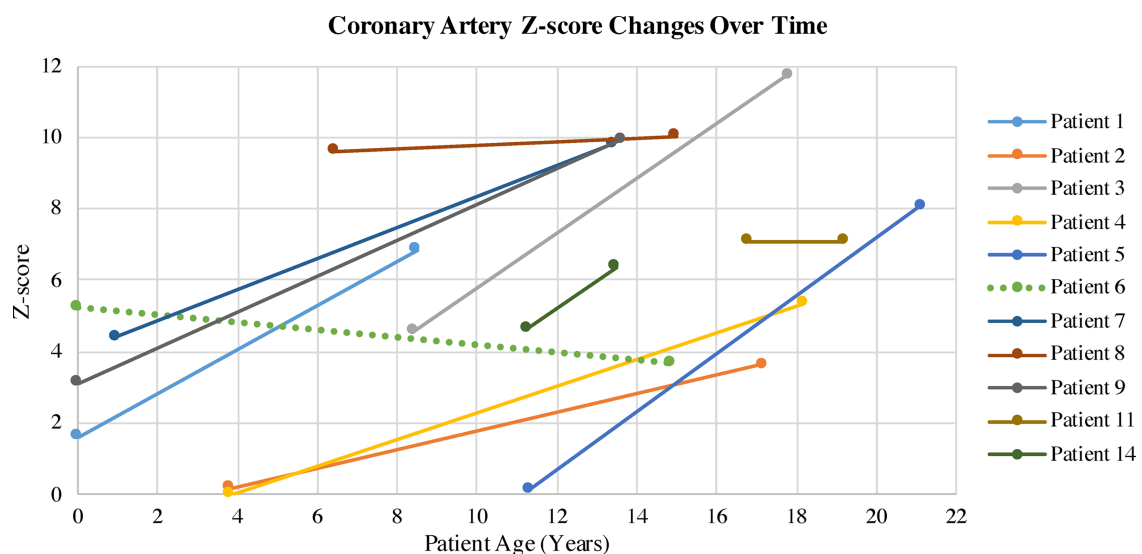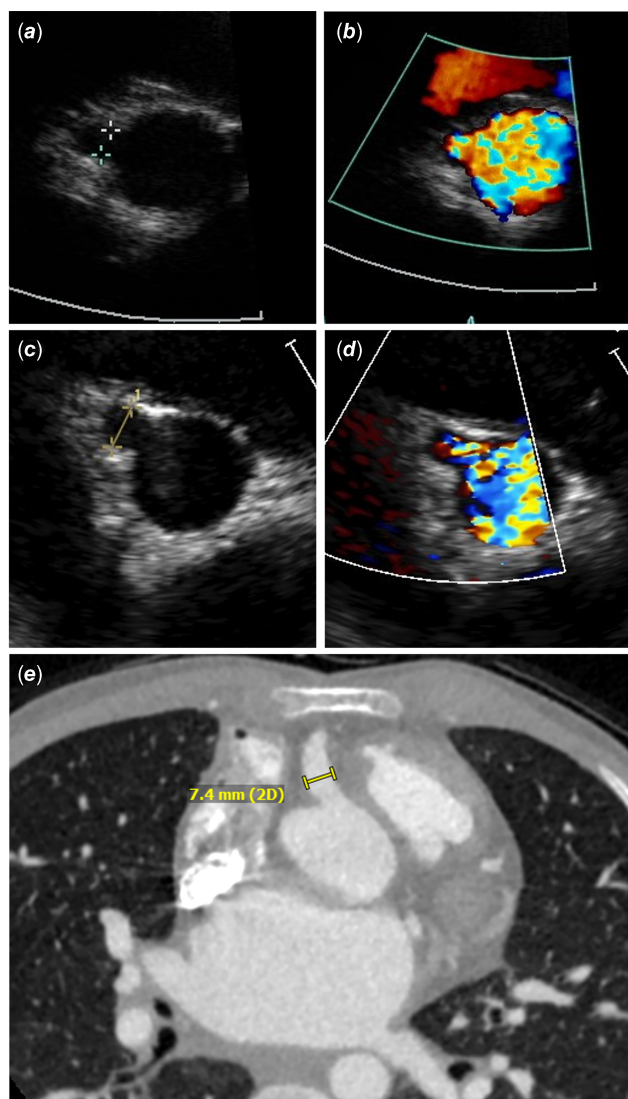

Figure 1. Coronary artery Z-score changes over time.

Figure 2. Coronary artery imaging by echocardiogram and CT for patient 7. Two dimensional and color Doppler echocardiogram of right coronary artery. a, b) 11 months (2.9 mm, Z =4.41). c and d) 13 years (7.0 mm, Z=9.83). e) 13 years (7.4 mm).

during follow-up. Vague symptoms were reported over the course of clinical follow-up in 10 (59%) patients: 6 had chest pain, 6 had fatigue, 5 had exercise intolerance, and 1 had palpitations. The most recent electrocardiogram showed nonspecific ST changes for 3 patients and 1 with associated mitral stenosis had ST depression in the inferolateral leads. None of the patients with electrocardiographic changes had symptoms.

Surgical or catheter-based interventions (Table 2) were performed in 14 (82%) children: 11 (65%) aortic valve balloon valvuloplasty procedures with 8 performed during infancy; 6 coarctation interventions, 4 aortic valve surgical repairs/replacements; 1 transcatheter aortic valve replacement.

Most patients (10; 59%) were prescribed aspirin for antiplatelet activity. Only 2 patients (both with repaired coarctation) were treated for systemic hypertension. No patient had an intervention specifically for coronary artery dilation, and none had clinical evidence of coronary thrombosis or myocardial infarction, with duration of follow-up ranging from < 1 year (5 patients) to 14 years. There were no deaths in this series.

Discussion

Our series of 17 patients with aortic valve disease and coronary artery dilation supports an association between these conditions that begins in early childhood and tends to progress. The ratio of males to females in this cohort was just over 3:1 (76% male), consistent with the predominance of males in the general bicuspid aortic valve population[18] as well as the predominance of males (90%) with bicuspid aortic valves and coronary artery dilation vs. bicuspid aortic valves and no coronary artery dilation (74%) reported in adult patients.[5] The right coronary artery was involved in 85% of our patients, similar to a prior report in which 3 children with bicuspid aortic valves and coronary artery dilation had right coronary artery involvement[6], and an adult series of patients with coronary artery aneurysms (although not exclusive to aortic valve disease) showed right coronary artery involvement in 87%.[19]

The factors driving coronary artery dilation in patients with aortic valve disease remain unclear. There is evidence that aortic root dilation is common in first-degree relatives of patients with bicuspid aortic valves even in the setting of a normal, trileaflet aortic valve.[20] Histopathologic studies of patients with bicuspid aortic valve demonstrate low fibrillin content and an increase in matrix metalloproteinase 2 activity which may contribute to degradation of the media and loss of elastic tissue in the aorta.[21,22] Some investigators have suggested a high-velocity jet through a stenotic valve into the coronary ostium promotes dilation[6], but, similar to our cohort, no correlation was shown between bicuspid aortic valve fusion pattern and the most severely dilated coronary artery in adults.[5] Despite aortic stenosis being common in our cohort, suggesting a role for this hemodynamic disturbance in the pathogenesis of coronary artery dilation, aortic stenosis severity was not statistically associated with the severity of coronary artery dilation in our group.

The majority (59%) of patients had aortic regurgitation, in many cases following aortic valve interventions. Any possible haemodynamic contribution of aortic regurgitation to the pathophysiology of coronary artery dilation could not be separated from the effect of aortic stenosis and the interventions. It is possible that aortic regurgitation may contribute to coronary artery dilation but, if so, systolic volume loading did not uniformly result in dilation of both coronary arteries and the degree of aortic regurgitation did not correlate with coronary artery Z-score. Interestingly, all 4 patients with both right and left main coronary artery dilation had aortic regurgitation, though the presence of coronary artery dilation in other patients with competent valves indicates other additional factors are involved.
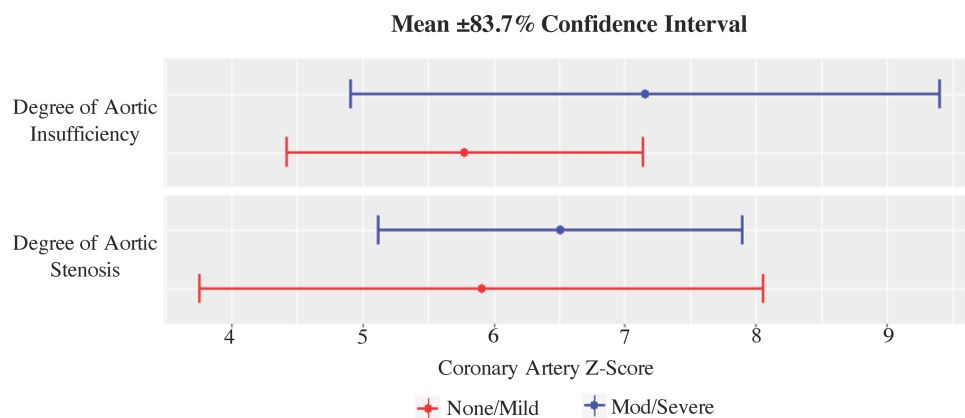
The process leading to dilation in this series appears to begin at a very young age for some children with the mean age for recognition at 6.4 years. Some patients may not have been diagnosed earlier due to the difficulty of measuring coronary artery dimensions in small, active children. The dilation of the ascending aorta associated with bicuspid/unicuspid aortic valves is well characterised, and the proportion of patients with bicuspid aortic valves, coronary artery dilation, and ascending aorta dilation was similar to the proportion with bicuspid aortic valves and ascending aorta dilation alone in adults.[5] Nearly half (47%) of our patients had accompanying ascending aorta dilation, slightly lower than the prevalence reported in the adult series (54% in the group with bicuspid aortic valve and coronary artery dilation vs. 70% in the group with bicuspid aortic valve without coronary artery dilation).

Medical management of the patients in this cohort varied but no interventions were performed to address coronary artery

Table 2. Catheter and surgical interventions.

Pt.	Age at balloon valvuloplasty (years)	Age in years and type of intervention for coarctation	Age in years at time of aortic valve intervention
1	0	–	–
2	0	–	17.3 (Transcatheter aortic valve replacement)
3	0.3	0.1 (Surgery)	
4	–	16.8 (Stent)	–
5	7.5	–	18 (Bioprosthetic aortic valve replacement)
6	3.3	–	–
7	0	0 (Surgery)	2.9 (Subaortic resection, aortic valvotomy) 7.0 (Subaortic resection, aortic valve repair) 10.0 (Subaortic resection, aortic valve repair) 13.6 (Ross Konno with ascending aorta aneurysm repair)
8	10.5	–	0 (Aortic valvotomy)
9	0	–	–
10	–	–	–
11	–	0 (Surgery) 16.8 (Stent)	–
12	0	0.5 (Surgery)	0.5 (Aortic valvotomy, supravalvar aortic patch)
13	0	–	–
14	0	0 (Surgery)	–
15	–	–	–
16	–	–	–
17	–	–	4.7 (Ross, ascending aorta aneurysm repair)

Pt. = Patient

Figure 3. Mean ±83.7% confidence interval.

dilation. In fact, coronary artery dilation did not receive immediate attention in over a third of patients as evidenced by a temporal lag in documentation in the clinical notes. This may be related to the lack of consensus opinion on what, if anything, can or should be done to mitigate progression. Although symptoms were reported in 10 patients, they were transient and nonspecific, and no patients had a focused evaluation for coronary insufficiency. No patient had coronary artery thrombosis or myocardial infarction, and there were no deaths. The sole patient with recent ST depression was symptom-free and on Coumadin for associated mitral stenosis. In adults, anticoagulation was once recommended for patients with coronary artery ectasia[23], though this has more recently been contested, and aspirin monotherapy is now considered as an alternative.[8] In our series, 10 patients were treated with aspirin, though several had additional post-operative indications. Whether children with coronary artery dilation and no other known risk factors for coronary artery disease should be managed based on thromboprophylaxis standards for adult coronary artery disease or by the recommendations for Kawasaki disease patients has not been studied and our series was too small to explore this question.[11] However, given adult data suggesting an association between ischaemia and coronary artery ectasia[9], additional studies are

needed to evaluate the true incidence and long-term impact of coronary artery dilation in children with bicuspid/unicuspid aortic valves.

Limitations

While this is the largest paediatric series for patients with bicuspid/unicuspid aortic valves and coronary artery dilation to date, it is limited by the small sample size and retrospective nature. Medical records were evaluated for all patients to search for symptoms of other causes of coronary artery dilation (e.g. Kawasaki disease). While no other causes were identified, they cannot be definitively ruled out in this retrospective cohort. Coronary artery imaging is standard for all first-time echocardiograms but is not standard for follow-up evaluations of bicuspid/unicuspid aortic valves unless requested. Additionally, our identification of coronary artery dilation in all patients with bicuspid/unicuspid aortic valves was dependent on its inclusion in the echo report. Therefore, our study likely undercounts the number of patients with coronary artery dilation and bicuspid/unicuspid aortic valves at our institution. Coronary artery Z-scores were applied to all imaging modalities in our study, despite Z-score measurements only being validated for echocardiogram measurements. Heterogeneity in interventions and follow-up isolated to a paediatric population limit our understanding of the natural history and potential long-term impact of this association.

Conclusions

Coronary artery dilation associated with bicuspid and unicuspid aortic valves begins in childhood and tends to progress. The right coronary artery is the most frequently involved artery. The long-term risk to these patients is uncertain, but no morbidity or mortality from these lesions was observed during childhood, and no coronary artery interventions were performed. Over half of the patients were treated with aspirin for antiplatelet activity. Increased awareness of the natural history of this phenomenon may allow more effective study of the pathogenesis and impact of this disease process and provide evidence-based recommendations for treatment.

Conflicts of interest. None.

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