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Abnormal Longitudinal Growth of the Aorta in Children with Familial Bicuspid Aortic Valve

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Abstract

Background—Bicuspid aortic valve (BAV) is the most common type of congenital heart defect (CHD) and is associated with clinically significant cardiovascular complications including valve calcification and ascending aortopathy (AscAo), predominantly occurring in adulthood. While a limited number of genetic etiologies for BAV have been defined, family members of affected individuals display BAV along with other left-sided CHD. This has led to guidelines from the American Heart Association and American College of Cardiology that recommend echocardiographic screening of first-degree relatives of affected adults. While potentially beneficial in adults, the yield of such screening in children is unknown. The purpose of this study was to investigate a cohort of children with familial BAV to determine the frequency of development of AscAo, and to identify risk factors that contribute to abnormal aortic growth. **Methods:** Echocardiograms over a 10 year follow up period were reviewed on 26 patients with familial BAV (22 male, 4 female; 22 with isolated BAV, 6 with BAV and aortic coarctation (CoA)). All had a family history of CHD and were recruited from 2005–2010 as part of a genetics research study. Four aortic segments (annulus, root, sinotubular junction, ascending aorta) on parasternal long axis echocardiographic images were measured by a single observer. The mean age at first echocardiogram was 7.1+/-5.5 years and 13.8+/-6.2 years on the last. Only patients with >2 echocardiograms in the 10 year period were included. Z score measurements of the aorta were plotted over time and based on these the cohort was divided into two groups: Group 1 (abnormal)

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Compliance with Ethical Standards

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– Z score for any segment >2 or a change in Z score >2 over follow up; Group 2 (normal) – Z score <2 throughout follow up and change in Z score <2.

Results—19 out of 26 children displayed abnormal aortic growth or dilation of the aorta. BAV with right/left cusp fusion was more frequent in Group 1(15/18) versus Group 2(3/7) ($p<0.05$). There were no significant differences in gender, aortic valve dysfunction, presence of CoA, family history, cardiac function, presence of left ventricular hypertrophy, or medication use between the 2 groups.

Conclusions—In our longitudinal study of children with familial BAV, the majority display evidence of abnormal growth of the ascending aorta during the follow up period consistent with AscAo and support the extension of current adult guidelines to the pediatric population. While we find that right/left cusp fusion is a risk factor for abnormal aortic growth, additional studies are needed to identify other factors to better select children who require serial screening.

Introduction

Bicuspid aortic valve (BAV) is the most common type of congenital heart defect (CHD), occurring in about 1–2% of the general population.¹ BAV occurs when the aortic valve has only two cusps instead of three due to fusion of 2 of the 3 valve leaflets and presents in three morphologic patterns. Right-left (R-L) cusp fusion is known to be more common (70%) than right-noncoronary (R-NC), with left-noncoronary (L-NC) being the least common.^{1, 2} BAV is a common cause of heart valve disease in adults due to its predisposition for calcification.³ BAV not only affects valvular function but is also associated with ascending aortopathy (AscAo).⁴ Thoracic aortic aneurysms are found in up to 50% of individuals with BAV and predispose up to 50% of those who are affected to aortic dissection and death.⁴ Accordingly, guidelines for the management of BAV in adult patients have been established in an attempt to reduce the morbidity and mortality associated with this lesion.^{5–7}

Among all types of CHD, numerous studies have demonstrated the high heritability of BAV along with other forms of left-sided CHD.⁸ It has been demonstrated that the family members of affected individuals display BAV along with other left-sided disease, with a prevalence of BAV nearly 10-fold higher in first-degree relatives of BAV patients than the general population.⁹ These findings have led to guidelines from the American Heart Association and American College of Cardiology which recommend echocardiographic screening of first-degree relatives of affected adults, and specifically in cases of premature onset of thoracic aortic disease and familial thoracic aortic aneurysm or dissection.¹⁰ The goal of such screening programs is to identify previously undiagnosed family members with BAV and initiate serial evaluation to potentially reduce the significant morbidity and mortality that can be associated with this disease. While identification of BAV is potentially beneficial in the adult population, the yield of early diagnosis of BAV using this type of screening approach in a pediatric population is unknown, especially since most complications from BAV present in adulthood.^{1, 9} Management of BAV in children remains a challenge, with imaging, medical, and surgical management strategies typically extrapolated from adult studies.¹¹ In children and adolescents with connective tissue disorders or BAV, the surgical threshold for aortic repair includes an absolute size of

aneurysm greater than 5cm, aneurysm growth rate exceeding 1cm per year, progressive aortic insufficiency, or a family history of early aortic dissection.¹¹

The purpose of this longitudinal study was to investigate a cohort of children with familial BAV to determine the frequency of abnormal growth of the ascending aorta. We hypothesized that serial echocardiographic screening in children with familial BAV for AscAo is of low-yield. In addition, we looked to identify factors that contribute to an increased rate of growth of the aortic root, sino-tubular junction, or ascending aorta.

Methods

The patients utilized in this study had been enrolled in a genetics research study and were recruited between 2005 and 2010. This study was approved by the institutional review board at Nationwide Children's Hospital. We found 38 patients with familial BAV, and we studied only those with the following criteria: having the diagnosis of BAV, having at least 2 echocardiograms performed during the 10 year follow-up period, age less than 21 years, and adequate echocardiographic images for measuring the aorta. Prior surgical or catheter intervention on the aortic valve was not an exclusion criterion.

A chart review of the electronic medical record was conducted to collect clinical information including age, gender, height, weight, body surface area, blood pressure at time of echocardiogram, and medications currently used. Surgical and catheter interventions were also noted. Family history of congenital heart disease and type of disease was previously collected as part of a genetics research study.

Four aortic segments (annulus, root, sinotubular junction, ascending aorta) on parasternal long axis echocardiographic images were measured by a single observer. Echocardiographic measurements were made in systole from inner edge to inner edge according to the American Society of Echocardiography guidelines for measuring the aorta.¹² Cusp fusion pattern was determined for each patient as right/non-coronary (R-NC), right/left (R-L), or left/non-coronary (L-NC). Aortic stenosis and regurgitation were classified as none, trivial, mild, moderate, or severe based on criteria listed in Table 1. Other echocardiographic data collected included coarctation location and Doppler velocity (if present), left ventricular M-mode measurements including left ventricular end diastolic dimension and left ventricular end diastolic dimension Z score, left ventricular ejection fraction, qualitative assessment of left ventricular dilation, and presence of left ventricular hypertrophy. EchoIMS (Merge, Richmond, VA) was used for the generation of Z scores for each aortic measurement and time point, based on the patient's age and body surface area. Z score measurements were plotted over time and based on these the cohort was divided: Group 1 (abnormal) having a Z score for any aortic segment greater than 2 or a change in Z score greater than 2 over the follow up period; Group 2 (normal) : Z score less than 2 throughout follow up and change in Z score of less than 2.

Results

Thirty-eight patients were included in the initial chart review. Twelve patients were excluded for the following reasons: only 1 available echocardiogram during the follow-up period, age

over 21 years, or interval between echocardiograms less than 1 year, if a patient had 2 echocardiograms only. Twenty-six patients with BAV were thus included, 22 male and 4 female. The mean age at first echocardiogram was 7.1 $\pm$ 5.5 years and 13.8 $\pm$ 6.2 years at last echocardiogram. Demographic data is listed in Table 2.

Twenty-two patients had isolated BAV, and 6 patients had associated CoA. As per the inclusion criteria, all patients had a family history of congenital heart disease. Among the 26 patients, 23 had a family history of aortic valve disease, 17 of which had a BAV. The other 4 patients had a family history notable for aortic valve stenosis and presumed BAV (Table 3). The most common forms of CHD for affected family members aside from BAV were other left-sided obstructive lesions including CoA and hypoplastic left heart syndrome.

Comparisons were made between the two groups for demographic and echocardiographic variables (Table 4). There were no significant differences between the 2 groups for initial degree of aortic valve dysfunction, presence of CoA, cardiac function, degree of left ventricular hypertrophy, or medication use. There was also no difference in the rate of complications or need for interventions between the two groups. The interventions/complications in the abnormal group included a Ross procedure, a surgical valvotomy, repairs of aortic arch coarctation, and balloon angioplasty of aortic coarctation with or without placement of stents. In the normal group there was one Ross procedure and one balloon aortic valvuloplasty.

The average follow up period for the cohort was 6.7 years (median 7, range 3–10). Predominantly, we found abnormal aortic growth and size in the aortic root and ascending aorta. In the aortic root, 6/26 had evidence of aortic dilation (z score > 2) while in the ascending aorta 13/26 had evidence of aortic dilation (z score > 2) and amongst these 13 patients, 7 had a z score > 3 (Figures 1 and 2). In addition, 2 patients met criteria for abnormal growth due to a z score > 2 in the annulus and 1 patient due to abnormal growth in the sinotubular junction. As expected, we did find that aortic dilation was more likely to be found in the ascending aorta (13/19), which is the most common location in patients with BAV.⁴ In summary, only 7/26 (27%) individuals in our cohort never displayed evidence of abnormal aortic growth or size over the follow-up period, which averaged 6 years (median 6, range 3–10) for Group 2. The remaining patients (19/26=73%) did show evidence of abnormal aortic growth or size and approximately one third of the patients (9/26) had significant aortic dilation with a z score > 3 . Interestingly, BAV with R-L cusp fusion was more frequent in the children with abnormal aortas (Group 1, 15/18) versus those with no evidence of AscAo (Group 2, 3/7) (Table 3, $p < 0.05$). One patient was on a cardiac medication, which was an ACE inhibitor.

Discussion

Despite guidelines regarding echocardiographic screening of first degree adult relatives of patients with BAV, the extension of screening to pediatric first degree relatives remains unclear. Here, we took advantage of a unique population of children with familial BAV that we have longitudinal follow over a 10 year period. In our study, only 7 out of 26 individuals never displayed evidence of abnormal aortic growth over the follow-up period, while the

majority of the cohort had evidence of aortic dilation or relatively rapid aortic growth. None of the patients required intervention for AscAo but early identification of abnormal aortic growth may be important in the long term medical management of these children.

Our findings suggest potential interventions to prevent aortopathy in BAV may need to be considered in childhood. Options for medical management in BAV to prevent or stop the progression of aortic dilation have not been well proven, though guidelines for timing of surgical intervention are established.⁶ Studies in patients with Marfan syndrome have shown benefit in the use of beta blockers¹³ and angiotensin receptor blockers¹⁴ in the prevention of aortic growth. Data extrapolated from these studies may be used clinically in the BAV population despite the differing genetic, histopathologic, and mechanical basis of disease. Numerous prior studies have attempted to identify risk factors for aortic valve disease in adults with BAV. A prospective adult study of 115 patients with asymptomatic BAV followed over a 5 year period showed that family history of aortic valve disease was associated with a significantly increased risk of increasing ascending aortic size, while no correlations with cusp fusion pattern or aortic valve dysfunction were found.¹⁵ Other studies have shown additional risk factors, including a study of 68 adult patients with BAV showing that aortic insufficiency or stenosis may increase the development of ascending aorta dilatation.¹⁶ Similarly, a large study of children with isolated BAV examined the incidence and rate of dilation of the ascending aorta versus a control population found that the BAV group had a larger ascending aorta initially and it increased in size over the follow-up period.¹⁷ In fact, the majority of children with BAV in the cohort showed progressive ascending aorta dilatation, worsening over time. Higher initial aortic valve gradients were associated with higher aortic z scores. This study suggests that both hemodynamic and intrinsic factors promote ascending aorta dilatation in children with BAV. In our study, children with R-L cusp fusion were more likely to display aortic dilation or more rapid growth of the ascending aorta. Other studies have attempted to link cusp fusion with clinical BAV outcomes including a large study of familial BAV, where they found R-NC morphology was more likely to manifest aortic valve disease in childhood, while R-L morphology more likely to manifest aortic valve disease in adulthood.¹⁸ A large retrospective study in children found R-NC cusp fusion was associated with aortic valve disease.¹⁹ A retrospective study in adults and children showed that patients with R-NC fusion were more likely to have dilation of the ascending aorta, and aortic root dilation was more likely in patients with R-L fusion.²⁰ Though cusp fusion may play a role, there are likely additional factors that contribute to aortic dilation in the BAV population.

Along these lines, several genes have been linked in the molecular basis of bicuspid aortic valve. Specifically, mutations in *NOTCH1* and *GATA5*, have been associated with bicuspid aortic valve in humans.^{21, 22} Consistent with findings in humans, dilation of the aorta has been reported in murine models with mutation of *Notch1*, consistent with a role for Notch1 signaling in the development of the ascending aortic wall.^{23, 24} Notch1 along with other genes are known to be important for the development of the aortic valve and ascending aorta, and it has been proposed that genetic abnormalities that result in BAV may also result in histopathologic changes, which predispose to aneurysm development.^{22, 25} In addition, there is an increasing amount of evidence supporting a role for hemodynamic stress induced by abnormal flow across the BAV in the development of aortopathy. Specifically,

investigators have demonstrated that regional hemodynamic differences and elevated aortic wall shear stress in the ascending aorta in the setting of BAV.^{22, 25} It is likely that abnormal genetics and hemodynamics together lead to pathogenic cellular and ECM remodeling in the proximal aorta and ultimately ascending aortic dilation.

Despite the majority of our cohort showing evidence of abnormal aortic growth over the follow-up period, there were no interventions for aortopathy over the study period. Previous publications have identified BAV being a risk factor for aortic dissection in a young population.²⁶ However, the financial implications of widespread screening are brought into question as we do not know the true benefit of screening children in terms of outcome or need for intervention prior to adulthood. A study in *Pediatrics* highlights the relative cost-effectiveness in screening siblings of patients with BAV versus the cost of complications in adulthood.²⁷ Detection of aortopathy in children, though not requiring intervention, may prove useful for several reasons. First, lifestyle modification can begin in childhood. As many adults will require a surgical intervention for BAV requiring cardiac bypass, lowering risk factors for coronary disease, hypertension, and diabetes can mitigate surgical risks in adulthood. In one study, 42% of adults with BAV experienced a cardiovascular medical or surgical event over a 20 year follow-up period highlighting that BAV is not a benign condition.²⁸ Further, many patients are lost in the transition from pediatric to adult care. Setting the stage for the importance and need for long-term follow-up may make adults with BAV more likely to continue care. Our study showed that the majority of children with familial BAV will display evidence of aortopathy. Without guidelines regarding initiation of screening and interval, there is a lot of practice variation and therefore opportunities for inadequate or excessive screening. The exact plan of care remains unknown, though earlier detection may help set the stage for timelier screening and earlier intervention in adulthood.

There are several limitations to our study. First, our population is small and of varied ages. Also, in our cohort, 4 patients in the abnormal group were classified as abnormal because of a change in z score of greater than 2 during the follow-up period. Despite the growth, the z scores for these patients were not out of the normal range. Essentially, this growth did not lead to the diagnosis of aortopathy, though it is worth noting that the trajectory of growth may also necessitate closer follow-up. Additionally in Group 2, 4 patients in this group had 2 echocardiograms during the follow-up period, only 1 with adequate images for measuring the ascending aorta. This finding points to a limitation of echocardiography, and also suggests that there may have been more patients in Group 1 (the abnormal group) had the ascending aorta been able to be measured. Lastly, the study is limited by its retrospective nature and the aortic measurements being measured by only one operator.

Conclusions

In our study of children with familial BAV, the majority displayed evidence of AscAo within our follow up period. Our results support the extension of current adult guidelines to the pediatric population, though the clinical value in asymptomatic children remains unknown. Additional studies are needed to identify other factors to better select children who require serial screening. Potential treatment for aortopathy for those with BAV may need to be initiated in childhood, and warrants study.

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Figure 1.

Longitudinal growth of aortic root in familial bicuspid aortic valve cohort. Z-scores of aortic root measurements obtained at the first and last echocardiogram are shown for each patient. Red lines signify abnormal aortic root diameter or abnormal growth. Yellow line marks z score = 2. *, z score noted to be greater than 2 on interim echocardiogram during follow up period.

Figure 2.

Longitudinal growth of ascending aorta in familial bicuspid aortic valve cohort. Z-scores of ascending aorta measurements obtained at the first and last echocardiogram are shown for each patient. Red lines signify abnormal ascending aorta diameter or abnormal growth. Yellow line marks z score = +2. *, z score noted to be greater than 2 on interim echocardiogram during follow up period.

Table 1**Aortic Stenosis/Regurgitation Classification Criteria**

	Trivial	Mild	Moderate	Severe
Aortic stenosis	<2 m/sec	2.0–2.9 m/sec	3.0–4.0 m/sec	>4.0 m/sec
Aortic regurgitation	Short narrow jet, limited to leaflet tips; no holodiastolic flow reversal; no LV dilation	<25% jet width/LVOT width, no holodiastolic flow reversal, no LV dilation	25–50% jet width/LVOT width, holodiastolic flow reversal in ascending aorta and transverse arch, usual LV dilation	>50% jet width/LVOT width, holodiastolic flow reversal in the aortic arch and abdominal aorta, LV dilation

LV = left ventricle

LVOT, left ventricular outflow tract

Table 2

Demographic and echocardiographic data

	First echocardiogram	Last echocardiogram
Age	7.1 ± 5.5 years	13.8 ± 6.2 years
BSA	0.95 ± 0.5	1.55 ± 0.6
Valve function		
No AS	12	8
Mild AS	7	13
Moderate AS	7	4
Severe AS	0	1
No AR	10	8
Trivial AR	5	3
Mild AR	9	8
Moderate AR	2	6
Severe AR	0	1
Annulus (mm)	15.4 ± 5.9	21.2 ± 5.3
Root (mm)	20.2 ± 7.0	27.1 ± 7.0
ST junction (mm)	16.4 ± 6.2	22.1 ± 5.4

	Demographics (N=26)
Female	4
Cusp fusion	
R/L	18
R/NC	6
L/NC	2
Coarctation	6
Hypertension	1
Medications	1

BSA = body surface area

AS = aortic stenosis

AR = aortic regurgitation

ST = sinotubular

R = right

L = left

NC = noncoronary

Table 3

Family History of Congenital Heart Disease

Bicuspid aortic valve	17
Aortic stenosis	4
HLHS	5
Coarctation	5
TOF	1
Mitral valve disease	2

HLHS, hypoplastic left heart syndrome

TOF, tetralogy of Fallot

Table 4

Comparison between abnormal and normal groups

	Group 1 – abnormal N=19	Group 2 – normal N=7	P value
Male	16	6	0.45
No AR	6	3	0.07
Trivial AR	5	1	
Mild AR	6	3	
Moderate AR	2	0	
Trivial AS	8	4	0.11
Mild AS	6	1	
Moderate AS	5	2	
Coarctation	5	1	0.35
Complications	7	2	0.38
R/L	15	3	<0.05
R/NC	3	3	
L/NC	1	1	
Positive family history BAV	12	5	0.34
Abnormal function	1	0	0.73
LVH	3	1	0.46
Medications	1	0	0.78

AR = aortic regurgitation

AS = aortic stenosis

R = right

L = left

NC = noncoronary

BAV = bicuspid aortic valve

LVH = left ventricular hypertrophy