CONGENITAL HEART DISEASE

Dilatation of the ascending aorta in paediatric patients with bicuspid aortic valve: frequency, rate of progression and risk factors

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Objectives: To describe the incidence and rate of dilatation of the ascending aorta in children with bicuspid aortic valve (BAV) and to determine factors that predict rapid aortic dilatation.

Design: Retrospective cohort study.

Setting: Regional tertiary care children's hospital.

Patients: All children aged 0–18 years seen at the authors' institution between 1990 and 2003 with an "isolated" BAV. All patients had had more than one technically adequate echocardiogram, at least six months apart, with concomitant height and weight data.

Interventions: Offline echocardiographic measurements of multiple levels of the aortic root were completed for each participant at each serial echocardiogram. These measurements were then compared with expected measurements derived from a normal local control population.

Main outcome measures: Rate of change of the ascending aorta size over time, where aortic size is expressed as the number of standard deviations above or below the mean size expected for a given body surface area (z score).

Results: 279 echocardiograms spanning a period of from 9 months to 13.3 years were analysed for 88 patients with BAV. The ascending aorta in the BAV group was larger than expected for body surface area at diagnosis and continued to increase in relative size at each of the four subsequent follow-up echocardiograms. Ascending aortic z score increased at an average rate of 0.4/year. A faster rate of increase in z score was predicted by both larger initial aortic valve gradient and non-use of β blockers.

Conclusions: Children with BAV are at risk of having a dilated ascending aorta. This risk increases with longer follow up.

Bicuspid aortic valve (BAV) is one of the most common congenital heart abnormalities, being found in 1–2% of adults.^{1–3} In recent years BAV has also been found to be a risk factor for proximal aortic dilatation and dissection.^{4–10} Recently, a study in a large group of adults suggested that the presence of aortic insufficiency or stenosis may alter the risk of developing ascending aorta dilatation in an adult population with BAV.¹¹ Indeed, nearly all of the studies conducted to date have reported on adults.¹² Yet aortic dissection and rupture in the setting of BAV may also appear in children and adolescents.^{9 10 13 14} The risk of developing a dilated ascending aorta in the setting of BAV is unknown for children, as are the risk factors for rapid progression and the optimal method and interval for patient follow up. This study sought to answer those questions.

METHODS

Patients

Patients were selected through a review of both the institutional cardiology and echocardiography databases. The cardiology database contains prospectively entered data on all patients seen in the local and outreach clinics performed by members of the Division of Pediatric Cardiology at the IWK Health Centre, a tertiary care university children's hospital affiliated with Dalhousie University in Halifax, Nova Scotia, Canada. Paediatric cardiology consultant services and paediatric echocardiography are unavailable in the Canadian Maritimes outside of these clinics. The echocardiography database contains echocardiographic data on all patients undergoing echocardiography either locally or through one of the outreach clinics.

The cardiology database uses a specific code for patients with a BAV and the echocardiography database has both code and free-text entry options. Both databases were searched for patients listed under the BAV code. In addition, the echocardiography database was searched for patients with the words bicuspid, bifoliate or bicommissural in the text of the echocardiogram report.

The echocardiograms for all patients identified were then located and both the tapes and reports were reviewed. All echocardiograms had been recorded by either a Hewlett Packard Sonos 5500, General Electric Vivid 5 or Acuson XP128 echocardiograph.

Children were included if they satisfied the following criteria: less than 18 years old at the time of echocardiography; echocardiographic confirmation of a diagnosis of BAV; at least two technically adequate previous echocardiograms, at least six months apart; concomitant height and weight measurements available for at least two echocardiograms; and adequate two-dimensional imaging of the ascending aorta at the level of the right pulmonary artery, in the parasternal long-axis view, to allow for offline measurements of the ascending aorta.

Children were excluded if they had one or more of the following criteria: prior aortic surgery or aortic prosthesis (including balloon valvuloplasty); coexistent aortic coarctation; cardiomyopathy; Marfan's syndrome or a family history of same; any other coexistent complex congenital heart disease.

Two hundred and sixty-nine patients with a diagnosis of isolated BAV and more than one echocardiogram were identified for potential inclusion. Of these, 131 were excluded

because their records lacked concomitant height and weight data or adequate ascending aorta images on at least two echocardiograms. Forty-four patients had prior aortic surgery, making them ineligible. Five had Marfan's syndrome and one had cardiomyopathy. All of them were excluded. This left 88 patients for analysis. These 88 patients had undergone a total of 279 echocardiograms. Each echocardiogram with technically adequate images was reviewed for inclusion in the study.

A control group was selected by searching the echocardiography database for patients with normal hearts who had been seen between 1998 and 2004. This period was chosen because of the increased likelihood of concomitant height and weight data being recorded on the chart and because these images were stored on site. Control subjects had been referred for echocardiography for a variety of reasons, with the main reason for referral being the presence of an asymptomatic murmur. Five hundred and thirty-four potential control subjects were found on the initial search. A random number generator was used to select control subjects from this pool. If the selected subject met inclusion and exclusion criteria, the echocardiogram was reviewed and data were entered into the study. If not, another potential subject was chosen in the same manner. This process was continued until the same number of control subjects as patients with BAV had been identified. Of subjects initially selected, 33 were excluded because of inadequate imaging of the ascending aorta, 95 for a lack of available concomitant height and weight data and one for a medical condition or family history concern that was believed to be a potential confounder. This left 317 subjects in the pool.

Variables

Table 1 lists the variables recorded for each echocardiogram.

Measurements

The diagnosis of BAV was first confirmed through chart and echocardiogram review. Echocardiographically, the diagnosis was made when only two aortic valve cusps were identified on parasternal short-axis imaging, or when there was commissural fusion along one of the commissures, resulting in a "tricommissural but bifoliate" aortic valve.¹⁵

Studies for both controls and patients were digitised and offline measurements were made with proprietary standard software in the Hewlett Packard Sonos 5500 echocardiograph. Measurements were made in systole to capture the largest diameter of the structure being measured and to maintain comparability between other similar studies, which have also made systolic measurements.¹⁶ Measurements were taken in the parasternal long-axis view at the level of the aortic annulus (hinge points of the aortic valve), sinuses of Valsalva, sinotubular junction and ascending aorta. The ascending aorta was measured at the level of the right pulmonary artery. All measurements were made in a

Figure 1 Relationship between untransformed ascending aorta diameter and body surface area (BSA). Lines represent mean and 99% confidence intervals. Rsq, amount of variance explained by the model.

direction perpendicular to the direction of blood flow. Measurements were made from inner edge to inner edge. Interobserver variability was tested through a random sample of 10 participants whose echocardiograms were selected for review. Two observers made measurements for these participants. The Pearson correlation for the association between the two measurements is reported as a measure of agreement.

Other echocardiographic variables such as left ventricular measurements, degree of aortic insufficiency and transvalvar gradient were recorded from the echocardiogram report.

Analysis

All data were analysed with the SPSS V.11.5 for Windows statistical package (SPSS Inc, Chicago, Illinois, USA).

Log normalised body surface area (BSA) and log normalised aortic measurements from control subjects were analysed by linear regression. This method of analysis was chosen for consistency with the prediction equations of Daubeney *et al.*¹⁶ which are used for other structures in our echocardiographic laboratory. The derived regression equation and the BSA at the time of echocardiography for each patient with BAV was used to calculate a predicted measurement for each level of aortic measurement. The predicted measurement and the actual measurement, along with the root mean square error, was used to derive a z score for each measurement made.¹⁶

The rate of change of z scores over time for each patient was then calculated. Survival curves for time to development of a z score > 2 were derived. Cox regression, based on default settings, was used to define predictors for a shorter time to develop a z score > 2. Logistic regression also based on default settings was used to determine predictors of a rapid rate of change of the z score, defined as a change of > 2

Table 1 Variables recorded for patients with bicuspid aortic valve

Height
Weight
Blood pressure (systolic, diastolic)
Degree of aortic insufficiency
Degree of aortic stenosis
Aortic gradient
Aortic annulus diameter
Aortic sinus diameter
Sinotubular junction diameter
Ascending aorta diameter at the level of the right pulmonary artery

Table 2 Regression equations for aortic measurements at various points as predicted by body surface area

Location	Multiplier	Intercept	Root mean square error	Correlation coefficient
Aortic annulus	0.426	2.732	0.10392	0.92
Aortic sinuses	0.443	3.021	0.10173	0.93
Sinotubular junction	0.434	2.819	0.10961	0.91
Ascending aorta	0.421	2.898	0.09111	0.93

Table 3 Left ventricular function and degree of aortic stenosis or insufficiency over a series of five echocardiograms

Variable	Echocardiogram				
	1	2	3	4	5
Ejection fraction (%)	78 (7)	79 (6)	79 (6)	80 (6)	82 (6)
Minimum	62	66	62	68	74
Shortening fraction (%)	41 (7)	41 (8)	41 (6)	42 (7)	44 (7)
Minimum	27	30	27	31	36
Peak instantaneous gradient (left ventricle to aorta)	28 (16)	30 (20)	34 (18)	44 (19)	41 (21)
Severity of aortic regurgitation					
None	34 (45.3%)	28 (35%)	16 (34%)	2 (10%)	1 (7.7%)
Mild	37 (49.3%)	43 (53.8%)	26 (55.3%)	13 (65%)	6 (46.2%)
Moderate	4 (5.3%)	9 (11.3%)	4 (8.5%)	4 (20%)	5 (38.5%)
Severe	0	0	1 (2.1%)	1 (5%)	1 (7.7%)

Data are mean (SD) or number (valid percentage).

SD above the mean annual rate of change. Variables tested were sex, age at first echocardiogram, presence and degree of aortic insufficiency, initial transvalvar aortic gradient, initial systolic and diastolic blood pressures, use of β blockers and duration of follow up.

A value of $p < 0.05$ was considered significant.

RESULTS

Interobserver Agreement

For the 10 randomly selected echocardiograms that were measured by two observers, the correlation coefficient for agreement between observers was 0.995.

Controls

Figure 1 shows control data depicting the relationship between the size of the ascending aorta and BSA prior to log normalisation. Table 2 shows the regression equations derived from natural log normalised data. Equations take the form $y = \text{multiplier} \times (\ln \text{BSA}) + \text{intercept}$, where y is the natural log of the expected size of the ascending aorta.

For all measurement locations, the multiplier, intercept and root mean square error are provided. With these data, the regression equation for estimation of the expected size of the ascending aorta is $y = 0.421(\ln \text{BSA}) + 2.898$, where y is the natural log of the expected ascending aorta measurement. This model accounts for 87% of the variance in the measurement ($R^2 = 0.87$).

Patients with BAV

Patients underwent an average of 3.2 echocardiograms each (range 2–13). The average age at initial echocardiography was 6 years (range 3 days to 15.6 years). The mean duration of follow up was 4.7 years (range 9.3 months to 13.2 years). The average transvalvar maximum instantaneous gradient at the initial echocardiogram was 29 mm Hg with a range of between 0 and 72 mm Hg (SD 15 mm Hg). Forty-seven patients (53%) had no aortic insufficiency, 37 (42%) had trivial or mild aortic insufficiency, and four (4.5%) had moderate aortic insufficiency. No patients had greater than moderate aortic insufficiency. There was an apparent increase

in the average maximum gradient over the course of follow up, as well as an apparent increase in the proportion of patients with moderate or greater aortic insufficiency. The absolute numbers in the group with moderate or greater aortic insufficiency remained essentially unchanged. Measures of left ventricular function did not change through the course of the follow-up period (table 3). Only six patients (6.8% of the sample) were taking β blockers, although all had started taking them as a result of a dilated ascending aorta.

Table 4 provides average blood pressures at the first five echocardiograms.

Table 5 provides the average z scores of the various aortic segments for the first five echocardiograms.

Whereas the ascending aorta z scores increased serially from diagnosis, the aortic annulus, sinuses of Valsalva and sinotubular junction z scores remained within the normal ranges. The frequency of an ascending aorta z score > 2 (on any echocardiogram) was 65 of 88 (73.9%), whereas 45 of 88 (51.1%) had a z score of > 3 on at least one study. The average rate of change of z score was 0.3928 (SD 0.0432)/year.

Figure 2 shows the Kaplan–Meier curve of time to development of a z score > 2 . The mean time from diagnosis to the development of an increased z score was 5.5 years (SE 0.37 years, 95% confidence interval (CI) 4.82 to 6.28 years). Cox analysis showed that, among variables tested, only a longer duration of follow up was predictive of a shorter time to the development of a z score > 2 . Multiple logistic regression analysis showed that, of the factors tested, only a higher initial left ventricular gradient was predictive of a high rate of ongoing dilatation of the ascending aorta (odds ratio (OR) 1.1, 95% CI 1.02 to 1.16; $p = 0.026$). Only use of β blockers protected against rapid dilatation (OR 0.004, 95% CI 0 to 0.776; $p = 0.04$).

DISCUSSION

BAV is a common congenital heart lesion.^{1 2} The follow up of patients with this condition requires assessment of the degree of stenosis and insufficiency of the valve and assessment of the size of the ascending aorta. Assessing the size of the

Table 4 Average blood pressures (BPs) at initial and subsequent four echocardiograms

BP (mm Hg)	Echocardiogram				
	1	2	3	4	5
Systolic	103 (13.3)	105 (12.8)	105 (13.7)	104 (19.1)	107 (16.4)
Diastolic	63 (8.5)	63 (9.2)	63 (9)	62 (9.5)	64 (7.1)
Range	80–138/50–87	80–145/36–82	81–130/40–90	82–170/44–77	88–140/54–80

Data are mean (SD).

Table 5 Average z scores at each aortic measurement level over a series of five echocardiograms

Location	Echocardiogram				
	1	2	3	4	5
Aortic annulus	0.29 (1.59)	0.86 (1.32)	1.11 (1.40)	1.07 (1.84)	1.84 (1.77)
Number	86	86	49	21	13
Aortic sinuses	0.14 (1.65)	0.56 (1.43)	0.58 (1.52)	0.53 (1.69)	1.07 (1.79)
Number	86	86	49	21	13
Sinotubular junction	0.29 (1.66)	0.81 (1.50)	0.98 (1.49)	0.86 (1.77)	1.84 (1.66)
Number	85	84	49	20	13
Ascending aorta	1.20 (1.88)	2.27 (1.61)	2.58 (1.67)	3.51 (1.91)	4.1 (1.35)
Number	88	87	50	22	13

z scores are mean (SD).

ascending aorta is necessary because of the infrequent but serious complication of aortic dissection and rupture, which occurs in some patients with this disease.³ This is believed to be more likely in patients with a dilated ascending aorta. Our study shows that the ascending aorta dilates, as defined by a z score > 2, in 74% of children with BAV followed up serially. Moreover, the dilatation tends to worsen over time, as manifest by an increasing z score with longer follow up.

In contrast with other conditions with similar aortic pathological features, notably Marfan's syndrome,¹⁷ our patients did not have dilatation of the aortic sinuses. This is consistent with the findings of Nistri *et al*,¹⁸ who reported a relative lack of dilatation of the aortic sinuses, sinotubular junction and aortic annulus in adults with BAV in comparison with the degree of dilatation of the ascending aorta. In contrast, Hahn *et al*¹⁹ noted significantly increased aortic sinus and sinotubular junction sizes in addition to the increased size of the proximal ascending aorta in his patients.

Dilatation is known to progress in the aortas of adults with BAV. Dore and colleagues²⁰ reported an average rate of increase of 0.7 mm/year. As absolute measurements are less meaningful in growing children, we chose to calculate z scores for our patients. We provide for the first time a published regression equation for calculation based on BSA of the expected size of the ascending aorta in children, which allows calculation of z scores. When z scores are calculated for our patients with BAV, our results confirm those of adult studies in that the ascending aorta z score increases over time in patients with BAV.²⁰ The average rate of change of z score was 0.3928/year. This suggests that, depending on the initial

z score, a follow-up interval of 2–4 years is required to detect important changes in the size of the ascending aorta.

In our analysis of risk factors, a higher initial aortic valve gradient was found to be associated with a higher aortic z score. This contrasts with the findings of other investigators that aortic dilatation is independent of the degree of stenosis.¹² Similarly, although others have found the degree of aortic dilatation to be associated with the degree of aortic insufficiency,¹⁹ our multivariate analysis did not show any association between aortic insufficiency and the degree of ascending aorta dilatation. This finding must be considered in light of the infrequent occurrence of more than mild aortic insufficiency in our population. This suggests that those with higher initial aortic valve gradients may require more frequent follow up, although this is likely to be done independently as part of the ongoing surveillance of patients with aortic stenosis.

There are no definitive data to support the use of drug treatment in patients with a dilated ascending aorta in the setting of a BAV. Empirically, clinicians sometimes prescribe β blockers to slow the rate of aortic dilatation in a manner similar to that observed in patients with Marfan's syndrome.²¹ The number of patients taking β blockers in our series was small, making it impossible to come to any meaningful conclusion about the utility of such an approach. Although the multivariate analysis did suggest that the use of β blockers may be associated with a less rapid rate of increase in ascending aortic z score, this was not seen in the univariate analysis. The benefit of β blockade for this population is, therefore, best viewed as unknown.

Limitations

This was a retrospective study, which made digitisation of taped images with subsequent offline calibration and measurement necessary. This may have introduced some error into the measurement process. We attempted to minimise systematic error by using a single reviewer to complete measurements, by measuring in a standard location and by checking for interobserver agreement. The exclusion of a substantial number of potential patients with BAV due to the lack of available height and weight data or images of the ascending aorta is another potential limitation. As the patients included spanned all age groups and years of study, we believe it is unlikely that they differed so substantially as to negate the findings of the study. Lastly, as patients with a dilated aorta were more likely to be followed up often, it is possible that the study suffers from ascertainment bias. This effect may be partly responsible for the apparent significant increase in z score over time.

Conclusions

Expected measurements of the ascending aorta in children can be predicted from BSA on the basis of a regression

Figure 2 Kaplan-Meier survival curve for children with bicuspid aortic valve showing time to development of dilated ascending aorta. A z score > 2 indicates an ascending aorta measurement > 2 SD above the mean.

equation derived from a group of normal children. This equation should be used to define the limits of normal ascending aorta size. Children with BAV are at risk of developing a dilated ascending aorta. This dilatation is progressive. In serial echocardiographic follow up of a group of children with BAV in the Canadian Maritimes, ascending aortic z scores increased at an average rate of 0.39/year, suggesting that a follow up interval of three years would be appropriate for most paediatric patients with this condition. A higher initial left ventricular outflow tract gradient predicts more rapid aortic dilatation. Although the number of patients taking them was small, the non-use of β blockers also predicted more rapid aortic dilatation.

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