Pediatric Cardiology (2021) 42:148–157
https://doi.org/10.1007/s00246-020-02464-2

ORIGINAL ARTICLE

Characterization of the Rate of Aortic Dilation in Young Patients with Thoracic Aortic Aneurysm

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Received: 5 June 2020 / Accepted: 16 September 2020 / Published online: 1 October 2020

Abstract

Longitudinal changes in aortic diameters of young patients with thoracic aortic aneurysm (TAA) have not been completely described, particularly over long periods of follow-up. This retrospective study sought to characterize the rates of proximal aortic dilation in young patients, identify risk factors for TAA progression, and evaluate the predictive utility of early echocardiographic follow-up. Inclusion criteria were: (1) TAA or TAA-predisposing genetic diagnosis, (2) age < 25 years at first echocardiogram, and (3) minimum of 5 years of echocardiographic follow-up. Proximal aortic diameters were measured by echocardiography and *Z*-scores calculated to index for body surface area. TAA severity was classified as no TAA (*Z*-score < 2), mild (*Z*-score 2 to 4), or at least moderate (*Z*-score > 4). Among 141 included patients, mean age at first echocardiogram was 7.3 ± 3.5 years. Mean follow-up duration was 9.8 ± 3.5 years. Fifty five patients had a genetic syndrome, and 38 of the non-syndromic patients had bicuspid aortic valve (BAV). The rate of aortic dilation was significantly higher at the ascending aorta than other aortic segments. BAV and age > 10 years at first echocardiogram were associated with increased rate of ascending aorta dilation. At the ascending aorta, over 25% of patients had categorical increase in TAA severity between first and last echocardiograms, and such patients demonstrated higher rate of dilation within their first 2 years of follow-up. These longitudinal findings highlight progressive ascending aorta dilation in young patients, which may worsen around adolescence. This may help determine timing of follow-up and target ages for clinical trials.

Keywords Thoracic aortic aneurysm · Bicuspid aortic valve · Marfan syndrome · Aortopathy

Introduction

Thoracic aortic aneurysm (TAA) is an aortopathy which predisposes to sudden, life-threatening aortic dissection or rupture [1]. Patients who progress to severe aortic dilation often require prophylactic aortic repair surgery, which frequently occurs in adulthood. Genetic conditions associated with TAA include Marfan syndrome (MFS) and Loeys–Dietz syndrome, and congenital bicuspid aortic valve (BAV) predisposes to TAA. Identifying TAA or establishing a genetic diagnosis at a young age, and early in disease course, facilitates monitoring and clinical interventions aiming to halt progression. Ultimately, this may prevent an aortic dissection or the need for prophylactic aortic surgery [2]. Optimizing clinical decision-making for young patients depends upon a thorough understanding of the longitudinal characteristics of aortic dilation over time. TAA groups including BAV, MFS, and idiopathic TAA have been individually described longitudinally; however, prior studies were limited by having variable follow-up intervals and including patients with short periods of follow-up [3–5]. Previous cross-sectional studies of young patients with BAV have observed increased severity of TAA in older age groups [6], but understanding how TAA progresses as children and young adults age has been limited by a paucity of longitudinal data spanning age groups. The first objective of this study was to characterize the rate of aortic dilation in young patients with TAA or a TAA-predisposing genetic diagnosis who have received care at our institution. The second

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00246-020-02464-2) contains supplementary material, which is available to authorized users.

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objective was to compare the rate of aortic dilation between diagnosis groups, hypothesizing that the rate of aortic root dilation is highest in MFS and the rate of ascending aorta dilation is highest in BAV. Thirdly, we evaluated the role of age in rate of aortic dilation and whether the trajectory of aortic dilation at early echocardiographic follow-up was associated with the long-term changes in TAA severity.

Materials and Methods

Cases were retrospectively identified by queries of the electronic medical record and echocardiography databases at Riley Hospital for Children at Indiana University School of Medicine (IUSM) among patients seen from 1999 to 2018. The study was approved by the IUSM Institutional Review Board. Inclusion criteria were: (1) age < 25 years at the time of first echocardiogram; (2) at least 5 years between the first and last echocardiogram available for review; and (3) TAA involving the aortic root or ascending aorta or a genetic diagnosis that predisposes to TAA development. Patients with complex congenital heart disease or previous cardiac surgery were excluded. Demographic and clinical data were collected by review of the electronic medical record. The cohort was subdivided into diagnosis groups based on genetic diagnosis and aortic valve morphology. Patients were categorized as having MFS or other genetic syndrome if the diagnosis was established by positive genetic testing or a clinical diagnosis was established in a clinical genetics consultation. Patients were included as "suspected MFS" if TAA was present and cardiology notes documented MFS, but the diagnosis was not able to be conclusively verified by review of a clinical genetics evaluation. Patients with TAA and BAV were included as BAV. Patients with trileaflet aortic valve and TAA who did not meet study criteria for the MFS, suspected MFS, or other syndromic groups were included as idiopathic TAA. Two patients with MFS who also had BAV were categorized as MFS. Patients were counted as taking medical therapy if it was documented in a clinical encounter between the first and last echocardiogram. Family history of TAA was defined as having a first- or second-degree relative with TAA. Five patients (two with MFS, two with idiopathic TAA, and one with BAV) required aortic root surgery within 5 years of their first echocardiogram and were therefore excluded.

Each patient's first and last echocardiograms were selected for study. When available, an early follow-up echocardiogram performed within 1 to 2 years after the first echocardiogram was also selected. Each echocardiogram was reviewed by 2 independent readers (APW, BJL). Aortic diameters were measured in the parasternal long axis window from inner edge to inner edge at the levels of the aortic annulus, aortic root, sinotubular junction (STJ) and ascending aorta, according to consensus guidelines [7]. The maximum diameter in systole was recorded by each reader. The mean diameter values between two readers were used for analysis. In order to optimize measurement precision, the differences in the measured diameters between the two primary readers were tabulated for each aortic segment and those with differences ≥ 2.5 percentile identified. For these, a third reader (TMC) measured the diameter and the nearest two of the three measurements were used for analysis. Intraclass correlations between the measurements used for analysis were ≥ 0.89 for all measured aortic segments, indicating good inter-reader reliability consistent with a prior report [8]. Diameters were adjusted for body surface area to calculate *Z*-scores using nomograms from Boston Children's Hospital (zscore.chboston.org) [9]. Aortic valve stenosis or insufficiency and the presence of mitral valve prolapse were recorded if identified on any echocardiography reports reviewed.

Categorical variables are presented as count and percent of total. Continuous variables are presented as mean ± standard deviation. The annual rate of change in aortic diameters and *Z*-scores were calculated using each patient's first and last echocardiogram. Levels of TAA severity were defined as: (1) no TAA (*Z*-score < 2), (2) mild TAA (*Z*-score 2 to 4), and (3) at least moderate TAA (*Z*-score > 4). To display the rates of aortic dilation for each patient, beeswarm plots were generated using the beeswarm package (https://cran.r-project.org/web/packages/beeswarm/index.html) in R: Project for Statistical Computing, version 4.0.0. Analysis of variance (ANOVA) was used to test for differences in rate of change in aortic diameter *Z*-scores between aortic segments. Post hoc comparisons between each pair of aortic segments utilized Student *t*-test that assumed unequal variances. Demographic and clinical characteristics were compared between diagnosis groups using ANOVA for continuous variables and Pearson's χ^2 test for categorical variables. Testing for factors associated with the rate of change in aortic diameter *Z*-score or absolute diameter was performed using ANOVA and were adjusted for the baseline diameter measured on the first echocardiogram. Least squares means were used to estimate effects and identify variables associated with progression compared with no change. Analysis for an association between the long-term change in class of TAA severity and rates of aortic dilation at a 1- to 2-year follow-up echocardiogram utilized Student *t*-test that assumed unequal variances. The alpha threshold used to determine statistical significance was 0.05. Statistical analyses were performed using SAS software (Cary, NC).

Results

The study included 141 patients. Demographic and clinical data are shown in Table 1. The mean age at first echocardiogram was 7.3 ± 3.5 years. The mean interval between first

and last echocardiogram was 9.8 ± 3.5 years. Most patients (*N* = 99, 70%) received medical therapy for TAA, including beta blockers (*N* = 82), angiotensin II type 1 receptor blockers (*N* = 48), and angiotensin-converting enzyme inhibitors (*N* = 5). Aortic valve stenosis or regurgitation, when present, was typically mild; only 3 (2%) patients had moderate aortic valve stenosis and 5 (4%) had moderate aortic valve regurgitation. Hypertension was infrequent (*N* = 7, 5%).

Changes in Aortic Diameters over Time in the Whole Cohort

The mean rate of aortic growth was 0.05 ± 0.04 cm/year (0.01 ± 0.19 *Z*/year) at the aortic annulus, 0.09 ± 0.05 cm/year (0.02 ± 0.16 *Z*/year) at the aortic root, 0.08 ± 0.05 cm/year (0.03 ± 0.20 *Z*/year) at the STJ, and 0.09 ± 0.05 cm/year (0.07 ± 0.21 *Z*/year) at the ascending aorta. The rate of change in aortic *Z*-score was significantly different between these aortic segments ($p = 0.008$) and significantly higher at the ascending aorta compared with the other segments (Fig. 1). Categorically, twice as many patients increased in TAA severity at the ascending aorta than at the aortic root (38 vs. 19 patients, respectively) (Fig. 2). This included 32 patients who progressed from having no evidence of TAA at the ascending aorta on their first echocardiogram to having at least mild TAA of the ascending aorta at their last echocardiogram. Notably, 11 of the 22 patients with at least moderate TAA on their last echocardiogram initially did not have TAA on their first echocardiogram. Overall, these data are consistent with a trend for increasing *Z*-scores over time for all of the aortic segments although this varied between patients. Progressive worsening in aortic dilation was most common at the ascending aorta.

Table 1 Demographic and clinical data for study cohort (*N* = 141)

Characteristic	*N* (%)
Sex	
Male	80 (57)
Female	61 (43)
Race	
Caucasian	126 (89)
Black or African American	14 (10)
Pacific Islander	1 (1)
Diagnosis group	
MFS	47 (33)
Suspected MFS	26 (18)
BAV	38 (27)
Idiopathic	22 (16)
Other syndrome	8 (6)
Aortic dilation on first echocardiogram (*Z* > +2)	
Annulus	58 (41)
Root	88 (62)
STJ	73 (52)
Ascending	40 (29)
None	40 (29)
Family history of TAA	26 (18)
Aortic valve stenosis[a]	21 (15)
Aortic valve regurgitation[a]	28 (20)
Mitral valve prolapse	39 (28)
Hypertension	7 (5)
Prescribed medical therapy for TAA	99 (70)

BAV bicuspid aortic valve, *MFS* Marfan syndrome, *STJ* sinotubular junction, *TAA* thoracic aortic aneurysm

[a]At least mild degree

Changes in Aortic Diameters Among Different Subgroups of TAA

In order to understand rates of aortic dilation between different categories of TAA, the cohort was subdivided into diagnosis groups of MFS (*N* = 47), suspected MFS (*N* = 26), BAV (*N* = 38), idiopathic TAA (*N* = 22), or other syndrome (*N* = 8). The latter group included Loeys–Dietz syndrome (*N* = 4), Ehlers–Danlos syndrome (*N* = 1), 22q11.2 deletion syndrome (*N* = 1), Melnick–Needles syndrome (*N* = 1), and Williams syndrome (*N* = 1). A

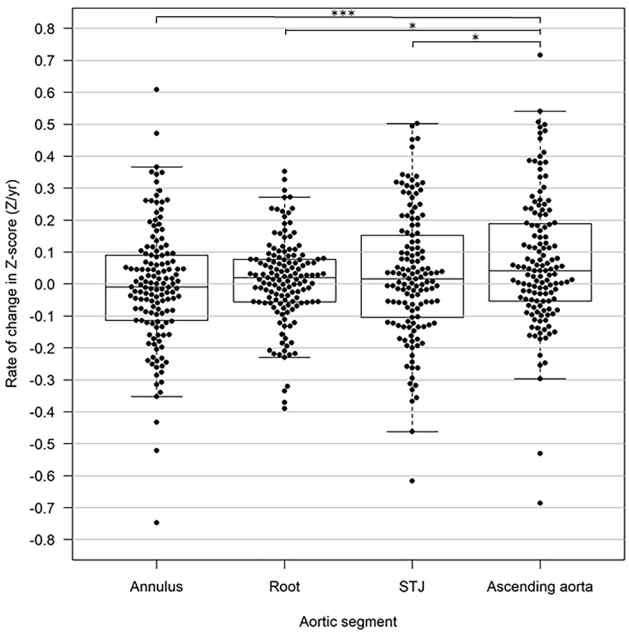

Fig. 1 Rate of change in aortic *Z*-score between first and last echocardiogram by aortic segment. The rate of change in aortic *Z*-score is shown for each patient (circles) at the aortic annulus, root, sinotubular junction (STJ) and ascending aorta. The rate of dilation at the ascending aorta was significantly higher than other aortic segments. One patient with rate of aortic root dilation of 1.05 *Z*/year is not shown to optimize data visualization. Boxes indicate the median and 1st and 3rd quartile values. *$p < 0.05$, ***$p < 0.001$

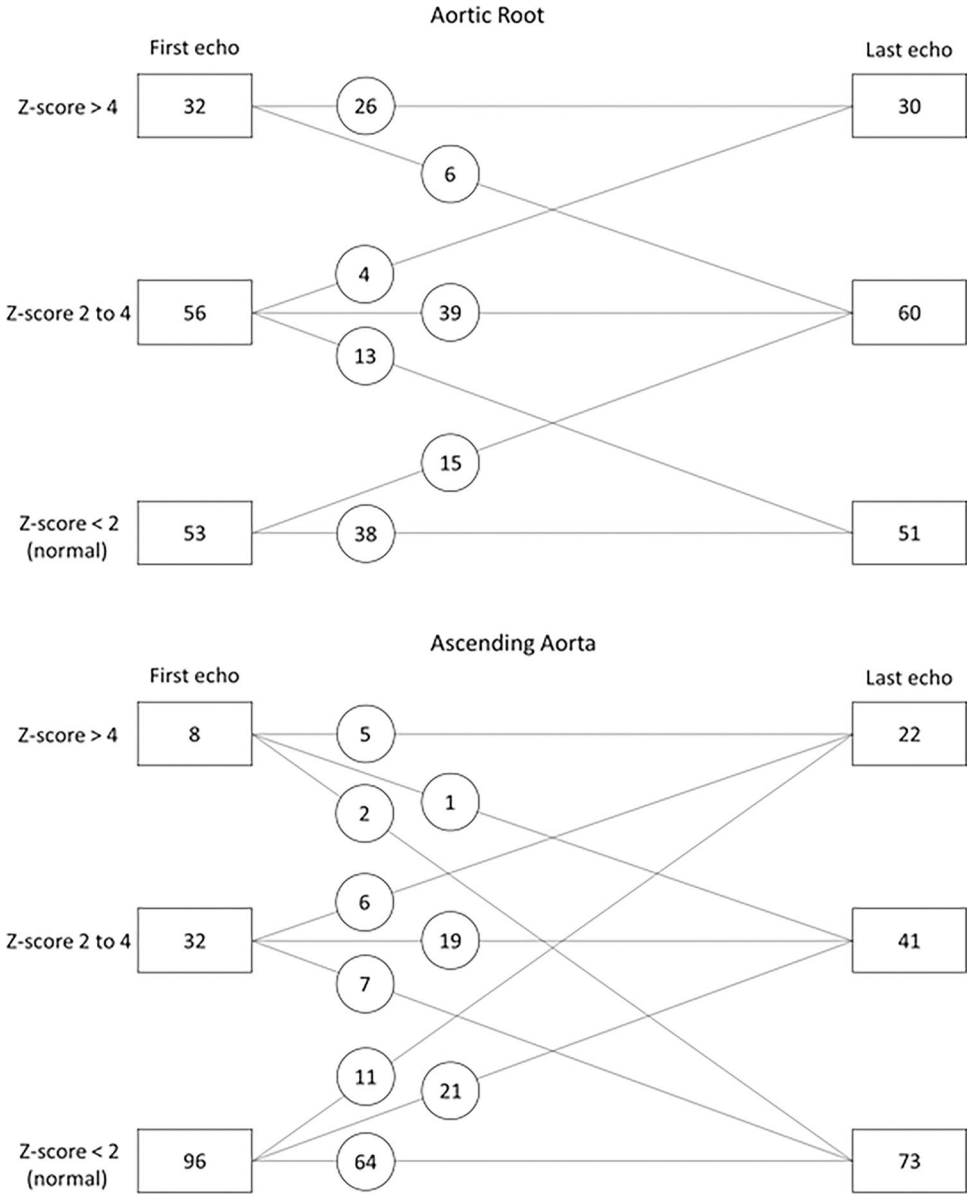

Fig. 2 Categorical changes in TAA severity between first and last echocardiogram for the aortic root and the ascending aorta. TAA severity was stratified into three categories. Boxes contain the number of patients in each severity category at the time of first echocardiogram (left) and last echocardiogram (right). The lines between boxes show the numbers of patients who changed TAA severity categories (diagonals) or remained in the same category (horizontals)

diagnosis of BAV, MFS, or other syndrome was already established prior to study entry in 25 of the 93 patients (27%) in these diagnosis groups. Age, sex, and duration of echocardiographic follow-up were similar between groups (Table 2). The BAV group had smaller aortic root diameter on first echocardiogram, and fewer patients in the BAV group received medical therapy than other groups. Rates of aortic dilation were variable among patients within each diagnosis group (Fig. 3). At the aortic root, neither the rate of change in *Z*-score ($p = 0.32$) nor absolute diameter ($p = 0.18$) differed significantly between groups. The MFS group was the only group to demonstrate an increase in aortic root *Z*-score over time that was significantly different from no change (estimated effect 0.05 ± 0.02 *Z*/year, $p = 0.04$) (Table 3). In contrast to the aortic root, diagnosis group was significantly associated with rate of change in ascending aorta *Z*-scores ($p = 0.002$) and absolute diameters ($p = 0.0004$). As was hypothesized, patients with BAV displayed significantly higher rates of ascending aorta dilation than other groups (Fig. 3). The estimated effect of BAV on ascending aorta *Z*-score rate was 0.18 ± 0.03 *Z*/year ($p < 0.0001$) (Table 3). In multivariate ANOVA, diagnosis group was significantly associated with the rate of ascending aorta *Z*-score change ($p = 0.004$), while sex ($p = 0.85$) and medical therapy ($p = 0.69$) were not. Notably, 18 of 28 (64%) patients in the BAV group who had TAA at the ascending aorta on the last echocardiogram did not have TAA on their first echocardiogram (Fig. 4). This included 8 patients (22% of the overall BAV group) who progressed from normal ascending aorta to at least

Table 2 Comparison of demographic and clinical characteristics between diagnosis groups

Characteristic	MFS ($N=47$)	Suspected MFS ($N=26$)	BAV ($N=38$)	Idiopathic ($N=22$)	Other syndrome ($N=8$)	p value
Age at first echo (years), mean ± SD	8.0 ± 5.8	9.0 ± 4.7	6.6 ± 5.6	6.5 ± 5.9	3.5 ± 3.0	0.09
Male, *N* (%)	22 (47)	15 (58)	27 (71)	10 (45)	6 (75)	0.12
Prescribed medical therapy, *N* (%)	42 (89)	22 (85)	16 (42)	13 (59)	6 (75)	< 0.001
First aortic root diameter (cm), mean ± SD	2.7 ± 0.6	3.0 ± 0.6	2.1 ± 0.6	2.3 ± 0.7	2.2 ± 0.7	< 0.001
First aortic root *Z*-score, mean ± SD	3.0 ± 1.8	3.5 ± 1.3	1.3 ± 1.5	2.7 ± 1.3	4.0 ± 3.3	< 0.001
First aortic root *Z*-score > 2, *N* (%)	33 (70)	24 (92)	12 (32)	13 (59)	6 (75)	< 0.001
First ascending aorta diameter (cm), mean ± SD	2.1 ± 0.5	2.2 ± 0.3	2.0 ± 0.6	1.8 ± 0.5	1.7 ± 0.4	0.07
First ascending aorta *Z*-score, mean ± SD	1.0 ± 1.4	0.9 ± 1.0	1.6 ± 1.5	1.4 ± 1.7	2.2 ± 1.6	0.11
First ascending aorta *Z*-score > 2, *N* (%)	13 (28)	3 (12)	14 (37)	7 (37)	3 (43)	0.18
Follow-up time (years), mean ± SD	9.6 ± 3.3	8.7 ± 2.8	11.1 ± 3.3	9.6 ± 3.8	8.9 ± 4.7	0.13

BAV bicuspid aortic valve, *MFS* Marfan syndrome, *SD* standard deviation

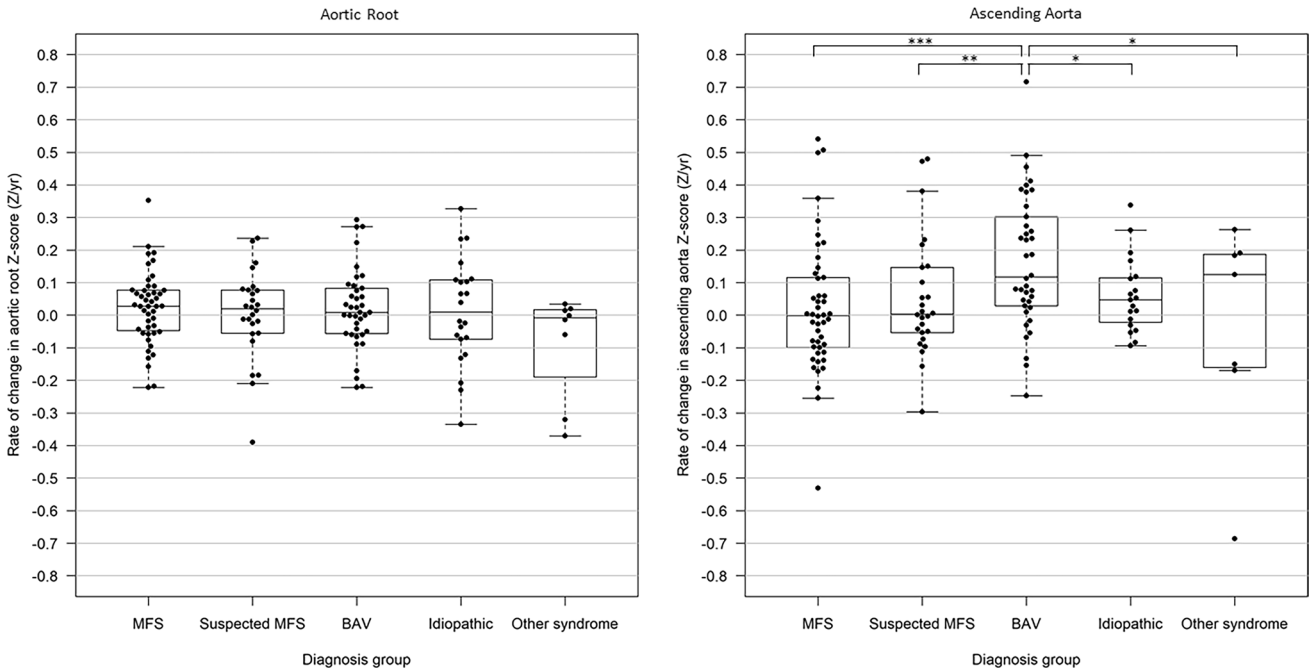

Fig. 3 Rate of change in aortic *Z*-score between first and last echocardiogram among diagnosis groups. The rates of change in *Z*-score are shown for each patient (circles). The rate of aortic root dilation was not significantly different between diagnosis groups ($p=0.32$) (left panel). One patient with MFS and rate of aortic root dilation of 1.05 *Z*/year is not shown to optimize data visualization. The rate of ascending aorta dilation was significantly different between diagnosis groups ($p=0.002$), whereby patients with bicuspid aortic valve (BAV) had the highest rates (right panel). Boxes indicate the median, 1st and 3rd quartile values. *MFS* Marfan syndrome. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

moderate TAA by last echocardiogram. In the BAV group, there was not a significant difference in the rate of change in ascending aorta *Z*-score between patients who were on medical therapy ($N=16$) compared with those not on medical therapy ($N=22$) ($p=0.74$). Overall, patients in the BAV group had more rapid dilation of the ascending aorta than other TAA groups, including many who developed TAA over time.

Table 3 Results of least squares means analysis to estimate the effect of clinical group on the rate of change in aortic *Z*-scores

Diagnosis group	Aortic root		Ascending aorta	
	Effect estimate, *Z*-score/year (SE)	*p* value	Effect estimate, *Z*-score/year (SE)	*p* value
MFS	**0.05 (0.02)**	**0.04**	0.01 (0.03)	0.70
Suspected MFS	0.01 (0.03)	0.74	0.03 (0.04)	0.35
BAV	0.01 (0.03)	0.82	**0.18 (0.03)**	**< 0.0001**
Idiopathic TAA	0.01 (0.03)	0.73	0.07 (0.04)	0.11
Other syndrome	− 0.07 (0.06)	0.19	0 (0.07)	0.97

SE standard error

The effect estimates with *p* value < 0.05 are highlighted in bold

Changes in Aortic Diameters Relative to Age

To assess the role of age on rate of aortic dilation, the cohort was stratified by age at the time of the first echocardiogram. Age category was not significantly associated with the rate of aortic root *Z*-score change by ANOVA ($p = 0.15$), although the age group of 10 to 15 years displayed a relatively increased rate (Table 4). In contrast, age category was significantly associated with the rate of ascending aorta *Z*-score change ($p = 0.04$). In particular, the categories including patients who were at least 10 years old at the time of first echocardiogram were associated with increased rate of ascending aorta dilation.

Analysis of Patients with Early Echocardiographic Follow-Up

Eighty two patients in the cohort had a follow-up echocardiogram performed 1 to 2 years after their first echocardiogram, which we used to assess the predictive utility of early echocardiographic follow-up. Categorically, TAA severity increased at the aortic root between the first and last echocardiogram in 11 of these 82 patients (13%). The rate of change in aortic root *Z*-score between the first and early (1 to 2 year) follow-up echocardiogram was not associated with increase in TAA severity category by the

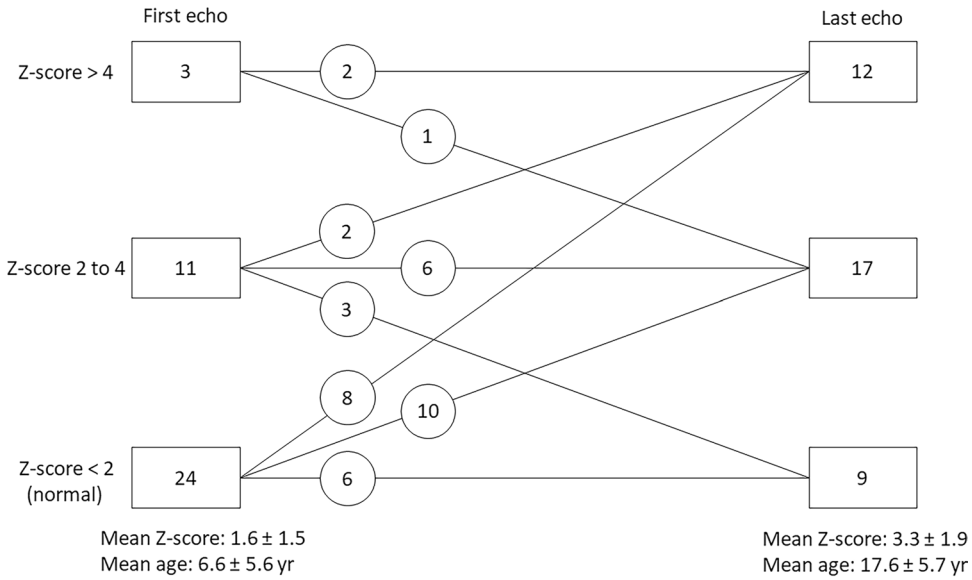

Fig. 4 Categorical changes in TAA severity between first and last echocardiogram at the ascending aorta in patients with bicuspid aortic valve (BAV)

Table 4 Results of least squares means analysis to estimate the effect of age at first echocardiogram on the rate of change in aortic *Z*-scores

Age category (*N*)	Aortic root		Ascending aorta	
	Effect estimate, *Z*-score/year (SE)	*p* value	Effect estimate, *Z*-score/year (SE)	*p* value
< 5 years (61)	0.01 (0.02)	0.79	0.04 (0.03)	0.11
5 to 10 years (38)	− 0.01 (0.03)	0.62	0.05 (0.03)	0.16
10 to 15 years (27)	**0.07 (0.03)**	**0.02**	**0.10 (0.04)**	**0.01**
> 15 years (15)	0.04 (0.04)	0.29	**0.20 (0.05)**	**< 0.001**

SE standard error

The effect estimates with *p* value < 0.05 are highlighted in bold

time of the last echocardiogram ($p = 0.39$) (Fig. 5). At the ascending aorta, TAA severity increased between first and last echocardiogram in 26 patients (32%). The mean rate between first and early follow-up echocardiogram was 0.6 *Z*/year for patients who ultimately increased in TAA severity category versus − 0.1 *Z*/year for those who did not increase in TAA severity category ($p = 0.002$) (Fig. 5). The subset of 26 patients who increased in severity at the ascending aorta included 14 patients in the BAV group (54%) and 12 who were not in the BAV group (46%). The characteristics of the 59 excluded study patients who did not have an early follow-up echocardiogram were not significantly different from the 82 included patients (Supplemental Table 1). These findings suggest that long-term risk for clinical changes in ascending aorta dilation may be identified within 1 to 2 years after initial echocardiogram in patients with or without BAV.

Discussion

In this study, we sought to characterize the long-term rate of aortic dilation in young patients with TAA who have been followed at our center. We found that many patients experienced increasing severity of aortic dilation over time, especially at the ascending aorta segment. As hypothesized, patients with BAV had the highest rates of aortic dilation at the ascending aorta. Many patients with BAV had initially normal aorta which worsened to at least mild TAA at the last follow up. Patients who had their first echocardiogram

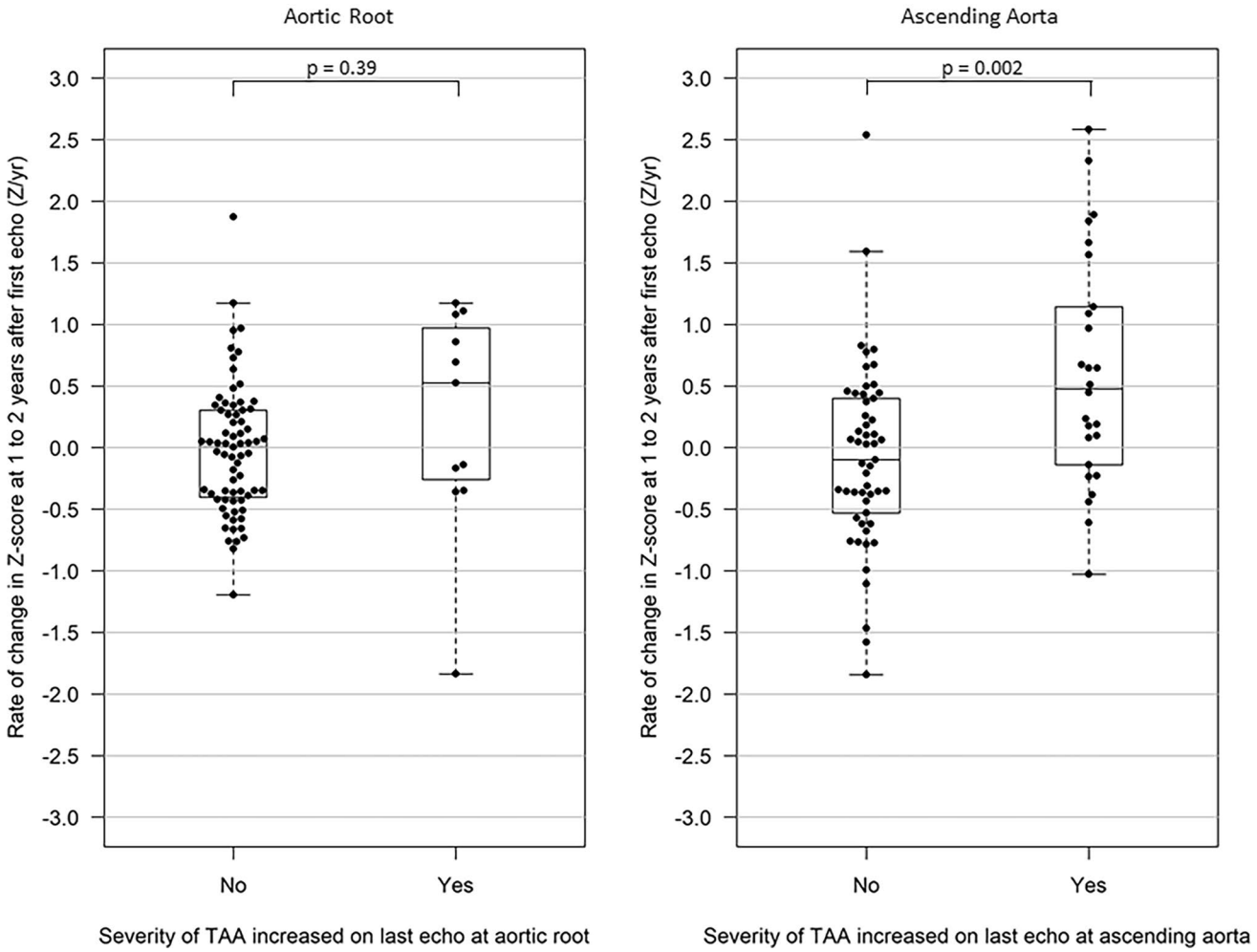

Fig. 5 Test for association between the early rate of aortic dilation and categorical worsening of TAA severity upon last follow-up. Study patients who had an echocardiogram performed 1 to 2 years after the first echocardiogram were included ($N = 82$). Patients who ultimately increased in category of TAA severity at the aortic root by the time of their last echocardiogram did not have a significantly different rate of aortic root dilation at 1 to 2 years after the first echocardiogram (left panel). In contrast, patients who increased in TAA severity at the ascending aorta had significantly higher rates of ascending aorta dilation at 1 to 2 years after the first echocardiogram (right panel). Boxes indicate the median and 1st and 3rd quartile values

performed at a later age had increased rates of ascending aorta dilation. The changes in *Z*-score between the first echocardiogram and a follow-up echocardiogram performed 1 to 2 years after the first were associated with the degree of TAA severity at later timepoints.

Overall, the ascending aorta segment was less dilated at study entry than the aortic root but was the segment most prone to progressive enlargement. Half of patients who had at least moderate TAA at the ascending aorta on their last echocardiogram had a normal ascending aorta on the first echocardiogram. Patients with BAV displayed the strongest predisposition for progressive ascending aorta dilation. This finding corroborates prior studies [10–12]. The novel aspects of this study's finding are that BAV patients were directly compared to other TAA groups and the periods of echocardiographic follow-up were longer than in prior studies. In the present study, the effect of BAV on ascending aorta *Z*-scores was 0.18 *Z*/year. This closely matches dilation rates observed in a previous study of patients with BAV [3], but is higher than was observed in other reports [11, 12]. A possible reason for the discrepancies is that the studies with lower rates included significant numbers of patients with BAV who also had coarctation of the aorta, which was associated with decreased rate of dilation [12]. In the current study, patients in the BAV group were less likely to be on medical therapy for TAA. Medical therapy did not significantly impact the rate of ascending aorta dilation in the whole cohort or within the BAV subgroup, suggesting that the different rates of dilation between groups were not due to medical therapy status. However, because of limitations in retrospective data collection and variations in clinical practice for when to start medical therapy, the study does not exclude a possible effect of medical therapy in some patients. A lack of randomized prospective medical therapy trials for patients with BAV represents a significant gap in knowledge. This study's evidence that TAA frequently worsened in young patients with BAV highlights this deficiency.

While the ascending aorta displayed more rapid progression, aortic root *Z*-scores increased in approximately half of patients during follow-up. In patients with a confirmed diagnosis of MFS, the aortic root *Z*-score increased significantly over time despite nearly 90% of these patients receiving medical therapy. Though the study by Lacro et al. showed reduction in aortic root *Z*-score when patients with MFS were treated with atenolol or losartan, our patients were not as rigorously monitored as they were in that trial [2]. Of note, we also observed increasing *Z*-scores at the aortic root or ascending aorta in many patients who did not have syndromic TAA or BAV. This highlights the need to monitor these patients and identify medical therapies that may be effective for this less well-characterized subset of TAA.

This study suggests that the rate of aortic dilation may accelerate after age 10 for both the root and the ascending aorta. Thus, the risk of progression may increase at older ages. This finding requires further investigation but may be an important consideration for medical therapy, cardiac screening and clinical monitoring decisions. Optimization of the timing and frequency of cardiac surveillance in patients with TAA or who are at risk for TAA, such as those with a normally functioning BAV, would improve safety and cost-effectiveness of longitudinal care. In this study, the changes in ascending aorta *Z*-score within the first two years of initial imaging were associated with TAA severity at much later ages. Also, many patients developed TAA during follow-up. Thus, until more precise prognostic markers of risk are developed, the study's findings support obtaining aortic imaging with echocardiogram or other modality on at least an annual basis, which is consistent with current recommendations for patients with TAA or MFS [13, 14]. This may not only help to identify TAA development early but also may provide prognostic information. Identifying robust predictors of TAA development and progression may help to optimize future strategies in cardiac imaging surveillance.

A strength of this study compared with prior reports was the long duration of echocardiographic follow-up available for all study patients. This is important because TAA does not typically progress rapidly. Another strength of this study was the inclusion of patients with diverse TAA etiologies, which facilitated novel longitudinal comparisons between TAA groups and makes the study's findings broadly applicable to TAA in the young. The findings affirm existing knowledge that the aortic root is often more severely involved for patients with MFS, while the ascending aorta is more frequently problematic in those with BAV [15]. The underlying mechanistic basis for these patterns is not well understood, but different embryological origins of proximal aortic smooth muscle cells may have a role in segmental heterogeneity between TAA subtypes [16]. Clinically, interventions in young patients with TAA may include initiation of medical therapy and activity restriction in attempt to reduce TAA progression and risk for dissection. These, however, may also have negative health or psychosocial repercussions. This study confirms that there is wide variability in the longitudinal changes of TAA in young patients, even within diagnosis groups. Identifying which patients have higher or lower long-term risk for worsened aortic dilation and aortic dissection promises not only to help clinicians recommend treatments where needed, but also to avoid unintended harm or overutilization of resources.

Limitations of this retrospective study included its reliance on clinical data documented in the medical record and that the schedules for imaging were not standardized. As a single-site study there is risk for ascertainment bias; however, our center's statewide catchment of patients increases the likelihood that the findings are generalizable. Genetic testing was not performed for every patient.

Patients with isolated BAV who did not have a diagnosis of TAA during follow-up were not included to focus strictly on TAA in this population. Therefore, the results do not provide information about the overall risk for TAA development in BAV but do indicate that there is a nontrivial risk for TAA to develop during the pediatric age ranges. Patients who required aortic surgery within 5 years of their first echocardiogram were not included because the study's objective was to define the long-term, longitudinal course of TAA. This may have led to under-representation of some severe cases, but this study was focused on patients whose TAA had not already worsened to the point where surgery was imminent before the diagnosis of TAA was made. Including two patients with MFS who had BAV in the MFS group may have modestly impacted comparisons between the groups but likely only biased toward finding no difference between groups. The number of patients that were included in the analysis of early follow-up echocardiograms was relatively small, although the characteristics of this subgroup were similar to the overall cohort. The finding may have been influenced by the timing of the first echocardiogram.

In conclusion, this study describes a cohort of 141 young patients followed clinically for TAA for a minimum of 5 years and mean of approximately 10 years. This study significantly increases understanding of the nature of TAA progression over extended clinical follow-up in a young TAA cohort. The ascending aorta segment appears to have particular risk for progressive dilation. Progression was variable between individual patients, highlighting the need to develop risk classification models that may include genetic and phenotypic factors to tailor evaluations and therapies [5, 17]. Progression may be most significant as patients approach adolescence, suggesting that this may be a time for more frequent imaging follow-up and medical therapy considerations. Increases in ascending aortic *Z*-score at 1- to 2-year follow-ups should trigger increased concern for long-term risk. Taken together, the data establish a baseline model of the rates of aortic dilation in young patients that can be a useful reference for clinicians managing patients and investigators designing clinical trials.

Acknowledgements Dr. Eric Ebenroth at Riley Hospital for Children generously provided assistance with clinical database queries.

Author Contributions APW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing-original draft, Writing-review and editing. ZY: Formal analysis, Validation, Writing-review and editing. TMC: Data curation, Writing-review and editing. LWM: Writing-review and editing. BJL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Administration, Validation, Writing-review and editing.

Funding Dr. Wheeler received support for this study from the Suzanne P. Murphy Foundation (Indianapolis, IN, USA). Dr. Landis received support from the National Institutes of Health (Bethesda, MD, USA) K23HL141667 Award.

Data Availability Original data can be made available upon request.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Approval of this retrospective chart review was obtained from the Institutional Review Board at Indiana University School of Medicine (No. 1509977311R005).

Informed Consent A waiver of consent for this retrospective chart review was granted by the Institutional Review Board at Indiana University School of Medicine.

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