Knowledge of aortic growth in patients with bicuspid aortic valve (BAV) is essential to identify patients at risk for dissection, but data on children remain unclear. We retrospectively evaluated the aortic diameters of all pediatric BAV patients, identified through an echocardiographic database (2005 to 2013). Medical records were reviewed and aortic diameters re-measured on echocardiographic images at diagnosis and if available on variable mid- and endpoints follow-up. Dilatation (z-score >2) was based on 2 different z-score equation methods (Gautier/Campens). In 234 of the total 250 BAV patients, aortic diameters were analyzed; median age was 6.1 years (interquartile range 1.7 to 10), of which 63% were male. Aortic coarctation was present in 81 (36%) patients, 23% had a ventricular septal defect. BAV morphology according to Sievers was as follows: type 0 in 128 patients (55%), type 1 in 96 (41%), and type 2 in 10 (4%). Ascending aortic (AA) dilatation was present in 24% (Gautier) and 36% (Campens) at inclusion. Median follow-up was 4.7 years. The AA was the only location where mean z-scores progressed significantly with age: 0.06 (Gautier) and 0.09 (Campens) units per year between ages 5 and 15 years. Associations for higher AA z-scores at older age were an initial z-score >2 (p <0.001) and aortic valve stenosis (p <0.05). Neither dissection nor preventive aortic surgery occurred. In conclusion, only the AA seems at risk for complication, although no aortic complications occurred in this pediatric BAV cohort. BAV morphology seems associated with larger AA z-scores and valvular dysfunction. © 2017 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). (Am J Cardiol 2017;120:131–136)
Aortic valve regurgitation was present in 132 children. Aortic valve stenosis (AS) was described with 5th order polynomials (quintics) constructed from a linear mixed-effects model, allowing single and serial measurements, unequal intervals, and a random intercept per subject. A likelihood ratio test assessed differences between subgroups. This model only allowed a univariate approach.

Analyses were performed in SPSS 20 (IBM Corp.).

**Results**

Of 11,792 children who underwent echocardiography, BAV was reported in 286. A total of 36 patients were excluded from the study because of incorrect diagnosis (n = 32), missing images (n = 1) or cardiac surgery distorting original valve anatomy before 2005 (n = 3). Of the 250 (2.1%) remaining patients, aortic diameters could be assessed in 234 (Ross procedure after 2005, n = 1; image storage errors, n = 4; inadequate images, n = 7; no height or weight data, n = 4), providing 580 studies. Table 1 describes their baseline characteristics, categorized by valve type.

Young children are lacking, we nevertheless chose to apply these methods. For this reason, we also performed additional regression analysis on absolute diameters at first examination. A z-score > 2 was considered abnormal. Only Gautier’s method was used for analysis of aortic growth in various subgroups. To account for dependency of serial measurements, the mean z-score over time was described with 5th order polynomials (quintics) constructed from a linear mixed-effects model, allowing single and serial measurements, unequal intervals, and a random intercept per subject. A likelihood ratio test assessed differences between subgroups. This model only allowed a univariate approach. p-values < 0.05 were considered statistically significant. Analyses were performed in SPSS 20 (IBM Corp.).

![Sievers classification](image)
Figure 3 shows a regression analysis of the absolute AA diameters at first examination of all patients and of 11 patients with isolated and, during follow-up, normally functioning BAV, including a correction for body surface area. Absolute AA diameter growth was 1.04 mm/year. We did not observe clinically relevant differences in subjects with aortic coarctation or valve dysfunction.

Figure 4 shows that an AA z-score >2 at inclusion was associated with a higher AA z-score at older age, compared with patients with an initial z-score <2 (p < 0.001). However, the z-score progression rate (Δz/Δt) was only minimally different between both groups and thus larger AA diameter was not associated with “faster” AA growth. Presence of AS also resulted in significantly higher AA z-scores (p < 0.05), but was associated to type 2 valve morphology (Table 1). However, the latter was present in only 10 patients. The presence of an initial z-score >2 was not associated to the presence of AS. Comparing patients with versus without aortic regurgitation, aortic arch and valve interventions, and specifically a history of coarctation did not result in significant differences in estimated z-score course.

For the SOV, a z-score >2 at inclusion (p < 0.001), male gender (p < 0.01), Sievers’ type 2 (p < 0.01), syndromes (p < 0.001), and absence of AS (p < 0.05) were associated with higher z-scores (Supplementary Figure 5). However, these factors were not independent: subjects with a syndrome more often had an initial z-score >2 (23% vs 6%, p < 0.05) and less often had AS (28% vs 60%, p < 0.01). Subjects with AS less often had an initial z-score >2 (4% vs 13%, p < 0.05). Higher STJ z-scores were observed in syndromes (p < 0.05), subjects with an initial z-score >2 (p < 0.001), and right-non coronary cusp fusion subtype within Sievers’ type 1 valve morphology (p < 0.01; Supplementary Figure 6), but again, they were nonprogressive.

Discussion

In this large population of children with BAV, we observed no rupture, dissection, or need for preventive aortic surgery. Only the AA z-score progressed with time, showing that the main emphasis on follow-up should lie on the aortic diameters at this location. An initial z-score >2...
and presence of AS were clinical markers for higher z-scores in early adulthood, but z-score progression was not faster. Indeed, aortic pathology in the context of BAV seems not a clinical problem in childhood. Previous studies compared contributing factors using numerical growth rates. This is the first study providing a visualized comparison of aortic diameter growth in children with a BAV. \(^{8,10,17–19}\)

As expected, BAV was common in our pediatric cardiology department and clearly associated with valve- and non-valve-related morbidity such as coarctation of the aorta,\(^{2,26}\) but also with other anomalies such as ventricular septal defects and patent ductus arteriosus, for which only putative associations were mentioned.\(^{5–7,27–29}\) Awareness and echocardiographic screening for other anomalies in clinical practice is mandatory. Similar to Fernandes et al.,\(^9\) valve interventions occurred in a minority and mainly early in life, typically for aortic stenosis. Most importantly, no intervention for aortic dilatation was needed and no complications of aortic dilatation occurred. However, some follow-up seems warranted as we do not want to miss the individual patient with rapid increase in diameter. For the patient with isolated, normally functioning BAV, we suggest to perform echocardiography every 5–10 years.

The AA shows the largest relative diameter and clearly grows faster than can be expected based on body growth and/or age. No significant differences in absolute AA diameter were observed between patients with isolated BAV and BAV patients with associated lesions or valve dysfunction. However, the isolated BAV group was only small. Although patients with an initial z-score >2 and patients with AS had a higher initial z-score, they all had similar AA growth, which makes AA diameter growth predictable. The progression of 0.06 to 0.09 z-score units per year was notably similar to literature that likewise used z-scores,\(^8,10\) as was absolute aortic diameter growth. Fernandes et al.\(^8\) earlier concluded that young patients initially presenting with higher z-scores seem to be at highest risk for aortic dilatation at later age, and this seems valid for all locations. It seems logical that only the AA is at risk for dilatation-related complications, as it is the only location showing z-score progression, but whether these patients indeed have an elevated need to undergo (preventive) aortic surgery at later age is not well studied. We propose regular follow-up for patients entering young adulthood to overcome this gap in knowledge.

Earlier studies suggested protective effects of a coarctation history on AA z-score progression, but we could not confirm this finding.\(^8,13,15\) Also, aortic regurgitation and aortic or valvular interventions were not associated with aortic size. Previous studies reported conflicting data on the increase of aortic dimensions at the level of the SOV.\(^{8,10,17–19}\) We found no z-score progression at this level. The clinical relevance of having an underlying syndrome on STJ diameters remains unclear, mainly because of the heterogeneity of this group.

It is suggested that in adult cohorts, BAV morphology is associated with valve dysfunction and complications.\(^3–6\) Our study confirms this in a pediatric cohort. Valve morphology should be determined at young age, for which in our opinion Sievers’ classification is applicable. Distribution of BAV morphology differed from Sievers’ original study, possibly because of differences in age category.\(^20\) Comparing studies that included BAV morphology is challenging because of a large variety in classifications. Many studies applied morphologic classification named after localization of 1 supposed fusion line (right-left, right-non and left-non coronary cusp fusion), whereas Sievers’ classification also allows 0 and 2 fusion lines.\(^5,8,9\) Given the visual similarities between type 0 anteroposterior orientation and type 1 right-left coronary cusp fusion and between type 0 lateral orientation and type 1 right-left or left-non coronary cusp fusion (Figure 1), distribution of morphology, valve dysfunction, and interventions were notably similar to the literature.\(^3,9\)

\(z\)-score equation methods by Gautier et al. and Campens et al regrettably are not designed for use in patients below 2 years, causing z-scores in these subjects to be only based on extrapolated data and difficult to interpret.\(^20,22\) Both methods provide clearly different results in this age group, with Campens’ method appearing the least accurate. For this reason, we calculated the annual z-score progression in children between 5 and 15 years. As we clinically found children presenting with AA z-scores >2 to have larger AAs in adolescence, we urge the need for \(z\)-score validation in
cohorts with sufficient representation of neonates and toddlers, for the clinician to be aware of the expected growth. Instead of using the z-score, we propose to use Figure 3 to evaluate whether a specific AA diameter is abnormal for a child with a BAV and possibly associated with complications later in life. This could be of benefit especially in patients younger than 5 years of age as the z-score has clear limitations here. Patients with an AA diameter above the 95% prediction interval of our BAV cohort should therefore probably be controlled more frequently.

All limitations of a retrospective study apply. We studied subjects in our tertiary center, introducing a selection bias. Two-dimensional echocardiography might not represent the 3-dimensional aortic shape and might have been subject to technical improvement during the study. We nonetheless believe in the reproducibility of this study with high interobserver agreement and observed differences within reported measurement variability.23 Echocardiography is still the primary investigation of choice for diagnosis and follow-up of children with a BAV, making our results applicable to most clinical situations. Our predictions lack external validation and we hope other research groups will provide this in the near future. The elementary shape of a 5th order polynomial might influence results in the extreme ages, although accuracy is suggested by the population size.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amjcard.2017.03.245.


