Cardiology in the Young

cambridge.org/cty

Trivial aortic valve regurgitation in children and adolescents with structurally normal hearts: physiologic or pathologic?

James J. Joyce[1,2], Thomas R. Joyce[2,3] and Sunita J. Ferns[1,4]

[1]Pediatric Cardiology Division, Wolfson Children's Hospital, Jacksonville, FL, USA; [2]Jacksonville Pediatric and Adult Congenital Cardiology, Jacksonville, FL, USA; [3]The University of Queensland School of Medicine, Brisbane, QLD, Australia and [4]Department of Pediatrics, University of Florida College of Medicine, Jacksonville, FL, USA

Original Article

Cite this article: Joyce JJ, Joyce TR, and Ferns SJ (2024) Trivial aortic valve regurgitation in children and adolescents with structurally normal hearts: physiologic or pathologic? *Cardiology in the Young* **34**: 131–136. doi: 10.1017/S1047951123001270

Received: 30 October 2022
Revised: 2 May 2023
Accepted: 4 May 2023
First published online: 31 May 2023

Keywords:
Aortic valve regurgitation; physiologic; children; adolescents

Corresponding author: J. J. Joyce;
Email: jaxpaccardiology@comcast.net

Abstract

Background: Trivial regurgitation from a normal aortic valve is rarely seen in healthy children and adolescents. The aim of this study was to evaluate timing of presentation, associated conditions, and medium-term prognosis of this incidental finding. *Methods:* Paediatric patients observed to have trivial aortic valve regurgitation with otherwise normal echocardiograms were retrospectively analysed. Clinical and echocardiographic parameters were measured and categorised on presentation and follow-up. *Results:* Sixty patients (39 males) were identified over a 13-year period. Age at presentation was 14.8 years (IQR 12.9–16.0), height z-score was + 0.71 (95% CI + 0.48– + 0.94), and body mass index z-score was + 0.66 (95% CI + 0.40– + 0.92). Median aortic regurgitation vena contracta diameter was 1.0 mm (IQR 0.8–1.3). Aortic valve strands were visualised in 28% and physiologic mitral regurgitation in 32%. Aortic annulus, sinotubular junction, and mid-ascending aorta diameters were normal, and mean aortic sinus diameter was only slightly increased (z-score + 0.23, 95% CI + 0.02– + 0.44). Follow-up data were obtained in 36 patients from 1 to 6.7 years later (median 2.1). Aortic regurgitation was no longer detectable in 28%, and none exhibited worsening. Mitral regurgitation prevalence was lower in those with aortic regurgitation resolution versus persistence (10% versus 50%, $p = 0.03$). *Conclusions:* Trivial aortic regurgitation in paediatric patients with normal hearts is more common in adolescents and is associated with an increased prevalence of aortic valve strands and physiologic mitral regurgitation. These findings do not worsen during growth and may resolve consistent with being physiologic rather than pathologic.

Echocardiographic colour Doppler studies of normal healthy children and adolescents commonly detect trivial regurgitation in tricuspid and pulmonic valves, much less frequently in the mitral valve, and only rarely in the aortic valve.[1–3] This incidentally noted aortic regurgitation is typically trivial and central (see Fig. 1 and Supplementary material video S1). In adulthood, the prevalence of regurgitation in trileaflet aortic valves increases with ageing, initially gradually then more rapidly after 50 years of age.[4] Among adult patients presenting for aortic valve replacement surgery for pure chronic regurgitation at the Mayo Clinic in 2019, 54% had a trileaflet valve and 24 % of these did not have any associated aortic root dilation.[5] Thus, regurgitation in a trileaflet aortic valve in adults can be significantly progressive. To the best of our knowledge, there are no published studies that have evaluated for factors associated with the early development of aortic regurgitation in otherwise normal aortic valves among children or for prognosis during the remainder of growth and maturation in adolescence.

Materials and methods

Study population

Paediatric patients (age < 21 years) seen for cardiology consultation between June 2008 and June 2021, who were found to have trivial regurgitation from an otherwise normal appearing aortic valve on echocardiography, were identified retrospectively from the database of Jacksonville Pediatric and Adult Congenital Cardiology. Consecutive echocardiogram studies across all ages from neonates to 20-year-olds were reviewed to identify the study sample. Exclusion criteria were any additional abnormality on echocardiography, especially any aortic valve deformity (such as leaflet fusion, asymmetry, thickening, or prolapse), ventricular septal malalignment, asymmetric septal hypertrophy, subaortic membrane, aortic ectasia (aortic valve or ascending aorta diameter z-score > +2.05, which is the 98th%ile), mitral valve prolapse, history of rheumatic fever or suspected rheumatic heart disease, Kawasaki disease, or any

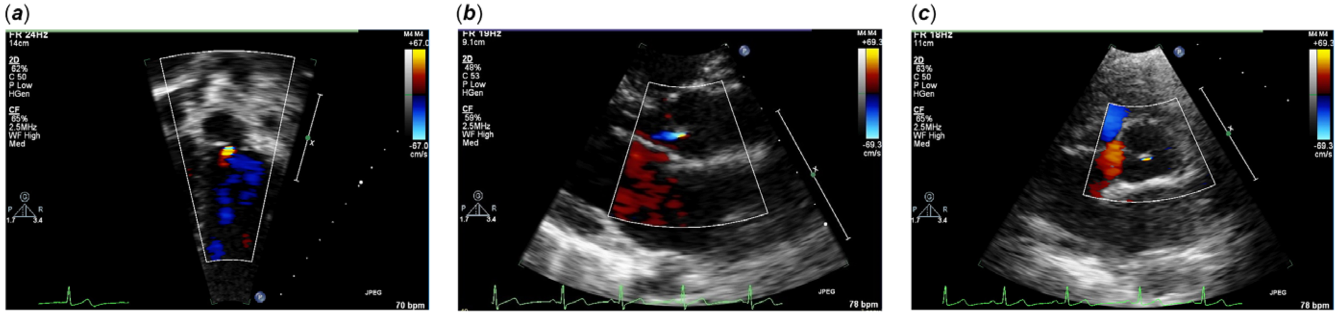

Figure 1. Trivial aortic regurgitation in (*a*) Apical 5-chamber view, (*b*) Parasternal long-axis view, and (*c*) Parasternal short-axis view.

autoimmune, systemic, or genetic disease. Rheumatic fever is quite rare in this region of the world.

Clinical data collected

The indication for cardiology referral, demographics, significant physical exam findings, past medical history, and athletic involvement history were obtained from the clinical record. Body surface area (BSA) was calculated using the formula of Haycock.[6] Body mass index (BMI) was normalised for age and sex, ranked by percentiles, and converted to z-scores (www.cdc.gov/healthyweight/bmi/calculator).[7] Resting clinic systolic and diastolic blood pressures were obtained using the Dinamap Monitor PRO 100 (Critikon, Tampa, FL) automated oscillometric device while sitting, and the average of three readings were standardised for age, sex, and height, then given a percentile rank and converted to z-scores (www.bcm.edu/bodycomplab/BPappZjs/BPvAgeAPPz.html).[8] Patients who returned for recommended follow-up evaluation had the results of their most recent assessment tabulated for comparison. Institutional Review Board approval was obtained for this retrospective study from Baptist Health Care Florida, Jacksonville [45 CRF 46.104 (d) (4)].

Echocardiography

Echocardiograms were obtained using iE33 model echocardiographic instruments (Philips Healthcare, NA) with 2–8 mHz probes following the guidelines and standards for performance of a paediatric echocardiogram recommended by the American Society of Echocardiography.[9] All echocardiographic measurements were performed off-line in DICOM format using the Philips Xcelera analysis package according to the recommendations for quantification methods of the American Society of Echocardiography.[10] Aortic regurgitation was diagnosed by the presence of colour Doppler flow reversal through the aortic valve persisting throughout diastole. The degree of aortic regurgitation was estimated using the vena contracta diameter measured in the zoomed parasternal long-axis view with a Nyquist limit of 60–75cm/sec. Valve regurgitation was graded by the indexed vena contracta diameter, as introduced by Colan and Sleeper,[11] where the vena contracta diameter in millimetres is divided by the square root of the BSA in metres. Aortic regurgitation was graded trivial if < 1.5 mm/m. A central location of the aortic regurgitation jet with direction towards the left ventricular apex was also required to rule out any subtle leaflet prolapse or asymmetry. The presence of any mitral valve regurgitation was also recorded. Other echocardiographic measurements catalogued were aortic annulus, aortic sinus, sinotubular junction, and mid-ascending aorta diameters by 2-D imaging in the parasternal long-axis view. Echocardiogram findings were tabulated, and aortic diameter z-scores based on BSA were estimated using the Boston Children's Hospital calculator.[12] The presence of a valve strand (filiform Lambl excrescence),[13–14] defined as a thin (≤ 1 mm wide) undulating filamentous echo-dense strand seen along the line of valve closure on the ventricular surface of the aortic valve, was also noted when at least 5 mm in length to avoid uncertainty with an artefact (see Fig. 2 and Supplementary material video S2).

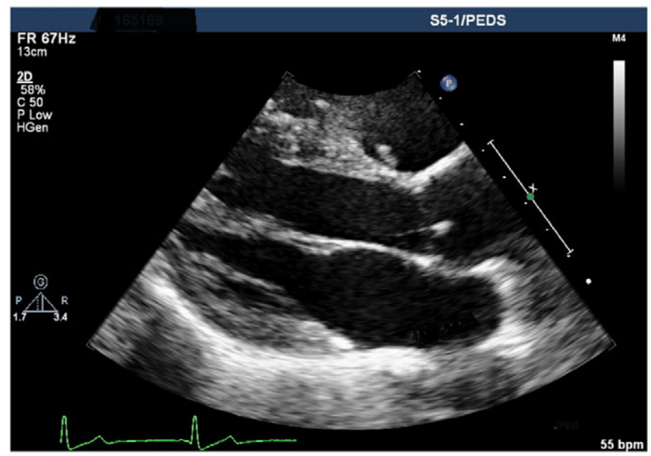

Figure 2. Aortic valve strand in parasternal long-axis view.

Statistical analysis

Results are presented as mean ± standard deviation for normally distributed parameters and as median with interquartile range (IQR) for non-normal quantitative data. The presence of a normal distribution was determined using the Shapiro–Wilk test. Data were indexed to BSA, height, age, and sex as appropriate. Available z-scores were estimated and reported as mean with 95 per cent confidence intervals (95% CI). When comparing categorical groups, Fisher's exact test was used for non-paired data and McNemar chi-square test was used for paired data. For normally distributed quantitative data, the paired and unpaired t-tests were used. With non-normal quantitative data, the Wilcoxon test or Mann–Whitney U-test were used as appropriate. A multivariable-adjusted logistic regression analysis was performed to compare patients with persistent aortic regurgitation at follow-up and those without aortic regurgitation at follow-up with the primary independent variable of interest being the presence or absence of mitral regurgitation. Variables were inputted into the model using a forward stepwise selection. A p-value < 0.05 was considered statistically significant. Statistical analysis was carried out using SPSS Statistics for Windows, version 27.0, IBM Corp., Armonk, NY.

Results

Study population at presentation

A total of 60 children and adolescents, 21 females and 39 males, were identified with trivial aortic regurgitation and otherwise normal echocardiograms. Ages at presentation ranged from five and a half to 19 years-old with only six children under 10 years of age. Presenting chief complaints that led to cardiology consultation were heart murmur in 20, syncope in 16, abnormal screening electrocardiogram in 8, close family history of hypertrophic cardiomyopathy or sudden cardiac death in 5, asymptomatic irregular heart rhythm due to unifocal isolated premature complexes in 4, chest pain with exercise in 4, and early stage 1 hypertension in 3. Some of these patients had more than one of the above complaints. Additionally, 10 were noted to have mild to moderate pectus excavatum, one had mild pectus carinatum, and one had straight back syndrome. Abnormalities noted on cardiology clinic 12-lead electrocardiograms were voltage criteria for left ventricular hypertrophy in four, non-specific T wave changes in three, mild left axis deviation in two, and one each with mild right axis deviation and mild non-specific intraventricular delay. Eleven patients (18%) were obese (BMI > 95th%ile) with six of these severely obese (> 99th%ile). Only one patient was underweight (BMI < 5th%ile). Thirty-four (57%) were involved in some form of athletics and 26 (43%) reported a relatively sedentary lifestyle. Seven patients were on a stimulant medication for attention-deficit disorder and 10 were using a salbutamol inhaler as needed for asthma symptoms. Demographics and echocardiographic parameters at the time of clinic presentation are listed in Table 1. Aortic regurgitation vena contracta diameters ranged from 0.3 to 1.8 mm, 0.3 to 1.4 mm/m when indexed to BSA$^{0.5}$, and 2% to 9% when expressed as a percentage of aortic annulus diameter. Aortic valve strands that were visualised had a median length of 9 mm with interquartile range of 8 to 14 mm.

Table 1. Trivial aortic regurgitation: demographics and clinical data at presentation.

n = 60	At presentation
Age (years)	14.8 (IQR 12.9–16.0)
Height (cm)	168 (IQR 160–174)
z-score by age and sex	+ 0.71, 95% CI + 0.48– + 0.94
Weight (kg)	61.0 (IQR 49.5–75.4)
Body surface area (m^2)	1.69 (IQR 1.50–1.95)
Body mass index (kg/m^2)	21.4 (IQR 18.8–23.9)
z-score by age and sex	+ 0.66, 95% CI + 0.40– + 0.92
Heart rate (bpm)	74 (IQR 67–81)
Systolic blood pressure (mmHg)	112 (IQR 107–122)
z-score by age, height, and sex	+ 0.30, 95% CI + 0.05– + 0.55
Diastolic blood pressure (mmHg)	63 (IQR 58–68)
z-score by age, height, and sex	–0.14, 95% CI –0.24– + 0.06
Aortic valve annulus diameter (mm)	21 ± 2
z-score by BSA	+ 0.23, 95% CI 0.00– + 0.46
Aortic sinus diameter (mm)	28 ± 3
z-score by BSA	+ 0.23, 95% CI + 0.02– + 0.44
Sinotubular junction diameter (mm)	22 ± 3
z-score by BSA	+ 0.03, 95% CI –0.19– + 0.24
Mid-ascending aorta diameter (mm)	24 ± 3
z-score by BSA	–0.13, 95% CI –0.36– + 0.10
Ascending aorta peak velocity (m/s)	1.25 ± 0.20
Vena contracta diameter (mm)	1.0 (IQR 0.8–1.3)
indexed to BSA$^{0.5}$ (mm/m)	0.8 ± 0.3
Aortic valve strand visualised	17 (28%)
Physiologic mitral valve regurgitation	19 (32%)

Data are reported as median (IQR = interquartile range), mean ± standard deviation, or percentile, and z-scores are reported as mean, 95% CI = 95% confidence intervals
BSA = body surface area

Follow-up evaluation

Thirty-six of the original patients (60%), 12 females and 24 males, were re-evaluated from 1.0 to 6.7 years after the initial visit (median 2.1, IQR 1.7–2.7). Follow-up data were compared to those at presentation (see Table 2 and Fig. 3). The box and whisker plots of aortic diameters in Figure 3 include any outliers. While height, weight, BSA, and BMI increased as expected with growth, the z-scores of the four aortic diameters and the percentages of mitral regurgitation and aortic valve strands did not change significantly. When followed serially, none had worsening of aortic regurgitation. Mitral regurgitation prevalence was lower in those with aortic regurgitation resolution versus persistent aortic regurgitation (10% vs. 50%, $p = 0.03$) (see Supplementary material Table S1). Although not statistically significant, there was also a lower prevalence of aortic valve strands in those with aortic regurgitation resolution. Multivariable logistic regression analysis showed that the only variable of significance was mitral regurgitation. Compared to those patients with no mitral regurgitation, those with mitral regurgitation had higher odds of having aortic regurgitation at follow-up (adjusted OR = 1.28, 95% CI = 1.2–2.12, R = 0.49, $p = 0.03$). Furthermore, when adjusted for BMI z-score and even height z-score, the analysis did not show an independent effect of BMI ($p = 0.543$) or height ($p = 0.786$) z-scores. Additionally, there was no statistical change in the Nagelkerke R (0.49–0.48) with the adjusted analysis.

Discussion

Using transthoracic echocardiography in normal children and adolescents, the prevalence of left heart valvular regurgitation has been reported at 0%–0.4% in the aortic valve and 2%–13% in the mitral valve.[1–3] Valve strands, also known as filiform Lambl excrescences, are composed of a connective tissue core covered by endocardium and appear most often at the central nodulus of Arantius in aortic valves. These have been detected at autopsy on normal aortic valves at all ages, including neonates, and are almost universal after 10 years of age.[13] Phillips et al using modern transthoracic echocardiography in normal paediatric patients visualised these aortic valve strands at a prevalence of 2.6% and found no relationship to age from infancy to 18 years.[14] During a median follow-up of 66 months in their study, no neurologic

https://doi.org/10.1017/S1047951123001270 Published online by Cambridge University Press

Table 2. Trivial aortic regurgitation: demographics and clinical data at follow-up.

n = 36	Initial	Follow-up	p-Values
Age (years)	14.9 (IQR 12.3–16.0)	17.1 (IQR 14.9–18.2)	< **0.01**
Height (cm) **z-score by age and sex**	166 (IQR 158–174) + 0.61, 95%CI + 0.30– + 0.92	172 (IQR 165–181) + 0.67, 95%CI + 0.36– + 0.98	< **0.01** 0.49
Weight (kg)	57.1 (IQR 49.3–68.9)	66.7 (IQR 59.4–76.5)	< **0.01**
Body surface area (m^2)	1.62 (IQR 1.47–1.86)	1.79 (IQR 1.68–1.95)	< **0.01**
Body mass index (kg/m^2) **z-score by age and sex**	21.1 (IQR 18.9–23.1) + 0.54, 95%CI + 0.23– + 0.85	22.3 (IQR 20.6–25.0) + 0.58, 95%CI + 0.25– + 0.91	< **0.01** 0.69
Heart rate (bpm)	73 (IQR 65–84)	70 (IQR 65–82)	0.09
Systolic BP (mmHg) **z-score by age, height, and sex**	112 (IQR 107–122) + 0.38, 95%CI + 0.07– + 0.69	118 (IQR 111–122) + 0.26, 95%CI −0.03– + 0.55	0.10 0.41
Diastolic BP (mmHg) **z-score by age, height, and sex**	61 (IQR 58–70) −0.11, 95%CI −0.41– + 0.19	63 (IQR 57–70) −0.36, 95%CI −0.62 – −0.10	0.91 0.07
Aortic valve annulus D (mm) **z-score by BSA**	20.4 ± 2.5 + 0.36, 95%CI + 0.13– + 0.59	21.5 ± 2.4 + 0.35, 95%CI −0.06– + 0.76	< **0.01** 0.91
Aortic sinus D (mm) **z-score by BSA**	28 ± 3 + 0.37, 95%CI + 0.17– + 0.57	29 ± 3 + 0.33, 95%CI + 0.07– + 0.59	< **0.01** 0.57
Sinotubular junction D (mm) **z-score by BSA**	22 ± 3 + 0.14, 95%CI −0.06– + 0.34	23 ± 2 + 0.24, 95%CI −0.03– + 0.51	< **0.01** 0.31
Mid-ascending aorta D (mm) **z-score by BSA**	24 ± 3 −0.02, 95%CI −0.24– + 0.20	25 ± 3 −0.14, 95%CI −0.50– + 0.22	< **0.01** 0.18
Ascending aorta velocity (m/s)	1.25 ± 0.21	1.19 ± 0.20	**0.04**
Aortic valve strand visualised	10 (28%)	9 (25%)	0.77
Trivial aortic regurgitation	36 (100%)	26 (72%)	< **0.01**
Physiologic mitral regurgitation	13 (36%)	14 (39%)	0.66

Data are reported as median (IQR = interquartile range) or mean ± standard deviation, and z-scores are reported as mean, 95% CI = 95% confidence interval, p values for initial versus follow-up BSA = body surface area; D = diameter

events or endocarditis were noted. No difference in male versus female prevalence has been reported for either valve regurgitation or valve strands in normal children and adolescents.

Our study of children and adolescents with the rare incidental echocardiographic finding of trivial aortic regurgitation and otherwise normal appearing trileaflet aortic valves suggests that it is more prevalent in adolescents, males, and those with taller stature and larger body mass index adjusted for age and sex. Among our 60 patients with trivial aortic regurgitation, 10 had mild to moderate pectus excavatum and 1 had the straight back syndrome. Both orthopaedic conditions decrease the anterior–posterior diameter of the thorax and may distort the cardiac structures to some extent. Mishiro et al demonstrated a relationship between this flattening of the chest and physiologic mitral regurgitation in normal young adults but did not report the presence or absence of aortic valve regurgitation.[15] We found no relationship between aortic regurgitation and athletic participation history. Our clinic blood pressures were obtained with the oscillometric method and compared to available normal population ranges based on the auscultatory method. A meta-analysis comparison of oscillometric and auscultatory measurements in children found that the oscillometric systolic blood pressure estimate is on average 2.5 mmHg higher, while there is no difference in diastolic blood pressure values.[16] In our study patients with trivial aortic regurgitation, the mean oscillometric systolic blood pressure z-score using auscultatory norms was slightly increased (+ 0.30, 95% CI + 0.05– + 0.55), and the mean diastolic blood pressure z-score was not different than zero. Thus, given the difference in measurement methods, there was no conclusive evidence of elevated blood pressure in our aortic regurgitation patients. The average aortic annulus, sinotubular junction, and mid-ascending aorta diameters were normal, while that for the aortic sinus was slightly increased (mean z-score + 0.23, 95% CI + 0.02– + 0.44). Patients in our study with aortic regurgitation demonstrated a relatively high prevalence of concomitant physiologic mitral valve regurgitation and aortic valve strands.

Among those re-evaluated on follow-up, over one-fourth had resolution of aortic regurgitation and the rest had unchanged aortic regurgitation without worsening. Those with persistent aortic regurgitation also had a slightly increased prevalence of associated mitral valve regurgitation, while those with resolved aortic regurgitation had a decrease in mitral regurgitation percentage. Aortic valve strand prevalence was also somewhat lower in those with aortic regurgitation resolution but not significantly. Thus, the presence of aortic regurgitation, valve strands, and mitral regurgitation trended together. Colan and Sleeper recently demonstrated in healthy paediatric patients without evidence of heart disease that there is significant temporal variation in the presence of cardiac valve regurgitation.[11] The interval between exams in their study was 2.7 ± 1.9 years, and they noted that study-to-study variability was as frequently resolution as new-onset regurgitation in all four valves. They concluded that new-onset

https://doi.org/10.1017/S1047951123001270 Published online by Cambridge University Press

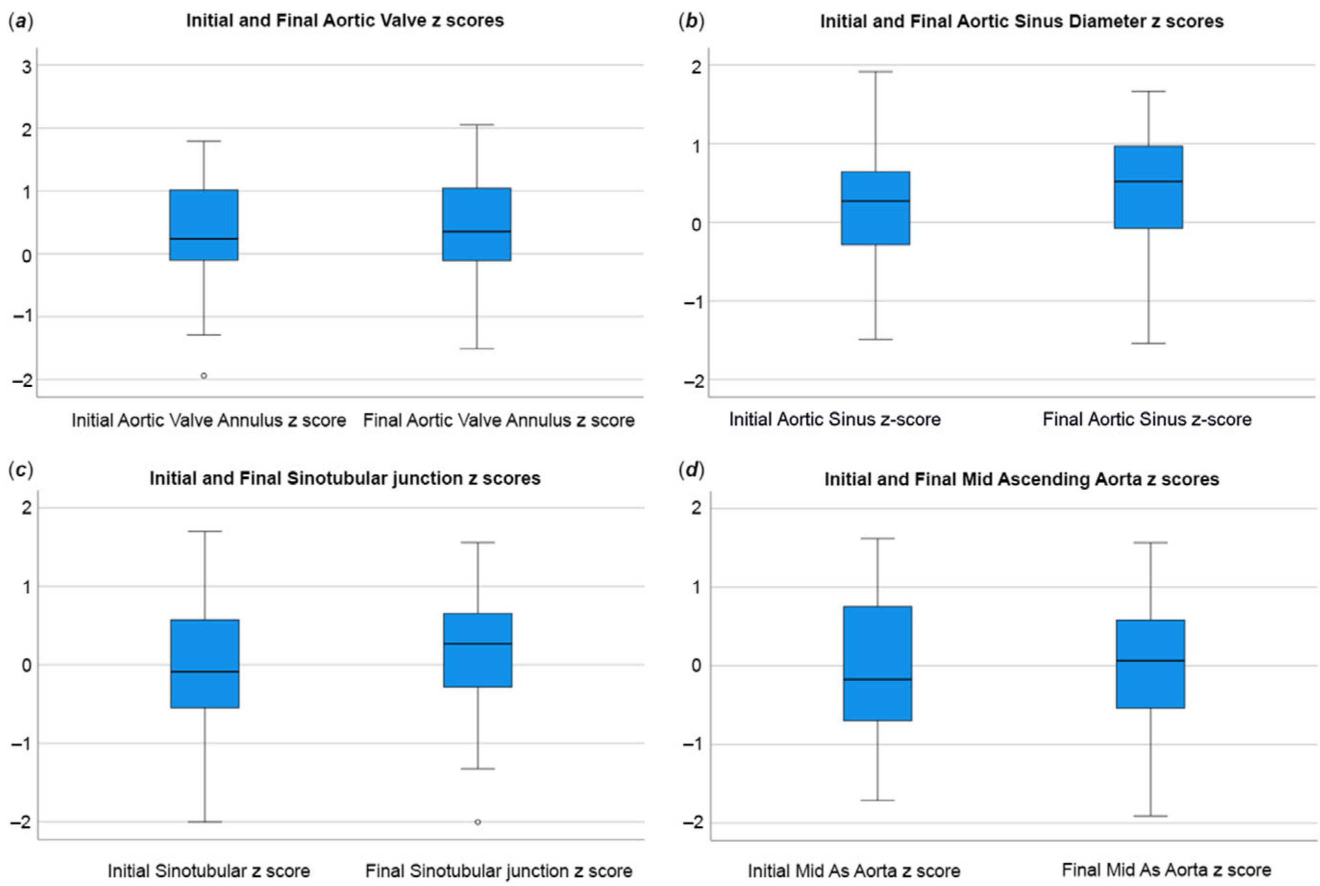

Figure 3. Initial and final aortic diameter z-scores in the follow-up group.

valve regurgitation requires the presence of greater than mild severity or additional evidence of valve abnormality in order to be classified as pathologic rather than physiologic.

In the adult years, the prevalence of left-sided heart valve regurgitation increases sooner in the mitral valve and later in the aortic valve. Healthy adults younger than 50 years of age have been shown to have gradually increasing colour Doppler evidence of regurgitation from 11% to 72% in the mitral valve and from 1.3% to 7% in the aortic valve, usually trivial to mild.[17–20] Young adult athletes have not been shown to have a higher prevalence of aortic regurgitation than control patients,[21–22] unless they are male competitive weightlifters where aortic regurgitation is associated with progressive aortic root dilation that correlates with duration of high-intensity strength training.[23] Older adults at 50 years and beyond have a 58%–74% prevalence of mitral valve regurgitation and a substantially increased rate of aortic regurgitation at 17%–23% with more regurgitation in the moderate to severe range.[18–19] Associated risk factors for the development of aortic regurgitation in adults have been demonstrated to be older age,[4–5,18–19,24–25,27–28] male sex,[4–5,24,27] and aortic root dilation.[5,19,24–25,27–28] Of aortic root dimensions, the sinotubular junction diameter has shown the strongest association with moderate to severe aortic regurgitation.[27–28] Systolic hypertension has been related to aortic regurgitation only in older adults consistent with very prolonged blood pressure elevation.[5,25–26,28] In the adult population, aortic regurgitation has not been shown to be related to body mass index [4,20,25–26] and, to the best of our knowledge, there are no studies that evaluated for a relationship to height alone. The prevalence of aortic valve strands in healthy adults is 14%–27%, persists unchanged over time, and is equally frequent among adults of all age groups and between men and women.[29–30] Like our study results, the lengths of these valve strands in healthy adults have been reported at 9.1 ± 3.4 mm.[31] Aortic valve strands in adults have not been shown to be associated with atherosclerosis, inflammation, or thrombogenesis.[31] Furthermore, in agreement with the paediatric research of Phillips et al,[13] recent adult research studies adjusting for comorbidities have also revealed that valve strands do not appear to be a source of embolic stroke.[29–31]

Limitations

The study is limited by its retrospective design; however, the identification of aortic valve regurgitation was logged in the echocardiogram reports at the time of patient encounters prospectively, minimising selection bias. The identification of valve strands is influenced by technical aspects of scanner settings, the patient's acoustic windows with transthoracic imaging, and the reading cardiologist's awareness of their possible presence. Part of our standard imaging protocol was to zoom in on the left ventricular outflow tract in the parasternal long-axis view and to use harmonic imaging, both of which increase the chances of detecting an undulating valve strand. The sample size of the study was small due to the rarity of the condition, and compliance with follow-up evaluations was incomplete. However, enough patients returned for re-evaluation to allow some conclusions about medium-term prognosis. A larger prospective study should be considered in the future to expand on these findings.

https://doi.org/10.1017/S1047951123001270 Published online by Cambridge University Press

Conclusions

Trivial aortic valve regurgitation in paediatric patients with otherwise normal echocardiograms appears to be more common in adolescents, particularly in those who are relatively taller and heavier, and in males. Trivial aortic regurgitation is associated with an increased prevalence of aortic valve strands and physiologic mitral valve regurgitation. During later adolescence, this valve regurgitation does not worsen and may even resolve, consistent with being physiologic rather than pathologic at this stage of development. Thus, we recommend that routine follow-up for this benign incidental finding is not necessary.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951123001270.

Acknowledgements. We are grateful for the excellent work of our former and current lead cardiac sonographers: Amanda Whitlow, Shaina Jackson, and Ashley Sheehan. The authors would like to thank Dr Gautam Shiva for his invaluable assistance with statistical analysis.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. None.

References

1. Clark BC, Krishnan A, McCarter R, Scheel J, Sable C, Beaton A. Using a low-risk population to estimate the specificity of the world heart federation criteria for the diagnosis of rheumatic heart disease. J Am Soc Echocardiogr 2016; 29: 253–258.
2. Thomson JD, Allen J, Gibbs JL. Left sided valvar regurgitation in normal children and adolescents. Heart 2000; 83: 185–187.
3. Brand A, Dollberg S, Keren A. The prevalence of valvular regurgitation in children with structurally normal hearts: a color doppler echocardiographic study. Am Heart J 1992; 123: 177–180.
4. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinates of mitral, tricuspid, and aortic regurgitation (the framingham heart study). Am J Cardiol 1999; 83: 897–902.
5. Yang L-T, Michelena HI, Maleszewski JJ, Schaff HV, Pellikka PA. Contemporary etiologies, mechanisms, and surgical approaches in pure native aortic regurgitation. Mayo Clin Proc 2019; 94: 1158–1170.
6. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated infants, children, and adults. J Pediatr 1978; 93: 62–66.
7. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Center for disease control and Prevention 2000 Growth charts for the United States: improvements to the 1977 National center for health statistics version. Pediatrics 2002; 109: 45–60.
8. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017; 140: e20171904.
9. Lai WW, Geva T, Shirali GS, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the task force of the pediatric council of American society of echocardiography. J Am Soc Echocardiogr 2006; 19: 1413–1430.
10. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the pediatric measurements writing group of the American society of echocardiography pediatric and congenital heart disease council. J Am Soc Echocardiogr 2010; 23: 465–495.
11. Colan SD, Sleeper LA. Longitudinal variation in presence and severity of cardiac valve regurgitation in healthy children. J Am Soc Echocardiogr 2020; 33: 1400–1406.
12. Boston Children's Hospital Heart Center. Echocardiographic Z-score calculator., https://zscore.chboston.org.
13. Hurle JM, Garcia-Martinez V, Sanchez-Quintana D. Morphologic characteristics and structure of surface excrescences (Lambl's excrescences) in the normal aortic valve. Am J Cardiol 1986; 58: 1223–1227.
14. Phillips AL, Qureshi MY, Eidem BW, Cetta F. Lambl's excrescences in children: improved detection via transthoracic echocardiography. Congen Heart Dis 2018; 13: 251–253.
15. Mishiro Y, Oki T, Iuchi A, et al. Echocardiographic characteristics and causal mechanism of physiologic mitral regurgitation in young normal subjects. Clin Cardiol 1997; 20: 850–855.
16. Duncombe SL, Voss C, Harris KC. Oscillometric and auscultory blood pressure measurement methods in children: a systematic review and meta-analysis. J Hypertens 2017; 35: 213–224.
17. Jobic Y, Slama M, Tribouilloy C, et al. Doppler echocardiographic evaluation of valve regurgitation in healthy volunteers. Br Heart J 1993; 69: 109–113.
18. Lavie CJ, Hebert K, Cassidy M. Prevalence and severity of Doppler-detected valvular regurgitation and estimation of right-sided cardiac pressures in patients with normal two-dimensional echocardiograms. Chest 1993; 103: 226–231.
19. Klein AL, Burstow DJ, Tajik AJ, et al. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. J Am Soc Echocardiogr 1990; 2: 54–63.
20. Reid CL, Anton-Culver H, Yunis C, Gardin JM. Prevalence and clinical correlates of isolated mitral, isolated aortic regurgitation, and both in adults aged 21 to 35 years (from the CARDIA study). Am J Cardiol 2007; 99: 830–834.
21. Douglas PS, Berman GO, O'Toole ML, Hiller WD, Reichek N. Prevalence of multivalvular regurgitation in athletes. Am J Cardiol 1989; 64: 209–212.
22. Vasconcelos DF, Jungueira Junior LE, Sanchez Osella OF. Doppler echocardiographic comparison of valvular dynamics in bicycle, running, and football athletes, and sedentary subjects. Arq Bras Cardiol 1993; 61: 161–164.
23. Babaee Bigi MA, Aslani A. Aortic root size and prevalence of aortic regurgitation in elite strength trained athletes. Am J Cardiol 2007; 100: 528–530.
24. Andell P, Li X, Martinsson A, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017; 103: 1696–1703.
25. Vriz O, Bertin N, Bossone E, Palatini P. Aortic diameters and mild functional aortic regurgitation in hypertensive and normotensive people. J Ultrasound Med 2018; 37: 2171–2180.
26. Rahimi K, Mohseni H, Kiran A, et al. Elevated blood pressure and risk of aortic valve disease: a cohort analysis of 5.4 million UK adults. Eur Heart J 2018; 39: 3596–3603.
27. Wenzel J-P, Petersen E, Nikorowitsch J, et al. Aortic root dimensions as a correlate for aortic regurgitation's severity. Int J Cardiovasc Imaging 2021; 37: 3439–3449.
28. Yang L-T, Enriquez-Sarano M, Michelena HI, et al. Predictors of progression in patients with stage B aortic regurgitation. J Am Coll Cardiol 2019; 74: 2480–2492.
29. Roldan CA, Shively BK, Crawford MH. Valve excrescences: prevalence, evolution and risk for cardioembolism. J Am Coll Cardiol 1997; 30: 1308–1314.
30. Roldan CA, Schevchuck O, Tolustrup K, et al. Lambl's excrescences: association with cerebrovascular disease and pathogenesis. Cerebrovasc Dis 2015; 40: 18–27.
31. Omron SS, Chaker S, Lerario MP, Merkler AE, Navi BB, Kamel H. Relationship between Lambl's excrescences and embolic strokes of undetermined source. Eur Stroke J 2020; 5: 169–173.