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Age-related changes in diastolic function in children: Echocardiographic association with vortex formation time

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Abstract

Background: This study aims to understand the age-related changes in vortex formation time (VFT) index in children, and thus, describe the ranges of VFT in different pediatric age groups with the ultimate goal of assessment of diastolic function.

Methods and results: Transthoracic echocardiograms in healthy (n = 84) subjects from birth to 20 years were analyzed to compute VFT and diastolic performance. LV apical and short-axis views were used. Three separate measurements were performed, and the mean was used to derive VFT and other indices. Statistical comparisons were made amongst the groups, stratified by age.

Results: Vortex formation times in neonates (median 1.79, interquartile range 1.31–1.92) and infants (1.38, 1.07–1.72) were found to be significantly lower ($P < .05$) than the older age groups (1–5 years 2.47, 1.87–2.94, 5–10 years 2.18, 1.89–2.53, 10–20 years 2.34, 1.84–2.96). The changes in VFT correlate to the changes in diastolic function in children.

Conclusion: Our results show that unlike adults, VFT changes along with the growth-related myocardial adaptations in children, and its range may be used to evaluate diastolic function. The present study is the first to test the significance of the trans-mitral VFT in children by comparing different age groups of healthy subjects.

KEYWORDS

echocardiography, pediatric diastolic dysfunction, Shone's complex, vortex formation time

1 | INTRODUCTION

In adults, efficient left ventricular (LV) diastolic function is due to a complex synergy between the LV suction and left atrial contraction, which establishes optimal LV circulation, energy conservation and transfer of blood flow momentum.[1-4] The dual mechanisms of the trans-mitral jet's added mass effect and vortex ring formation allow blood to optimally propagate from the LA toward the aorta.[5] The trans-mitral vortex ring develops due to the negative intraventricular suction force applied to the cardiac base, similar to a piston-cylinder mechanism, that opens the mitral valve and ensues a trans-mitral starting jet.[6,7] Therefore, quantifying the trans-mitral pulsed flow provides a good estimate of the LV diastolic performance.

Vortex formation time (VFT) has been established and validated as a nondimensional measure to quantify LV vortex formation during diastolic filling in adults. VFT is calculated based on the stroke ratio of the trans-mitral flow, mitral valve diameter and LV geometry, as described by Gharib et al[2] Optimal vortex formation occurs when there is synchrony between adequate LV expansion and mitral valve opening signified by a desired trans-mitral jet stroke ratio (~3.5 to 5.5).[2,8] Lower VFT values have been observed in adult patients with diastolic dysfunction, denoting suboptimal propulsion across the

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mitral valve.[1,8,9] Concurrently, higher VFT values can be attributed to turbulence through the LV.[10-12]

In children, considerable heterogeneity exists in the published reference ranges of diastolic function indices, thus complicating the assessment of diastolic function.[13] Furthermore, there has been no report on how VFT changes in children. The present pilot study aims to better understand the diastolic changes and trans-mitral flow by quantifying VFT and its range in different age groups of healthy children.

2 | METHODS

2.1 | Study groups

A retrospective study of transthoracic echocardiograms in 84 subjects (birth to 20 years) from Bronx Lebanon Hospital Center between January 2015 and March 2017 was performed. The local institutional review board approved this study. All echocardiograms were performed in the outpatient echocardiographic laboratory for standard of care clinical indications. We followed the institutional protocol based on the American Society of Echocardiography (ASE) guidelines on performing and quantifying pediatric echocardiograms.[14]

The study subjects consisted of 84 healthy subjects. Indications for echocardiograms in these subjects included: heart murmurs, palpitations, or chest pain. Echocardiograms with low image quality due to subject movement, mitral valve E-A wave fusion or poor echo windows were excluded from the study. In addition, subjects with any other form of congenital heart disease (CHD), including atrial septal defect and patent ductus arteriosus, or with abnormal electrocardiograms were excluded. All subjects were in sinus rhythm at the time of the acquiring echocardiograms.

2.2 | Image acquisition

Echocardiography was performed on a Vivid E9 XD clear ultrasound system (GE Healthcare) using appropriate transducers. Two-dimensional images with separate focused views of the LA and the LV in the apical 4-chamber, 2-chamber and of the LV in the parasternal short-axis views were obtained (Figure 1). Left ventricular stroke volume (SV) and ejection fraction (EF) were calculated using the biplane Simpson's method of summation of disks.[14] Pulse wave cursor was placed at the tip of the mitral valve leaflets to obtain LV inflow Doppler in the apical 4-chamber view. The velocity time integrals (VTI) of the mitral E- and A-waves were measured (cm). The mitral valve's (MV) geometric orifice area (GOA) (cm^2) was obtained in the parasternal short-axis view in a plane perpendicular to the mitral valve leaflets, as shown in Figure 1.[15] The largest open dimension was traced along the mitral valve leaflets inclusive of the commissures in diastole, by direct visual assessment using planimetry (Figure 1). Left atrial volume (LAV) was obtained using the biplane Simpson's method of summation of disks by tracing the left atrial area in the apical 4-chamber and 2-chamber views at end-systole (mL).[14] Pulse wave e′ tissue Doppler velocities (cm/s) were obtained with a 2-mm pulse Doppler gate placed within 1 cm of the mitral valve annulus at the interventricular septum in the apical 4-chamber view, per ASE guideline.[16] A mean of 3 separate cardiac cycle measurements was used for all calculations. To avoid inter-observer variability in image acquisition, a single operator (DG) made all the measurements. LAV was indexed to body surface area for subsequent statistical comparisons (LAVI). For further analyses and computation of trans-mitral VFT, de-identified data were sent to KLAB (Edwards Lifesciences Center for Advanced Cardiovascular Technology at UC Irvine) after an inter-institutional agreement for data exchange.

2.3 | Vortex formation time (VFT)

The following calculations were performed to obtain the trans-mitral VFT:

$$\mathrm{VFT} = \frac{4(1-\beta)}{\pi}\alpha^3 \times \mathrm{EF} \tag{1}$$

where, β is the fraction of stroke volume contributed from the atrial component of LV filling (A-wave) and α^3 describes a dimensionless LV volume parameter, as described before.[1,2] Since, the LV stroke volume is equal to the summation of blood flows that enter the LV during A-wave (β) and E-wave (ε), $\varepsilon = 1 - \beta$ was used for calculation of VFT as:

$$\mathrm{VFT} = \frac{4\varepsilon\alpha^3}{\pi} \times \mathrm{EF} \tag{2}$$

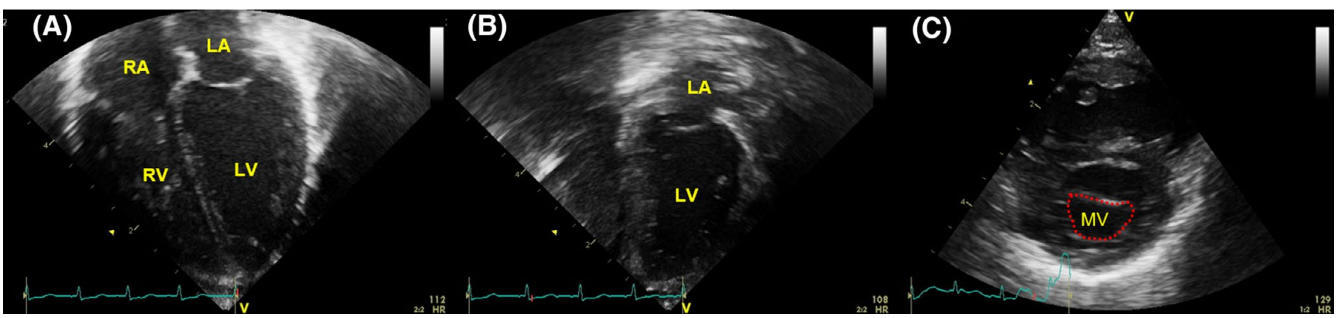

FIGURE 1 Representative images of left ventricular apical 4-chamber (A), 2-chamber (B) and short-axis (C) views used to obtain echocardiographic data in this study (LA = left atrium; LV = left ventricle; MV = mitral valve). The dotted line in C represents the MV geometric orifice area

where ε is the fraction of stroke volume contributed by early filling (E-wave).

2.4 | Statistical analysis

Descriptive data were expressed as mean ± standard deviation or median ± interquartile range. Kolmogorov–Smirnov test was conducted on all variables to test for normality of distribution. Student's *t*-test, one-way ANOVA and post hoc Tukey test were used for parametric and Mann–Whitney *U* test was used for nonparametric data comparisons. Pearson's product correlation was performed to obtain regression to the best fit for VFT. Echocardiographic measurements and corresponding VFT calculations were repeated on 10 subjects more than 3 months after the first measurements to derive inter-observer (DG and AK) and intra-observer (DG) VFT correlations using Bland–Altman analysis. A *P*-value <.05 was considered significant for all comparisons. Statistical analysis was performed using commercially available software, R Commander (plug-in EZR version 1.33).

3 | RESULTS

Baseline study patient characteristics are described in Table 1. This group of healthy subjects had an almost equal distribution of males (47.6%) and females.

3.1 | VFT in healthy children and age-related changes

Vortex formation time is a continuous parameter; however, to better understand the effect of age on quantified parameters, we divided the study subjects into the following age groups: birth—1 month (n = 23), 1 month–1 year (n = 11), 1–5 years (n = 9), 5–10 years (n = 18) and 10–20 years age (n = 23), as shown in Table 2. Subjects in birth-1 month (median 1.79, interquartile range (IQR) 1.31–1.92) and 1 month–1 year age groups (1.38, IQR 1.07–1.72) had significantly lower VFT compared to subjects at 1–5 years (2.47, IQR 1.87–2.94), 5–10 years (2.18, IQR 1.89–2.53) and 10–20 years age (2.34, IQR 1.84–2.96) as shown in Figure 2 ($P < .05$). Routine Doppler-derived echocardiographic parameters of mitral valve E- and A-waves, and e′ velocity were significantly lower in birth-1 month and 1 month-1 year compared to older groups (Table 2). Neonates had a higher peak atrial flow velocity (A-wave) with E/A ratio < 1 and higher E/e′ suggestive of altered relaxation (Table 2 and Figure 3).

TABLE 1 Baseline characteristics of all subjects

	Healthy children (n = 84)
Age (years)	5.9 ± 5.9
Sex: male (%)	40 (47.6)
BSA (m^2)	0.8 ± 0.6

Abbreviation: BSA = body surface area.

3.2 | Inter- and intra-observer variations

Bland–Altman comparisons for inter-observer variability of VFT showed good agreement (mean difference 0.26, confidence interval CI: −1.11 to 1.64). Similar results were obtained for intra-observer VFT variability (mean difference 0.63, CI: −1.05 to 2.31) as shown in Figure 4.

4 | DISCUSSION

This study investigates the possible association between VFT and age-related changes in LV diastolic function in children from birth to 20 years. Our pilot study results show that VFT ranges in children are totally different than in adults; they change rapidly in the first year of life and rises to adult levels by the second decade.

4.1 | VFT and diastolic function in healthy children

The neonates' and infants' LV are known to have altered relaxation characteristics that progressively change over the first year of life, and subsequently reach adult levels.[17] The results of the routinely derived echocardiographic parameters in our cohort corroborate with the previous studies that have shown relatively lower Doppler-derived trans-mitral velocities (E- and A-waves) and lower e′ in neonates and infants.[13,18,19] Diastolic function indices in older adolescents are comparable to adults[13]; however, these values cannot be applied to younger children. A considerable variation exists in the published reference ranges of diastolic function indices in children.[13] Our study's results, for the first time, suggest that the normal ranges of VFT (1.5–3) in children are totally different than the adults' normal range (3.5–5.5).

The age-related changes of diastolic function in children may have multiple reasons. The adult LV is known to have a "wringing" systolic movement created by counterclockwise rotation of the apex and a clockwise rotation of the base.[20] Alternatively, the neonatal LV has a low peak torsion and untwisting velocity compared to older children and adults. It has been suggested that somatic growth and LV maturation result in progressively farther myofiber connections between the base and apex and progressive increase in torsion and twist.[21] Thus, greater negative intraventricular pressure gradients form within the LV as the child grows.[21] Furthermore, relatively faster heart rates in children may be associated with adaptations in LV relaxation and perhaps LV twisting/untwisting. We hypothesize that the low VFT values found in neonates and infants are related to the "ineffective twisting",[21] due to the smaller LV dimensions and faster heart rates,[22] compared to adults. This combination may not allow the trans-mitral vortex to fully form during early diastole, and therefore, it is likely that neonates and infants have shorter duration of trans-mitral jet. Our results indicate that VFT is attenuated in neonates and infants and increases to the adults' normal range by adolescence. In our opinion, it may be misleading to characterize

TABLE 2 Temporal changes in traditional echocardiographic diastolic function parameters

	Birth–1 mo, n = 23	1 mo–1 y, n = 11	1–5 y, n = 9	5–10 y, n = 18	10–20 y, n = 23	*P*-value
Mitral E (cm/s)	47 (40–57)	91 (82–97)*	90 (88–102)*	100 (93–110)*	93 (88–107)*	<.01*
Mitral A (cm/s)	50 (47–54)**	82 (65–91)	58 (49–59)	48 (38–60)**	44 (40–52)**	<.05**
Septal e′ (cm/s)	4.0 (3.0–5.0)**	8.3 (7.8–10.5)*	12.1 (11.7–13.5)*,**	13.2 (12.0–14.7)*,**	14.3 (12.8–15.5)*,**	<.01* <.05**
E/A	0.97 (0.87–1.23)	1.09 (0.92–1.34)	1.53 (1.39–1.86)*	2.16 (1.58–2.64)*,**	2.07 (1.85–2.32)*,**,***	<.01* <.05** <.05***
E/e′	11.7 (9.4–14.4)	9.9 (8.9–11.4)	7.6 (7.2–8.7)*,**	8.1 (7.4–8.5)*,**	6.4 (6.0–7.8)*,**	<.01* <.05**
LAVI (mL/m^2)	8.8 (7.1–11.4)	12.5 (11.3–16.8)	18.8 (15.6–21.5)*	18.3 (16.6–21.8)*	20.7 (15.4–25.7)*,**	<.01* <.05**
EF (%)	60 (58.6–65.4)	57.9 (56.4–60.7)	56.6 (55.5–58.3)	55.5 (53.6–58.2)	55.5 (53.3–57.4)	NS

Abbreviations: EF = ejection fraction; LAVI = Indexed left atrial volume.
*Significant *P* value < .001 compared to birth–1 mo group.
**Significant *P* value < .05 compared to 1 mo–1 y group.
***Significant *P* value < .05 compared to 1–5 y group; data are presented as median and interquartile range in table.

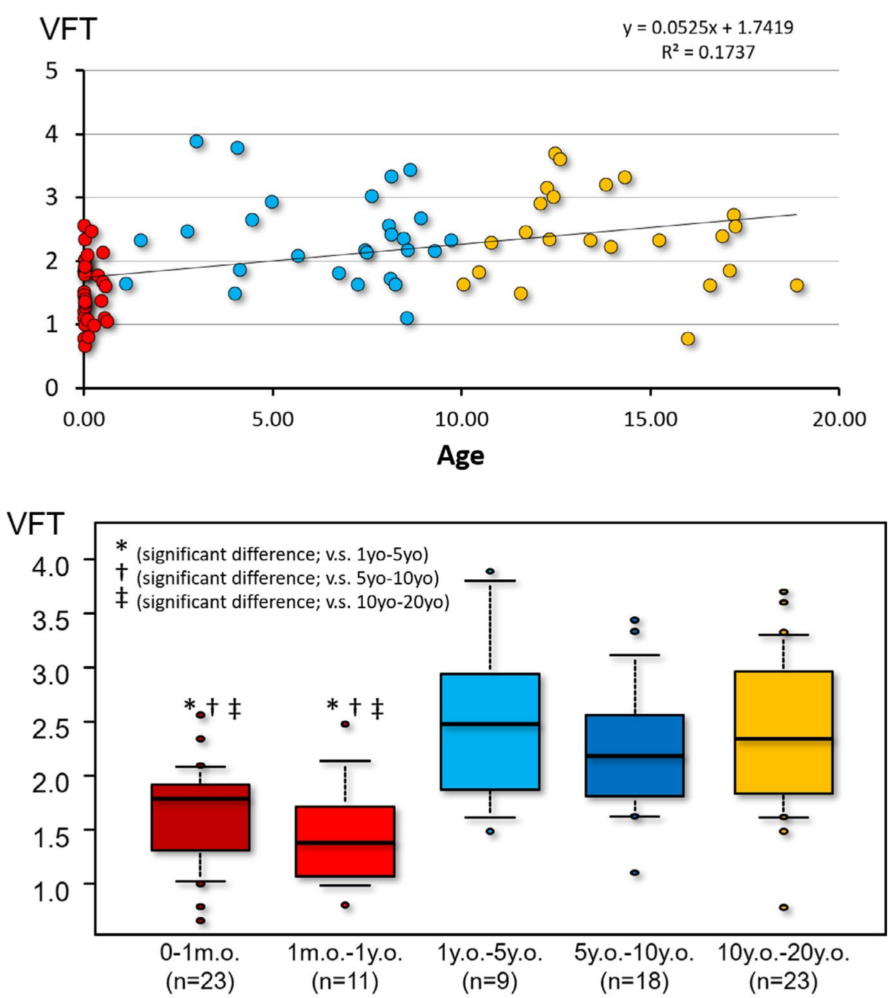

FIGURE 2 Normal ranges of vortex formation time from birth to 20 y of age

the maturation-related LV adaptation in infants akin to the altered ventricular stiffness that occurs in adults' diastolic dysfunction (as observed in patients with Heart Failure with Preserved Ejection Fraction).[23]

4.2 | Clinical application to congenital heart disease

Diastolic dysfunction remains an under-recognized disease in pediatric congenital heart disease, mainly due to the lack of standardized

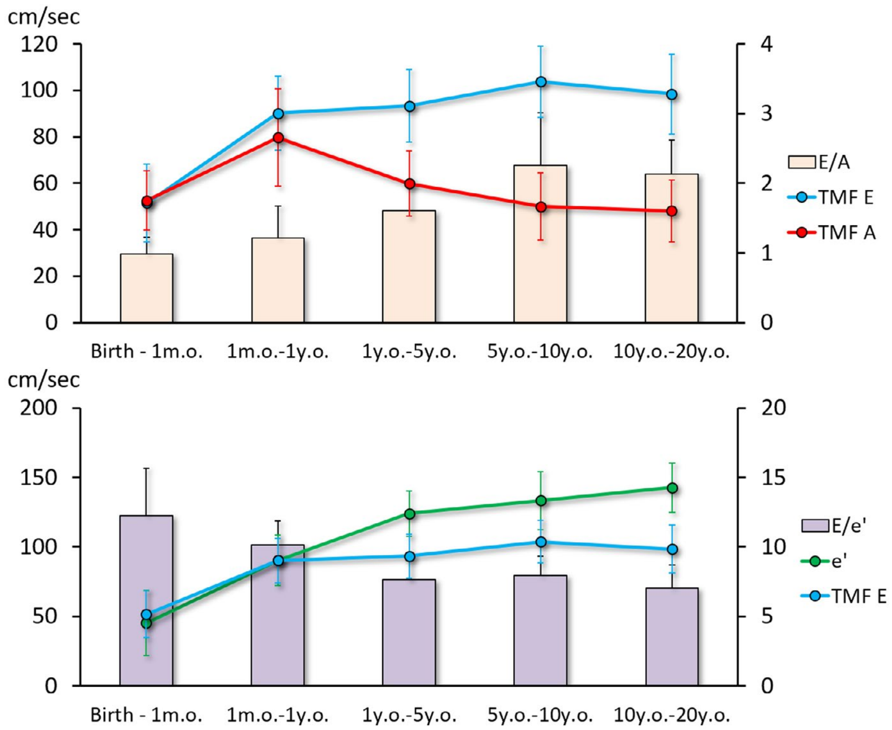

FIGURE 3 The upper panel illustrates the changes in trans-mitral flow's E-wave, A-wave and E/A ratios from birth to 20 y of age. The lower panel illustrates the changes in trans-mitral flow's E-wave, myocardial tissue Doppler-derived e′ velocities and E/e′ ratios for the same age ranges

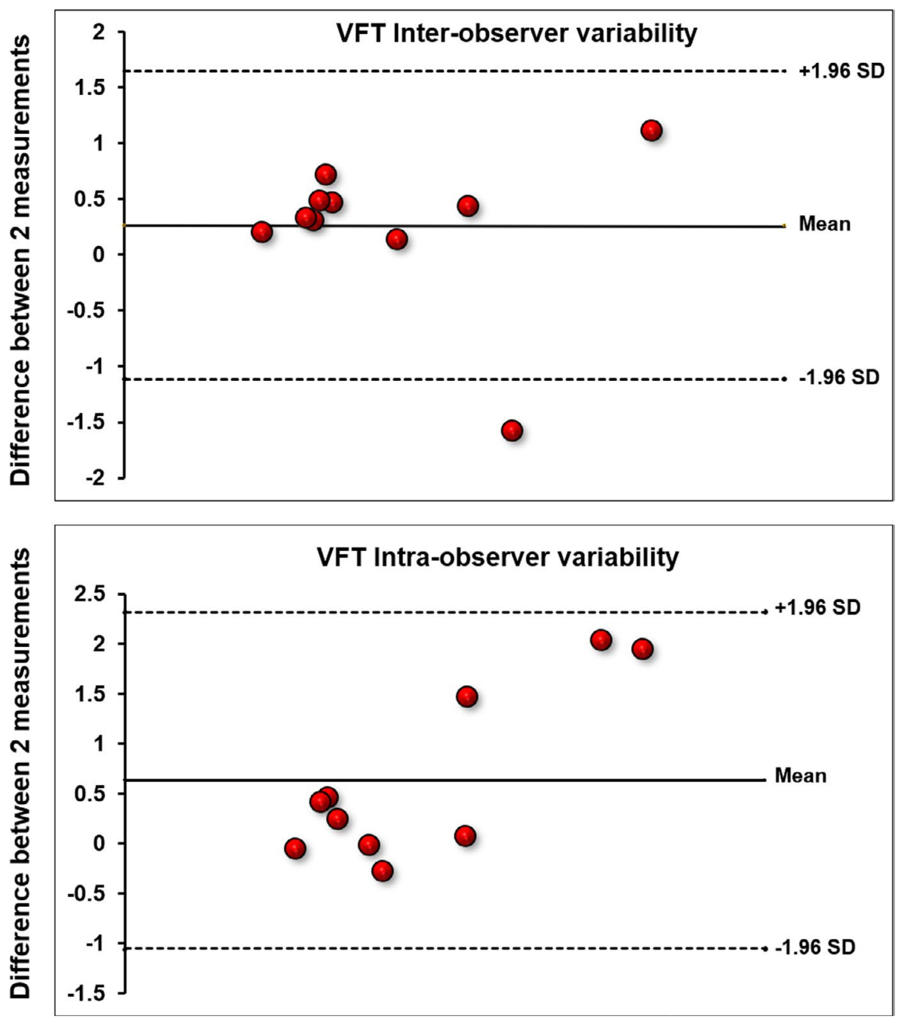

FIGURE 4 Bland–Altman correlations of inter-observer (left panel) and intra-observer (right panel) variability in vortex formation time measurements

reference normative data.[13] Additionally, certain forms of CHD such as left to right shunt lesions alter mitral Doppler inflow velocities and contribute to misleading assessments.

We also quantified VFT in a pilot application in 5 subjects with Shone's complex related congenital mitral stenosis (MS) from parachute mitral valve and without any left ventricular outflow tract (LVOT) obstruction. All 5 subjects had mild stenosis with a mean gradient of 5.1 ± 1.0 mm Hg across the mitral valve. These subjects had abnormal VFTs of 4.99 ± 1.58. We hypothesize that in this group of patients with a smaller mitral valve orifice, the trans-mitral jet velocity is disproportionately increased, which led to higher VFT.[2,5] The trans-mitral vortex pinch-off tends to occur in infinity, or alternatively may never occur. In this situation, the blood flow momentum is mainly transferred through the jet that lead to high-energy dissipation and incoherent flow structures.[12,24]

Understanding the fluid dynamics and in particular trans-mitral vortex dynamics would help further understanding the mechanisms of heart failure due to CHD in pediatric age groups.

4.3 | Limitations

The mitral valve has a time-varying diastolic exit diameter and the area changes continuously throughout diastole.[2] The largest diameter derived from the GOA was used for VFT calculations, as has been used in previous studies.[1,25] Limitations of temporal and spatial resolution in routinely performed echocardiograms preclude the use of any other diameter. There is a negligible delay to achieving the largest diameter from the mid-diastolic phase of mitral valve inflow on echocardiograms.[1] Mathematical calculation of all echocardiographic indices such as ejection fraction is subject to assumptions of an ellipsoid shape of the LV and minimal variations from beat to beat. Such assumptions are inherent to the calculation of VFT. This study involved a relatively small number of subjects and may not be representative of the entire population. Effects of the controlled variation in VFT with HR could not be investigated in this study, due to its retrospective nature. Direct correlation to catheterization derived diastolic function indices could not be performed, due to the ethical constraints of performing cardiac catheterizations in healthy children.

5 | CONCLUSIONS

This study, for the first time, computes and compares VFT in groups of healthy children from birth to 20 years of age. In contrast to adults, our data suggest that VFT is significantly lower in healthy neonates and infants (IQR- 1.3–1.7) and rises subsequently during transition to adulthood. VFT changes mainly in the first year of life, because of the unique adaptive changes in the LV of the neonates and infants, and eventually reaches the adult threshold by the second decade of life. This pilot study lays the foundation for larger validation studies into the contribution of VFT in evaluating diastolic function in the pediatric age group.

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CONFLICT OF INTEREST

None.

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