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Z Scores and Reference Values for Tissue Doppler Imaging Velocities and Timings of Healthy Egyptian Children

Rania S. Elzayat[1]*, Wael A. Bahbah[1], Shaimaa S. Soliman[2] and Basim A.E. El-Gazzar[1]
[1]Pediatric Department and [2]Public Health and Community Medicine Department,
Faculty of Medicine, Menoufia University, Egypt
***Corresponding author:** Rania Salah Elzayat, **Tel:** +201018268286, **E-Mails:** rania.elzayat@med.menofia.edu.eg ; raniaelzayat1@yahoo.com,**ORCID ID:** https://orcid.org/0000-0003-1145-1141

ABSTRACT

Background: Tissue Doppler Imaging (TDI) modality is frequently utilized to evaluate cardiac function. TDI velocities and timings vary with age and growth. Data about normal TDI values in the first two years of life is limited. Also, reference values of TDI differ according to racial and environmental factors.

Objective: This research aimed to identify the normal values and introduce Z scores for left ventricular pulsed TDI timings and velocities in Egyptian children as well as investigate the impact of age, heart rate (HR), body surface area (BSA), and gender on TDI timings and velocities.

Methods: For 208 healthy children with an age range between two months and two years, a pulsed TDI examination was applied using the apical four chamber view at the septal and lateral mitral annuli during ventricular systole and early and late diastole. We measured systolic, early and late diastolic velocities, isovolumic contraction, isovolumic relaxation and ejection times (ETs). Also, mitral closure to opening time (MCOT) and Tie index were obtained. The association between TDI velocities and timings and different demographic variables were analyzed using linear regression model.

Results: Normal values and Z score graphs for most of left ventricular TDI velocities and time intervals were demonstrated. TDI velocities and timings were positively correlated with age and BSA while negatively correlated with HR and not affected by sex. **Conclusion:** We present reference values of left ventricular TDI parameters in pediatric Egyptian children from two months to two years of age and demonstrate the effect of growth on TDI velocities.

Key Words: Tissue Doppler imaging, Pediatrics, Left ventricle, Myocardial velocity.

INTRODUCTION

Echocardiography is the diagnostic method of choice for pediatric cardiac diseases. The availability of normal ranges for measurements is a crucial component of this modality **(1)**. Tissue Doppler Imaging (TDI) is an ultrasonic technology that assesses the myocardium's contraction and relaxation velocities **(2)**. It is a useful echocardiographic technique for evaluating systolic and diastolic myocardial function. It captures the high-amplitude, low-velocity signals produced by myocardial motion **(3)**. Its value as a diagnostic and prognostic tool for various pediatric cardiac disorders has been recognized **(4-10)**. In contrast to the well-established normal reference values for TDI in adult patients, data about normal TDI measurements in pediatric patients is sparse, with some limitations regarding the segments evaluated and limited age distribution. Although cardiac structures are affected by normal physical growth in the first 2 years of life, prior studies have provided a single standard reference value for all infants under the age of one year without taking into consideration the accelerated growth during this period **(11-13)**.

Therefore, this research aimed to establish normal reference values and z scores for left ventricular timings and velocities measured by pulsed TDI in healthy Egyptian infants and toddlers aged from 2 months to 2 years and to investigate the effect of age, body surface area (BSA), heart rate (HR), and gender on the measured parameters.

PATIENTS AND METHODS

Study population

This prospective observational research was applied at the Pediatric Cardiology Unit of Menoufia University Hospital. Healthy children aged 2 months to 2 years were enrolled. The existence of a heart murmur, chest pain, an enlarged cardiac silhouette on a chest radiograph, or an abnormal ECG were all causes for an echocardiographic referral. Any child with a final diagnosis of structural cardiac diseases, arrhythmia, acute illness, or chronic disease, including chromosomal abnormalities, was excluded from the study.

Study process and interventions:

A detailed history, a thorough clinical examination, and an echocardiographic examination of all the eligible children were all performed. At the time of the echocardiography, each patient's age, gender, HR, weight, and length were recorded. BSA was estimated by Haycock formula **(14)**. Participants were divided into 4 age-related subgroups: 2–6 months, >6–12 months, >12–18 months, and >18–24 months.

Echocardiographic Examination

Transthoracic echocardiography and TDI were performed to each participant. Conventional two-dimensional echocardiography verified that the hearts

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were structurally normal. Children were either at rest or under the influence of chloral hydrate (50–75 mg/kg PO, 1 g maximum dose) when being examined.

The echocardiographic examinations were carried out using Philips HD 11 ultrasound device (manufactured by Philips Medical Systems, Netherlands) with a 3-8 MHz transducer, based on the age and size of the child. Echocardiograms were recorded digitally and were subsequently analyzed from the stored images. The two authors, who have experience with echocardiography, performed the examination (first and last authors). Since these young children cannot hold their breath, three cardiac cycles were recorded and then averaged to minimize the respiration effect on myocardial velocities.

For each participant, a standard complete two-dimensional, color flow and pulsed Doppler examination was applied. The sample volume was positioned at the tips of the mitral valve leaflets in the apical 4-chamber view, and the pulsed Doppler technique was used to assess the peak early diastolic velocity (E) and the peak atrial systolic velocity (A).

Pulsed TDI images were acquired from the apical 4-chamber view at mitral valve annular level with the sample volumes placed at two locations: the subendocardial portion of the interventricular septum and the left ventricular lateral wall (for simplification will be named as septal and lateral respectively). As much as possible, the Doppler beam was aligned parallel to the myocardial wall. Angle correction was not used. Doppler sample volume size was reduced to <5 mm, the sweep rate was tuned to a minimum of 100 mm/s, and the lowest acceptable gain was used to improve the quality of the Doppler signal.

TDI measurements from each myocardial wall segment included peak systolic myocardial velocity (Ś), peak early diastolic myocardial velocity (È) and peak late diastolic myocardial velocity (À). The ratio of early-diastolic velocity of conventional mitral inflow to early diastolic velocity of the mitral annulus (E/È) was calculated. Isovolumic contraction time (ICT) is the time from end of À wave to the beginning of the Ś wave. Isovolumic relaxation time (IRT) is the time from the end of the Ś wave to the beginning of the following È wave. Ejection time (ET) is the time from start to the end of Ś wave. Mitral closure to opening time (MCOT) was estimated as sum of (ICT+ IRT+ ET). Myocardial performance or Tei Index (MPI) was estimated as sum of ICT plus IRT divided by ET (15).

Ethical Approval:

The guardian of each participant provided an informed consent. All research procedures were approved by the Institutional Research Committee of Menoufia University (IRB: 10/2022 PEDI-11-1). This study complied with the 2013 revision of the Helsinki Declaration of 1964.

Statistical analysis

Version 20.0 of the Statistical Package for the Social Sciences (SPSS) was used to analyze the data (IBM Corp, Armonk, NY). The studied variables were tested for normality by Shapiro–Wilk test. The Pearson's coefficient (r) was utilized to determine the correlation among tissue Doppler readings and other parameters (age, BSA, and HR), with higher values of (r) denoted stronger correlation. Linear regression analysis was utilized to test the effect of age, gender, BSA and HR on TDI measurements, then to detect the best predictor for each dependent variable and find an equation to predict its value. The coefficient of determination (R^2) was utilized to describe the degree of variation in the TDI measurements that is predictable from the independent variables. Stepwise linear regression analysis (multivariate analysis) was performed to identify which demographic factor had the greatest impact on each TDI parameter. The best predictor for each TDI parameter, as indicated by the largest R^2 in multiple linear regression analysis, was used to construct Z score graphs, that represent the respective regression line (mean) and intervals of Z score±1 and Z score±2 for each TDI parameter at each of the sampling sites [mitral septal and lateral annuli]. The effect of HR on time interval measurements was eliminated by applying Bazett's correction (16). The threshold for statistical significance was a two-sided P value of ≤ 0.05.

Reproducibility of TDI measurements:

To test for interobserver variability, a second echocardiographer (the last author) blindly repeated the measurements previously recorded by the first echocardiographer (the first author) during the same clinic visit. The first author then blindly repeated the TDI measurement at the 2 sampling sites 7 days after the initial visit for 53 infants (25% from study population) to assess intraobserver variability. Cronbach's Alpha was used to test for inter observer variability, while paired t-test was used to test for intraobserver variability.

RESULTS

Of the 208 healthy infants enrolled in this study, 121 were boys (58.2%). The mean age of the studied participants was 10.65±6.77, ranging from 2 to 24 months. Their BSA ranged from 0.24–0.59 m^2 and HR ranged from 110–166 beat/min. Their mean weight (±SD) was 8.56 (±2.37) kg, mean length/height (±SD) was 0.75±0.11 meter. The mean ± SD of ejection fraction, fractional shortening, left ventricular (LV) end-diastolic diameter and LV end-systolic diameter were 68.46 ± 55.55%, 36.18 ± 5.52, 2.44 ± 0.32 cm, and 1.54 ± 0.22 cm respectively. The mean ± SD of mitral peak E velocity, peak A velocity, E deceleration time and E/A ratio were 97.18 ±10.27 cm/sec, 68.02 ±8.52 cm/sec, 102.8±12.25 cm/sec and 1.44 ± 0.16 respectively.

Pulsed TDI velocities and time intervals in healthy infants were demonstrated in table 1.

Table 1: Pulsed wave tissue doppler velocities and time intervals in healthy children by age group

TDI measurement	**Age (Months)**			
	2 – 6	**>6 – 12**	**>12 – 18**	**>18 – 24**
	(n = 72)	**(n = 72)**	**(n = 24)**	**(n = 40)**
Lateral mitral annulus				
É (cm/s)	9.82±1.09 (7.68–12.90)	11.19 ± 1.28 (8.47–15.30)	12.08±1.17 (9.87–13.70)	12.60±1.17 (10.50–15.50)
Á (cm/s)	6.55±0.83 (5.03–7.91)	6.81±0.74 (5.21–7.75)	7.03±0.52 (5.84–7.82)	7.13±0.53 (5.76–7.98)
É/Á	1.51±0.17 (1.11–1.86)	1.65±0.15 (1.37–1.97)	1.72±0.15 (1.47–1.98)	1.77±0.12 (1.63–2.08)
E/É	9.40±0.92 (7.03–11.43)	8.58±0.96 (6.59–10.77)	8.49±1.03 (6.28–10.23)	8.61±0.48 (7.71–9.45)
Ś (cm/s)	6.26±0.81 (5.0–7.72)	6.72±0.71 (4.89–7.75)	6.81±0.65 (5.77–8.0)	7.13±0.54 (5.86–8.19)
ICT (msec)	27.14±3.55 (20.0–32.0)	35.28±1.92 (31.0–38.0)	39.63±1.34 (37.50–42.0)	43.45±2.05 (40.0–47.50)
IRT (msec)	15.26 ± 2.06 (11.50–19.0)	20.73±1.38 (18.0–22.50)	23.54±0.79 (22.50–25.0)	28.08±2.55 (24.50–33.0)
ET (msec)	164.1±10.88 (139.0–182.0)	190.9±4.54 (182.0–196.0)	198.7 ± 2.81 (196.0 – 202.0)	207.1±3.64 (202.0–216.0)
MCOT (msec)	206.5±16.10 (172.0–230.5)	246.9±7.54 (231.5–256.5)	261.8±4.45 (256.0–269.0)	278.9±7.44 (266.5–291.0)
MPI	0.26±0.02 (0.22–0.29)	0.29±0.01 (0.27– 0.31)	0.32±0.01 (0.31–0.33)	0.35±0.02 (0.32–0.39)
Septal mitral annulus				
É (cm/s)	9.19±0.94 (7.35–12.0)	10.28 ± 1.0 (7.82–12.20)	11.11±1.11 (9.03–12.80)	11.51±0.98 (9.40–13.20)
Á (cm/s)	6.60±0.71 (4.75–7.63)	6.64±0.79 (4.94–7.91)	6.99 ± 0.49 (6.14–7.54)	7.04±0.48 (6.49–7.96)
É/Á	1.40±0.18 (1.10–1.85)	1.56±0.15 (1.29–1.87)	1.60 ± 0.20 (1.39–1.97)	1.64±0.17 (1.39–1.97)
E/É	10.02±0.91 (7.56–11.66)	9.32 ± 1.0 (7.44–11.66)	9.20±0.89 (7.53–10.43)	9.41±0.39 (8.67–10.0)
Ś (cm/s)	6.47±0.60 (5.47–7.72)	6.93±0.59 (5.49–7.91)	7.11±0.66 (6.05–8.38)	7.53±0.66 (5.77–8.45)
ICT (msec)	27.19±3.78 (21.0–32.0)	35.60 ±1.79 (33.0–38.0)	40.17±1.15 (38.50–42.0)	43.45±1.55 (40.0–47.0)
IRT (msec)	16.29±2.0 (12.50–18.50)	21.29±1.53 (19.0–24.0)	25.33±0.76 (24.0–27.0)	30.60±2.77 (26.0–34.50)
ET (msec)	166.4±10.85 (135.0–182.0)	190.2±5.01 (182.0–196.0)	201.3±1.27 (198.0–202.0)	209.7±4.87 (202.0–216.0)
MCOT (msec)	209.9±16.29 (170.0–232.5)	246.7 ± 7.91 (234.0–258.0)	266.8±2.64 (262.0–271.0)	280.7±9.50 (256.0–295.0)
MPI	0.26±0.02 (0.22–0.29)	0.30±0.01 (0.28–0.32)	0.33±0.01 (0.31–0.34)	0.36±0.02 (0.33–0.40)

É = Early diastolic velocity, Á = Late diastolic velocity, É/Á = ratio between early diastolic velocity and late diastolic velocity, E/É = Early diastolic velocity by PWD / early diastolic velocity by TDI, Ś = Systolic Velocity, ICT = Isovolumic contraction time, IRT = Isovolumic relaxation time, ET = Ejection time, MCOT = Mitral closure to opening time, MPI = Myocardial performance index. Data expressed as mean ± SD (minimum-maximum).

Correlation between mitral septal and lateral TDI measurements and different growth parameters were demonstrated in table 2. All septal and lateral mitral TDI velocities and timings were correlated positively with both age and BSA and negatively with HR except for E/É ratio which showed significant negative correlation with age and BSA and positive correlation with HR.

Table 2: Correlation between mitral septal and lateral TDI measurements and different demographic variables in studied children

TDI Parameters	Age (Months)		BSA (m^2)		HR (beat/min)	
	r	p	r	p	r	p
Lateral annulus						
É (cm/s)	0.663	<0.001	0.649	<0.001	-0.678	<0.001
Á (cm/s)	0.292	<0.001	0.281	<0.001	-0.277	<0.001
É/Á	0.545	<0.001	0.544	<0.001	-0.584	<0.001
E/É	-0.313	<0.001	-0.291	<0.001	0.394	<0.001
Ś (cm/s)	0.373	<0.001	0.332	<0.001	-0.343	<0.001
ICT (msec)	0.945	<0.001	0.896	<0.001	-0.967	<0.001
IRT (msec)	0.965	<0.001	0.900	<0.001	-0.944	<0.001
ET (msec)	0.892	<0.001	0.885	<0.001	-0.962	<0.001
MCOT (msec)	0.928	<0.001	0.903	<0.001	-0.971	<0.001
MPI	0.943	<0.001	0.877	<0.001	-0.919	<0.001
Septal annulus						
É (cm/s)	0.668	<0.001	0.667	<0.001	-0.678	<0.001
Á (cm/s)	0.260	<0.001	0.225	0.001	-0.207	0.003
É/Á	0.445	<0.001	0.482	<0.001	-0.507	<0.001
E/É	-0.262	<0.001	-0.255	<0.001	0.343	<0.001
Ś (cm/s)	0.524	<0.001	0.485	<0.001	-0.484	<0.001
ICT (msec)	0.935	<0.001	0.899	<0.001	-0.972	<0.001
IRT (msec)	0.981	<0.001	0.897	<0.001	-0.925	<0.001
ET (msec)	0.918	<0.001	0.904	<0.001	-0.968	<0.001
MCOT (msec)	0.928	<0.001	0.900	<0.001	-0.967	<0.001
MPI	0.946	<0.001	0.880	<0.001	-0.919	<0.001

r: Pearson coefficient, É = Early diastolic velocity, Á = Late diastolic velocity, É/Á = ratio between early diastolic velocity and late diastolic velocity, E/É = Early diastolic velocity by PWD / early diastolic velocity by TDI, Ś = Systolic Velocity, ICT = Isovolumic contraction time, IRT = Isovolumic relaxation time, ET = Ejection time, MCOT = Mitral closure to opening time, MPI = Myocardial performance index.

Univariate regression analysis showed significant association between all TDI parameters (velocities, ratios, timings, and indices) and demographic features (age, HR and BSA) but not with sex (Table 3). Regarding multivariate regression analysis, lateral and septal É velocity, É/Á and E/É ratios were best predicted from HR (R^2= 0.46; 0.459, 0.341; 0.257 and 0.155; 0.118 respectively). Lateral and septal Á and Ś velocities were best predicted from age (R^2= 0.085; 0.068 and 0.139; 0.275 respectively). All corrected time intervals (ICT, IRT, ET, MCOT) were best predicted from age at the mitral valve lateral and septal sides (Table 3).

Table 3: Linear regression analysis for the effect of age, sex, body surface area and heart rate on mitral lateral and septal TDI measurements of studied children

TDI measurement	**Age (months)**		**Sex**		**BSA** (m^2)		**HR (beat/min)**		**Best predictor with equations**
	R^2	**p**	**R^2**	**p**	**R^2**	**p**	**R^2**	**p**	
Lateral mitral annulus									
É (cm/s)	0.44	<0.001	0.016	0.065	0.421	<0.001	0.46	<0.001	20.250-(0.069×**HR**)
Á (cm/s)	0.085	<0.001	0.02	0.083	0.079	<0.001	0.077	<0.001	6.464+(0.032×**Age**)
É/Á	0.297	<0.001	0.001	0.806	0.296	<0.001	0.341	<0.001	2.529-(0.007×**HR**)
E/É	0.098	<0.001	0.01	0.141	0.085	<0.001	0.155	<0.001	5.621+(0.024×**HR**)
Ś (cm/s)	0.139	<0.001	0.015	0.083	0.111	<0.001	0.117	<0.001	6.191+(0.043×**Age**)
ICTc (m/sec)	0.893	<0.001	0.002	0.553	0.803	<0.001	0.873	<0.001	40.404+(0.971×**Age**)
IRTc (m/sec)	0.931	<0.001	0.001	0.923	0.809	<0.001	0.849	<0.001	21.500+(0.812×**Age**)
ETc (m/sec)	0.796	<0.001	0.002	0.505	0.784	<0.001	0.601	<0.001	259.191+(1.412×**Age**)
MCOTc (m/sec)	0.862	<0.001	0.002	0.563	0.815	<0.001	0.796	<0.001	321.013+(3.205×**Age**)
MPI	0.889	<0.001	0.001	0.968	0.769	<0.001	0.845	<0.001	0.389+(0.004×**Age**)
Septal mitral annulus									
É (cm/s)	0.447	<0.001	0.02	0.06	0.445	<0.001	0.459	<0.001	17.882-(0.058×**HR**)
Á (cm/s)	0.068	<0.001	0.014	0.084	0.051	0.001	0.043	0.003	6.457+(0.027×**age**)
É/Á	0.198	<0.001	0.001	0.63	0.232	<0.001	0.257	<0.001	2.367-(0.006×**HR**)
E/É	0.068	<0.001	0.008	0.191	0.065	<0.001	0.118	<0.001	6.859+(0.020×**HR**)
Ś (cm/s)	0.275	<0.001	0.031	0.074	0.235	<0.001	0.234	<0.001	6.310+(0.056×**age**)
ICTc (msec)	0.875	<0.001	0.002	0.542	0.808	<0.001	0.863	<0.001	40.726+(0.967×**Age**)
IRTc (msec)	0.961	<0.001	0.001	0.73	0.804	<0.001	0.810	<0.001	22.148+(0.922×**Age**)
ETc (msec)	0.842	<0.001	0.001	0.665	0.816	<0.001	0.654	<0.001	260.606+(1.471×**Age**)
MCOTc (msec)	0.861	<0.001	0.001	0.587	0.81	<0.001	0.820	<0.001	324.210+(3.255×**Age**)
MPI	0.895	<0.001	0.001	0.684	0.775	<0.001	0.844	<0.001	0.393+(0.005×**Age**)

BSA: body surface area, HR: heart rate, É = Early diastolic velocity, Á = Late diastolic velocity, É/Á = ratio between early diastolic velocity and late diastolic velocity, E/É = Early diastolic velocity by PWD / early diastolic velocity by TDI, Ś = Systolic Velocity, ICTc = Isovolumic contraction time corrected for heart rate, IRTc = Isovolumic relaxation time corrected for heart rate, ETc = Ejection time corrected for heart rate, MCOTc = Mitral closure to opening time corrected for heart rate, MPI = Myocardial performance index.

We provided Z score graphs for the septal and lateral mitral TDI parameters in children between the ages of 2 months and 2 years in figures 1 and 2, respectively.

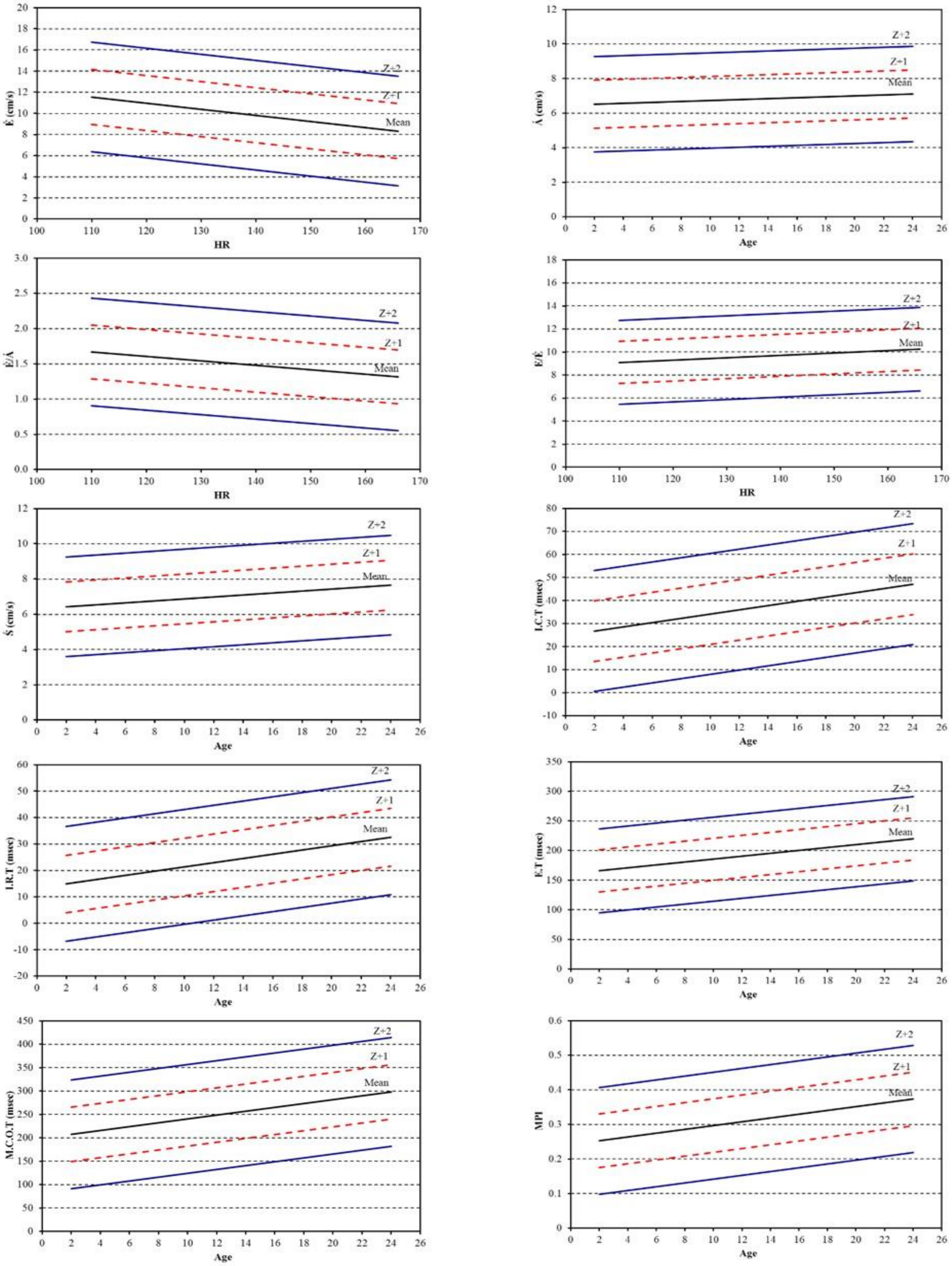

Figure 1: Z score graphs of septal mitral TDI paramaters. The two broken red lines and the two solid blue lines represent z scores ± 1 and ± 2, respectively. The black line represent the regression line (mean)

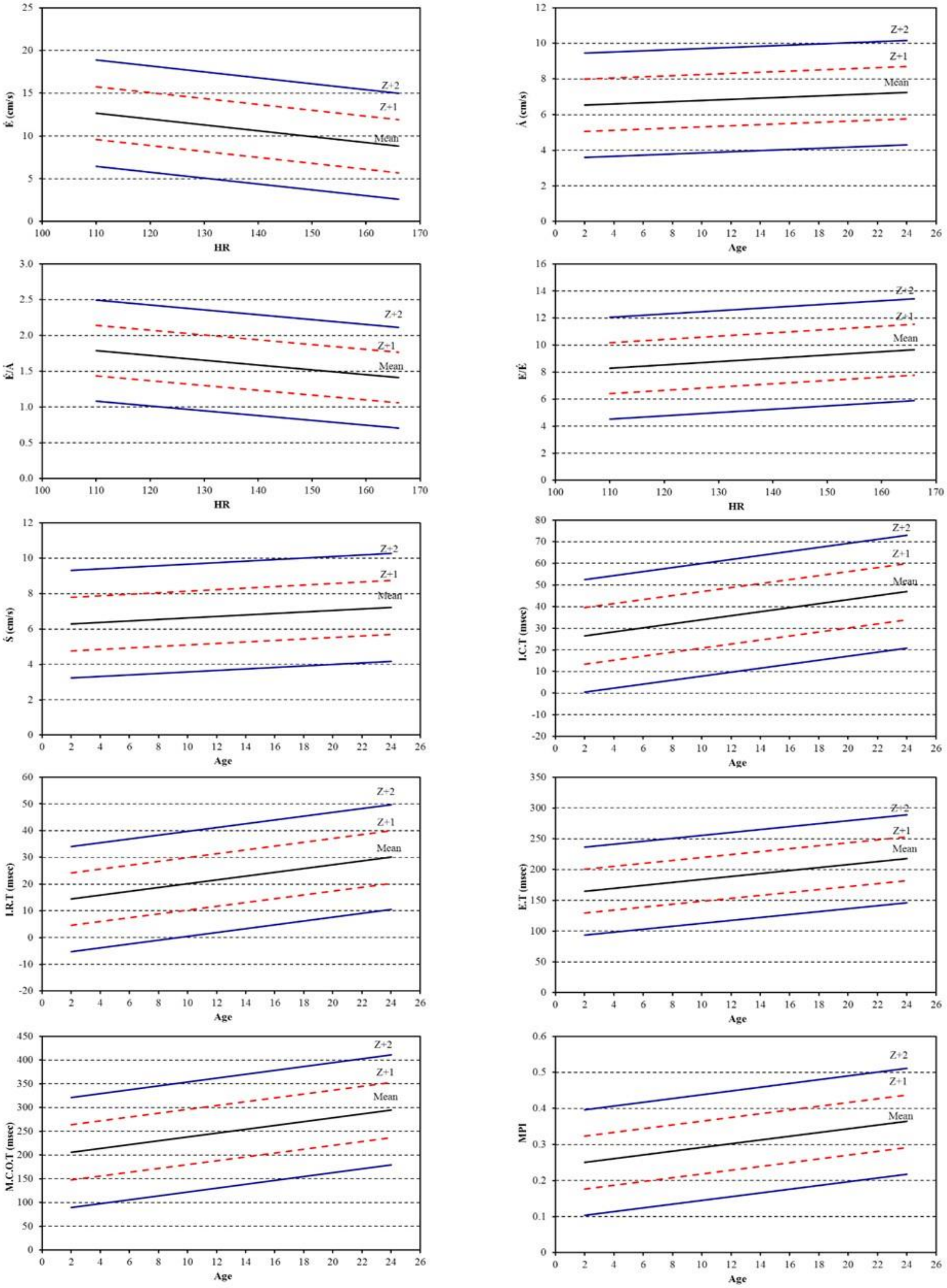

Figure 2: Z score graphs of lateral mitral TDI paramaters. The two broken red lines and the two solid blue lines represent z scores ± 1 and ± 2, respectively. The black line represent the regression line (mean)

No significant difference was detected among the first and second readings of the first author for any of the mitral septal or lateral TDI parameters (P > 0.05). There was excellent agreement between the two observers for all the mitral septal and lateral measurements (P <0.001).

DISCUSSION

The longitudinally directed TDI is increasingly being used to quantitatively assess cardiac function in children who suffered from congenital and acquired heart diseases **(17-20)**. TDI is quite helpful in this population because it is easily applicable, noninvasive, relatively load independent, and does not depend on geometric assumptions.

Our study data were collected from a cohort of healthy children (208 participants) aged from 2 months to 2 years, overcoming one of the limitations of previous researches that had smaller sample sizes, particularly in this younger age group. Our study covers a gap in the present pediatric nomograms for mitral valve TDI measurements. **Cantinotti *et al.* (21)** revealed that the values of the mitral E and A velocities changed during infancy and stabilized at 2 years of age. This highlights how crucial it is to create percentiles or z scores for TDI measurements in this age group.

Our study's mean TDI velocities and timings for healthy children are slightly different from previous reports **(12, 22, 23)**. This may be due to racial and environmental differences. There was significant correlation among TDI parameters and age, BSA, and HR. At the septal and lateral mitral annuli, a highly significant positive correlation among age and TDI velocities (systolic, early diastolic, and late diastolic velocities) was discovered. The considerable rise in systolic and diastolic TDI velocities in the first two years of life may be due to the maturation of the ventricular myocardium during this time of development. In studies by **Hiarada *et al.* (2)** and **Eidem *et al.* (12)**, systolic (Ś) and early diastolic (É) velocities at the septal and lateral mitral annuli were significantly positively correlated with age, whereas late diastolic (Á) velocities were not. This may be explained by the wide age range of children in these studies, with only a tiny percentage of those under 2 years old. A significant positive correlation between age and BSA and a negative correlation between HR were found for the septal and lateral É/Á ratios. According to **Ichihashi *et al.* (24)**, the right ventricle's É/Á remained constant after birth while the left ventricle's É/Á elevated with more than 5 years. These alterations indicate that aging results in a maturation of left ventricular diastolic function.

We found that E/É ratio negatively correlated with both age and BSA and positively correlated with HR. **Eidem *et al.* (12)** also found that E/É ratio was highest in neonates and decreased gradually during childhood because of increasing early diastolic velocity (É) during childhood.

The best predicting variable (age, BSA, HR or sex), as determined by multivariate analysis, was utilized to create Z-score graphs for the most frequently used mitral TDI velocities and timings. As a result, we offered reliable normal values for the pediatric population. Time intervals, which included ICT, IRT, ET and MCOT, were best predicted from age after correction for HR. Similarly, **Cui *et al.* (25)** found that ICT and IRT were best predicted by age but ET was predicted best with HR, but this study lacks the mean normal values of ET after correction for HR. **Dallaire *et al.* (26)** found time intervals to be correlated with BSA, while **Eidem *et al.* (12)** introduced normal values of the time intervals for age but didn't subject their measurements to regression models to conclude the most influencing factor. MPI was predicted best with age at both mitral septal and lateral annuli, and this agreed with **Cui *et al.* (25)**.

Limitations: It was a single center research and we did not use color TDI. Despite the fact that pulsed-wave TDI may only be obtained from one spot at a time, in contrast to color TDI which creates several time traces from different regions using a single cine loop, pulsed-wave TDI is more frequently used in daily clinical settings.

CONCLUSION

We introduced normal values and Z score graphs for most of the left ventricle tissue Doppler velocities and time intervals for Egyptian children aged 2 months to 2 years. Our observations suggest that all TDI corrected time intervals and most of velocities were best predicted from age and that all studied TDI measures are not affected by gender. TDI parameters differ according to racial and environmental factors so, each country should use its own reference values.

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