The diastolic inflow and longitudinal movement of the heart in the African full-term newborn infant

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ABSTRACT

Introduction: **Echocardiography is essential in the assessment of systolic and diastolic left ventricular (LV) function. The diastolic component of the cardiac cycle which is a crucial aspect of cardiac output has been less researched in the neonatal population.**

Aim: **To determine normal echocardiographic references for diastolic inflow and longitudinal movement of both the left and right heart in healthy full-term Black African neonates.**

Methodology: **A descriptive, bidirectional study design was undertaken. Healthy African (Black) full-term newborn infants who met inclusion criteria were recruited at the Chris Hani Baragwanath Academic Hospital. Left and right ventricular (RV) systolic and diastolic function were assessed using various echocardiographic M-mode, flow Doppler and tissue Doppler measurements. Statistical analysis was performed using Excel and Statistica version 13.1. Normal ranges were calculated using means ± standard deviations.**

Results: **Two hundred and ninety-two neonates (142 males, 152 females; median gestational age 39 weeks, range 37–42 weeks) were included in the study. Most subjects (175/292;60%) were born by caesarean section. Median body surface area was 0.20 m^2 (range 0.16–0.25 m^2). Median weight was 3.12 kg (range, 2.5–4.43 kg). Median post-delivery age at echocardiography was 31 hours (range 12–216 hours). The following measurements (means ±SD) were documented: LVEF and LVFS were 73.56% (±8.93) and 40.34% (±7.91) respectively. Mitral valve (MV) peak E = 0.58 m/s (±0.113), MV peak A = 0.59 m/s (±0.123), MV peak E/A ratio = 1.01 (±0.21), MV E' = 0.058m/s (±0.012), MV E/E' ratio = 10.38 (±2.65), MV S' = 0.052 m/s (±0.009) and LV Tei = 0.306 (±0.139). Measurements pertaining to the RV function were: TAPSE = 7.51 mm (±1.304), tricuspid valve (TV) peak E = 0.512 m/s (±0.126), TV peak A = 0.616 m/s (±0.127), TV E/A = 0.845 (±0.199), TV E' = 0.079 m/s (±0.021), TV E/E' ratio = 6.78 (±2.02), TV S' = 0.071 m/s (±0.045) and RV Tei = 0.283 (±0.132).**

Conclusion: **This large study established normal reference values for diastolic function and longitudinal systolic and diastolic movement of the heart in healthy full-term African neonates using echocardiography.**

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INTRODUCTION

Accurate diagnosis of heart disease using echocardiography depends on establishing normal values of cardiac dimensions.(1)

Echocardiography is a cost-effective, non-invasive diagnostic modality for the detection of both structural and functional heart disease in all age groups.(2,3)

However, there is little information regarding diastolic function of the neonatal heart and even less data about the African newborn infant.

Cantinotti and Lopez, et al. conducted a literature search and discovered there were only 33 published studies evaluating diastolic function in children,(4) but most have small sample sizes with few neonatal subjects.

The diastolic function patterns that are reproducible in older children cannot be extrapolated to neonates as neonates have much smaller cardiac chambers, a faster heart rate, and a rapidly changing physiological pattern particularly in the early neonatal period.[4] This lack of diastolic function data in the healthy neonate offers an opportunity to establish normal values that can be used in the evaluation of myocardial function of neonates with heart disease, particularly in the African population.

Several studies have established that ethnicity is a significant determinant of cardiac chamber size and therefore ethnic-specific reference values for echocardiographic interpretations should be considered.[5-9] Although when Lopez, et al. compared the paediatric heart network (PHN) database Z-scores to previously published Z-scores found that models based on body surface area (BSA) were not affected by age, sex, race, or ethnicity.[10] The disregard for ethnic differences may have consequences if management decisions hinge on normative values based on other population groups.[8,9,11]

This study is therefore the first to report on normal values for systolic and diastolic function in healthy Black African neonates.

METHODS

The echocardiographic data were acquired with consent from each mother during the study "Human Research Ethics Committee (Medical)" on 26 May 2017 – Ethics Clearance certificate no. M170524.

Three hundred and twenty-five healthy neonates aged 12 hours or more were recruited in the post-natal wards of Chris Hani Baragwanath Academic Hospital, which is an African tertiary care centre situated on the outskirts of Johannesburg. The hospital serves the indigent population of Soweto, southern Gauteng, and the North West province. The final sample size was reduced to 292, due to some participants not meeting the inclusion criteria. Participant identifiers were omitted and were replaced with a study number to maintain participant anonymity.

Qualifying criteria included healthy African newborn infants delivered by normal vertex (NVD) or caesarean section (C/S) with structurally normal hearts, who were full term, aged 12 hours and older before discharge, and had a birth weight of ≥ 2.5 kg.

Exclusion criteria comprised neonates who were older than 30 days, non-Africans (non-Black), congenital heart disease diagnosed echocardiographically, and a haemodynamically significant patent ductus arteriosus > 2 mm in diameter.

The following demographic data was collected from patient paper records: Date of birth, weight (kg), length (cm), gender (M/F), and gestational age in weeks.

Echocardiographic assessment

Echocardiographic parameters were acquired according to the American Society of Echocardiography Paediatric and Congenital Heart Disease Council guidelines 2010.[12] Myocardial performance index was acquired according to Tei, et al.[13]

All images were recorded by a MV13-0034 Rev2: GE Healthcare Vivid E compact digital ultrasound console BT12 machine (General Electric, Milwaukee, United States) using a 5–6 MHz transducer.

Ejection fraction (EF) and fraction shortening (FS) was measured using M-mode with the standard leading-edge to leading edge technique.

Tricuspid annular plane systolic excursion (TAPSE), which is a determination of the longitudinal movement of the TV annulus, was measured using M-mode where the cursor was aligned perpendicular to the tricuspid lateral annulus in the apical 4 chamber view. The sample volume in the LV was measured at the tips of the MV leaflets (distal to the annulus) where early diastole / passive filling represented by the peak of the E wave and late filling was represented by the peak of the A wave. The RV measurements were done in the same fashion with the sample volume taken from the TV.

The pulsed wave tissue Doppler imaging (TDI) was measured in the apical 4 chamber view by taking a sample volume from the septal border of the mitral annulus and RV free wall of the tricuspid annulus. The velocities measured included the mitral valve septal E', A' and S' waves, and tricuspid valve lateral E', A' and S' waves and reflected the longitudinal movement of the mitral and tricuspid annuli during diastole and systole.

The myocardial performance index (MPI) of the RV and LV were calculated using measurements taken in the apical 4 chamber view for mitral and tricuspid valve inflow patterns, and the apical 5 chamber view for the aortic valve outflow Doppler envelope in the case of the LV MPI and the parasternal short axis view for the pulmonary valve outflow measurement in the case of RV MPI. The pulsed wave Doppler sample volume was set at 4 mm width. The sample volume was taken at the tips of the mitral valve / tricuspid valve leaflets in diastole, while the second sample volume was taken at the left ventricular outflow tract (LVOT), right below the aortic valve cusps. No angle correction was used.

Statistical analysis

All statistical analysis was performed using Excel and Statistica version 13.1. (TIBCO Statistica 2016). Raw data was captured on Excel. Normal ranges were calculated using means ± standard deviations. Categorical data were expressed in frequencies and percentages. Confounding factors were fitted to determine the effects on the recorded variables using multiple regression analysis. A p-value of < 0.05 was considered statistically significant. Z-scores were also calculated for the variables. The Shapiro-Wilk test was used to assess the normality of distribution; a probability value of < 0.05 was considered to not be normally distributed. Exploratory statistical testing for normality of the measured data was done using the Breusch-Pagan and White test to check for the presence of heteroscedasticity. Intraclass correlation coefficient (ICC) was used to analyse the reliability between the interraters.

Reproducibility

Inter-observer and intra-observer bias were analysed. Data from 131 echocardiographical studies were re-analysed in a blinded fashion by a second observer. The inter-observer variability was calculated using the ICC.

RESULTS

Demographic data

Two hundred and ninety-two (n = 292) neonates met the inclusion criteria and participated in the research. The gender distribution was almost equal with a slight female preponderance (Table I). There were 142 (49%) male and 150 (51%) female neonates who participated in the study (Table I). The gestational

TABLE I: Baseline demographic and echocardiography characteristics (n=292).

Variable	n	Mean	Median	Minimum	Maximum	Std. Dev
Gender: Male	142					
Female	150					
Gestational age range (weeks)			39	37	42	
Neonatal age range (hours)			31	12	216	
Mode of delivery						
C/S	175					
NVD	117					
Birth weight (kg)		3.2	3.1	2.5	4.4	0.4
Birth length (cm)		50.5	50.0	40.0	60.0	3.1
BSA m^2		0.2	0.2	0.2	0.3	0.0
Age (hrs)		40.1	31.0	12.0	216.0	29.2
Variable	**Valid N**	**Mean**	**Median**	**Minimum**	**Maximum**	**Std. Dev**
Left Ventricle M-Mode						
LV EF%	291	73.6	74.0	51.0	95.0	8.9
LV FS%	291	40.2	40.0	24.0	65.0	7.9
Doppler measurements						
MV PEAK E (m/s)	292	0.583	0.585	0.290	0.900	0.113
MV PEAK A (m/s)	292	0.592	0.580	0.340	1.100	0.123
MV E/A RATIO	292	1.011	1.000	0.455	1.686	0.210
MV E' (m/s)	289	0.058	0.060	0.040	0.110	0.012
MV E/E' ratio	289	10.375	10.000	4.833	18.250	2.653
MV S' (m/s)	289	0.052	0.050	0.030	0.090	0.009
LV Tei	283	0.306	0.300	0.040	0.930	0.139
Right ventricle measurements M-mode						
TAPSE (mm)	152	7.5	7.5	4.8	11.4	1.3
Doppler measurements						
TV PEAK E (m/s)	226	0.512	0.495	0.260	1.060	0.126
TV PEAK A (m/s)	226	0.616	0.615	0.360	1.170	0.127
TV E/A RATIO	226	0.845	0.807	0.480	1.980	0.199
TV E' (m/s)	214	0.079	0.080	0.040	0.190	0.021
TV E/E' RATIO	214	6.783	6.424	2.786	15.800	2.016
TV S' (m/s)	215	0.071	0.070	0.030	0.700	0.045
RV Tei	205	0.283	0.260	0.020	0.730	0.132

n: number of participants, C/S: caesarean section, NVD: normal vertex delivery; KG: kilograms, CM: centimetre, BSA: body surface area; LV EF: left ventricular ejection fraction, LV FS: left ventricular fraction shortening. Std. Dev: standard deviation. MV peak E: mitral valve - early diastolic filling measured by pulsed Doppler, MV Peak A: mitral valve - late diastolic filling measured by pulsed Doppler, MV E/A: mitral valve - early diastolic filling / late diastolic filling ratio, TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI, MV E/E': mitral valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - aystolic wave representing peak myocardial systolic velocity at the septal MV annulus measured by TDI, LV Tei: myocardial performance index. TAPSE: tricuspid annular plane excursion; TDI TV E': tricuspid valve - peak myocardial velocity in early diastole measured by TDI, TV E/E': tricuspid valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus measured by TDI, RV Tei: myocardial performance index.

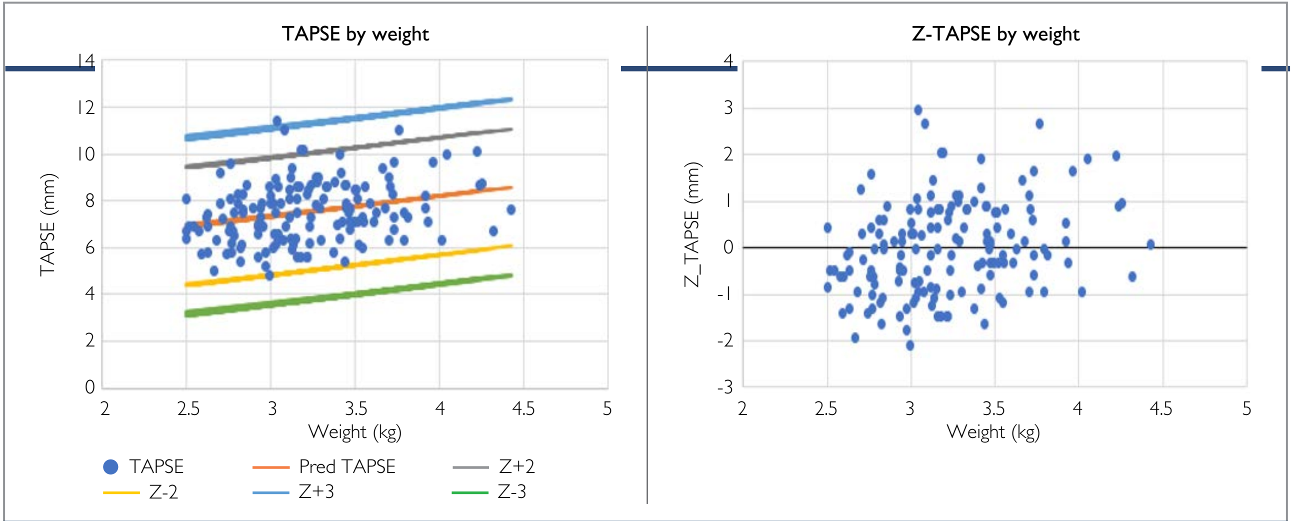

FIGURE 1: TAPSE scatterplots and Z-score boundaries.

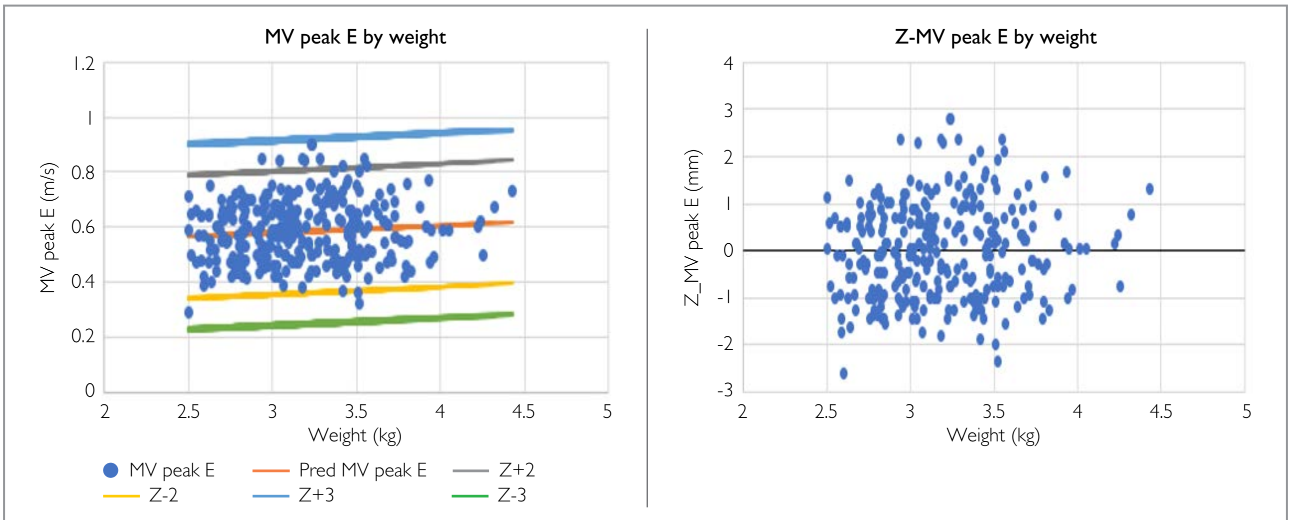

FIGURE 2: MV peak E scatterplot and Z-score boundaries.

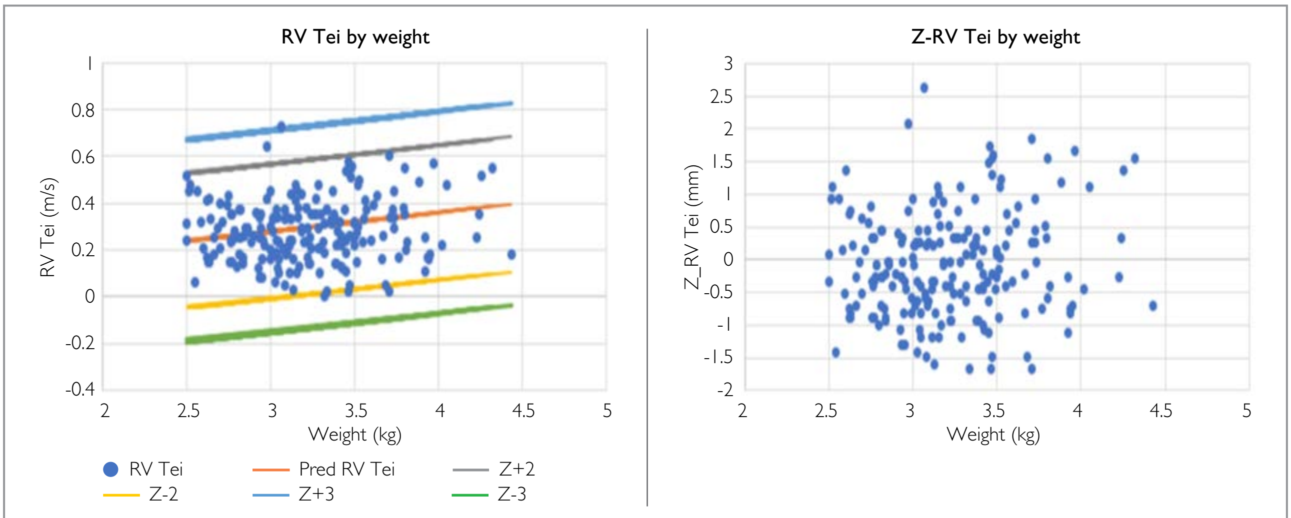

FIGURE 3: RV Tei scatterplot and Z-score boundaries.

TABLE II: Univariate regression analysis of confounding factors.

Variables	BW (kg)		BH (cm)		BSA		GA		MOD		Gender		Age	
	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value	b	p-value
LV EF%	-2.985	0.401	0.124	0.408	129.337	0.266	-0.047	0.912	1.693	0.115	0.407	0.698	0.020	0.275
LV FS%	-2.021	0.521	-0.275	0.383	97.879	0.342	-0.037	0.923	1.401	0.141	0.215	0.817	0.018	0.245
MV PEAK E	0.023	0.610	-0.001	0.888	0.836	0.035	0.007	0.197	0.006	0.663	-0.011	0.420	0.000	0.421
MV PEAK A	0.045	0.014	0.000	0.964	-0.283	0.858	-0.005	0.436	0.019	0.206	-0.023	0.110	0.000	0.489
MV E/A RATIO	-0.210	0.011	-0.008	0.342	5.274	0.052	0.020	0.049	-0.038	0.125	0.029	0.250	0.000	0.728
MV E'	-0.001	0.764	0.000	0.616	0.081	0.619	0.000	0.653	0.000	0.893	-0.002	0.290	0.000	0.675
MV E/E'	-0.034	0.974	0.025	0.812	6.849	0.843	0.067	0.599	-0.107	0.740	-0.105	0.739	0.005	0.339
MV S'	0.002	0.040	0.000	0.537	0.030	0.783	0.001	0.004	0.000	0.745	0.000	0.648	0.000	0.027
LV Tei	0.040	0.474	-0.002	0.722	-0.708	0.697	0.005	0.462	-0.004	0.826	-0.003	0.846	0.000	0.136
TAPSE	0.875	0.001	0.087	0.009	20.879	0.001	0.003	0.973	-0.020	0.930	-0.175	0.414	0.000	0.960
TV PEAK E	-0.037	0.492	-0.010	0.075	2.291	0.194	0.000	0.956	0.040	0.023	0.003	0.835	0.000	0.099
TV PEAK A	-0.005	0.918	-0.010	0.087	1.279	0.471	-0.011	0.096	0.033	0.064	0.003	0.844	0.001	0.017
TV E/A RATIO	-0.065	0.440	-0.002	0.856	2.293	0.417	0.018	0.099	0.022	0.442	0.013	0.636	0.000	0.683
TV E'	0.005	0.593	0.000	0.741	0.142	0.632	-0.002	0.109	-0.003	0.322	-0.003	0.360	0.000	0.405
TV E/E'	-0.912	0.292	-0.116	0.199	27.793	0.331	0.098	0.380	0.481	0.098	0.111	0.687	0.007	0.089
TV S'	-0.013	0.498	-0.001	0.657	0.377	0.562	-0.004	0.159	0.008	0.241	0.004	0.468	0.000	0.821
RV Tei	0.014	0.841	-0.009	0.226	2.540	0.277	0.004	0.706	-0.053	0.031	-0.031	0.178	-0.001	0.007

b: beta coefficient, BW: body weight, BH: birth length, BSA: body surface area, GA: gestational age, MOD: mode of delivery, AGE: age in hours. LV EF: left ventricular ejection fraction, LV FS: left ventricular fraction shortening, MV peak E: mitral valve - early diastolic filling measured by pulsed Doppler, MV Peak A: mitral valve - late diastolic filling measured by pulsed Doppler, MV E/A: mitral valve - early diastolic filling / late diastolic filling ratio, TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI, MV E/E': mitral valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - systolic wave representing peak myocardial systolic velocity at the septal MV annulus measured by TDI, LV Tei: myocardial performance index, TAPSE: tricuspid annular plane excursion, TV peak E: tricuspid valve - early diastolic filling measured by pulsed Doppler, TV peak A: tricuspid valve - late diastolic filling measured by pulsed Doppler, TV E/A: tricuspid valve - early diastolic filling / late diastolic filling ratio, TDI TV E': tricuspid valve - peak myocardial velocity in early diastole measured by TDI, TV E/E': tricuspid valve - early diastolic filling / peak myocardial velocity in early diastole ratio, TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus measured by TDI,
RV Tei: myocardial performance index, Std.Dev: standard deviation.

age ranged between 37–42 weeks (median = 39 weeks) (Table I). The neonatal age at the time of echocardiographical study ranged between 12 hours to 216 hours (median = 31 hours). According to mode of delivery, 175 (59.9%) of the sample was born via C/S, of whom 86 (29.5%) were females and 89 (30.5%) were males. There were 117 (40.1%) neonates who was born via NVD of whom 64 (21.9%) were females and 53 (18.1%) were males (Table I).

Population characteristics

The BSA for the study cohort ranged between a minimum of 0.16 m^2 and a maximum of 0.25 m^2 (median = 0.2 m^2). The body weight (BW) ranged between a minimum of 2.5kg and a maximum of 4.43 kg (median = 3.12 kg) (Table I). One hundred and seven (36.6%) participants weighed between 2.5 kg–3 kg, 101 (34.6%) weighed between 3.1–3.4 kg and 84 (28.8%) weighed 3.5 kg and more.

Echocardiographic measurements

M-mode measurements

Left ventricular systolic function was assessed using EF and FS derived from M-mode measurements. Out of the 292 participants, 291 (99.65%) had LV EF% and LV FS% measurements with LV EF% ranging from 51%–95% (mean, 73.56% and median 74%). LV FS% ranged from 24%–65% (mean, 40.3% and median, 40%) (Table I).

There was no correlation between LV EF (r = 0.029), LV FS (r = 0.027) and birth weight. Most (LV EF 96.6%, LV FS 95.5%) of the population clustered within the -2 and +2 Z-Score. TAPSE was used as a measure of right ventricular longitudinal systolic function. The TAPSE was determined in 152 participants, ranging from 4.8 mm–11.4 mm with a mean of 7.5 mm and a median of 7.5 mm (Table I). TAPSE displayed a weak to moderate positive correlation (r = 0,277), with birthweight. A scatterplot and predicted Z-score boundaries are shown in Figure 1.

Doppler measurements

The left heart

Doppler echocardiography was used to determine left ventricular diastolic function (Table I). The majority of the LV measurements showed no correlation with birth weight.

There was no correlation between MV peak E (r = 0.09) and birth weight. Most (96%) of the population plotted between the -2 and +2 Z-score (Figure 2).

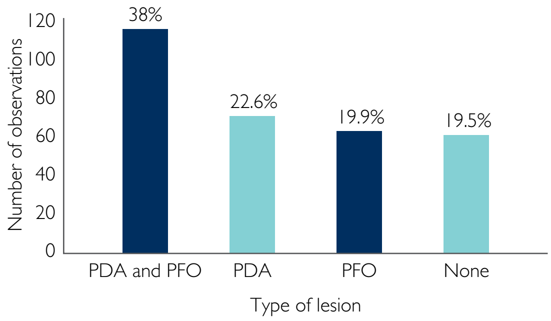

FIGURE 4: Cardiac findings.

The MV peak A (r = 0.142) showed a very weak positive correlation with weight. Most (95%) of the population plotted between the -2 and +2 Z-scores.

Most (MV E/A: 95% and MV E/E' 95%) of the population plotted between -2 and +2 Z-scores. LV Tei (r = 0.035) showed no correlation with weight.

The right heart

Doppler and tissue Doppler echocardiography were used to assess right ventricular diastolic function (Table I). The majority of the parameters did not show any correlation with birth weight except for TV E' (r = 0.12) and RV Tei (r = 0.113) which showed weak correlations.

RV Tei (r = 0.113) showed a very weak but positive correlation with birth weight. Most (99%) of the population plotted between -2 and +2 Z-scores (Figure 3).

Cardiac findings

A large number (235/80.5%) of neonates were found to have clinically insignificant expected cardiac lesions (Figure 4). The most common findings consisted of the patent ductus arteriosus (PDA) and patent foramen ovale (PFO). There were (111/38%) with PDA and PFO (66/23%) with PDA only and (58/20%) with PFO only. No PDA or PFO was present in the remaining (57/19.5%) patients.

Left and right heart systolic and diastolic parameters displayed for use in the clinical setting.

Left heart and right heart measurements for clinical use are displayed in Table III and Table IV, standard deviation / Z- scores of -3 and +3 are included.

Effects of confounding factors

In the univariate regression analysis, birth weight (BW), birth length (BL), body surface area (BSA), gestational age (GA), mode of delivery (MOD), gender and age in hours were independent variables (predictor variables) as shown in Table I. MV peak A (p = 0.014), MV S' (p = 0.040) and TAPSE (p = 0.001) showed a significant increase when there was a corresponding increase in birth weight, whereas MV E/A ratio (p = 0.011), showed a significant decrease when there was an increase in weight. TAPSE (p = 0.009) also showed a significant increase with an increase in BL. MV peak E (p = 0.035) and TAPSE (p = 0.001) showed a significant increase with an increase in BSA. MV S' showed a significant increase in velocity with an increase in gestational age. TV peak E (p = 0.023) showed an increase in the C-section group, whereas RV Tei (p = 0.031) showed a significant decrease in the C-section group. Gender did not affect any of the variables. MV S' (p = 0.027), TV peak A (p = 0.017) and RV Tei (p = 0.007) showed a significant increase with an increase in age in hours post-delivery (Table II).

Inter-observer variability

Inter-observer variability was calculated using ICC. Measurements were performed by an independent, experienced paediatric cardiologist and a senior cardiac technologist (the researcher) and compared. Most of the measurements between the observers showed a significant strong similarity / relationship, except for MV E/A ratio, LV Tei, and TV S' which had a R-value of less than moderate similarity / relationship.

DISCUSSION

The study aimed to establish reference values for systolic and diastolic function in term newborn infants of African ethnicity. Normal values are required to interpret the presence of abnormalities. This may indicate pathology or changes that may be positive or negative responses to treatment.[1]

The strength and limitations of published paediatric nomograms for echocardiographic functional parameters have not been critically evaluated, especially in the neonatal population[4] and in particular, the African neonatal population. Regardless of the importance of these measurements in practice, an all-inclusive set of normative data to assist in the evaluation of myocardial function of neonates in the sub-Saharan region has not been established to now.[14,15]

The definition of what is "normal" varies widely according to age, BSA, gender, and race. These changes may be more apparent in paediatrics as cardiac chamber dimensions change with somatic growth.[5,15] Therefore, it is imperative to normalise echocardiographic measurements according to body size.

Several echocardiographic references have been published, but the majority are derived from North America and the European populations. In addition, these study cohorts from which most of the current data are obtained are mostly derived from Caucasian and some from Asian populations, which may not apply to other populations. Several studies have established that ethnicity is a significant determinant of cardiac chamber sizes. Therefore, ethnic-specific reference values for echocardiographic interpretations are recommended.[4-9,15] Furthermore, study methodology varies widely amongst publications. Many studies have small sample sizes, heterogeneous methodologies, and the

TABLE III: Left heart systolic and diastolic measurements for clinical use.

Predicted values (mean ± SD) variables expressed by weight			
Variables	Weight group 1 2.5–3 kg	Weight group 2 3.1–3.4 kg	Weight group 3 = > 3.5 kg
+3 SD	101.881	99.103	100.133
+2 SD	92.354	90.592	91.384
LV EF%	73.300	73.572	73.886
-2 SD	54.246	56.551	56.387
-3 SD	44.720	48.040	47.638
+3 SD	65.099	62.911	63.971
+2 SD	56.742	55.358	56.152
LV FS%	40.028	40.253	40.514
-2 SD	23.314	25.148	24.875
-3 SD	14.957	17.596	17.056
+3 SD	1.994	2.118	1.972
+2 SD	1.781	1.867	1.772
LA/AO RATIO	1.356	1.364	1.373
-2 SD	0.931	0.861	0.974
-3 SD	0.718	0.610	0.775
+3 SD	0.876	0.949	0.940
+2 SD	0.775	0.827	0.826
MV PEAK E (m/s)	0.572	0.583	0.597
-2 SD	0.370	0.340	0.367
-3 SD	0.268	0.218	0.253
+3 SD	0.889	0.970	1.026
+2 SD	0.784	0.844	0.889
MV PEAK A (m/s)	0.574	0.592	0.614
-2 SD	0.364	0.341	0.339
-3 SD	0.259	0.215	0.201
+3 SD	1.672	1.655	1.593
+2 SD	1.455	1.440	1.396
MV PEAK E/A ratio	1.021	1.011	1.000
-2 SD	0.587	0.582	0.604
-3 SD	0.370	0.367	0.406
+3 SD	0.092	0.109	0.098
+2 SD	0.081	0.092	0.085
MV E' (m/s)	0.058	0.058	0.059
-2 SD	0.035	0.025	0.033
-3 SD	0.024	0.008	0.020
+3 SD	17.898	18.373	18.888
+2 SD	15.340	15.709	16.114
MV E/E' ratio	10.222	10.381	10.567
-2 SD	5.104	5.052	5.019
-3 SD	2.546	2.388	2.245
+3 SD	0.079	0.078	0.075
+2 SD	0.069	0.069	0.068
MV S' (m/s)	0.051	0.052	0.053
-2 SD	0.032	0.034	0.039
-3 SD	0.023	0.026	0.031
+3SD	0.697	0.703	0.827
+2 SD	0.565	0.571	0.656
LV Tei	0.301	0.306	0.313
-2 SD	0.037	0.042	-0.031
-3 SD	-0.094	-0.090	-0.202

LV EF: left ventricular ejection fraction (%), LV FS: left ventricular fraction shortening (%), LA/AO ratio: left Atrium / Aorta ratio MV peak E: mitral valve - early diastolic filling, measured by pulsed Doppler (m/s), MV peak A: mitral valve - late diastolic filling, measured by pulsed Doppler (m/s). MV E/A: mitral valve - early diastolic filling/ late diastolic filling (ratio), TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI (m/s), MV E/E': mitral valve - early diastolic filling /peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - systolic wave representing peak myocardial systolic velocity at the septal MV annulus, measured by TDI (m/s), LV Tei: myocardial performance index.

TABLE IV: Right heart measurements for clinical use.

Predicted values (mean ± SD) variables expressed by weight			
Variables	Weight group 1 2.5–3 kg	Weight group 2 3.1–3.4 kg	Weight group 3 = > 3.5 kg
+3 SD	10.431	11.870	11.492
+2 SD	9.333	10.405	10.304
TAPSE	7.136	7.475	7.928
-2 SD	4.940	4.544	5.552
-3 SD	3.842	3.079	4.364
+3 SD	0.813	0.903	0.947
+2 SD	0.711	0.772	0.804
TV PEAK E	0.507	0.512	0.518
-2 SD	0.302	0.251	0.232
-3 SD	0.200	0.121	0.089
+3 SD	1.052	1.035	1.147
+2 SD	0.922	0.912	0.988
TV PEAK A	0.663	0.666	0.670
-2 SD	0.403	0.420	0.351
-3 SD	0.273	0.296	0.192
+3 SD	1.435	1.503	1.510
+2 SD	1.257	1.299	1.300
TV PEAK E/A	0.901	0.891	0.879
-2 SD	0.545	0.483	0.459
-3 SD	0.367	0.279	0.248
+3SD	0.136	0.134	0.166
+2 SD	0.116	0.116	0.138
TV E' (m/s)	0.076	0.079	0.082
-2 SD	0.036	0.042	0.026
-3 SD	0.016	0.023	-0.002
+3 SD	14.260	14.667	16.052
+2 SD	12.133	12.430	13.383
TV E/E' ratio	7.880	7.955	8.044
-2 SD	3.626	3.480	2.706
-3 SD	1.499	1.242	0.036
+3 SD	0.112	0.114	0.120
+2 SD	0.285	0.224	0.234
TV S' (m/s)	0.115	0.118	0.122
-2 SD	-0.054	0.012	0.009
-3 SD	0.030	0.029	0.024
+3 SD	0.647	0.789	0.994
+2 SD	0.518	0.624	0.774
RV Tei	0.261	0.294	0.334
-2 SD	0.003	-0.036	-0.106
-3 SD	-0.126	-0.201	-0.326

TAPSE: tricuspid annular plane excursion (mm), TV peak E: tricuspid valve - early diastolic filling measured by pulsed Doppler (m/s), TV peak A: tricuspid valve - late diastolic filling, measured by pulsed Doppler (m/s), TV E/A: tricuspid valve - early diastolic filling / late diastolic filling ratio. TDI TV E': tricuspid valve - peak myocardial velocity in early diastole, measured by TDI (m/s), TV E/E': tricuspid valve - early diastolic filling / peak myocardial velocity in early diastole (ratio) TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus, measured by TDI (m/s), RV Tei: myocardial performance index.

use of variable body size parameters and regression equations, which have resulted in a wide range of Z-scores for a single measurement.[14,15]

This study aimed to address the gap in the lack of global cardiac function nomograms for neonates in the sub-Saharan African region. To our knowledge, the study represents the first such study from the sub-Saharan region showing normal values for diastolic inflow and longitudinal movement of the full-term neonatal heart. The study population included 292 African (Black) neonatal participants and thus represents the largest studied neonatal population to date.

Few previous studies included neonatal sex and mode of delivery (Supplementary Table I). Male neonates were predominant in the other studies, whereas in our study, females were dominant.[16-18] Our study also showed a higher number of C/S deliveries than NVDs than the other studies.[16-18] The need for C/S delivery depends on complications experienced by the mother during delivery, parents' choice, or the obstetricians' experience. Another reason could be that Chris Hani Baragwanath Hospital is a tertiary hospital where mothers in labour are admitted following referral from other centres for complications for which a C/S may be required.

Neonatal age varied widely amongst studies; 4 studies enrolled neonates who were 24 hours of age post-delivery,[16,17,19,20] 2 studies enrolled neonates who were between 1–7 days of age post-delivery,[18,21] and 4 studies were undertaken between zero days to just less than a month post-delivery. The number of hours post-delivery was not specified.[22-24] The majority (an average of 7 studies) of the neonatal studies indicated that a study limitation was the small sample size of the study population.

Our study cohort numbered 292 and enrolled neonates with a mean age of 40.1 hours and a median of 31 hours post-delivery.

Overbeek, et al., Abushaban, et al., and Cantinotti, et al. demonstrated that BSA, body weight, and gestational age correlated well with the cardiac measurements but concluded that it was better to present neonatal measurements in relation to body / birth weight since the neonatal BSA range is small and varies slightly when compared to older and bigger subjects.[25-27]

An increase in birth weight in the current study was associated with a significant increase in certain left heart measurements (MV peak A, MV S'), and a significant increase in TAPSE. Only the MV S' velocity showed a very small but significant increase with gestational age. There was little to no correlation of cardiac function measurements with body size (weight, length, and BSA). The C/S group showed a significant increase in the TV peak E velocity whereas the RV Tei showed a decrease in the C/S group, there was no valid explanation that could be found which could explain the above. Not all studies made a comparison between mode of delivery and cardiac function differences, so it is difficult to compare the similarities.

M-mode

Ejection fraction (EF) and fractional shortening (FS)

Normal values for linear LV function using M-mode have been established in children, with FS reported to be 28%–46%, and EF 56%–78%.[28,29] This study documented M-mode FS as mean: 40.25% and EF mean: 73.56% in neonates which is similar to previously published normal values (Supplementary Table II).[18,22]

The disadvantage of M-mode is that one assumes a cylindrical shape of the LV, and if the LV function is reduced the estimation of FS can be under- or over-estimated.[30]

In addition, if the M-mode cursor is not placed correctly over the myocardium, errors in measurement may also result.[29] The LV shape and consequently the calculation of M-mode derived parameters may be skewed in the presence of congenital heart defects (CHD), change in loading conditions (preload and afterload), and may also be affected by RV dysfunction which causes a change in the shape of the LV because of ventricular interdependence.[29]

Tricuspid annular plane systolic excursion (TAPSE)

While the physiological significance of the right ventricle is often undervalued, it is crucial to assess its function in various diseases such as pulmonary hypertension to predict prognosis.[30]

TAPSE is an important measurement of the longitudinal function of the right ventricle since the majority of the right ventricle ejection depends on the longitudinal contraction of the right ventricular myocardium.[24,31,32] Normal ranges of TAPSE have been determined for children.[24,31,32] However, there are no established reference values for neonates and children in the sub-Saharan Africa. The TAPSE values in our study ranged from 4.8 mm–11.4 mm with a mean of 7.5 mm (Table I); lower than those described in previous studies (Supplementary Table II).[23,24] There was a significant positive correlation between TAPSE and weight, length, and body surface area, most likely due to an increased excursion of the tricuspid valve annulus in a bigger heart in a bigger neonate.[23,24]

Pulsed Doppler

Non-invasive pulse Doppler measurements of transmitral flow have been widely used for assessment of left ventricular relaxation abnormalities in all age groups including neonates.[18] In this study the mean mitral valve (MV) peak E velocity (0.583 m/s) was slightly less than the mean MV peak A velocity (0.592 m/s) with a MV E/A ratio of 1.01. The mean tricuspid valve (TV) peak E was 0.51 m/s, the TV peak A was 0.61 m/s, with a TV E/A ratio of 0.845. MV peak E velocity increased with an increase in the body surface area, while the MV peak A velocity seemed to decrease with increasing BSA, although not significant. MV peak E and MV peak A velocities were measured to be marginally higher than other publications (Supplementary Table III).[17-19,22]

There was some variability regarding the ratio of MV E to A velocities across the various studies (Supplementary Table III) which may be explained by the heterogeneity amongst the studies such as the smaller patient numbers in some studies as well as the differences in the age of the neonates at the time of data acquisition.[17,18,20-22] The cardiovascular system of the neonate undergoes dramatic changes within the first few hours of birth from a high pulmonary vascular resistant dominance to a systemic vascular resistance dominance which persists throughout life. These haemodynamic changes may explain why [22] the MV E velocity was the dominant velocity compared to the other studies.[17,18,20-22] This is reflective of a higher systemic vascular resistance state of the neonate at an older age.[33]

TV peak E velocity showed a significant positive relationship with delivery by C/S.[34] The higher TV E velocity may reflect an element of diastolic dysfunction associated with a less compliant RV. The risk of respiratory distress secondary to transient tachypnea of the newborn, surfactant deficiency and pulmonary hypertension are increased in neonates after delivery by C/S and may explain some of the differences according to the mode of delivery.[33] TV peak A velocity showed a positive significant relationship with age in hours post-delivery. This demonstrates that the compliance of the RV increases with age.[35]

Tissue Doppler imaging

Tissue Doppler imaging (TDI) is used to analyse longitudinal movement and function as well as diastolic function of both ventricles which is preload independent and which is in contrast to pulse Doppler evaluation.[21,30,36,37] MV S' showed a correlation with birth weight, gestational age, and age after delivery. MV E' velocity and MV E/E' ratios did not show any association. A possible implication is that the bigger the baby, the bigger the heart and the bigger the excursion of the MV annulus during systole. Adult values for early mitral annular or septal E' wave velocities are higher (< 0.08 m/s) compared to neonates (0.06 m/s +/- 0.01 m/s).[21,38] In contrast the E/E' ratio, which correlates with invasively measured pulmonary wedge pressure, of a normal adult LV (7.7 ± 3.0) is lower than a neonate (10.38).[21,29,39,40] This higher value in the neonate is reflective of a sudden higher left ventricular filling pressure of the newborn infant following separation from the placenta which is associated with an abrupt increase in systemic afterload.[33]

In our study the mean MV septal S' velocity which represents the mitral annular movement towards the left ventricular apex during systole, was found to be 0.05 m/s, which was slightly higher than Mori, et al. and Taksande (0.04 m/s).[21,22] These differences demonstrate the heterogeneity amongst the studies where measurements may have been done at different times after delivery.

The TV E' velocities and E/E' ratio showed no correlation with any of the independent variables in contrast to Tao, et al.[34] who demonstrated TV E/E' ratio to be significantly higher in the C/S group compared to the NVD group.

The current study showed the mean MV E/E' ratio of 10.38 m/s, to be higher than the mean TV E/E' 6.78 m/s which is similar to the Mori's, et al. study.[21] This may be attributed to the relatively higher left ventricular filling pressures soon after birth which represents an adaptation of the LV myocardium to the sudden increase in post-natal systemic afterload.[33]

The mean TV S' velocity in the study population was noted to be higher than the mean MV S' velocity which is similar to findings by Mori and Taksande (Supplementary Table III).[21,22] The higher TV S' velocity is a normal finding because the right ventricle is intrinsically more dependent on longitudinal movement against a lower afterload during systole, whereas the left ventricular contraction is more complex and also incorporates twisting and circumferential shortening components.[21,40]

Myocardial performance index (Tei index)

The Tei index reflects both systolic and diastolic function and can be applied to both the left and the right ventricle and correlates well with invasive measurements of systolic and diastolic function.[22,41,42] Its value is independent of chamber geometry, heart rate, or age.[41,43,44]

The RV Tei index showed a moderate, but not significant, positive correlation with birth weight in our study where the RV Tei mean was 0.28 and LV Tei mean was 0.31 at a mean age of 40.13 hours. The study by Bokoniec showed the mean ventricular Tei indexes to be slightly higher (RV Tei mean of 0.42 and the LV Tei index mean of 0.37). However, the neonatal cohort was much younger (≤ 24 hours) post-delivery (Supplementary Table III).[16] The Bokiniec study also showed a decrease in the mean RV Tei index towards the end of the neonatal period, from 0.42–0.29 which may reflect the physiological drop in pulmonary artery pressures with age.[16] The LV Tei remained unchanged.[16,33]

Clinical use table

A unique clinical use table has been compiled with predicted values and Z-scores to be used in an African setting to assist in decision-making regarding the longitudinal systolic function of both ventricles as well as diastolic function of the newborn infant (Table III and IV).

Reproducibility and inter observer variability

ICC was conducted between the 1st and the 2nd observer as a test for reproducibility. The overall ICC average was 71.86% which shows a strong correlation between the 2 observer measurements. Núñez-Gil and Iwashima, Seguchi and Ohzeki with ICCs of 0.74 and 0.91 respectively showed a similar correlation.[18,24]

Local versus International values

The findings of this study were compared to obtainable international values (Supplementary Table III).

The mean weight of the current study was similar to 2 Asian studies,[19,20] but the mean age assessment was 40 hours compared to the same Asian study where measurements were done at 24 hours post-delivery. The sample size (n = 292) is much larger than other studies performed on healthy full-term neonates and is therefore highly powered and provides a high level of confidence in the variation of normality in term African neonatal cardiac function.[21,45]

Study strengths and limitations

This study is one of the largest and most recent undertaken in the neonatal population worldwide. It is also strongly powered in terms of the large sample size, a strong ICC, and the incorporation of other cardiac function parameters (Tei index and tissue Doppler) not included in other studies.[16,17,19,20,31]

Due to the lack of availability, cardiac speckle-tracking and strain, a measure of tissue deformation, was omitted.[46]

CONCLUSION

This study has established normal reference values for systolic and diastolic function using various echocardiographic modalities in full-term African neonates. It is the first such study to be done in sub-Saharan Africa with a population cohort of 292 subjects, which is the largest worldwide. Comparisons with other studies have confirmed differences between various ethnic groups.

Conflict of interest: none declared.

SUPPLEMENTARY TABLE I: Gender and mode of delivery (Local vs. international values).

	This study 2019 (South Africa) n = 292	Riggs, et al. 1989 (Northern America) n = 22	Iwashima, Seguchi and Ohzeki 2005 (Asia) n = 55	Bokiniec, at al. 2016 (Europe) n = 29
Gender - M/F	142M/150F	-	31M/24F	18M/11F
Mode of delivery - C/S: NVD	175:117	05:17	18/37	11:18

M: male, F: female, C/S: caesarean section, NVD: normal vertex delivery.

SUPPLEMENTARY TABLE II: M-mode measurements (Local vs. international values).

	This study 2019 (Africa) n = 292	Mori, et al. 2004 (Asia) n = 135	Iwashima, Seguchi and Ohzeki 2005 (Asia) n = 55	Núñez-Gil, et al. 2011 (Europe) n=30	Uysal, Boston and Çil 2015 (Europe) n = 22	Taksande 2018 (Asia) n = 15
Mean weight (kg)	3.18	2.95	2.46	-	-	2.56
Mean BSA (m^2)	0.202	-	-	0.23	< 0.25	-
LV EF (%)	73.56 (± 8.93)	-	71.20 (± 6.5)	-	-	-
LV FS (%)	40.25 (± 7.91)	31 (± 0.06)	-	-	-	39.06 (± 3.72)
TAPSE(mm)	7.516 (± 1.30)	-	-	10.56 (± 7.26)	9.09 (± 5.91)	-

n: number of participants in study, BSA: body surface area, m^2: metre squared, LV EF: left ventricular ejection fraction, LV FS: left ventricular fraction shortening, TAPSE: tricuspid annular plane systolic excursion. Data is expressed as mean ± standard deviation.

SUPPLEMENTARY TABLE III: Doppler measurements (Local vs. international values).

	This study 2019 (Africa) n = 292	Riggs, et al. 1989 (Northern America) n = 22	Harada, et al. 1994 (Asia) n = 16	Shiota, Harada and Takada 2002 (Asia) n = 45	Mori, et al. 2004 (Asia) n = 135	Iwashima, Seguchi and Ohzeki 2005 (Asia) n = 55	Koestenberger, et al. 2012 (Europe) n = 83	Bokiniecet, et al. 2016 (Europe) n = 29	Taksande 2018 (Asia) n = 15
Mean weight (kg)	3.18	3.44	3.09	3.06	2.95	2.46	-	3.443	2.56
Mean BSA (m^2)	0.20	-	-	-	-	-	0.22	-	-
MV PEAK E	0.58 (± 0.11)	0.50 (± 7.9)	-	0.53 (± 9)	0.52 (± 9.5)	0.54 (± 13.6)	-	-	0.46 (± 0.88)
MV PEAK A	0.59 (± 0.12)	0.49 (± 8.3)	-	0.44 (± 5)	0.48 (± 8.0)	0.48 (± 8.5)	-	-	0.54 (± 0.85)
MV E/A RATIO	1.01 (± 0.21)	1.00 (± 0.25)	-	1.19 (± 0.15)	-	1.14 (± 0.15)	-	-	0.86 (± 0.18)
MV E'	0.06 (± 0.01)	-	-	-	0.05 (± 0.9)	-	-	-	0.03 (± 0.88)
MV E/E'	10.38 (± 2.65)	-	-	-	7.0 (± 1.6)	-	-	-	-
MV S'	0.05 (± 0.00)	-	-	-	0.04 (± 0.7)	-	-	-	0.04 (± 0.75)
LV Tei	0.31 (± 0.14)	-	-	-	-	-	-	0.37 (± 0.10)	0.30 (± 4.77)
TV PEAK E	0.51 (± 0.13)	0.47 (± 8.5)	0.42 (± 7.3)	-	0.38 (± 7.1)	-	-	-	-
TV PEAK A	0.62 (± 0.13)	0.53 (± 9.9)	0.49 (± 7.9)	-	0.49 (± 7.5)	-	-	-	-
TV E/A RATIO	0.84 (± 0.20)	0.85 (± 0.23)	0.87 (± 0.17)	-	-	-	-	-	-
TV E'	0.08 (± 0.02)	-	-	-	0.08 (± 1.3)	-	-	-	0.09 (± 0.14)
TV E/E'	6.78 (± 2.01)	-	-	-	5.2 (± 1.2)	-	-	-	-
TV S'	0.07 (± 0.05)	-	-	-	0.07 (± 1.2)	-	0.07 (± 4.75)	-	0.09 (± 0.14)
RV Tei	0.28 (± 0.13)	-	-	-	-	-	-	0.42 (± 0.14)	0.40 (± 5.24)

n: number of participants in study, BSA: body surface area, MV peak E: mitral valve - early diastolic filling measured by pulsed Doppler, MV peak A: mitral valve - late diastolic filling measured by pulsed Doppler, MV E/A: mitral valve - early diastolic filling/late diastolic filling ratio, TDI MV E': mitral valve - peak myocardial velocity in early diastole measured by TDI, MV E/E': mitral valve- early diastolic filling / peak myocardial velocity in early diastole ratio, TDI MV S': mitral valve - Systolic wave representing peak myocardial systolic velocity at the septal MV annulus measured by TDI, LV Tei: myocardial performance index, TV peak E: tricuspid valve - early diastolic filling measured by pulsed Doppler, TV peak A: tricuspid valve - late diastolic filling measured by pulsed Doppler, TV E/A: tricuspid valve – early diastolic filling / late diastolic filling ratio,
TDI TV E': tricuspid valve - peak myocardial velocity in early diastole measured by TDI, TV E/E': tricuspid valve – early diastolic filling / peak myocardial velocity in early diastole ratio, TDI TV S': tricuspid valve - systolic wave representing peak myocardial systolic velocity at the lateral TV annulus measured by TDI, RV Tei: myocardial performance index.

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