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Nomograms of pulsed Doppler velocities, times, and velocity time integrals for semilunar valves and great arteries in healthy Caucasian children

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1. Introduction

Doppler velocities are key echocardiographic parameters employed for functional evaluation of semilunar valve and great vessels at all the ages [1]. In adults the range of normality for Doppler measurements in the semilunar valves and great arteries have been recently reported by a few recent multicenter studies with appropriate sample sizes (e.g. from 449 to 1396 normal subjects, >18 years) [2–6]. In contrast, references values for aortic and pulmonary Doppler in children are limited [7–14]. Few recent studies have reported normal values for single parameters [7–10], including the velocity time integrals (VTI) for the aorta [7,10], the pulmonary valve [7], the right ventricular outflow tract [9], maximal Doppler velocities at the aortic level [10], and the pulmonary artery acceleration times (PAAT) [8,14]. A few of these studies had large (e.g. from 756 to 1193 healthy children, age: 0–18 years) [8,10], or relatively large (e.g. 349 subjects, age 0–20 years) [7] sample size, while others were numerically limited (e.g. 75 children, age 1.3–12.6 years) [14]. However, comprehensive pediatric nomograms on Doppler velocities derived from a large sample size, and including complete dataset of measurements (e.g. VTI, maximal systolic velocity, acceleration/deceleration times) at semilunar valves and great vessels are lacking. In particular, it is surprising that normal data on maximal Doppler velocities, that are basic parameters commonly employed to distinguish among normal and pathologic and to grade valve defect severity, are very limited [10]. The aim of the present study was to prospectively establish pediatric nomograms for Doppler velocities, acceleration and deceleration time derived gradients and VTI for the great arteries at different sites in a large pediatric cohort.

2. Methods

2.1. Study population

Selected healthy Caucasian children evaluated from April 2017 to May 2018 in the outpatient pediatric cardiology department at the Fondazione CNR-Regione Toscana G. Monasterio of Massa for congenital heart disease (CHD) screening were prospectively recruited. Neonates and infants mostly were evaluated for "innocent murmurs" while older children and young adolescents usually come in our outpatients for suspicion of CHD after sport screening. Our population includes 400 healthy children already analyzed for recent publications on other measurements [15,16]. The inclusion and exclusion criteria have been reported elsewhere [15,16]. Briefly, only those with technically adequate echocardiographic examinations were enrolled in the study. The presence of intra-cardiac defects that represent normal circulatory physiology such as a patent foramen ovale was considered normal [15,16]. All subjects with clinical, electrocardiographic, or echocardiographic evidence of CHD or acquired heart disease were excluded. Other exclusion criteria consisted of patients with known or suspected neuro-muscular disease, genetic syndromes, or chromosomal abnormalities; body mass index (BMI) ≥95th percentile for children ≥2 years old [17,18] or weight-for-length *Z*-score ≥ 2 based on the World Health Organization (WHO) Child Growth Standards for children <2 years old [17,18]; pulmonary hypertension [19]; systemic hypertension (for children >4 year of age), connective tissue disease; or family history of genetic cardiac disease (such as Marfan syndrome or cardiomyopathy), [15,16]. All non-Caucasian subjects were also excluded to avoid racial variability bias. All patients underwent a complete 2-dimensional examination and images were digitally stored for subsequent off-line analysis. Images were collected only in quiet and cooperative children. Infants were allowed to bottle feed and (for older children) to watch cartoons during the examinations. No child was sedated. Approval for this study was obtained from the Local Ethics Committee (Study "Bet" N.390). Parents or legal guardians of all the children were informed and accepted to participate in the study by signing a written consent.

2.2. Echocardiographic examination

Echocardiographic measurements included: pulsed Doppler velocities (cm/s), acceleration/deceleration times (ms), ejection times (ms), and VTI measurements (cm) at

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multiple sites including the aortic valve, the pulmonary valve and the aortic arch (at the level of the third vessel branch). Vessel diameters (e.g. sub-aortic, pulmonary artery and aortic isthmus diameters) were calculated in order to derive stroke volume (SV) (ml) and cardiac output (CO) (L/min) using the formula. $SV = VTI * \pi * (\text{vessel diameter}/20)^2$; $CO = SV \times \text{heart rate}$. Measurements were performed according to international recommendations [1]. The measurements and sites are detailed in Table 1A. Echocardiograms were performed using Philips-iE33 systems (Philips, Bothell, USA) with phase array 12 Mhz, 8 Mhz, and 5 Mhz transducers, and off-line measurements on Philips-Q-Lab-9 (Philips, Bothell, USA). Measurements were only made if excellent and unambiguous views were available. Two independent experienced pediatric cardiologists (M.C., E.F.) acquired images and performed measurements.

2.3. Statistical methods

The sample size was calculated based on previous observations [15,16,19–28]. The sample size necessary to obtain nomograms with sufficient statistical power dividing the population into 6 major age stages (Group 1 neonates: 0–30 days; Group 2, infancy: 31 days-12 months; Group 3, toddlers: 13 months-2 years; Group 4, early childhood: 2–5 years; Group 5, middle childhood: 6–11 years; Group 6, early adolescence 12–17 years) is at least 600 patients [15,16,23,24]. To examine the relationship between parameters of body size, heart rate, age and each of the echocardiographic variables, multiple models using linear, logarithmic, quadratic, cubic, power, exponential, and square root equations were tested [15,16]. Among the models that satisfied the assumption of homoscedasticity, the model with the highest R^2 value was considered to provide the best fit. The presence or absence of heteroscedasticity, a statistical term used to describe the behavior of variance and normality of the residuals, was tested by the White test and the Breusch-Pagan test as described previously [20,21]. To test the normality of residuals, the Shapiro-Wilk and Lilliefors (Kolmogorov-Smirnov) tests were used [26,27]. Age, weight, height, heart rate (HR) and body surface area (BSA) [15,16] were used as independent variables in different regression analyses to predict the mean values of each echocardiographic measurement. The Haycock formula was used to calculate BSA [22]. This formula is commonly employed in the pediatric population since it underestimates less at low BSA (e.g > 0.7 m2) [15,16]. Outliers to be excluded from analysis were identified visually and using the Leverage values and the Studentized error residuals, the observations were omitted in the final analysis if they significantly deviated from the models. The effect of sex was also evaluated as covariate in these models [15,16]. Inter and intra-rater agreement of measurements was based on coefficient of variation (CV), and intraclass correlation coefficients (ICC) in 20 subjects. The Inter- and Intra CV were calculated like an average value calculated from the individual CVs for all of the duplicates. Inter CVs of <15% are generally acceptable, while Intra CVs should be <10%. The Statistical Package for Social Sciences (SPSS) Release 23.0 (Chicago, Illinois) and Stata Version 13 for Windows (Stata Corp, 2001) were used for analyses.

3. Results

3.1. Subjects

The final study population comprised 712 subjects (age 31 days-17 years; 48.6% female). Mean age of the study population was 92.2 months (median 89.6 months, inter-quartile range 51.7–136.6 months). Body weight ranged from 2.6 to 92.5 kg (median 26 kg; inter-quartile range 17–42 kg); height ranged from 46 to 185 cm (median 125 cm; inter-quartile interval 103–149 cm); and BSA ranged from 0.19 to 2.15 m^2 (median 0.94 m^2; inter-quartile interval 0.70–1.32 m^2). Heart rate ranged from 46 to 189 beats per minute (b.p.m.), median 87, inter-quartile interval 76–101 b.p.m.. Demographic data is shown in Tables 1B and Supplemental Table 1.

3.2. Relationship of echocardiographic parameters with BSA, HR, and age

Relationship of echocardiographic parameters with BSA, HR and age are reported in Table 2a. At all the sample points VTI, ejection time, diameter, SV and CO were directly correlated with BSA and age and indirectly with HR (r at least 0.6 and $p < 0.001$). Low correlation coefficients—positively with BSA and age and negatively with HR were observed for maximal systolic velocity, acceleration time and deceleration time (r 0.4 or less and $p < 0.001$) indicating a weak relationship of these measurements with BSA, age and HR. When maximal velocities and decelerations times were corrected by ET, correlations remained low and significant (all $p < 0.001$) but became negative with age and BSA and positive with heart rate.

3.3. Data normalization

For each parameter we tested the relationship with BSA, HR and age using three univariate regression models where the parameter was the dependent variable and BSA, HR and age were the independent variable (tested in three univariate models). Different models using linear, logarithmic, quadratic, cubic, power, exponential, and square root equations were tested, and the equation with highest coefficient of determination (R^2) that satisfied the assumption of homoscedasticity and normality of residuals was chosen. At all the sample points for all the parameters (except for ejection time) the association with BSA was stronger than HR and age (Supplemental Table 2). Only for ejection time HR was superior, but the model did not satisfy the assumption of homoscedasticity and normality of residuals, and therefore BSA was used for normalization of all the parameters. The best fit models for each measurement were the exponential ($\ln[y] = a + b^*\ln[x]$), linear ($y = a + b^*x$) or cubic ($y = a + b1^*x + b2^*x2 + b3^*x3$) (Table 2a, 2b, 2c). For some of the measurements, low R^2 were noted (Table 2a, 2b, 2c). The predicted values and *Z*-scores boundaries are presented where R^2 was acceptable (Tables 3A and B). For the other measurements, mean observed values and standard deviations are reported (Supplemental Table 3). When the influence of gender was evaluated by multiple linear regression models incorporating it as covariate along with BSA, HR and age, no significant effects were found for most measurements (Supplemental Table 4).

Table 1A
Measurements.

Site of measurement	Projection	Measurements
Aortic valve	5 chamber view	Max. velocity (cm/s)
		Systolic acceleration and deceleration time (ms)
		Systolic duration (ms)
		VTI (cm)
	Long axis view	Sub-aortic diameter (mm)
Pulmonary valve	Short axis view	Max. velocity (cm/s)
		Systolic acceleration and deceleration time (ms)
		Systolic duration (ms)
		VTI (cm)
	Short axis view	Pulmonary diameter (mm)
Aortic Arch at the level of the third vase	Supra-sternal view	Max. velocity (cm/s)
		Systolic acceleration and deceleration time (ms)
		Systolic duration (ms)
		VTI (cm)
	Supra-sternal view	Aortic arch diameter after the origin of the third vessel(mm)

VTI = velocity time integral.

Table 1B
Distribution of BSA calculated with the Haycock formula.

BSA	N	%
[0.15–0.25)	10	1.4
[0.25–0.3)	13	1.8
[0.3–0.35)	18	2.5
[0.35–0.4)	26	3.6
[0.4–0.45)	30	4.2
[0.45–0.5)	21	2.9
[0.5–0.6)	37	5.2
[0.6–0.7)	48	6.7
[0.7–0.8)	52	7.3
[0.8–0.9)	57	8.0
[0.9–1.0)	56	7.9
[1.0–1.1)	51	7.2
[1.1–1.2)	50	7.0
[1.2–1.3)	45	6.3
[1.3–1.4)	46	6.4
[1.4–1.5)	49	6.8
[1.5–1.6)	50	7.0
[1.6–2.1)	53	7.4
Total	712	100

BSA = body surface area.

3.4. Reproducibility

Intra-observer and inter-observer agreement were assessed by calculating both the intraclass correlation coefficient (ICC) and coefficient of variation (CV). As detailed in Supplemental Table 5 the ICC were high for all the measurements, showing an almost perfect agreement. Furthermore, CV was very low confirming the excellent agreement.

4. Discussion

We report normal values for Doppler velocities, acceleration and deceleration times and VTI for the semilunar valves and great arteries in a large population of healthy children. This is the first study in children comprehensively evaluating Doppler nomograms for the great arteries at multiple sites. Previous reports were limited to single [8–10] or few parameters [7]. For example, VTI was calculated at the aortic valve [7], at the pulmonary valve [7], and on the right ventricular outflow tract [9].

Pulmonary acceleration times (PAAT) have been reported in healthy children and in patients with pulmonary hypertension (PH) [8,13]. A few studies had large [8], or relatively large [7] sample size, while others were numerically limited [14]. Our group [8] established *Z*-scores for PAAT in a large pediatric sample and also demonstrated its correlation with pulmonary vascular resistance in children with pulmonary hypertension (ρ=−0.497). We have also established Z-scores for the right ventricle outflow tract (RVOT) VTI [9] and showed high specificity of RVOT VTI Z-score for atrial septal defects.

Solinsky et al. [7] have reported normal values for semilunar valve VTI in 349 children and young adults from 0 to 20 years. They demonstrated aortic VTI values to have 73% sensitivity for the diagnosis of hemodynamically significant patent ductus arteriosus (PDA), while pulmonary artery VTI had 84% sensitivity in identifying significant atrial septal defect. Another report from our group [15] that evaluated pulsed-wave Doppler systolic velocities, deceleration time, wave duration, and two-dimensional vessel diameters in 853 subjects noted significant variations in these parameters with age. At lower ages, Doppler peak velocity was steeper, pulsed-wave shorter and pulsatility limited.

In the present study the VTI, ejection time, diameter, SV and CO positively correlated with BSA and age but negatively with HR (r at least 0.6 and $p < 0.001$) at all the sample points. A weak correlation (r about 0.4 or less; $p < 0.001$) of maximal systolic velocity, acceleration time and deceleration time with BSA, age and HR were observed. Similar observations were made by Pees et al. [10] in a retrospective cohort of healthy children and young adults (0–20 years) in that aortic VTI positively correlated with age and BSA ($r = 0.685$ and 0.645 respectively), and negatively with HR ($r = -0.710$). PAAT [8] has also been shown to positively correlate with age and BSA ($r = 0.848$ and $r = 0.856$,) and negatively with heart rate ($r = -0.906$). A negative correlation of semilunar valve VTI with heart rate was shown by Solinsky and colleagues, [7] particularly in children <7 years of age.

The concept of correlation (r) is not to be confused with the coefficient of determination (R2). Pearson correlation coefficients (r) are sensitive only to a linear relationship between two variables, i.e. may be present even when one variable is a nonlinear function of the other. The coefficients of determination are calculated using several relationships including linear, logarithmic, quadratic, cubic, power, and exponential between two variables. The presence of low correlation coefficients implies that a linear equation would not describe the relationship between X and Y, but the two variables could be related in a quadratic or cubic equation. For nomograms, coefficients of determination (R^2) is typically used [16]. In the present series, we presented z-scores when there was satisfactory R^2 among echocardiographic variables and body size measurements, and the remaining measurements are reported as mean values plus or minus standard deviation. The use of z-score equations with low R^2 may generate confusion as the intervals of normality derived may be highly inaccurate. For example, for a

Table 2a
Aorta: Coefficients for regression equations relating echocardiographic measurements and body surface area, the Standard Error of the Estimate, the determination coefficient. Normality test: Shapiro-Wilk and Lilliefors (Kolmogorov-Smirnov). Heteroscedasticity test (White test and Breusch-Pagan test).

Measurement	Intercept	B	SEE (√MSE)	R^2	SW	KS	BP	W
BSA HAYCOCK. (ln[y] = a + b*ln[x]); Z value = (ln[Measurement] −(Intercept + B*ln[BSA]))/√MSE								
Ao VTI (cm)	3.160	0.353	0.188	0.459	0.067	0.193	0.468	0.085
Ao ejection time (ET) (ms)	5.687	0.209	0.112	0.459	0.062	0.087	0.074	0.264
sub Ao diameter (mm)	2.694	0.477	0.098	0.851	0.334	0.200	0.452	0.719
Ao Max vel/ET	−5.450	−0.079	0.197	0.038	0.868	0.200	0.044	0.033
Ao Acceleration Time (AT) (ms)	4.309	0.314	0.282	0.233	<0.001	<0.001	<0.001	<0.001
Ao AT/Ao ET	−1.374	0.109	0.290	0.033	<0.001	<0.001	<0.001	0.010
Ao Deceleration Time (DT) (ms)	5.383	0.180	0.162	0.230	<0.001	<0.001	0.184	0.724
Ao DT/ET	−0.301	−0.029	0.141	0.010	<0.001	<0.001	0.306	0.249
AO SV (ml)	3.686	1.324	0.243	0.878	0.868	0.200	0.064	0.053
AO CO (L/min)	1.224	0.902	0.247	0.759	0.601	0.200	0.971	0.234
BSA HAYCOCK. (y = a + b*x); Z value = (Measurement − (Intercept + B*BSA))/√MSE								
Ao VTI/ET	0.067	0.013	0.014	0.130	<0.001	<0.001	0.001	0.016
Ao max systolic velocity (m/s)	1.072	0.193	0.196	0.146	<0.001	<0.001	<0.001	0.003

BSA HAYCOCK. ($y = a + b_1*x + b_2*x^2 + b_3*x^3$); Z value = (Measurement − ($a + b_1*BSA + b_2*BSA^2 + b_3*BSA^3$))/√MSE

Measurement	a	b_1	b_2	b_3	SEE (√MSE)	R^2	SW	KS	BP	W
Ao VTI*HR	3018.8	−2944.8	2683.3	−731.8	489.16	0.038	<0.001	<0.001	0.011	0.091

Table 2b
Pulmonary artery:

BSA HAYCOCK. (ln[y] = a + b*ln[x]); Z value = (ln[Measurement] –(Intercept + B*ln[BSA]))/√MSE

Measurement	Intercept	B	SEE (√MSE)	R^2	SW	KS	BP	W
PA VTI (cm)	3.102	0.277	0.169	0.378	0.401	0.200	0.014	0.084
PA diameter (mm)	2.857	0.476	0.121	0.771	0.188	0.200	0.764	0.381
PA Acceleration time (AT) (ms)	4.656	0.379	0.264	0.325	<0.001	<0.001	<0.001	<0.001
PA AT/ET	−1.082	0.180	0.248	0.107	0.413	0.156	0.049	0.019
PA SV (ml)	3.957	1.215	0.287	0.794	0.456	0.200	0.376	0.665
PA Co (L/min)	1.495	0.815	0.282	0.633	0.699	0.200	0.483	0.324

BSA HAYCOCK. ($y = a + b_1*x + b_2*x^2 + b_3*x^3$); Z value = (Measurement – ($a + b_1*BSA + b_2*BSA^2 + b_3*BSA^3$))/√MSE

Measurement	a	b_1	b_2	b_3	SEE (√MSE)	R^2	SW	KS	BP	W
PA ejection time (ET) (ms)	140.9	335.1	−188.8	33.59	36.41	0.409	<0.001	<0.001	0.026	0.147
PA VTI/ET	0.086	−0.049	0.043	−0.009	0.013	0.076	<0.001	<0.001	0.005	0.115
PA max systolic velocity (m/s)	1.220	−0.463	0.438	−0.103	0.180	0.048	<0.001	<0.001	0.003	0.471
PA max vel/ET	0.007	−0.008	0.006	−0.001	0.001	0.223	<0.001	<0.001	<0.001	<0.001
PA Deceleration time (DT) (ms)	103.5	233.0	−171.2	40.77	34.53	0.128	<0.001	<0.001	0.001	0.067
PA DT/ET	0.727	−0.016	−0.120	0.057	0.112	0.055	<0.001	<0.001	0.005	0.005
PA VTI*HR	3327	−3791	3161	−827.3	423.4	0.107	<0.001	<0.001	0.157	0.086

given child with BSA 0.5 m^2, had we used the best model obtained (ln[y] = a + b*ln[x]); Z value = (ln[Measurement] –(Intercept + B*ln [BSA]))/√MSE) with an R^2 of 0.233, the derived range of normality was 34.0 to105.1 ms, while the observed values were from 40.0 to 87.0 ms.

Doppler velocities and VTI measurements have been reported as absolute values and corrected for systolic time interval [11,13]. Adult studies [11,13] showed how correction of aortic acceleration times by ejection time increased the accuracy in aortic stenosis estimation. In a pediatric series of pulmonary hypertension, Levy et al. [14] demonstrated good accuracy of PAAT <90 ms and PAAT/RVET <0.31 across wide ranges of pulmonary hemodynamics. In this series, however correction of Doppler velocities and VTI for ejection time did not yield benefit. For both semilunar valves, the R2 for SV and CO were good (0.633 to 0.878), but a factor of correction to relate aortic and pulmonary variables could not be defined. As a result, the clinical utility of SV and CO for the calculation of the pulmonary to systemic flow ratio (QP: QS) seem to be limited, while they may be helpful to evaluate alterations in cardiac output [7]. Because strong negative correlations have been found among VTI values and HR by multiple authors [7,8,10], Solinski et al. [7] have proposed percentiles of the product of aortic and pulmonary VTI and HR as a surrogate of CO. They proposed normalization of VTI X HR values for ventricular length instead of the BSA, since BSA may not adequately reflect the need for CO in obese or athletic children. The R2 of VTI X HR with the ventricular length was not reported by these authors [7], so it is unclear whether normalization for ventricular length may be superior.

4.1. Limitations

Since the population in our region is mainly constituted by Caucasian, we limited our study to this ethnic group. Thus, data from different ethnic backgrounds are lacking in the present study. However, this eliminated bias of differing racial compositions, and would potentially allow comparisons with populations of different races and ethnicities [15,16]. A complete set of measurements was not available for all the studied subjects. The impossibility to perform *Z*-scores with a sufficient statistical power for few measurements is a limitation of the present studies. However, it has been demonstrated that in children when Doppler parameters are evaluated, normalization by age, BSA or other body size variables is often challenging [29]. Of interest parameters with higher R2 were ejection times and VTI as has been shown in

Table 2c
Aortic arch.

BSA HAYCOCK. (ln[y] = a + b*ln[x]); Z value = (ln[Measurement] –(Intercept + B*ln[BSA]))/√MSE

Measurement	Intercept	B	SEE (√MSE)	R^2	SW	KS	BP	W
Arch VTI (cm)	3.279	0.450	0.190	0.566	0.581	0.200	0.028	0.160
Arch ejection time ET (ms)	5.634	0.219	0.117	0.449	<0.001	0.014	0.156	0.532
Arch VTI/ET	−2.360	0.225	0.174	0.279	0.098	0.089	0.608	0.901
Arch diameter (mm)	2.461	0.460	0.136	0.723	0.622	0.200	0.325	0.544
Arch max velocity (m/s)	0.354	0.183	0.150	0.259	0.234	0.200	0.810	0.559
Arch Acceleration time (AT) (ms)	4.543	0.403	0.309	0.286	<0.001	<0.001	<0.001	<0.001
Arch AT/ET	−1.087	0.176	0.320	0.066	<0.001	<0.001	<0.001	<0.001
Arch deceleration time (ms)	5.195	0.130	0.208	0.084	<0.001	<0.001	<0.001	0.008
Arch DT/ET	−0.443	−0.103	0.189	0.064	<0.001	<0.001	0.024	0.209
Arch SV (ml)	3.337	1.365	0.300	0.826	0.135	0.200	0.040	0.125
Arch CO (L/min)	0.874	0.989	0.296	0.713	0.225	0.200	0.165	0.408

BSA HAYCOCK. ($y = a + b_1*x + b_2*x^2 + b_3*x^3$); Z value = (Measurement – ($a + b_1*BSA + b_2*BSA^2 + b_3*BSA^3$))/√MSE

Measurement	a	b_1	b_2	b_3	SEE (√MSE)	R^2	SW	KS	BP	W
Arch max vel/ET	0.006	−0.003	0.002	0.0003	0.001	0.033	<0.001	<0.001	0.590	0.894
Arch VTI*HR	2620	−1597	1790	−523.9	507.0	0.043	<0.001	<0.001	0.220	0.853

AO = aorta, PA = pulmonary artery; AT = acceleration time, CO = cardiac output, DT = deceleration time, ET = ejection time, PA = pulmonary artery, SV = stroke volume, VTI = velocity time integral.
BP=Breusch-Pagan test KS=Kolmogorov–Smirnov test SEE = standard error of the estimate, MSE = mean square error, R2 = coefficient of determination, W=White test, SW=Shapiro-Wilk test.

Table 3
Predicted values (Mean ± 2SD) of measured echocardiography variables expressed by body surface area (BSA) (Haycock).

A

	0.10	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**	**0.50**	**0.60**
	7.18	8.28	9.17	9.92	10.58	11.17	11.71	12.67	13.51
Ao VTI (cm)	**10.46**	**12.07**	**13.35**	**14.45**	**15.41**	**16.27**	**17.06**	**18.45**	**19.68**
	15.23	17.57	19.45	21.04	22.44	23.70	24.84	26.88	28.67
	145.7	158.6	168.4	176.5	183.3	189.3	194.7	204.0	211.9
Ao ejection time (ET) (ms)	**182.3**	**198.4**	**210.7**	**220.8**	**229.4**	**236.9**	**243.6**	**255.2**	**265.1**
	228.1	248.3	263.7	276.2	287.0	296.4	304.8	319.3	331.7
	4.05	4.92	5.64	6.28	6.85	7.37	7.85	8.74	9.53
Sub Ao diameter (mm)	**4.93**	**5.98**	**6.86**	**7.63**	**8.33**	**8.96**	**9.55**	**10.63**	**11.59**
	6.00	7.28	8.35	9.29	10.13	10.91	11.62	12.93	14.10
	1.16	1.99	2.91	3.91	4.98	6.11	7.29	9.80	12.47
AO SV (ml)	**1.89**	**3.24**	**4.74**	**6.36**	**8.10**	**9.93**	**11.86**	**15.93**	**20.28**
	3.08	5.26	7.70	10.35	13.17	16.15	19.28	25.90	32.97
	0.26	0.37	0.49	0.59	0.70	0.80	0.91	1.11	1.31
AO CO (L/min)	**0.43**	**0.61**	**0.80**	**0.97**	**1.15**	**1.32**	**1.49**	**1.82**	**2.15**
	0.70	1.01	1.31	1.60	1.88	2.16	2.44	2.98	3.52
	8.38	9.38	10.16	10.80	11.36	11.86	12.31	13.09	13.77
PA VTI (cm)	**11.75**	**13.15**	**14.24**	**15.15**	**15.93**	**16.63**	**17.26**	**18.36**	**19.31**
	16.48	18.44	19.97	21.24	22.34	23.32	24.20	25.74	27.07
	99.7	114.2	127.8	140.6	152.5	163.7	174.1	192.6	208.4
PA ejection time (ET) (ms)	**172.6**	**187.0**	**200.6**	**213.4**	**225.3**	**236.5**	**246.9**	**265.4**	**281.2**
	245.4	259.9	273.5	286.2	298.2	309.3	319.7	338.3	354.1
	4.57	5.54	6.35	7.06	7.71	8.29	8.84	9.83	10.72
PA diameter (mm)	**5.82**	**7.06**	**8.09**	**9.00**	**9.81**	**10.56**	**11.26**	**12.52**	**13.65**
	7.41	8.99	10.31	11.46	12.50	13.45	14.34	15.94	17.39
	1.80	2.94	4.17	5.47	6.82	8.23	9.68	12.69	15.84
PA SV (ml)	**3.19**	**5.22**	**7.40**	**9.71**	**12.11**	**14.61**	**17.18**	**22.53**	**28.12**
	5.66	9.26	13.14	17.23	21.50	25.93	30.50	40.00	49.92
	0.39	0.54	0.68	0.82	0.95	1.08	1.20	1.44	1.67
PA Co (L/min)	**0.68**	**0.95**	**1.20**	**1.44**	**1.67**	**1.90**	**2.11**	**2.53**	**2.94**
	1.20	1.67	2.11	2.53	2.94	3.33	3.71	4.46	5.17
	6.44	7.73	8.80	9.73	10.56	11.32	12.02	13.29	14.43
Arch VTI (cm)	**9.42**	**11.31**	**12.87**	**14.23**	**15.44**	**16.55**	**17.58**	**19.44**	**21.10**
	13.77	16.53	18.82	20.80	22.58	24.21	25.70	28.42	30.85
	133.7	146.1	155.6	163.4	170.1	175.9	181.2	190.2	198.0
Arch ejection time ET (ms)	**169.0**	**184.7**	**196.7**	**206.5**	**214.9**	**222.3**	**228.9**	**240.4**	**250.2**
	213.5	233.3	248.5	261.0	271.6	280.9	289.3	303.7	316.1
	3.10	3.73	4.26	4.72	5.13	5.51	5.86	6.49	7.06
Arch diameter (mm)	**4.06**	**4.90**	**5.59**	**6.19**	**6.73**	**7.23**	**7.69**	**8.52**	**9.26**
	5.33	6.43	7.34	8.13	8.84	9.49	10.09	11.18	12.16
	0.67	1.16	1.72	2.33	2.98	3.68	4.42	5.99	7.69
Arch SV (ml)	**1.21**	**2.11**	**3.13**	**4.24**	**5.44**	**6.71**	**8.05**	**10.92**	**14.01**
	2.21	3.85	5.70	7.73	9.91	12.23	14.68	19.90	25.53
	0.14	0.20	0.27	0.34	0.40	0.47	0.54	0.67	0.80
Arch CO (L/min)	**0.25**	**0.37**	**0.49**	**0.61**	**0.73**	**0.85**	**0.97**	**1.21**	**1.45**
	0.44	0.66	0.88	1.10	1.32	1.53	1.75	2.18	2.61

B

	0.7	**0.8**	**0.9**	**1.0**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**
	14.27	14.96	15.59	16.18	16.74	17.26	17.75	18.22	18.67	19.10	19.52
Ao VTI (cm)	**20.78**	**21.79**	**22.71**	**23.57**	**24.38**	**25.14**	**25.86**	**26.54**	**27.20**	**27.82**	**28.43**
	30.27	31.73	33.08	34.33	35.50	36.61	37.66	38.66	39.61	40.52	41.40
	218.9	225.1	230.7	235.8	240.5	245.0	249.1	253.0	256.7	260.1	263.5
Ao ejection time (ET) (ms)	**273.8**	**281.6**	**288.6**	**295.0**	**300.9**	**306.5**	**311.6**	**316.5**	**321.1**	**325.5**	**329.6**
	342.6	352.3	361.0	369.1	376.5	383.4	389.9	396.0	401.7	407.2	412.4
	10.26	10.93	11.56	12.16	12.72	13.26	13.78	14.27	14.75	15.21	15.66
Sub Ao diameter (mm)	**12.48**	**13.30**	**14.07**	**14.79**	**15.48**	**16.13**	**16.76**	**17.37**	**17.95**	**18.51**	**19.05**
	15.18	16.18	17.11	17.99	18.83	19.63	20.39	21.13	21.83	22.52	23.18
	15.30	18.26	21.34	24.53	27.83	31.23	34.72	38.30	41.96	45.71	49.53
AO SV (ml)	**24.87**	**29.68**	**34.69**	**39.88**	**45.25**	**50.77**	**56.45**	**62.27**	**68.23**	**74.31**	**80.52**
	40.44	48.26	56.40	64.85	73.57	82.55	91.78	101.24	110.92	120.82	130.92
	1.50	1.70	1.89	2.08	2.26	2.45	2.63	2.81	2.99	3.17	3.35
AO CO (L/min)	**2.47**	**2.78**	**3.09**	**3.40**	**3.71**	**4.01**	**4.31**	**4.61**	**4.90**	**5.20**	**5.49**
	4.04	4.56	5.07	5.57	6.07	6.57	7.06	7.55	8.03	8.52	8.99
	14.37	14.91	15.41	15.86	16.29	16.68	17.06	17.41	17.75	18.07	18.37
PA VTI (cm)	**20.15**	**20.91**	**21.60**	**22.24**	**22.84**	**23.39**	**23.92**	**24.42**	**24.89**	**25.34**	**25.76**
	28.25	29.32	30.29	31.19	32.02	32.80	33.54	34.23	34.89	35.52	36.12
	221.7	232.5	241.2	248.0	253.0	256.4	258.4	259.3	259.3	258.5	257.1
PA ejection time (ET) (ms)	**294.5**	**305.3**	**314.0**	**320.8**	**325.8**	**329.2**	**331.3**	**332.2**	**332.1**	**331.3**	**330.0**
	367.3	378.2	386.9	393.6	398.6	402.0	404.1	405.0	404.9	404.1	402.8
	11.53	12.29	13.00	13.67	14.30	14.91	15.49	16.04	16.58	17.09	17.59
PA diameter (mm)	**14.69**	**15.65**	**16.56**	**17.41**	**18.22**	**18.99**	**19.72**	**20.43**	**21.12**	**21.77**	**22.41**
	18.71	19.94	21.09	22.18	23.20	24.19	25.13	26.03	26.90	27.74	28.55
	19.10	22.46	25.92	29.46	33.08	36.76	40.52	44.34	48.21	52.15	56.13

(continued on next page)

Table 3 (*continued*)

B											
	0.7	**0.8**	**0.9**	**1.0**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**
PA SV (ml)	**33.91**	**39.88**	**46.02**	**52.30**	**58.72**	**65.27**	**71.94**	**78.71**	**85.60**	**92.58**	**99.65**
	60.20	70.80	81.69	92.85	104.25	115.88	127.71	139.74	151.96	164.36	176.92
	1.90	2.12	2.33	2.54	2.74	2.94	3.14	3.34	3.53	3.72	3.91
PA Co (L/min)	**3.33**	**3.72**	**4.09**	**4.46**	**4.82**	**5.17**	**5.52**	**5.87**	**6.21**	**6.54**	**6.87**
	5.86	6.53	7.19	7.84	8.47	9.09	9.71	10.31	10.91	11.50	12.08
	15.46	16.42	17.32	18.16	18.95	19.71	20.43	21.12	21.79	22.43	23.05
Arch VTI (cm)	**22.61**	**24.01**	**25.32**	**26.55**	**27.71**	**28.82**	**29.88**	**30.89**	**31.86**	**32.80**	**33.71**
	33.07	35.11	37.02	38.82	40.52	42.14	43.69	45.17	46.59	47.97	49.29
	204.8	210.8	216.4	221.4	226.1	230.4	234.5	238.3	242.0	245.4	248.7
Arch ejection time ET (ms)	**258.8**	**266.4**	**273.4**	**279.8**	**285.7**	**291.2**	**296.3**	**301.2**	**305.8**	**310.1**	**314.3**
	327.0	336.7	345.5	353.5	361.0	367.9	374.4	380.6	386.4	391.9	397.1
	7.58	8.06	8.50	8.93	9.33	9.71	10.07	10.42	10.76	11.08	11.39
Arch diameter (mm)	**9.94**	**10.57**	**11.16**	**11.72**	**12.24**	**12.74**	**13.22**	**13.68**	**14.12**	**14.54**	**14.96**
	13.05	13.88	14.65	15.38	16.07	16.72	17.35	17.95	18.53	19.09	19.63
	9.49	11.39	13.37	15.44	17.59	19.80	22.09	24.44	26.86	29.33	31.86
Arch SV (ml)	**17.29**	**20.75**	**24.37**	**28.13**	**32.04**	**36.08**	**40.25**	**44.54**	**48.93**	**53.44**	**58.05**
	31.50	37.80	44.40	51.26	58.39	65.75	73.34	81.15	89.16	97.37	105.77
	0.93	1.06	1.19	1.33	1.46	1.59	1.72	1.85	1.98	2.11	2.24
Arch CO (L/min)	**1.68**	**1.92**	**2.16**	**2.40**	**2.63**	**2.87**	**3.11**	**3.34**	**3.58**	**3.81**	**4.05**
	3.04	3.47	3.90	4.33	4.76	5.19	5.62	6.04	6.47	6.90	7.32

The estimates values are in bold, the values above are -2SD and the values below are +2SD.
Only parameters with $R2 > 0.4$ are reported (PA VTI has an R2 of 0.378 and is also reported for completeness of data).
AO = aorta, PA = pulmonary artery; AT = acceleration time, CO = cardiac output, DT = deceleration time, ET = ejection time, PA = pulmonary artery, SV = stroke volume, VTI = velocity time integral.

previous studies [9,10]. Also derived stroke volumes and cardiac output data showed very good R2. We did not try to compute normalization of VTI values for cardiac measurements [7] which may be an interesting idea for future researches.

5. Conclusions

We report pediatric echocardiographic normal data for Doppler velocities, acceleration/deceleration times and VTI at multiple sites (aortic/pulmonary valve and aortic arch). This is the first pediatric study to report a comprehensive dataset of normal values for Doppler velocities and VTI. Our data would serve as a baseline Doppler evaluation in children with congenital heart disease, pulmonary hypertension and ventricular dysfunction of different nature. The influence of confounders including race and ethnic groups, need to be examined in future studies.

Conflict of interest

Authors' conflict of interest disclosure, research founding, employment or leadership: This work has been supported by Italian Health Ministry Finalized Research Young Research Award 2011-2012 "GR-2011-02350662.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.001.

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