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ORIGINAL INVESTIGATION

WILEY Echocardiography

Reference intervals and percentile curve for left ventricular outflow tract (LVOT), velocity time integral (VTI), and LVOT-VTI-derived hemodynamic parameters in healthy children and adolescents: Analysis of echocardiographic methods association and agreement

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Background: Echocardiographic reference intervals (RIs) for left ventricular outflow tract (LVOT) and velocity time integral (VTI) are scarce in pediatrics.

Aims: (a) to generate RIs and percentiles for LVOT, VTI, and hemodynamic variables in healthy children and adolescents from Argentina; (b) to analyze the equivalence between stroke volume (SV), cardiac output (CO), and cardiac index (CI) obtained from two-dimensional echocardiography (2D) and LVOT-VTI analysis with pulsed wave Doppler (PWD); and (c) to analyze the association between subjects' characteristics and VTI and LVOT-VTI-derived parameters.

Methods: Two-dimensional and PWD studies were done in 385 subjects (5–24 years). Mean and standard deviation age-related and body surface area (BSA)-related equations were obtained for VTI and LVOT-VTI-derived parameters (parametric regression methods based on fractional polynomials). BSA- and age-specific percentiles were determined.

Results: Pulsed wave Doppler- and 2D-derived parameters were positively correlated. However, PWD values were always lower than those from 2D. Specific RIs for PWD and 2D data were necessary. Covariance analysis showed that sex-specific RIs were required for LVOT, but not for VTI, VTI-derived CO and CI. Age-related RIs were obtained for LVOT, LVOT-VTI, and VTI-derived CO and CI. BSA-related RIs for VTI-derived CO and CI were obtained.

Conclusions: Stroke volume, CO, and CI data from 2D and PWD are not equivalent. An accurate analysis of LVOT-VTI-derived parameters requires considering age and BSA. In this study, age- and BSA-related RIs and percentiles for LVOT, VTI, and hemodynamic parameters in healthy children and adolescents were determined, discriminating data according to the methodological approach (2D or PWD).

KEYWORDS

adolescents, blood pressure, cardiac index, cardiac output, children, epidemiology, left ventricular outflow tract, pediatrics, reference values, velocity time integral

1 | INTRODUCTION

Severe heart failure diagnosis and management requires monitoring cardiac output (CO) and hemodynamic parameters.[1] While invasive CO determination through thermodilution using pulmonary artery catheterization remains as the traditional standard method, its routine use is controversial and limited due, among others, to availability, usefulness, and safety issues.[2–8] Noninvasive CO estimation through echocardiography has shown to be an accurate, confident, and easy tool to use in critically ill patients.[9,10] In 2014, the European Society of Intensive Care Medicine reported that echocardiography, rather than invasive methods, is the preferred modality to the early determination of the type of shock.[1] Two-dimensional echocardiography (2D) is ideally suited to evaluate cardiac function in critically ill patients, whereas pulse wave Doppler (PWD) provides additional hemodynamic data that allow to monitor circulatory parameters.[1]

Changes in CO and left ventricle (LV) stroke volume (SV) could be quantified through PWD determinations using the velocity time integral (VTI) and the LV outflow tract (LVOT) diameter. LVOT-VTI provides adequate information to follow changes in SV,[1,9,11–13] and it has been proposed to be included in the Rapid Ultrasound in Shock protocol.[9]

Despite the proven clinical usefulness of ultrasonic-derived CO indexes, there is lack of data regarding LVOT-VTI reference intervals (RIs), obtained from population-based studies in healthy people.[14,15] Additionally, there are no studies analyzing, in children and adolescents, the correlation or equivalence between hemodynamic data (SV, CO, and CI) obtained using 2D and those obtained from LVOT-VTI using PWD.

In this context, this work's main aims were as follows: (a) to generate RIs and percentile curves for VTI, LVOT, and hemodynamic variables obtained from PWD LVOT-VTI measurements (CO and CI) in subjects (children, adolescents, and young adults) from an Argentinean population, healthy and nonexposed to cardiovascular risk factors (CRFs); (b) to analyze the equivalence between SV, CO, and CI data obtained from 2D and data derived from LVOT-VTI measurements (PWD); and (c) to analyze the association between VTI and LVOT-VTI-derived parameters (CO and CI) with anthropometric, hemodynamic, and cardiovascular characteristics.

2 | MATERIALS AND METHODS

This research is part of a project started in 2014 in Tandil, Argentina, aimed at investigating the prevalence of CRFs.[16–20] RIs for several cardiovascular variables have recently been published.[20–22] This prospective study was developed after protocol approval by the Institutional Ethics Committee.

Asymptomatic children, adolescents, and young adults (5–24 years old) from the community were considered for enrollment. The maximum age was set to ensure body growth and development had been completed and adulthood reached.[23,24] Each subject was submitted to clinical interview, blood sampling evaluation, and anthropometric assessment. Inclusion and exclusion criteria (and their definitions) are detailed in Data S1. Briefly, included subjects were normotensive, nonexposed to CVRFs, and none of them had cardiovascular, renal, or pulmonary disease.[25–27] A total of 385 subjects were included (Table 1).

2.1 | Echocardiographic evaluation: 2D and PWD measurements

Echocardiographic studies were done by a single researcher using an Esaote MyLab 40 ultrasound system (Esaote, Genoa, Italy). Evaluations agreed with Recommendations for Cardiac Chamber Quantification.[28,29] Detailed data about the Echocardiographic evaluation are in Data S1.

2.2 | Two-dimensional echocardiographic measurements

Left ventricular outflow tract diameter data correspond to the average of 3 measures, manually obtained at mid-systole in the point of entry of aortic valve cusps (zoomed parasternal long-axis view).[30,31] LV end-diastolic and end-systolic dimensions (LVEDD and LVESD, respectively), end-diastolic and end-systolic interventricular septum thickness (EDIVST and ESIVST, respectively), end-diastolic and end-systolic posterior wall thickness (EDPWT and ESPWT, respectively), and end-diastolic aortic root diameter were obtained from 2D images.[28] LVEDD, EDIVST, and EDPWT, obtained from M-mode ultrasound, were used to calculate LV mass (LVM).[32] Left atrial (LA) dimensions were measured in parasternal long-axis views. LA volume was calculated using the disk summation algorithm. Then, it was indexed considering BSA.[28] LV end-diastolic volume, LV end-systolic volume, and LV ejection fraction (LVEDV, LVESV, and LVEF, respectively) were determined considering the biplane method of disk summation (modified Simpson's rule).

Finally, LVESV and LVEDV were used to calculate SV, CO, CI, and systemic vascular resistance (SVR):

$$SV_{2D} = LVEDV - LVESV \quad (1)$$

$$CO_{2D} = SV_{2D} \times HR \quad (2)$$

$$CI_{2D} = CO_{2D}/BSA \quad (3)$$

$$SVR_{2D} = MBP/CO_{2D} \quad (4)$$

The subindex 2D indicates the parameter was computed from 2D data.

2.3 | PWD echocardiographic measurements

Pulsed wave Doppler mitral inflow velocities were obtained from the apical four-chamber window, with the Doppler sample volume

positioned at the mitral valve tips. Then, peak velocities in early (E) and late (A) diastole were determined.

Left ventricular outflow tract peak velocity and VTI measurements were obtained from the apical 5-chamber view with the PWD sample positioned in the center of the LVOT, immediately below the hinge position of the aortic valve leaflets.[33] Filters were optimized to clearly visualize the border of the spectral Doppler signal. Then, the outer boundary of the signal was traced to calculate the VTI.

The following parameters were determined from PWD (and 2D) data[30,34,35]:

$$SV_{Doppler} = VTI \times LVOT\ area \quad (5)$$

where LVOT area was quantified as

$$LVOT\ area = \pi(LVOT\ diameter/2)^2 \quad (6)$$

$$CO_{Doppler} = SV \times HR \quad (7)$$

$$CI_{Doppler} = CO_{Doppler}/BSA \quad (8)$$

$$SVR_{Doppler} = MBP/CO_{Doppler} \quad (9)$$

The subindex "Doppler" indicates the parameter was obtained considering PWD data. Thus, they could also be considered as VTI-derived.

The intra-observer reproducibility was as follows: 2.0 ± 1.9% for LVOT, 2.3 ± 2% for LVEDD, 4.0 ± 3.8% for EDIVST, 4.2 ± 3.8% for LV mass, and 3.0 ± 2.5% for LVOT-VTI.

2.4 | Mathematical and statistical analysis

A stepwise data analysis was carried out as described below.

First, to determine whether specific RIs for PWD-derived hemodynamic parameters were necessary, the association (correlation) between 2D-derived (SV_{2D}, CO_{2D}, and CI_{2D}) and PWD-derived ($SV_{Doppler}$, $CO_{Doppler}$, and $CI_{Doppler}$) data was analyzed. Then, data equivalence (agreement) was analyzed (Bland–Altman) assessing mean and proportional differences (errors) and constructing limits of agreement. SV, CO, and CI data obtained by both methods (PWD and 2D) showed significant associations (Table 2). There were significant mean differences (systematic errors) between 2D- and PWD-derived data (SV mean error = −6.38 mL, $P < 0.0001$; CO mean error = −0.40 L/m, $P < 0.0001$; CI mean error = −0.22 L/m/m^2, $P < 0.0001$) (Table 2). Additionally, there were proportional errors when SV and CO data were analyzed (Table 2). As a result, specific RIs for PWD-derived parameters were defined as necessary (Table 2).

Second, potential variables associated with LVOT, VTI, and VTI-derived hemodynamic parameters were analyzed by means of simple bivariate and point-biserial correlations (Table 3). That enabled to identify variables that should be considered as cofactors in covariate analysis (ANCOVA).

Third, we evaluated whether LVOT, VTI, and VTI-derived parameters ($CO_{Doppler}$ and $CI_{Doppler}$) RIs for males and females were necessary. Sex influence was examined before and after adjusting for cofactors (covariance analysis, ANCOVA) (Table 4). Prior to ANCOVA, the equality of variances (Levene's test) and the homogeneity of regression slopes were evaluated and confirmed. As a result of the described analysis, sex-specific RIs for LVOT (but not for VTI and VTI-derived CO and CI) were considered as necessary (Table 4).

Fourth, age-related equations for mean and standard deviation (SD) values were obtained for LVOT (discriminated by sex), VTI, and VTI-derived parameters. To that end, parametric regression methods based on fractional polynomials (FPs) were implemented using MedCalc software (MedCalc, Ostend, Belgium). Those methods, described by Royston and Wright,[36] have been used by the European Arterial Stiffness Collaboration Group[37–39] and by our group to obtain RIs for arterial parameters in our Argentinean population.[20–22] Briefly, fitting FPs for age-specific LVOT, VTI, $CO_{Doppler}$ and $CI_{Doppler}$ mean, and SD regression curves were defined using an iterative procedure (generalized least squares, GLS). The obtained results enabled to estimate age-specific mean and SD for the different parameters (LVOT, VTI, $CO_{Doppler}$, and $CI_{Doppler}$). As an example, VTI mean equation could be: $=a + b * age^p + c*age^q + \ldots$, where a, b, c, … are the coefficients, and p, q, … are the powers, with numbers selected from the set (−2, −1, −0.5, 0, 0.5, 1, 2, 3) estimated from the regression for mean VTI curve, and likewise for the SD regression. Continuing the example, FPs with powers (1, 2), that is, with $p = 1$ and $q = 2$, illustrate an equation with the form $a + b * age + c * age^2$.[36] Residuals were used to assess the model fit, deemed appropriate if the scores were normally distributed, with a mean of 0 and a SD of 1, randomly scattered above and below 0 when plotted against age. The best-fitted curves, considering visual and mathematical criteria (Kurtosis and Skewness coefficients), were selected. Taking into account mean and SD equations, age-specific percentiles were defined using the standard normal distribution (Z) (Tables 5–7 for LVOT, Table 6 for VTI, and Tables 7,8 for VTI-derived data, respectively). Age-specific 1th, 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th, and 99th percentile curves were calculated as mean VTI + Zp * SD, where Zp assumed −2.3263, −1.9599, −1.6448, −1.2815, −0.6755, 0, 0.6755, 1.2815, 1.6448, 1.9599, and 2.3263 values, respectively. LVOT, VTI, $CO_{Doppler}$, and $CI_{Doppler}$ were expressed in mm, cm, L/m, and L/m/m^2, and age and BSA in years and m^2, respectively.

The minimum sample size required was defined considering a normal distribution of the covariate (age) in the sample (conservative way) and a 95% and 90% limit of reference and confidence interval (two-sided), respectively, with a 95% and 15% reference range and relative margin of error, respectively.[20–22] The minimum sample size required for RIs construction (ie, for males or females) was 168 subjects. Additionally, according to the central limit theorem, a normal distribution was assumed, considering Kurtosis and Skewness coefficients distribution and the number of subjects studied (sample size > 30).[40]

Continuous and categorical variables are expressed as mean value ± SD or percentage. Data analysis was done using MedCalc

TABLE 1 Children and adolescents characteristics

	All (n = 385)				Male (n = 210)				Female (n = 175)				*P* value
	MV	SD	Min.	Max.	MV	SD	Min.	Max.	MV	SD	Min.	Max.	(Male vs Female)
Age (years)	15.94	3.29	5.08	24.42	16.48	3.19	5.08	24.42	15.30	3.31	5.67	24.33	0.00
Body weight (kg)	59.96	14.84	19.00	110.00	64.81	15.47	22.00	110.00	54.13	11.65	19.00	88.00	0.00
Body height (cm)	164.25	12.98	108.00	197.00	169.43	12.52	114.00	197.00	158.04	10.61	108.00	176.00	0.00
BSA (m^2)	1.65	0.26	0.75	2.44	1.74	0.26	0.83	2.44	1.53	0.20	0.75	2.01	0.00
BMI (kg/m^2)	21.90	3.44	14.08	29.94	22.25	3.49	14.08	29.94	21.49	3.35	14.60	29.82	0.03
SBP (mm Hg)	110.27	8.95	90.00	138.00	112.71	9.00	91.00	138.00	107.34	7.99	90.00	131.00	0.00
MBP (mm Hg)	78.69	6.40	62.67	98.33	79.14	6.68	62.67	98.33	78.15	6.02	63.33	95.00	0.13
DBP (mm Hg)	62.90	6.46	46.00	80.00	62.36	6.84	46.00	80.00	63.55	5.93	50.00	78.00	0.07
PP (mm Hg)	47.37	7.83	30.00	83.00	50.35	7.82	31.00	83.00	43.79	6.19	30.00	65.00	0.00
HR (beats/minute)	67.88	11.69	45.00	112.00	65.16	10.65	45.00	112.00	71.13	12.07	45.00	107.00	0.00
Hematocrit (%)	40.83	2.41	37.00	45.00	40.66	2.34	37.00	45.00	41.03	2.47	37.00	45.00	0.13
Glycemia (mg/dL)	82.78	8.58	63.00	97.00	83.14	8.46	66.00	97.00	82.35	8.74	63.00	97.00	0.37
Creatinine (mg/dL)	0.85	0.13	0.57	1.12	0.85	0.14	0.57	1.12	0.84	0.13	0.59	1.12	0.29
Total cholesterol (mg/dL)	157.15	20.77	100.00	190.00	159.02	20.38	110.00	190.00	154.90	21.08	100.00	190.00	0.05
Triglycerides (mg/dL)	71.55	20.77	40.00	126.00	70.90	20.14	40.00	126.00	72.31	21.54	40.00	125.00	0.51
Cardiac and arterial structural properties													
LVEDD (mm)	49.52	4.74	35.00	59.80	51.70	4.42	35.00	59.80	46.91	3.68	37.70	55.80	0.00
LVESD (mm)	32.18	2.98	23.70	39.70	33.45	2.88	23.70	39.70	30.66	2.33	24.90	37.40	0.00
EDIVST (mm)	7.25	1.02	4.30	10.30	7.67	1.01	4.30	10.30	6.74	0.78	4.70	8.90	0.00
ESIVST (mm)	11.52	1.80	7.00	16.80	12.19	1.77	7.40	16.80	10.71	1.49	7.00	14.80	0.00
EDPWT (mm)	7.33	0.98	5.00	10.00	7.77	0.92	5.00	9.70	6.81	0.79	5.00	10.00	0.00
ESPWT (mm)	12.92	1.87	8.00	18.90	13.64	1.86	8.10	18.90	12.06	1.47	8.00	16.70	0.00
RWT	0.29	0.03	0.22	0.39	0.30	0.02	0.22	0.39	0.29	0.03	0.24	0.38	0.00
LVEDV (mL)	117.15	25.49	50.87	178.63	129.10	24.13	50.87	178.63	102.81	18.83	60.79	152.40	0.00
LVESV (mL)	42.10	9.32	19.54	68.76	46.15	9.14	19.54	68.76	37.24	6.92	22.10	59.64	0.00
LVM (g)	121.19	37.49	40.05	219.59	139.52	36.58	40.05	219.59	99.20	24.53	43.42	186.56	0.00
LVMI (g/m^2)	72.38	14.58	43.15	112.51	79.20	13.87	44.80	112.51	64.19	10.69	43.15	97.07	0.00
LVMI ($height^{2.7}$)	31.05	5.98	17.98	48.19	33.05	5.79	18.94	48.19	28.63	5.28	17.98	44.33	0.00
LA diameter (mm)	32.55	3.97	20.00	42.00	34.10	3.78	21.00	42.00	30.69	3.34	20.00	39.20	0.00
Aortic root diameter (mm)	26.94	3.39	17.70	36.20	28.45	3.20	17.70	36.20	25.13	2.64	18.00	35.60	0.00

(Continues)

TABLE 1 (Continued)

	All (n = 385)				Male (n = 210)				Female (n = 175)				*P* value
	MV	SD	Min.	Max.	MV	SD	Min.	Max.	MV	SD	Min.	Max.	(Male vs Female)
Cardiac functional properties													
E-wave amplitude (m/s)	1.01	1.54	0.58	31.10	1.07	2.09	0.58	31.10	0.94	0.15	0.58	1.45	0.41
A-wave amplitude (m/s)	0.46	0.11	0.17	0.95	0.45	0.11	0.17	0.95	0.47	0.11	0.28	0.93	0.09
E/A ratio	2.22	1.86	1.01	37.02	2.34	2.48	1.01	37.02	2.08	0.49	1.05	3.58	0.17
LVeSF (%)	34.97	1.75	30.45	45.21	35.26	1.76	30.45	43.05	34.62	1.66	31.03	45.21	0.00
LVmSF (%)	21.81	2.23	18.20	28.76	21.94	2.18	18.21	28.20	21.65	2.27	18.20	28.76	0.20
LVEF (%)	64.00	2.23	57.81	76.24	64.24	2.28	57.81	73.83	63.72	2.13	58.76	76.24	0.02
LVESS	66.39	9.76	47.37	100.62	66.51	9.78	48.19	100.62	66.24	9.76	47.37	97.88	0.79
LVPS	218.49	26.06	107.03	295.28	219.25	24.34	164.14	295.28	217.58	28.02	107.03	290.21	0.53
2DE-derived parameters													
SV (2DE-derived, mL)	75.05	16.80	31.33	113.07	82.95	15.82	31.33	113.07	65.56	12.53	38.69	99.06	0.00
CO (2DE-derived, L/min)	5.01	1.09	2.19	7.78	5.34	1.05	2.19	7.78	4.62	1.01	2.30	7.68	0.00
CI (2DE-derived, mL/m^2)	3.06	0.58	1.37	5.29	3.08	0.53	1.93	4.51	3.03	0.64	1.37	5.29	0.40
SVR (2DE-derived, mm Hg min/L)	1.23	0.29	0.64	2.42	1.16	0.26	0.64	2.42	1.32	0.29	0.71	2.37	0.00
SW (2DE-derived, mm Hg mL)	85.32	21.38	32.19	153.05	94.75	20.48	32.19	153.05	74.01	16.39	40.30	128.85	0.00
Doppler-derived parameters													
LVOT (mm)	20.49	2.34	13.30	28.10	21.48	2.33	14.30	28.10	19.31	1.72	13.30	24.30	0.00
LVOT-VTI (cm)	21.30	2.94	14.00	30.00	21.78	2.97	14.00	30.00	20.73	2.80	14.00	28.00	0.00
SV (VTI-derived, L/min)	68.66	12.77	33.41	106.82	73.41	12.16	40.88	100.79	62.98	11.06	33.41	106.82	0.00
CO (VTI-derived, L/min)	4.61	0.95	2.59	8.25	4.75	0.96	2.75	8.25	4.44	0.92	2.59	6.64	0.00
CI (VTI-derived, L/m^2)	2.84	0.62	1.46	6.32	2.77	0.63	1.46	6.32	2.92	0.59	1.80	4.52	0.02
SVR (VTI-derived, mm Hg min/L)	1.33	0.29	0.61	2.66	1.30	0.27	0.61	2.19	1.37	0.31	0.78	2.66	0.01

2DE = two-dimensional echocardiography; BMI = body mass index; BP = blood pressure; BSA = body surface area; CI = cardiac index; CO = cardiac output; DBP = diastolic blood pressure; EDIVST = end-diastolic interventricular septum thickness; EDPWT = end-diastolic posterior wall thickness; ESIVST = end-systolic interventricular septum thickness; ESPWT = end-systolic posterior wall thickness; HR = heart rate; LA = left atrial; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic dimension; LVeSF = left ventricle endocardial shortening fraction; LVESS = left ventricular end-systolic stress; LVESV = left ventricular end-systolic volume; LVMI = left ventricular mass index; LVmSF = left ventricular midwall shortening fraction; LVOT = left ventricular outflow tract; LVPS = left ventricular peak stress; MBP = mean blood pressure; PP = pulse pressure; PW-Doppler = pulsed wave Doppler; RWT = relative wall thickness; SBP = systolic blood pressure; SV = stroke volume; SVR = systemic vascular resistance; SW = stroke work; VTI = velocity time integral.
A $P < 0.05$ was considered statistically significant.

TABLE 2 Association and equivalence between VTI-derived and 2DE-mode–derived stroke volume, cardiac output, and cardiac index (Correlation and Bland–Altman analysis)

	Stroke volume (mL)		Cardiac output (L/min)		Cardiac index (L/min	
	Net difference	**% difference**	**Net difference**	**% difference**	**Net difference**	**% difference**
R		0.5908		0.6042		0.5437
R 95% CI		0.5217 to 0.6523		0.5367 to 0.6641		0.4692 to 0.6105
P value		**<0.0001**		**<0.0001**		**<0.0001**
	Stroke volume (mL)		**Cardiac output (L/min)**		**Cardiac index (L/min/m^2)**	
	Net difference	**% difference**	**Net difference**	**% difference**	**Net difference**	**% difference**
B. Bland and Altman						
Arithmetic mean (systematic) error	−6.3811	−7.9674	−0.403	−7.9674	−0.2231	−7.9674
95% CI	−7.7691 to −4.9930	−9.8708 to −6.0640	−0.4951 to −0.3108	−9.8708 to −6.0640	−0.2804 to −0.1657	−9.8708 to −6.0640
P (H_0: Mean = 0)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
SD	13.8522	18.9949	0.9195	18.9949	0.5724	18.9949
Lower limit	−33.5315	−45.1974	−2.2053	−45.1974	−1.345	−45.1974
95% CI	−35.9057 to −31.1572	−48.4532 to −41.9417	−2.3629 to −2.0477	−48.4532 to −41.9417	−1.4431 to −1.2469	−48.4532 to −41.9417
Upper limit	20.7693	29.2627	1.3993	29.2627	0.8988	29.2627
95% CI	18.3950 to 23.1436	26.0069 to 32.5184	1.2417 to 1.5569	26.0069 to 32.5184	0.8007 to 0.9970	26.0069 to 32.5184
Regression equation	y = 18.1619 + −0.3416x	y = 19.0828 + −0.3765x	y = 0.4101 + −0.1691x	y = 3.3663 + −2.3565x	y = −0.4466 + 0.07577x	y = −20.7296 + 4.3267 x
Intercept						
Coefficient	18.1619	19.0828	0.4101	3.3663	−0.4466	−20.7296
SE	3.6983	5.1768	0.2471	5.1446	0.1663	5.4916
t-value	4.9109	3.6862	1.6597	0.6543	−2.6857	−3.7748
P	**<0.0001**	**0.0003**	**0.0978**	**0.5133**	**0.0076**	**0.0002**
95% CI	10.8904 to 25.4333	8.9042 to 29.2614	−0.07572 to 0.8959	−6.7489 to 13.4816	−0.7735 to −0.1196	−31.5271 to −9.9321
Slope						
Coefficient	−0.3416	−0.3765	−0.1691	−2.3565	0.07577	4.3267
SE	0.05062	0.07086	0.05047	1.0508	0.0555	1.833
t-value	−6.7474	−5.3127	−3.3499	−2.2427	1.3652	2.3605
P	**<0.0001**	**<0.0001**	**0.0009**	**0.0255**	0.173	0.0188
95% CI	−0.4411 to −0.2420	−0.5158 to −0.2371	−0.2683 to −0.06983	−4.4225 to −0.2905	−0.03335 to 0.1849	0.7227 to 7.9306

2DE = two-dimensional echocardiography; CI = confidence interval; SD = standard deviation; SE = standard error.

In all cases, the arithmetical differences were obtained as the subtraction between the value obtained for the VTI-derived and the B-mode–derived parameter (in that order). A $P < 0.05$ was considered statistically significant. Bold values indicate statistical significance ($P < 0.05$).

TABLE 3 Association between VTI-derived parameters and demographic, anthropometric, cardiovascular risk factors, and cardiovascular parameters levels in children and adolescents

	LVOT (mm)	LVOT-VTI (cm)	CO (VTI-derived, L/min)	CI (VTI-derived, L/m^2)
A. Demographic, anthropometric, and cardiovascular risk factors				
Sex (1: female, 0: male)				
R	−0.464	−0.178	−0.159	0.121
P value	0.000	0.000	0.002	0.018
Age (years)				
R	0.581	0.086	0.188	−0.341
P value	0.000	0.094	0.000	0.000
Body weight (kg)				
R	0.741	0.266	0.362	−0.383
P value	0.000	0.000	0.000	0.000
Body height (cm)				
R	0.752	0.246	0.289	−0.445
P value	0.000	0.000	0.000	0.000
BSA (m^2)				
R	0.784	0.275	0.354	−0.427
P value	0.000	0.000	0.000	0.000
BMI (kg/m^2)				
R	0.468	0.213	0.325	−0.206
P value	0.000	0.000	0.000	0.000
SBP (mm Hg)				
R	0.329	0.138	0.222	−0.137
P value	0.000	0.007	0.000	0.007
MBP (mm Hg)				
R	0.202	−0.025	0.114	−0.114
P value	0.000	0.622	0.026	0.026
DBP (mm Hg)				
R	0.073	−0.133	0.015	−0.074
P value	0.155	0.009	0.764	0.148
PP (mm Hg)				
R	0.318	0.268	0.242	−0.097
P value	0.000	0.000	0.000	0.058
HR (beats/minute)				
R	−0.327	−0.222	0.490	0.709
P value	0.000	0.000	0.000	0.000
Hematocrit (%)				
R	−0.010	0.020	0.049	0.052
P value	0.840	0.690	0.342	0.308
Glycemia (mg/dL)				
R	−0.058	−0.067	−0.011	0.050
P value	0.253	0.192	0.830	0.331
Creatinine (mg/dL)				
R	0.016	−0.041	−0.005	−0.011
P value	0.749	0.426	0.920	0.837
Total cholesterol (mg/dL)				
R	0.088	−0.038	0.017	−0.003
P value	0.085	0.460	0.747	0.953
Triglycerides (mg/dL)				
R	0.032	−0.022	0.043	0.026
P value	0.531	0.670	0.397	0.605
B. Cardiac and arterial structural properties				
LVEDD (mm)				
R	0.735	0.236	0.213	−0.399
P value	0.000	0.000	0.000	0.000
LVESD (mm)				
R	0.715	0.232	0.213	−0.380
P value	0.000	0.000	0.000	0.000
EDIVST (mm)				
R	0.714	0.271	0.303	−0.293
P value	0.000	0.000	0.000	0.000
ESIVST (mm)				
R	0.523	0.127	0.085	−0.359
P value	0.000	0.013	0.094	0.000
EDPWT (mm)				
R	0.704	0.276	0.284	−0.295
P value	0.000	0.000	0.000	0.000
ESPWT (mm)				
R	0.566	0.161	0.167	−0.322
P value	0.000	0.001	0.001	0.000
RWT				
R	0.306	0.185	0.237	−0.023
P value	0.000	0.000	0.000	0.648
LVEDV (mL)				
R	0.732	0.230	0.203	−0.397
P value	0.000	0.000	0.000	0.000
LVESV (mL)				
R	0.710	0.224	0.204	−0.375
P value	0.000	0.000	0.000	0.000
LVM (g)				
R	0.769	0.255	0.251	−0.368
P value	0.000	0.000	0.000	0.000
LVMI (g/m^2)				
R	0.600	0.210	0.142	−0.246
P value	0.000	0.000	0.005	0.000
LVMI (height$^{2.7}$)				

(Continues)

TABLE 3 (Continued)

(Continues)

TABLE 3 (Continued)

	LVOT (mm)	LVOT-VTI (cm)	CO (VTI-derived, L/min)	CI (VTI-derived, L/m^2)
R	0.431	0.175	0.127	−0.111
P value	0.000	0.001	0.013	0.029
LA diameter (mm)				
R	0.682	0.213	0.195	−0.374
P value	0.000	0.000	0.000	0.000
Aortic root diameter (mm)				
R	0.794	0.141	0.260	−0.306
P value	0.000	0.005	0.000	0.000
C. Cardiac functional properties				
E-wave amplitude (m/s)				
R	−0.047	−0.026	−0.026	−0.011
P value	0.361	0.611	0.607	0.835
A-wave amplitude (m/s)				
R	−0.145	0.039	0.301	0.359
P value	0.004	0.443	0.000	0.000
E/A ratio				
R	−0.036	−0.001	−0.094	−0.083
P value	0.480	0.986	0.067	0.105
LV endocardial SF (%)				
R	0.165	0.041	0.029	−0.119
P value	0.001	0.421	0.567	0.019
LV medioventricular SF (%)				
R	0.132	0.103	0.126	0.034
P value	0.009	0.044	0.013	0.512
LVEF (%)				
R	0.054	0.003	−0.008	−0.062
P value	0.287	0.949	0.879	0.221
LV ES stress				
R	0.044	0.051	0.082	0.031
P value	0.389	0.314	0.106	0.546
LV peak stress				
R	−0.025	−0.046	−0.023	−0.071
P value	0.631	0.372	0.656	0.167
SV_{2DE} (mL)				
R	0.717	0.225	0.195	−0.395
P value	0.000	0.000	0.000	0.000
CO_{2DE} (L/min)				
R	0.491	0.076	0.604	0.142
P value	0.000	0.137	0.000	0.005
CI_{2DE} (mL/m^2)				
R	−0.109	−0.160	0.381	0.544
P value	0.033	0.002	0.000	0.000
SVR_{2DE} (mm Hg min/L)				
R	−0.441	−0.083	−0.549	−0.161
P value	0.000	0.106	0.000	0.001
SW_{2DE} (mm Hg mL)				
R	0.703	0.196	0.209	−0.379
P value	0.000	0.000	0.000	0.000
LVOT (mm)				
R	1.000	0.120	0.368	−0.232
P value		0.019	0.000	0.000
$LVOT\text{-}VTI_{DOPPLER}$(cm)				
R	0.120	1.000	0.556	0.311
P value	0.019		0.000	0.000
$SV_{DOPPLER}$ (L/min)				
R	0.681	0.804	0.631	0.098
P value	0.000	0.000	0.000	0.054
$CO_{DOPPLER}$ (L/min)				
R	0.368	0.556	1.000	0.674
P value	0.000	0.000		0.000
$CI_{DOPPLER}$ (L/m^2)				
R	−0.232	0.311	0.674	1.000
P value	0.000	0.000	0.000	
$SVR_{DOPPLER}$ (mm Hg min/L)				
R	−0.285	−0.534	−0.881	−0.648
P value	0.000	0.000	0.000	0.000

BMI = body mass index; BSA = body surface area; CI = cardiac index; CO = cardiac output; ES and ED = end-systolic and end-diastolic, respectively; HR = heart rate; LA = left atrium; LV = left ventricle; LVEF = left ventricle ejection fraction; LVOT = left ventricular outflow tract; SBP, MBP, DBP, and PP = systolic, mean, diastolic, and pulse blood pressure, respectively; SF = shortening fraction; SV = stroke volume; SVR = systemic vascular resistance; SW = stroke work; VTI = velocity time integral index.

A $P < 0.05$ was considered statistically significant.

statistical software (version 14.8.1., MedCalc Inc., Ostend, Belgium) and IBM SPSS 20.0 Software (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

3 | RESULTS

Anthropometric, biochemical, hemodynamic, and cardiovascular characteristics of the studied subjects (n = 385, males: 210) are summarized in Table 1.

Pulsed wave Doppler- and 2D-derived parameters showed significant positive correlations (Figure 1). PWD values were always lower

TABLE 4 Sex-related analysis of covariance (ANCOVA) adjusting by age and body surface area

		Before adjustment				After adjustment by covariates					Levene's test	Heterogeneity of slopes' test	Covariates' values:	
	n	MV	SD	SE	P	MV	SE	95% CI	P	R^2-adjusted	(P value)	(P value)	Age (years)	BSA (m^2)
LVOT (mm)														
Male	210	21.482	2.333	0.161	6.59175E-22	20.90	0.10	20.70–21.09	<0.0001	0.653	0.002	0.794	15.94	1.65
Female	175	19.305	1.720	0.130		20.01	0.11	19.79–20.22						
LVOT-VTI (cm)														
Male	210	21.779	2.972	0.205	0.000448462	21.48	0.20	21.08–21.88	0.2191	0.08556	0.185	0.078	15.94	1.65
Female	175	20.730	2.801	0.212		21.09	0.22	20.65–21.53						
$CO_{DOPPLER}$ (VTI-derived, L/min)														
Male	210	4.746	0.960	0.066	0.001757962	4.62	0.06	4.49–4.75	0.8158	0.1214	0.949	0.157	15.94	1.65
Female	175	4.442	0.924	0.070		4.60	0.07	4.45–4.74						
$CI_{DOPPLER}$ (VTI-derived, L/m^2)														
Male	210	2.770	0.626	0.043	0.017690294	2.87	0.04	2.79–2.95	0.308	0.186	0.128	0.552	15.94	1.65
Female	175	2.920	0.594	0.045		2.80	0.04	2.72–2.89						

CI = cardiac index; CO = cardiac output; LVOT = left ventricular outflow tract; MV = mean value; SD = standard deviation; SE = standard error; VTI = velocity time integral.

than those obtained from 2D studies (Table 2). Considering PWD data as the reference, the systematic differences between measurements (PWD minus 2D value) were as follows: −6.38 ± 13.85 mL for SV; −0.40 ± 0.92 L/m for CO, and −0.22 ± 0.57 L/m/m^2 for CI. There were also proportional errors between measurements. Then, the differences (absolute and relative) between data varied, depending on the value of the variable (Table 2, Figure 2). Figure 2 shows the graphical representation (Bland–Altman) of the differences between methods for SV, CO, and CI measurements.

Jointly analyzing our findings, it could be said that values obtained from PWD and 2D show significant statistical differences that could have clinical meaning.

3.1 | Association between LVOT-VTI-derived parameters and subject's characteristics

Table 3 shows bivariate and point-biserial correlations between LVOT-VTI-derived parameters and subjects' characteristics (ie, demographic, hemodynamic, anthropometric parameters, and CVRFs exposure). Anthropometric parameters (height, weight, BSA, and BMI), SBP, PP, and HR showed significant positive associations with VTI-derived parameters (Table 3). Aortic root and cardiac dimensions were positively associated with LVOT-VTI-derived parameters, age and sex. Additionally, as can be seen in Table 3 all the 2D-derived parameters (SV_{2D}, CO_{2D}, CI_{2D}, SVR_{2D}, and SW) show a significant association with LVOT-VTI-derived parameters.

Table 4 shows sex-related analysis of covariance (ANCOVA) adjusting for age and BSA. When LVOT, LVOT-VTI, and $CO_{Doppler}$ were analyzed before any model adjustment, males showed higher values than females. After covariate adjustment, only LVOT values showed significant sex-related differences. Consequently, specific sex-related RIs were not required for LVOT-VTI, $CO_{Doppler}$, and $CI_{Doppler}$ values. On the contrary, when LVOT was considered, specific RIs for males and females were necessary (Table 4).

3.2 | Mean and standard deviation age- and BSA-related equations for LVOT, VTI, and VTI-derived parameters: basis for z-scores calculation

Age- and BSA-related mean and SD equations for LVOT, VTI, $CO_{Doppler}$, and $CI_{Doppler}$ were obtained for all subjects, males and females (Table 9 and Data S1). The expected mean and SD values for a given age (and sex) can be calculated using the obtained equations. Then, by quantifying the *z*-scores: (*z*-score = [observed value − expected mean]/SD), it can be assessed how far (in SD units) are observed values from those anticipated (expected).

3.3 | RIs for LVOT diameter, LVOT-VTI, and VTI-derived parameters

For each year of age within the age range considered (5–24 years), specific percentiles and RIs were defined for the different variables.

TABLE 5 Age-related reference intervals (RIs) for left ventricular outflow tract (mm) for the entire population (n = 385), females (n = 175) and males (n = 210)

Age (years)	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
5.0											
All	8.38	8.93	9.41	9.98	10.94	12.05	13.19	14.24	14.89	15.45	16.11
Female	9.41	9.82	10.15	10.54	11.16	11.84	12.50	13.08	13.42	13.71	14.04
Male	3.00	4.23	5.29	6.52	8.56	10.83	13.10	15.14	16.37	17.43	18.66
6.0											
All	10.11	10.62	11.06	11.58	12.46	13.47	14.50	15.44	16.01	16.52	17.11
Female	11.11	11.50	11.83	12.20	12.81	13.48	14.13	14.70	15.04	15.33	15.66
Male	6.24	7.28	8.18	9.20	10.92	12.84	14.75	16.47	17.50	18.39	19.43
7.0											
All	11.52	12.00	12.42	12.91	13.73	14.67	15.62	16.50	17.03	17.49	18.03
Female	12.36	12.75	13.08	13.45	14.07	14.74	15.40	15.97	16.31	16.61	16.94
Male	8.79	9.68	10.45	11.34	12.81	14.46	16.11	17.59	18.47	19.24	20.14
8.0											
All	12.69	13.15	13.55	14.02	14.81	15.70	16.61	17.44	17.95	18.39	18.91
Female	13.33	13.72	14.06	14.44	15.06	15.75	16.42	17.01	17.35	17.65	18.00
Male	10.82	11.60	12.28	13.06	14.36	15.81	17.26	18.56	19.35	20.02	20.81
9.0											
All	13.65	14.10	14.49	14.95	15.73	16.61	17.50	18.31	18.80	19.23	19.74
Female	14.09	14.49	14.84	15.23	15.87	16.57	17.26	17.87	18.22	18.53	18.89
Male	12.45	13.16	13.77	14.47	15.65	16.95	18.26	19.43	20.13	20.74	21.45
10.0											
All	14.43	14.89	15.28	15.74	16.52	17.40	18.30	19.11	19.61	20.04	20.54
Female	14.70	15.12	15.47	15.88	16.54	17.26	17.97	18.60	18.97	19.29	19.65
Male	13.78	14.43	14.99	15.64	16.72	17.92	19.13	20.21	20.85	21.42	22.07
11.0											
All	15.07	15.54	15.95	16.42	17.21	18.11	19.03	19.86	20.36	20.80	21.32
Female	15.20	15.63	15.99	16.41	17.10	17.85	18.58	19.23	19.61	19.94	20.32
Male	14.86	15.47	16.00	16.61	17.63	18.76	19.90	20.91	21.52	22.05	22.67
12.0											
All	15.59	16.08	16.50	16.99	17.81	18.75	19.70	20.56	21.08	21.54	22.08
Female	15.60	16.05	16.43	16.86	17.57	18.35	19.11	19.78	20.18	20.52	20.91
Male	15.73	16.32	16.83	17.42	18.40	19.49	20.58	21.56	22.15	22.66	23.25
13.0											
All	16.00	16.51	16.95	17.47	18.34	19.32	20.32	21.22	21.77	22.26	22.82
Female	15.92	16.39	16.78	17.23	17.97	18.78	19.57	20.26	20.67	21.03	21.43
Male	16.43	17.01	17.51	18.09	19.05	20.12	21.19	22.16	22.74	23.24	23.82
14.0											
All	16.32	16.86	17.33	17.87	18.79	19.83	20.89	21.86	22.44	22.95	23.55
Female	16.19	16.67	17.08	17.55	18.31	19.15	19.97	20.69	21.12	21.48	21.90
Male	16.97	17.56	18.06	18.64	19.60	20.68	21.75	22.71	23.29	23.79	24.38
15.0											
All	16.56	17.14	17.63	18.21	19.19	20.30	21.43	22.46	23.08	23.63	24.27
Female	16.40	16.90	17.33	17.81	18.61	19.47	20.32	21.07	21.51	21.89	22.33
Male	17.40	17.99	18.50	19.09	20.07	21.16	22.25	23.23	23.82	24.33	24.92

(Continues)

TABLE 5 (Continued)

Age (years)	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
16.0											
All	16.73	17.34	17.87	18.49	19.54	20.73	21.93	23.04	23.70	24.29	24.98
Female	16.56	17.08	17.53	18.03	18.86	19.76	20.64	21.41	21.87	22.26	22.71
Male	17.71	18.32	18.84	19.45	20.46	21.58	22.71	23.72	24.33	24.85	25.46
17.0											
All	16.84	17.49	18.06	18.72	19.84	21.11	22.41	23.59	24.31	24.94	25.68
Female	16.69	17.23	17.69	18.21	19.07	20.00	20.91	21.72	22.19	22.60	23.07
Male	17.92	18.56	19.10	19.73	20.79	21.96	23.13	24.18	24.81	25.36	25.99
18.0											
All	16.88	17.58	18.19	18.90	20.10	21.46	22.86	24.13	24.90	25.58	26.37
Female	16.77	17.34	17.82	18.36	19.25	20.22	21.16	21.99	22.48	22.90	23.39
Male	18.05	18.71	19.29	19.95	21.05	22.28	23.51	24.62	25.28	25.85	26.52
19.0											
All	16.88	17.63	18.28	19.04	20.32	21.79	23.28	24.65	25.48	26.21	27.06
Female	16.83	17.42	17.91	18.48	19.40	20.40	21.38	22.24	22.75	23.18	23.69
Male	18.10	18.80	19.41	20.10	21.27	22.57	23.87	25.03	25.73	26.34	27.04
20.0											
All	16.84	17.63	18.33	19.14	20.51	22.08	23.68	25.15	26.04	26.83	27.74
Female	16.86	17.47	17.99	18.57	19.53	20.56	21.58	22.47	22.99	23.44	23.96
Male	18.08	18.82	19.47	20.21	21.44	22.82	24.19	25.43	26.17	26.81	27.55
21.0											
All	16.75	17.60	18.34	19.20	20.67	22.35	24.07	25.64	26.60	27.44	28.42
Female	16.87	17.50	18.03	18.64	19.63	20.70	21.75	22.67	23.21	23.68	24.21
Male	18.00	18.79	19.47	20.26	21.57	23.03	24.49	25.80	26.59	27.27	28.06
22.0											
All	16.62	17.53	18.31	19.24	20.80	22.59	24.43	26.12	27.14	28.04	29.10
Female	16.86	17.51	18.06	18.69	19.71	20.82	21.90	22.85	23.41	23.89	24.45
Male	17.86	18.70	19.43	20.26	21.66	23.21	24.77	26.16	27.00	27.72	28.57
23.0											
All	16.47	17.42	18.26	19.24	20.91	22.82	24.78	26.58	27.68	28.64	29.78
Female	16.82	17.50	18.07	18.72	19.78	20.92	22.04	23.02	23.60	24.09	24.66
Male	17.67	18.57	19.34	20.23	21.71	23.37	25.02	26.51	27.40	28.17	29.07
24.0											
All	16.28	17.29	18.18	19.22	20.99	23.02	25.11	27.03	28.21	29.24	30.45
Female	16.76	17.46	18.06	18.73	19.82	21.01	22.16	23.17	23.77	24.28	24.87
Male	17.43	18.39	19.21	20.16	21.74	23.50	25.26	26.84	27.79	28.61	29.57

Data are shown in Figure 3 and in Tables 5–8 (for LVOT, LVOT-VTI, $CO_{Doppler}$, and $CI_{Doppler}$, respectively). It is to note that LVOT data were analyzed considering the total number of subjects as well as males and females, separately.

To improve the visualization of the temporal evolution of the variables, they were analyzed as described above, but considering smaller age intervals. Resulting data are shown in Tables A–F (Data S1).

Since the studied variables were associated with BSA, specific BSA-related percentiles and RIs were defined considering 0.2-m^2 intervals within the BSA range analyzed (0.8–2.4 m^2). Data are summarized in Figure 4 and Table 9.

4 | DISCUSSION

Despite the recognized clinical value of echocardiographic CO estimation, the lack of RIs for LVOT-VTI-derived parameters obtained in healthy populations has contributed to limit their widespread use in clinical practice. On the other hand, available works have mainly

TABLE 6 Age-related reference intervals for left ventricular outflow tract velocity time integral (cm) for the entire population (n = 385)

Age	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
5.0	10.0	10.8	11.5	12.4	14.0	16.0	18.3	20.6	22.0	23.4	25.1
6.0	11.3	12.1	12.8	13.7	15.3	17.2	19.4	21.6	23.0	24.2	25.8
7.0	12.3	13.1	13.8	14.7	16.3	18.2	20.3	22.4	23.7	24.9	26.4
8.0	13.2	14.0	14.7	15.5	17.1	19.0	21.0	23.0	24.3	25.5	26.9
9.0	13.9	14.7	15.4	16.2	17.8	19.6	21.6	23.6	24.8	26.0	27.4
10.0	14.4	15.2	15.9	16.8	18.3	20.1	22.1	24.0	25.3	26.4	27.7
11.0	14.9	15.6	16.3	17.2	18.7	20.5	22.5	24.4	25.6	26.7	28.0
12.0	15.2	16.0	16.7	17.5	19.0	20.8	22.8	24.7	25.9	27.0	28.3
13.0	15.4	16.2	16.9	17.7	19.3	21.1	23.0	24.9	26.2	27.2	28.6
14.0	15.5	16.3	17.0	17.9	19.4	21.2	23.2	25.1	26.4	27.4	28.8
15.0	15.6	16.4	17.1	18.0	19.5	21.4	23.3	25.3	26.5	27.6	28.9
16.0	15.6	16.4	17.1	18.0	19.5	21.4	23.4	25.4	26.6	27.7	29.1
17.0	15.5	16.3	17.1	18.0	19.5	21.4	23.5	25.5	26.7	27.9	29.2
18.0	15.4	16.2	17.0	17.9	19.5	21.4	23.5	25.5	26.8	27.9	29.3
19.0	15.2	16.1	16.8	17.7	19.3	21.3	23.4	25.5	26.8	28.0	29.4
20.0	15.0	15.9	16.6	17.6	19.2	21.2	23.4	25.5	26.8	28.0	29.5
21.0	14.8	15.7	16.4	17.4	19.0	21.1	23.3	25.4	26.8	28.1	29.6
22.0	14.5	15.4	16.2	17.1	18.8	20.9	23.2	25.4	26.8	28.1	29.6
23.0	14.2	15.1	15.9	16.9	18.6	20.7	23.0	25.3	26.8	28.1	29.7
24.0	13.9	14.8	15.6	16.6	18.4	20.5	22.9	25.2	26.7	28.1	29.7

TABLE 7 Age-related reference intervals for VTI-derived cardiac output (L/m) for the entire population (n = 385)

Age	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
5.0	1.942	2.102	2.249	2.430	2.761	3.179	3.654	4.134	4.448	4.738	5.097
6.0	2.058	2.233	2.395	2.594	2.961	3.425	3.954	4.491	4.844	5.171	5.575
7.0	2.161	2.349	2.522	2.737	3.132	3.633	4.206	4.789	5.173	5.528	5.969
8.0	2.254	2.453	2.636	2.863	3.281	3.812	4.419	5.038	5.446	5.824	6.293
9.0	2.340	2.547	2.738	2.975	3.411	3.965	4.600	5.246	5.673	6.068	6.558
10.0	2.420	2.634	2.831	3.075	3.525	4.097	4.752	5.419	5.859	6.266	6.772
11.0	2.495	2.714	2.916	3.166	3.626	4.211	4.880	5.561	6.010	6.426	6.942
12.0	2.565	2.788	2.994	3.248	3.716	4.309	4.987	5.677	6.131	6.552	7.073
13.0	2.632	2.858	3.066	3.323	3.795	4.393	5.076	5.770	6.226	6.648	7.171
14.0	2.695	2.923	3.132	3.391	3.866	4.466	5.149	5.842	6.297	6.717	7.238
15.0	2.756	2.984	3.194	3.453	3.928	4.527	5.207	5.896	6.347	6.764	7.280
16.0	2.814	3.042	3.252	3.510	3.983	4.578	5.253	5.933	6.379	6.790	7.298
17.0	2.869	3.097	3.306	3.563	4.032	4.620	5.286	5.956	6.394	6.798	7.296
18.0	2.923	3.149	3.357	3.611	4.075	4.655	5.309	5.967	6.395	6.790	7.276
19.0	2.975	3.199	3.404	3.655	4.112	4.682	5.323	5.965	6.383	6.767	7.239
20.0	3.025	3.247	3.449	3.696	4.145	4.703	5.328	5.953	6.359	6.731	7.189
21.0	3.074	3.292	3.491	3.734	4.173	4.717	5.326	5.932	6.325	6.684	7.126
22.0	3.121	3.335	3.530	3.768	4.197	4.727	5.317	5.902	6.281	6.627	7.052
23.0	3.167	3.377	3.568	3.799	4.217	4.731	5.301	5.865	6.229	6.561	6.968
24.0	3.212	3.417	3.603	3.828	4.233	4.730	5.280	5.822	6.170	6.488	6.876

VTI = velocity time integral.

TABLE 8 Age-related reference intervals for VTI-derived cardiac index (L/m^2) for the entire population (n = 385)

Age	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
5.0	5.975	5.800	5.655	5.492	5.234	4.962	4.707	4.491	4.368	4.264	4.147
6.0	5.678	5.443	5.250	5.038	4.706	4.367	4.056	3.799	3.654	3.534	3.400
7.0	5.442	5.168	4.945	4.702	4.328	3.952	3.614	3.340	3.187	3.061	2.923
8.0	5.249	4.948	4.706	4.444	4.044	3.648	3.297	3.016	2.861	2.735	2.596
9.0	5.088	4.769	4.514	4.239	3.825	3.418	3.062	2.779	2.625	2.499	2.361
10.0	4.949	4.619	4.356	4.074	3.651	3.239	2.882	2.600	2.447	2.323	2.188
11.0	4.829	4.492	4.224	3.938	3.510	3.098	2.741	2.462	2.311	2.189	2.057
12.0	4.724	4.382	4.112	3.824	3.396	2.984	2.630	2.355	2.206	2.086	1.956
13.0	4.630	4.287	4.016	3.729	3.302	2.892	2.542	2.270	2.124	2.005	1.878
14.0	4.546	4.204	3.934	3.648	3.223	2.818	2.472	2.203	2.059	1.943	1.818
15.0	4.471	4.131	3.863	3.579	3.158	2.757	2.415	2.151	2.009	1.894	1.771
16.0	4.402	4.066	3.800	3.520	3.104	2.708	2.371	2.110	1.970	1.857	1.736
17.0	4.340	4.008	3.746	3.469	3.059	2.669	2.336	2.079	1.941	1.830	1.710
18.0	4.282	3.956	3.698	3.426	3.022	2.638	2.310	2.056	1.920	1.810	1.692
19.0	4.229	3.909	3.656	3.389	2.992	2.613	2.290	2.040	1.906	1.798	1.681
20.0	4.181	3.867	3.619	3.357	2.968	2.595	2.277	2.031	1.898	1.792	1.676
21.0	4.135	3.829	3.587	3.330	2.948	2.583	2.270	2.027	1.896	1.791	1.677
22.0	4.093	3.795	3.558	3.307	2.934	2.575	2.267	2.028	1.899	1.795	1.682
23.0	4.054	3.763	3.533	3.288	2.923	2.572	2.269	2.034	1.906	1.803	1.692
24.0	4.017	3.735	3.511	3.273	2.917	2.572	2.276	2.043	1.918	1.816	1.706

VTI = velocity time integral.

assessed a single parameter; obtained data from retrospective analysis; considered a unique cutoff value for the studied parameters, and/or did not analyze explanatory factors.[14,15]

In this context, this work provides age- and BSA-related RIs and percentile curves for hemodynamic variables (LVOT, VTI, CO, and CI) obtained from LVOT-VTI data in a cohort of healthy children, adolescents, and young adults nonexposed to CRFs. Compared to the use of single cut of values, the use of RIs and percentiles use would have the advantage of enabling a more accurate data interpretation (ie, considering explanatory growth-related factors).[41,42] In addition, in this work hemodynamic data were obtained considering two methodological approaches based on echocardiographic studies (2D and PWD). Correlation and agreement analyses showed that 2D- and PWD (LVOT-VTI)-derived SV, CO, and CI measurements were positively correlated, but showed mean and proportional errors. Then, 2D- and PWD-derived hemodynamic data are not interchangeable (Figures 1,2; Table 2). SV values obtained from LVOT-VTI were always lower than those obtained from 2D (volumetric) data. Hence, 2D-derived SV values would be "underestimated" by data obtained from LVOT-VTI. As was stated, the differences between measurements were statistically significant, but they could also be clinically significant in particular medical context. As an example, when SV exceeds 80 mL, the differences between measurements would be approximately equal to 10 mL. If we are not aware of methodological-related differences in SV and/or if we analyze SV values (or the resultant CO) without taking into account such differences, we could make significant clinical mistakes in patients' diagnosis and/or management. In our knowledge, this is the first study in which the equivalence between hemodynamic measurements obtained from 2D and LVOT-VTI (PWD) was analyzed, and consequently, the first in which their differences were demonstrated.

There were significant associations between some baseline characteristic (ie, anthropometric variables) of the studied subjects and echocardiographic parameters (Table 3). In this regard, LVOT diameter and VTI values showed significant correlations with body mass and surface. Higher LVOT dimensions and VTI-derived parameters were associated with higher weight, height, BSA, and BMI values. Data about the relationship between BSA and VTI in children and adolescents are scarce, controversial, and inconsistent, which could be explained, at least partially by methodological differences among studies.[12,14]

SBP rather than DBP showed significant associations with VTI-derived hemodynamic parameters. Then, VTI-derived hemodynamic parameters would be exclusively associated with "systolic load" indexes. Increased heart rate[43] and impaired ventricular function are predictors of worse prognostic in childhood heart failure.[44,45] Additionally, those markers were associated with lower VTI values.[12,41] In agreement with that, in our population HR levels were negatively associated with LVOT and LVOT-VTI values (Table 3).

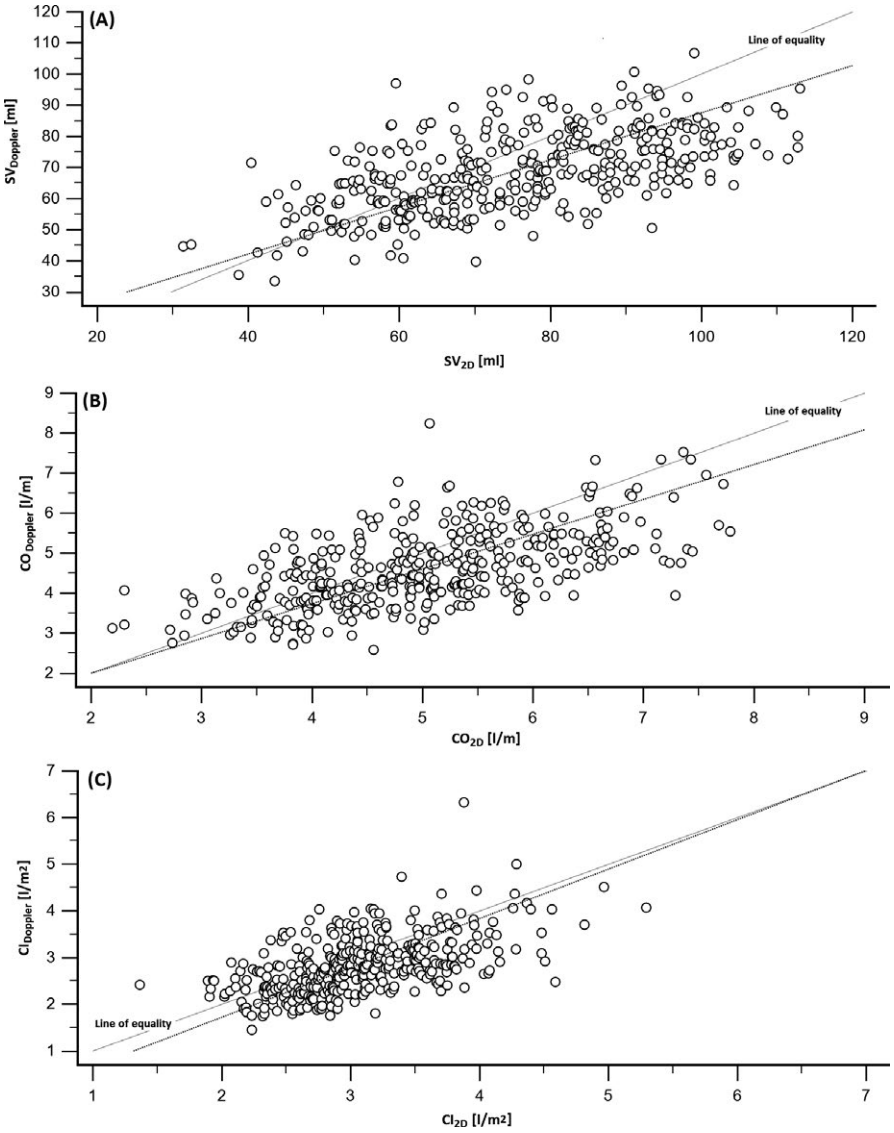

FIGURE 1 Correlation between velocity time integral-derived and 2D-derived methods, in terms of (A) stroke volume (SV), (B) cardiac output (CO), and (C) cardiac index (CI)

As was expected, larger LVOT was observed together with higher values of the structural cardiac parameters (ie, LV diameters, wall thickness, and atria dimensions).

Jointly analyzing our findings, it could be said that growth-related increases in LVOT-VTI in children and adolescents occur in conjunction with increases in LVOT cross-sectional area and cardiac structures (Table 3).

In agreement with Pees et al[14] findings, we found that sex-related RIs for LVOT-VTI data were not necessary. On the contrary, as was described, VTI and BSA were associated and BSA should be considered when analyzing VTI data. Related with that, Poutanen et al[46] found that increases in aortic VTI and those in BSA were associated in healthy subjects (n = 168; 11.1 ± 5 years). Pees et al also reported a strong correlation between aortic VTI and BSA in infants, children, and adolescents (n = 1200) distributed in 15 BSA groups (from 0.11 to 2.23 m^2).[14] In the present work, healthy children, adolescents, and young adults within a wide BSA range (mean 1.65 ± 0.26 m^2, range from 0.75 to 2.44 m^2) were studied and the associations between hemodynamic data and BSA were analyzed (assessing the potential role of BSA as an explanatory factor). Looking at our findings, it could be stated that LVOT and LVOT-VTI data depend on anthropometric characteristics. Then, the "size" of the subject should be considered at the time of analyzing LVOT and LVOT-VTI data in children and adolescents.

The lack of RIs for LVOT-VTI obtained from prospective population-based studies in healthy people makes it difficult to analyze our findings, comparing our results with those obtained by other authors. Pees et al[14] reported reference values for aortic VTI in 1200 children from 0 to 20 years. Figure 5 shows a comparative analysis between Pees et al and our work. It is noteworthy that 25th, 50th, 75th, and 95th percentiles curves were similar (similar profiles), but the values obtained in our work were on average 24.5% lower (17.4%–33.4%) than those reported by Pees et al.[14] The differences could be explained by methodological and/or technical issues. *First*, Pees et al. data were obtained retrospectively from the database of a University Hospital. On the contrary, our data were obtained from a prospective community-based study. *Second*, while Pees et al measured aortic VTI (and did not consider aorta dimensions),

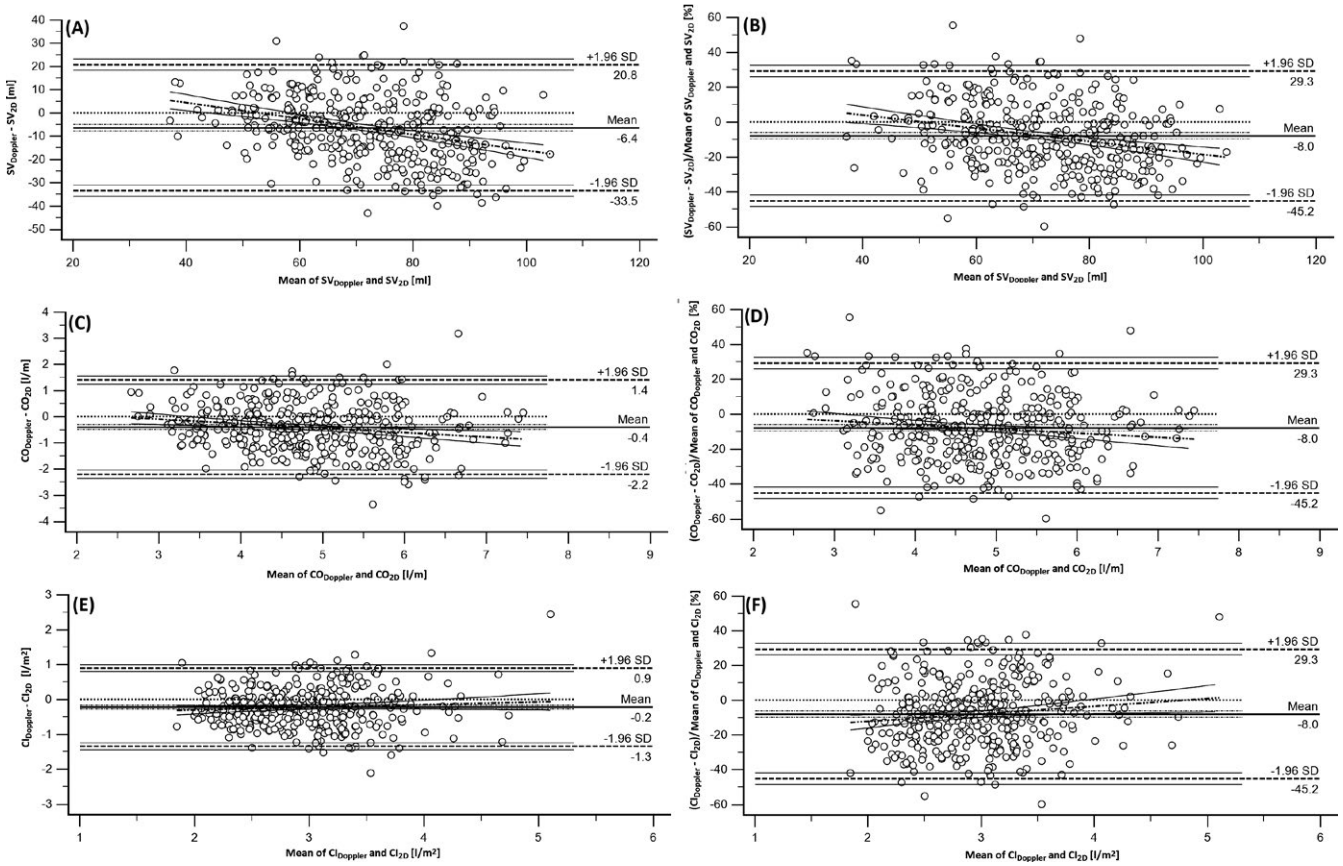

FIGURE 2 Bland–Altman representation of the net and proportional difference between methods is shown for stroke volume (SV) (A,B), cardiac output (CO) (C,D), and cardiac index (CI) (E,F)

we measured the LVOT-VTI, the most used and the preferred to assess SV and CO.[14,31,33,35] It is to note that VTI values measured in the aorta have shown to be 27.2% higher than those obtained in the LVOT.[41]

4.1 | Clinical implications

The advent of several echocardiographic techniques has provided new and more sensitive tools for the evaluation of cardiac function. They include 2DE, Doppler, three-dimensional echocardiography (3DE),[28,30,34,47] tissue Doppler imaging (TDI),[48] and speckle tracking echocardiography (STE);[49,50] all of them are associated with its own strengths and weaknesses. In daily clinical practice, CO evaluation through conventional echocardiography studies depends on a combination of measurements made in the 2D and LVOT blood flow assessment through Doppler. The cardiac structure usually used to measure SV and CO is the LVOT.[31,35] CO value is obtained by multiplying the SV by the HR. SV is calculated as, SV = VTI × LVOT area, where LVOT area = π (LVOT diameter/2)^2.[30,34,35] Thus, LVOT-VTI is a Doppler-derived measure of the distance travelled by the midstream blood through the LVOT in a single heartbeat, which is also called "stroke distance."[51,52] The correlation between CO measured by "stroke distance" and that obtained through cardiac catheterization evaluation has been validated.[31,53] Another approach to measure CO is the 2D-derived method based on end-diastolic and end-systolic LV volumes using the disk summation algorithm (Simpson's technique) and indexed using BSA values.

With conventional techniques, the measurement of the LVOT area is a potential and frequent source of error in the calculation of CO, since any inaccuracy in the measurement of the diameter will be squared increasing the impact of the error on estimation of SV. Consequently, it is necessary to have an accurate, reliable, and easy substitute to estimate changes in SV (and CO). The LVOT-VTI measurement has been proposed as a firm candidate to replace SV estimation. In this regard, since LVOT area would be considered constant, the changes in SV could be reflected in LVOT-VTI changes.[1,9] Available reports suggested that LVOT-VTI assessment could be considered enough to monitor short-term changes in SV. Furthermore, LVOT-VTI would be an appropriate and dynamic indicator of fluid responsiveness.[1,11]

The measurements of LVOT and VTI-derived parameters have some advantages: (a) providing a CO surrogate that can be obtained easily and quickly with standard equipment widely available in health centers; (b) a good intra- and interobserver repeatability;[54] and (c) being a useful tool to follow up or monitor SV changes[1,9,11] in different populations.[12,13] On the other hand, the limitations of LVOT and VTI-derived measurement include following ones: (a) As a Doppler-based technique, the obtained values with LVOT-VTI (as

TABLE 9 Body surface area-related reference intervals for left ventricular outflow tract (LVOT in mm), velocity time integral (VTI in cm), cardiac output (CO in L/min), and cardiac index (CI in L/m^2) for the entire population (n = 385)

BSA (m^2)	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
0.8											
LVOT	12.45	12.79	13.08	13.42	13.99	14.63	15.28	15.87	16.23	16.54	16.91
VTI	12.50	13.16	13.75	14.46	15.73	17.25	18.90	20.50	21.52	22.44	23.55
CO	2.320	2.444	2.555	2.689	2.927	3.215	3.529	3.833	4.027	4.203	4.415
CI	5.561	5.276	5.045	4.793	4.405	4.016	3.667	3.385	3.228	3.098	2.956
0.9											
LVOT	12.95	13.31	13.62	13.98	14.59	15.28	15.98	16.61	17.00	17.33	17.72
VTI	13.02	13.70	14.32	15.06	16.37	17.95	19.67	21.33	22.38	23.33	24.49
CO	2.349	2.493	2.624	2.782	3.066	3.413	3.796	4.172	4.413	4.633	4.901
CI	5.514	5.187	4.924	4.640	4.208	3.782	3.407	3.107	2.943	2.808	2.661
1.0											
LVOT	13.48	13.86	14.19	14.57	15.21	15.94	16.68	17.35	17.76	18.11	18.53
VTI	13.48	14.19	14.82	15.59	16.94	18.57	20.34	22.06	23.15	24.13	25.32
CO	2.389	2.551	2.698	2.877	3.199	3.598	4.041	4.480	4.763	5.022	5.340
CI	5.429	5.074	4.790	4.486	4.029	3.583	3.195	2.888	2.721	2.586	2.438
1.1											
LVOT	14.03	14.43	14.77	15.17	15.85	16.61	17.39	18.09	18.52	18.89	19.33
VTI	13.89	14.62	15.27	16.06	17.45	19.13	20.94	22.71	23.82	24.83	26.05
CO	2.439	2.615	2.776	2.972	3.328	3.770	4.265	4.758	5.079	5.372	5.733
CI	5.314	4.943	4.649	4.334	3.865	3.411	3.019	2.712	2.546	2.411	2.266
1.2											
LVOT	14.60	15.01	15.37	15.79	16.50	17.29	18.10	18.84	19.28	19.67	20.13
VTI	14.26	15.00	15.67	16.48	17.90	19.62	21.48	23.28	24.43	25.46	26.71
CO	2.498	2.686	2.858	3.069	3.453	3.932	4.470	5.010	5.361	5.683	6.080
CI	5.179	4.801	4.502	4.185	3.713	3.259	2.870	2.567	2.403	2.272	2.129
1.3											
LVOT	15.19	15.62	15.99	16.43	17.16	17.98	18.82	19.59	20.05	20.45	20.92
VTI	14.59	15.35	16.03	16.85	18.31	20.06	21.96	23.80	24.96	26.01	27.29
CO	2.564	2.763	2.945	3.168	3.575	4.084	4.658	5.235	5.612	5.958	6.385
CI	5.028	4.651	4.354	4.039	3.571	3.124	2.742	2.446	2.286	2.158	2.019
1.4											
LVOT	15.79	16.24	16.62	17.07	17.83	18.68	19.55	20.34	20.82	21.23	21.72
VTI	14.88	15.66	16.35	17.19	18.67	20.45	22.38	24.25	25.44	26.51	27.81
CO	2.638	2.845	3.035	3.269	3.694	4.228	4.831	5.437	5.833	6.198	6.648
CI	4.866	4.496	4.205	3.896	3.439	3.003	2.631	2.343	2.189	2.064	1.930
1.5											
LVOT	16.41	16.87	17.27	17.73	18.51	19.39	20.28	21.10	21.59	22.02	22.52
VTI	15.14	15.93	16.64	17.49	18.99	20.80	22.76	24.66	25.87	26.95	28.27
CO	2.719	2.933	3.130	3.371	3.812	4.364	4.989	5.617	6.027	6.405	6.871
CI	4.696	4.338	4.056	3.757	3.315	2.893	2.534	2.256	2.106	1.986	1.857
1.6											
LVOT	17.05	17.52	17.93	18.40	19.20	20.11	21.02	21.86	22.36	22.80	23.32
VTI	15.38	16.18	16.90	17.76	19.28	21.11	23.10	25.03	26.25	27.35	28.68
CO	2.807	3.027	3.228	3.476	3.928	4.494	5.133	5.776	6.196	6.582	7.059

(Continues)

TABLE 9 (Continued)

BSA (m^2)	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
CI	4.523	4.180	3.909	3.623	3.198	2.793	2.448	2.180	2.037	1.921	1.796
1.7											
LVOT	17.70	18.18	18.60	19.09	19.91	20.83	21.77	22.63	23.14	23.59	24.12
VTI	15.59	16.40	17.12	18.00	19.54	21.39	23.41	25.35	26.59	27.70	29.05
CO	2.901	3.126	3.331	3.583	4.042	4.617	5.265	5.916	6.340	6.730	7.211
CI	4.348	4.022	3.765	3.493	3.088	2.702	2.371	2.115	1.977	1.866	1.746
1.8											
LVOT	18.37	18.86	19.29	19.78	20.62	21.57	22.53	23.40	23.93	24.39	24.92
VTI	15.78	16.60	17.33	18.21	19.77	21.64	23.67	25.64	26.89	28.01	29.37
CO	3.002	3.230	3.438	3.692	4.156	4.734	5.385	6.037	6.461	6.851	7.332
CI	4.173	3.867	3.624	3.367	2.984	2.617	2.302	2.058	1.926	1.820	1.705
1.9											
LVOT	19.04	19.55	19.98	20.49	21.34	22.31	23.29	24.18	24.71	25.18	25.73
VTI	15.95	16.77	17.51	18.40	19.97	21.86	23.91	25.90	27.15	28.29	29.66
CO	3.110	3.339	3.548	3.804	4.268	4.846	5.494	6.141	6.562	6.948	7.422
CI	4.000	3.714	3.487	3.245	2.885	2.539	2.240	2.008	1.882	1.780	1.671
2.0											
LVOT	19.73	20.25	20.69	21.21	22.08	23.06	24.05	24.96	25.51	25.98	26.54
VTI	16.09	16.93	17.67	18.57	20.15	22.06	24.12	26.12	27.39	28.53	29.91
CO	3.225	3.454	3.663	3.918	4.380	4.953	5.593	6.230	6.643	7.021	7.486
CI	3.830	3.564	3.353	3.128	2.791	2.466	2.184	1.964	1.844	1.747	1.642
2.1											
LVOT	20.43	20.96	21.41	21.93	22.82	23.82	24.83	25.75	26.30	26.79	27.36
VTI	16.23	17.06	17.81	18.71	20.31	22.23	24.31	26.32	27.59	28.74	30.13
CO	3.346	3.575	3.782	4.035	4.491	5.055	5.682	6.304	6.706	7.073	7.523
CI	3.663	3.419	3.224	3.015	2.702	2.398	2.133	1.925	1.811	1.720	1.620
2.2											
LVOT	21.15	21.68	22.14	22.67	23.57	24.58	25.61	26.54	27.11	27.60	28.17
VTI	16.34	17.18	17.94	18.84	20.45	22.38	24.47	26.49	27.77	28.92	30.32
CO	3.475	3.701	3.906	4.155	4.602	5.152	5.762	6.364	6.752	7.105	7.537
CI	3.501	3.277	3.098	2.907	2.617	2.334	2.086	1.890	1.783	1.696	1.602
2.3											
LVOT	21.87	22.41	22.88	23.42	24.33	25.36	26.40	27.34	27.91	28.41	29.00
VTI	16.44	17.29	18.05	18.96	20.57	22.51	24.60	26.63	27.92	29.08	30.49
CO	3.611	3.833	4.033	4.277	4.713	5.246	5.834	6.411	6.782	7.119	7.530
CI	3.343	3.140	2.977	2.802	2.536	2.274	2.043	1.860	1.759	1.677	1.587
2.4											
LVOT	22.61	23.15	23.63	24.17	25.10	26.14	27.19	28.15	28.73	29.23	29.82
VTI	16.53	17.38	18.14	19.05	20.67	22.62	24.72	26.76	28.05	29.22	30.62
CO	3.754	3.970	4.166	4.402	4.823	5.336	5.897	6.446	6.798	7.116	7.503
CI	3.191	3.008	2.861	2.701	2.458	2.217	2.004	1.833	1.739	1.662	1.577

well as TDI)[34] were strongly dependent on the insonation angle and the specific location of the sample. Both the STE[49,50] and the 3D[28,47] overcome this weakness of the Doppler-based techniques; (b) the LVOT-VTI values reflect a surrogate of the SV without providing additional information on regional or global motility, while the TDI,[34,48] STE,[49,50] and the 3DE[28,47] provide specific and sensitive information for quantification of global and regional LV contractile function; (c) the dependency from geometric assumptions about LV and LVOT shape[33] (in contrast with STE[49,50] and 3DE techniques).[28,47]

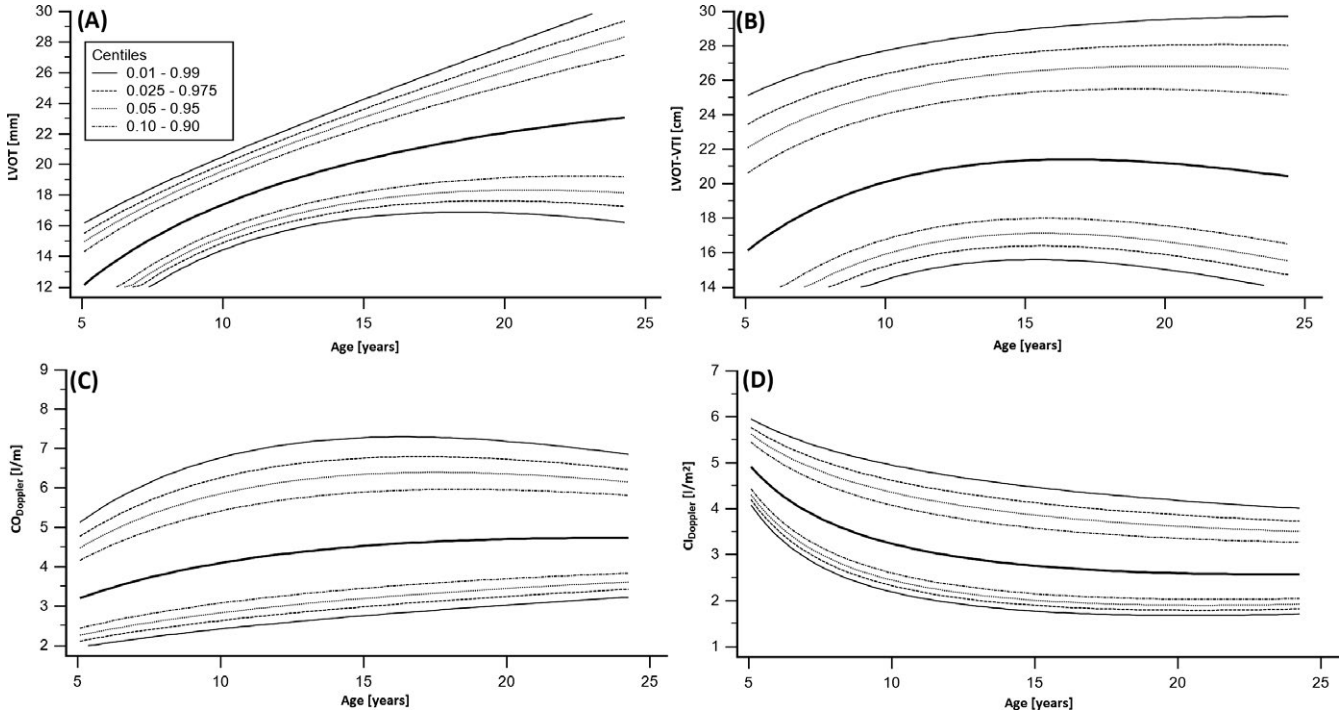

FIGURE 3 Age-specific percentiles curves for velocity time integral (VTI) (A), left ventricular outflow tract diameter (LVOT) (B), and cardiac output (CO) (C) and cardiac index (CI) (D) Doppler- or LVOT-VTI-derived, for the entire population of children and adolescents

The Guidelines for the Use of Echocardiography as a Monitor for Therapeutic Intervention in Adults considered a single cutoff value (18 cm) for LVOT-VTI.[34] That single cutoff value was established considering data from adults.[42,51] Similarly, it has been proposed to include in the RUSH protocol the measurement of LVOT-VTI as surrogate of SV, considering 18–22 cm as the reference range of normality.[9]

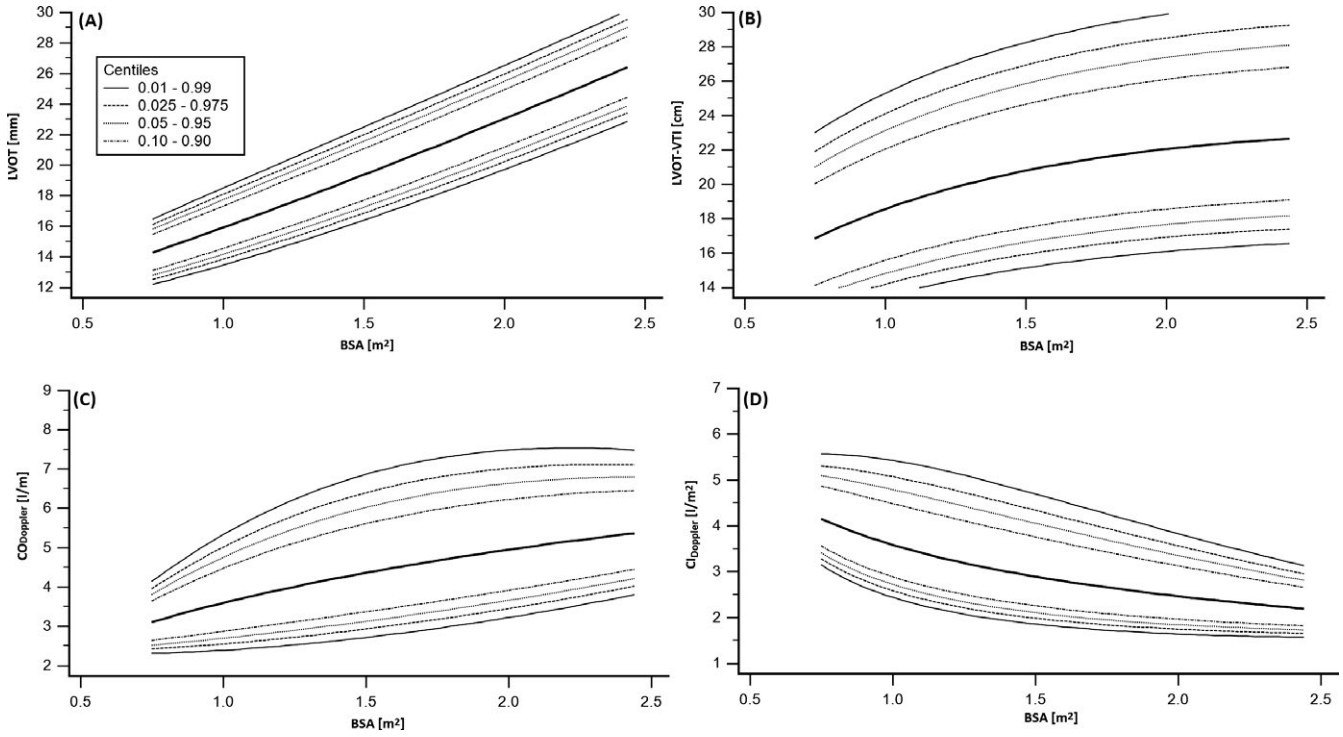

FIGURE 4 Body surface area-specific percentiles curves for left ventricular outflow tract (LVOT) diameter (A), left ventricular outflow tract velocity time integral (LVOT-VTI) (B), and cardiac output (CO) (C) and cardiac index (CI) (D) from Doppler- or LVOT-VTI-derived method, for the entire population of children and adolescents

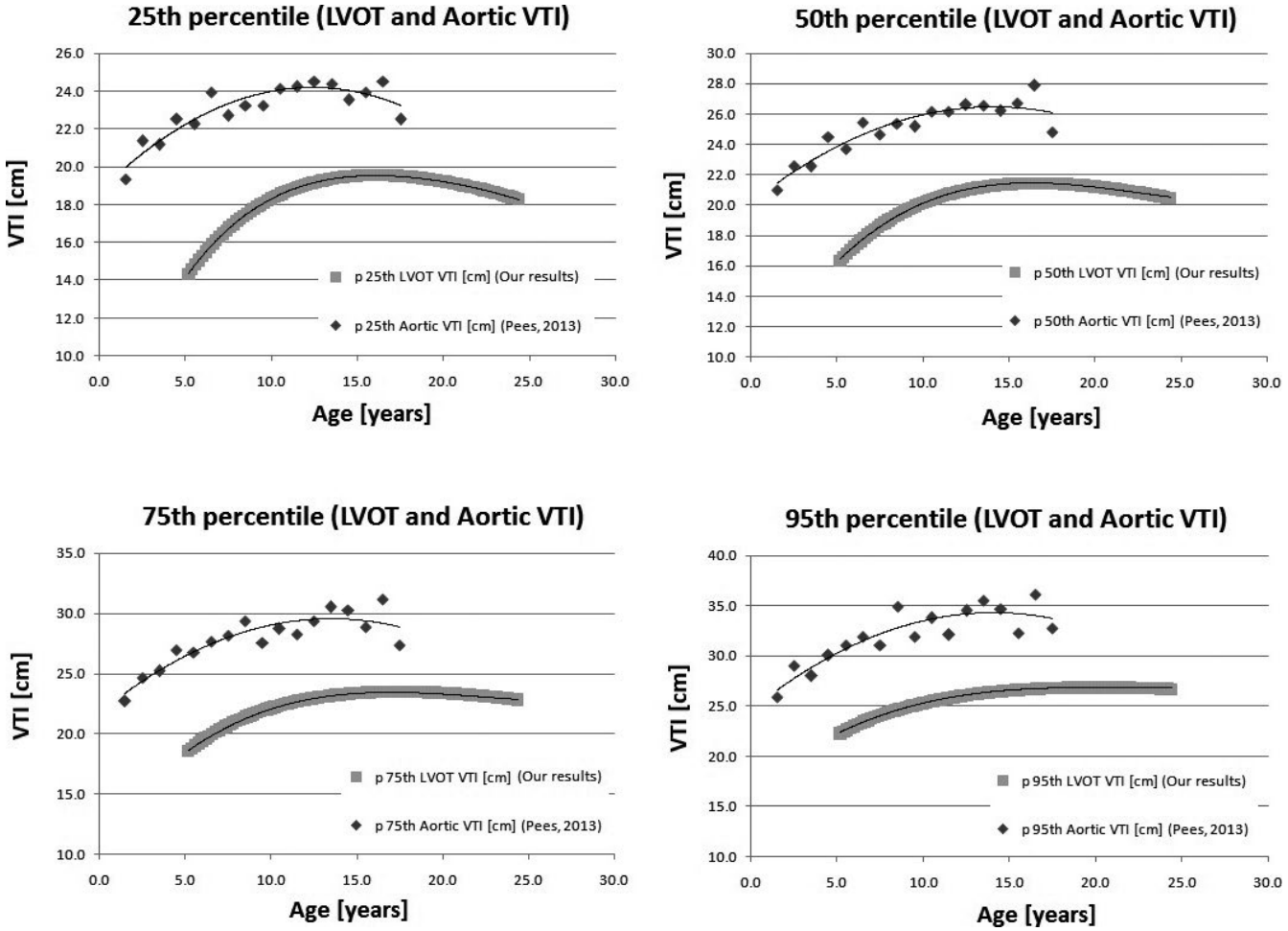

FIGURE 5 Age-specific velocity time integral (VTI) percentiles obtained in our population (LVOT-VTI) and those reported in children and adolescents from an Austrian population (Aortic VTI) (Pees 2013). Percentiles 25th, 50th, 75th, and 95th obtained showed that the Argentinean population has always the lowest VTI values

A recent work showed that LVOT-VTI outperforms ejection fraction and Doppler-derived CO, as predictor of outcomes in a select advanced heart failure cohort.[55] Moreover, a recent study in children and adolescents with dilated cardiomyopathy indicated that LVOT-VTI could be a useful (alternative) LV performance index.[12] In that research, a LVOT-VTI < 17 cm (PWD) or <22 cm (continuous wave Doppler) indicated impaired ventricular function.[12] Considering those values and our RIs for LVOT-VTI (Table 6), it is to note that approximately 50%, 25%, and 10% of healthy children <6, <8, and <11 years old, respectively, would have LVOT-VTI values below 17 cm. Then, if a fixed cutoff value equal to 17 cm were considered for subjects from our population, impaired ventricular function or low CO would be overdiagnosed. The use of adjusted age-related RIs could reduce those errors.

4.2 | Study limitations

This research used a cross-sectional design. Consequently, the age-related changes in the studied variables should be interpreted cautiously, since the real age-related changes could be misestimated. Further studies, comparing VTI-derived SV values with data obtained from invasive studies (gold standard) in different populations and/or hemodynamic conditions would be valuable.

5 | CONCLUSIONS

Hemodynamic parameters obtained from PWD and 2D data in children, adolescents, and young adults are correlated but could not be considered as equivalent since they show significant absolute and proportional error.

Specific age- and BSA-related RIs and percentiles curves for LVOT, LVOT-VTI, and derived hemodynamic parameters were defined from data obtained in healthy children, adolescents, and young adults from an Argentinean population, nonexposed to CVRFs.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplementary material.

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