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Stroke volume and cardiac output non-invasive monitoring based on brachial oscillometry-derived pulse contour analysis: Explanatory variables and reference intervals throughout life (3–88 years)

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Abstract

Background: *Non-invasive assessment of stroke volume (SV), cardiac output (CO) and cardiac index (CI) has shown to be useful for the evaluation, diagnosis and/or management of different clinical conditions. Through pulse contour analysis (PCA) cuff-based oscillometric devices would enable obtaining ambulatory operator-independent non-invasive hemodynamic monitoring. There are no reference intervals (RIs), when considered as a continuum in childhood, adolescence and adult life, for PCA-derived SV [SV(PCA)], CO [CO(PCA)] and CI [CI(PCA)]. The aim of the study were to analyze the associations of SV(PCA), CO(PCA) and CI(PCA) with demographic, anthropometric, cardiovascular risk factors (CVRFs) and hemodynamic parameters, and to define RIs and percentile curves for SV(PCA), CO(PCA) and CI(PCA), considering the variables that should be considered when expressing them.*

Methods: *In 1449 healthy subjects (3–88 years) SV(PCA), CO(PCA) and CI(PCA) were non-invasively obtained (Mobil-O-Graph; Germany). Analysis: associations between subject characteristics and SV(PCA), CO(PCA) and CI(PCA) levels (correlations; regression models); RIs and percentiles for SV(PCA), CO(PCA) and CI(PCA) (parametric methods; fractional polynomials).*

Results: *Sex, age, and heart rate would be explanatory variables for SV, CO, and CI levels. SV levels were also examined by body height, while body surface area (BSA) contributing to evaluation of CO and CI. CVRFs exposure did not contribute to independently explain the values of the dependent variables. SV, CO and CI levels were partially explained by the oscillometric-derived signal quality. RIs and percentiles were defined.*

Conclusions: *Reference intervals and percentile for SV(PCA), CO(PCA) and CI(PCA), were defined for subjects from 3–88 years of age, results are expressed according to sex, age, heart rate, body height and/or BSA.* (Cardiol J 2021; 28, 6: 864–878)

Key words: adolescents, adults, cardiac output, children, pulse contour analysis, reference intervals

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Introduction

Non-invasive assessment of left ventricle stroke volume (SV), cardiac output (CO) and cardiac index (CI) were shown to be useful for the evaluation, diagnosis and/or management of different clinical and physiological conditions in both pediatric, and adult populations [1, 2]. Several non-invasive and/or minimally invasive approaches have been proposed to determine SV, CO and CI (i.e. transpulmonary-thermodilution, thoracic bioimpedance-bioreactance, ultrasonography). Among them, echocardiography stands out as a method widely used and recommended in clinical practice [3–5]. However, different factors contribute to circumscribe the use of echocardiography to certain contexts and conditions, limiting its widespread use (i.e. for community-based epidemiological studies). Among those factors are: (1) physical (size) restrictions and cost of the devices, (2) operator-dependency and the need for a learning-curve, (3) inability to obtain adequate records in many subjects or conditions, (4) different acquisition approaches may affect measurement variability, (5) a relatively long period of time is required to complete a study and/or (6) ambulatory records or continuous monitoring of the variables cannot be obtained [6, 7]. Pulse contour analysis (PCA) of blood pressure (BP) waveforms obtained non-invasively would enable estimating the SV, CO and CI [8–12]. Among the different approaches and devices available, the cuff-based oscillometric devices would be of choice, in cases of population studies within a community, taking into account their portability, high speed of measurement (2–3 min), operator-independence and need for minimal collaboration of the subject (e.g. children) [13–15].

In both, pediatric and adult populations, there is scarce data about normal and reference values for SV, CO and CI at rest. That is particularly true for data obtained from PCA. Furthermore, available information acquired in specific (i.e. Asian) populations cannot not be extrapolated to other populations [16, 17]. The present group of researchers have been working on the identification and definition of particular characteristics (i.e. age-related changes, percentile curves, reference intervals [RIs]) of cardiovascular variables in several populations; with special emphasis which considers childhood, adolescence and/or adult life as a continuum [18–23].

The main aims herein, were to analyze the associations of SV(PCA), CO(PCA) and CI(PCA) with demographic, anthropometric, cardiovascular risk factors (CVRFs) and hemodynamic parameters, and to define percentile curves and RIs for SV(PCA), CO(PCA) and CI(PCA), taking into account the variables that should be considered when expressing them (e.g. age, sex, body surface area [BSA]).

Methods

Healthy subjects (n = 1449; 3–88 years) from the community were considered for enrolment (Table 1) [18–22]. Hypertension, diabetes or dyslipidemia were considered present if the subject reported being in treatment and/or a previous diagnosis of their condition. Subjects were classified as sedentary when the physical activity they performed was lower than a moderate intensity of physical load. Smoking at least one cigarette per week was defined as a current smoker. Family history of cardiovascular disease was defined by the presence of first-degree relatives with premature cardiovascular disease [18–22]. Body mass index (BMI) was calculated as the weight-to-squared height ratio converted into percentiles/z-scores (subjects < 18 years) [18–22].

Pulse contour analysis

Readings were obtained after 10 min of rest. The oscillometric-cuff (Mobil-O-Graph; I.E.M.-GmbH, Germany) was placed on the left arm. The device measured peripheral (brachial) mean BP (MBP) and determined peripheral systolic BP, diastolic BP and pulse pressure (pSBP, pDBP, pPP). Peripheral waveforms were calibrated to pDBP and calculated MBP (MBP = pDBP + pPP/3). From the peripheral measurements, the Mobil-O-Graph determined the central (aortic) BP waveform and quantified [14, 15]: (1) central systolic BP, diastolic BP and pulse pressure (cSBP, cDBP, cPP); (2) heart rate (HR); (3) pulse wave analysis (PWA)-derived parameters like P1 and P2, augmented pressure (AP), augmentation index without and with normalization to a HR = 75 beats/min (AIx, AIx@75), pulse wave velocity (PWV), forward (Pf) and backward (Pb) wave components, reflection coefficient; (4) SV, CO, CI, and total systemic vascular resistance. Only data from accurate waves were considered. Record quality was consigned as an in-device quality index: (1 — excellent, 2 — good, and 3 — minimally acceptable record). Data assigned to each subject were an average of at least three measurements.

Data analysis

Data analysis was done using MedCalc (v.18.5, MedCalc Inc., Belgium) and IBM-SPSS Statistical

Table 1. Subjects characteristics.

	Entire group (n = 1449)									Male (n = 745)									Female (n = 704)								
	MV	SE	SD	Min	p25th	p50th	p75th	Max	Range	MV	SE	SD	Min	p25th	p50th	p75th	Max	Range	Mean	SE	SD	Min	p25th	p50th	p75th	Max	Range
Sex (male)	51.4%																										
Age [years]	29.3	0.7	22.4	3.9	12.4	18.3	50.1	88.8	84.9	28.9	0.9	21.3	4.2	12.4	18.3	49.0	84.4	80.2	29.6	1.0	23.4	3.9	12.5	18.3	53.3	88.8	84.9
Body weight [kg]	61.6	0.7	22.8	13.2	48.9	61.9	76.5	134.7	121.5	67.1	1.0	24.2	14.3	53.0	69.0	82.7	134.7	120.4	56.1	0.8	19.9	13.2	46.4	57.0	67.1	115.0	101.8
Body height [cm]	157.0	0.6	20.1	97.0	149.0	162.0	171.0	197.0	100.0	1.6	0.0	0.2	1.1	1.5	1.7	1.8	2.0	0.9	1.5	0.0	0.2	1.0	1.5	1.6	1.6	1.8	0.9
BSA [m²]	1.61	0.01	0.39	0.59	1.43	1.66	1.87	2.65	2.06	1.71	0.02	0.41	0.67	1.51	1.80	1.99	2.65	1.98	1.50	0.01	0.34	0.59	1.41	1.58	1.70	2.23	1.63
BMI [kg/m²]	24.0	0.2	5.6	11.5	20.1	23.4	27.2	48.2	36.7	24.4	0.2	5.5	11.5	20.6	24.1	27.7	45.5	34.0	23.6	0.2	5.7	12.9	19.8	22.8	26.7	48.2	35.3
Z-score BMI* [SD]	1.10	0.08	1.93	-3.81	-0.13	0.64	1.88	9.64	13.45	1.32	0.12	2.15	-3.81	0.00	0.76	2.24	9.64	13.45	0.88	0.09	1.67	-3.00	-0.22	0.56	1.75	8.16	11.16
Sedentarism	44.2%									46.0%									42.3%								
Hypertension	20.5%									21.5%									19.6%								
Current smoke	9.8%									11.2%									10.2%								
Dyslipidemia	23.5%									24.6%									22.6%								
Diabetes	3.2%									3.4%									3.1%								
Familiar history of premature atherosclerosis-related disorder	10.8%									10.2%									12.4%								
Pharmacological treatment for hypertension	15.9%									14.9%									16.9%								
Pharmacological treatment for dyslipidemia	9.4%									12.2%									8.3%								
Pharmacological treatment for diabetes	3.7%									4.1%									3.9%								
Total cholesterol [mg/dL]	205	2	43	99	175	201	231	363	264	211	3	44	99	170	195	227	363	264	205	3	42	120	184	205	240	336	216
HDL cholesterol [mg/dL]	53	1	16	17	42	51	63	109	92	48	1	13	17	40	46	54	93	76	59	1	17	19	47	58	69	109	90
LDL cholesterol [mg/dL]	126	2	40	31	97	120	148	293	262	126	3	42	31	97	120	148	293	262	126	3	38	49	98	120	149	244	195
Triglycerides [mg/dL]	130	5	88	1	76	105	150	742	741	136	7	89	34	80	112	163	742	708	123	6	85	1	72	101	141	538	537
Glycemia [mg/dL]	95	1	20	64	86	93	100	296	232	95	1	14	65	88	94	101	172	107	95	2	25	64	85	91	99	296	232
Signal quality (continuous variable)	1.47	0.01	0.42	1.00	1.13	1.40	1.75	3.00	2.00	1.49	0.02	0.46	1.00	1.11	1.40	1.75	3.00	2.00	1.45	0.02	0.38	1.00	1.13	1.40	1.75	3.00	2.00
Signal quality (categorical variable):																											
1 ("Excellent")	61.3%									60.2%									62.4%								
2 ("Very good")	36.9%									36.7%									37.1%								
3 ("Poor")	1.8%									3.1%									0.5%								
pSBP [mmHg]	119	0.402	14	85	110	118	126	199	114	120	0.552	13	85	112	119	128	196	111	118	0.581	14	86	108	115	125	199	113
pMBP (calculated; form factor: 0.33) [mmHg]	86	0.329	11	54	79	85	93	148	94	87	0.467	11	61	79	86	93	148	87	85	0.462	11	54	78	84	91	140	86
pDBP [mmHg]	70	0.326	11	36	62	69	76	131	95	70	0.478	11	41	62	69	77	131	90	70	0.444	11	36	62	68	76	111	75
pPP [mmHg]	49	0.276	9	28	43	48	56	105	77	50	0.400	10	28	43	49	56	105	77	48	0.377	9	29	42	48	54	89	60
Heart rate (MOG) [beats/min]	73	0.410	14	33	62	71	81	135	102	70	0.539	13	33	60	68	78	121	88	76	0.595	14	41	66	74	84	135	94
aSBP [mmHg]	108	0.464	16	71	97	107	118	185	114	111	0.670	16	77	101	110	121	180	103	105	0.616	15	71	95	104	112	185	114
aDBP [mmHg]	71	0.326	11	38	63	70	78	133	95	72	0.477	11	41	64	70	79	133	92	71	0.444	11	38	63	70	77	112	74
aPP [mmHg]	37	0.332	11	15	30	35	42	88	73	40	0.503	12	15	32	38	45	88	73	35	0.409	10	15	28	33	39	82	67
P1 [mmHg]	101	0.394	13	67	92	100	109	162	95	105	0.580	14	74	96	104	112	162	88	97	0.486	12	67	89	96	104	151	84
P2 [mmHg]	108	0.464	16	71	97	107	118	185	114	111	0.669	16	77	101	110	121	185	114	105	0.616	15	71	95	104	112	185	114
AP [mmHg]	8	0.162	5	1	4	6	9	37	36	7	0.220	5	1	3	5	9	38	37	8	0.237	6	2	4	6	10	38	36
AIx [%]	19	0.320	11	-7	11	16	24	60	67	16	0.415	10	2	9	13	21	53	51	22	0.457	11	-7	14	19	28	60	67
AIx@75 [%]	18	0.342	12	-7	9	17	26	65	72	13	0.422	10	-7	5	12	20	43	50	22	0.463	11	-6	14	22	30	65	71
Pb [mmHg]	15	0.151	5	4	11	14	17	38	34	16	0.229	5	4	12	15	18	38	34	14	0.186	4	4	11	13	16	35	31
Pf [mmHg]	24	0.223	8	11	19	23	28	66	55	26	0.348	8	11	21	25	30	66	55	23	0.260	6	11	18	22	25	53	42
RC [%]	60	0.279	9	18	55	61	67	81	63	61	0.388	9	18	55	61	67	81	63	60	0.401	10	19	54	61	67	80	61
PVV [m/s]	6	0.060	2	4	5	5	7	15	12	6	0.077	2	4	5	5	7	13	9	6	0.092	2	4	5	5	7	15	12
SV [mL/beat]	73	0.981	15	33	62	73	84	125	91	78	0.646	15	40	67	80	88	125	85	67	0.609	15	33	58	68	77	114	81
CO [L/min]	5.09	0.02	0.74	3.10	4.54	5.06	5.63	7.10	4.00	5.28	0.03	0.74	3.40	4.73	5.28	5.82	7.10	3.70	4.91	0.03	0.70	3.10	4.43	4.86	5.40	6.68	3.58
SVR [s.mmHg/mL]	1.12	0.01	0.19	0.75	0.98	1.11	1.25	1.98	1.23	1.10	0.01	0.19	0.96	0.96	1.08	1.23	1.98	1.23	1.15	0.01	0.19	0.78	1.02	1.15	1.28	1.95	1.17
CI [L.min/m²]	3.32	0.90	0.03	1.53	2.68	3.15	3.70	6.77	5.23	3.26	0.04	0.93	1.53	2.60	3.03	3.73	6.77	5.23	3.37	0.04	0.86	1.88	2.80	3.23	3.68	6.67	4.78

*Calculated for subjects under 18 years old. Min — minimal value; Max — maximal value; SD — standard deviation; SE — standard error; BSA — body surface area; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; PP — pulse pressure; MBP — mean blood pressure; HDL — high density lipoprotein; LDL — low-density lipoprotein; MOG — Mobil-O-Graph; AP — augmented pressure; AIx — augmentation index; AIx and AIx@HR75 — augmentation index non-normalized and normalized considering a heart rate equal 75 beats/min; Prefix "p" and "a" — peripheral (brachial artery) and central (aortic); P1 and P2 — blood pressure at time 1 and 2, respectively; Pb and Pf — backward and forward aortic blood pressure component amplitude, respectively; RC — reflection coefficient; PVV — pulse wave velocity; SV — stroke volume; CO — cardiac output; SVR — systemic vascular resistances; CI — cardiac index

Software (v.20, SPSS Inc., USA). A p < 0.05 was considered statistically significant.

Associations between the subject characteristics (demographic, anthropometric, CVRFs, hemodynamic characteristics) and the SV(PCA), CO(PCA), CI(PCA) and signal-quality index levels were evaluated. To this end, simple and point-biserial correlations (Table 2) and multiple linear regression models (MLR, Stepwise) were considered (Table 3). After age, sex, BSA and height adjustment, there were no significant associations between the exposure to CVRFs and SV, CO or CI levels. Consequently, disregarding their exposure to CVRFs, all subjects studied could be considered in constructing the RIs.

As a result of the analysis described: (1) sex and age-specific RIs for SV(PCA), CO(PCA) and CI(PCA); (2) height specific RIs for SV(PCA) and (3) BSA specific RIs for CO and CI were considered necessary (Table 3). Then, age-related, height-related and BSA-related (always discriminated by sex) equations for mean and SD values were obtained for PCA-derived parameters. To this end, parametric regression methods based on fractional polynomials (FPs) were implemented [18–21, 24–27]. Briefly (as an example), mean and SD regression curves for age-specific SV(PCA), CO(PCA) and CI(PCA) were defined as fitting FPs. Thereafter, age-specific mean and standard deviation (SD) values could be obtained. As an example, CO(PCA) mean equation would be: $= a + b \times age^p + c \times age^q + \ldots$, where a, b, and c, are coefficients, and p, q, are powers, with numbers selected from the set [–2, –1, –0.5, 0, 0.5, 1, 2, 3], estimated from the regression for the mean CO(PCA) curve. Continuing the example, FPs with powers [1, 2], that is, with p = 1 and q = 2, illustrates an equation with the form $a + b \times age + c \times age^2$ [24]. Residuals were used to assess the model fit, deemed appropriate if the scores were normally distributed, with a mean equal to 0 and an SD equal to 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. From the mean and SD equations, and considering the standard normal distribution (Z) age-specific, HR-specific, height-specific and BSA-specific percentiles were defined (SV(PCA): Fig. 1; **Suppl. Tables S1–S6**; CO(PCA): Fig. 2; **Suppl. Tables S7–S12**; CI(PCA): Fig. 3; **Suppl. Tables S13–S18**). The 1th, 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th, and 99th percentile curves were calculated as mean + 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.

The minimum sample size required (n = 377 subjects) for RIs construction (i.e. for males or females) was defined considering a normal distribution for the covariate in the sample (conservatively), a 95% and 90% limit of reference and confidence interval (two-sided), respectively; with a 95% and 10% reference range and relative margin of error, respectively [18–21, 28]. 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) [29].

Results

SV(PCA), CO(PCA), CI(PCA): Impact of sex, age, HR and anthropometric characteristics

Table 1 describes characteristics of the 1449 subjects included in the study. Note the wide age range considered (3–88 years old) and the balanced sex distribution (male = 51.4%).

Table 3 shows explanatory variables for SV(PCA), CO(PCA) and CI(PCA) values (MLR models). The variables considered were those with statistically significant associations with PCA-derived data in bivariate analyses (Table 2). Sex, age, and HR would be explanatory variables for dependent variables (SV, CO, CI). SV levels were also explained by height, while BSA contributed to explain CO and CI. CVRFs did not contribute to explain, independently, the values of the dependent variables. Then, data from all the studied subjects could be considered for the RIs, which should be sex-specific and expressed taking into account age, HR and height or BSA) (Table 3). It is noteworthy that variations in SV, CO and CI were partially explained by the oscillometric-derived signal quality. A higher signal quality was associated with higher SV, CO and CI (Tables 2, 3).

SV(PCA), CO(PCA), CI(PCA): Percentile curves and RIs for children, adolescents and adults

Figure 1 shows age, HR and height-specific percentile curves for SV(PCA). **Supplementary Tables S1–S6** show sex-specific RIs for SV considering age, HR and height.

Age, HR and BSA-specific percentile curves for CO(PCA) and CI(PCA) in males and females are shown in Figures 2, 3. **Supplementary Tables S7–S12** show sex-specific RIs for CO considering

Table 2. Association (unadjusted and adjusted) between stroke volume, cardiac output or cardiac index and demographic, anthropometric, cardiovascular risk factors exposition, hemodynamic and cardiovascular parameters.

Columns are grouped as **Bivariate (unadjusted or Zero-order) correlations** (first 10 value columns) and **Bivariate (adjusted) correlations: Sex, Age, BMI and BSA** (last 10 value columns). Within each group: SV (MOG), CO (MOG), CI (MOG), Signal quality (continuous variable), Signal quality (categorical variable); each with R and p.

Variable and units	SV [mL/beat] R	p	CO [L/min] R	p	CI [L·min/m²] R	p	SQ cont R	p	SQ categ R	p	SV [mL/min] R	p	CO [L/min] R	p	CI [L·min/m²] R	p	SQ cont R	p	SQ categ R	p
Sex [Female: 1; Male: 0]	-0.340	< 0.001	-0.246	< 0.001	0.060	0.042	-0.050	0.092	-0.046	0.120	—	—	—	—	—	—	—	—	—	—
Age [years]	0.229	< 0.001	-0.096	0.001	-0.596	< 0.001	0.061	0.039	0.052	0.081	—	—	—	—	—	—	—	—	—	—
Body weight [kg]	0.503	< 0.001	0.329	< 0.001	-0.787	< 0.001	-0.044	0.138	-0.031	0.302	-0.236	< 0.001	-0.228	< 0.001	0.201	< 0.001	0.115	< 0.001	0.092	0.002
Body height [cm]	0.635	< 0.001	0.407	< 0.001	-0.774	< 0.001	-0.126	< 0.001	-0.105	< 0.001	0.225	< 0.001	0.266	< 0.001	-0.177	< 0.001	-0.138	< 0.001	-0.114	< 0.001
BSA [m²]	0.584	< 0.001	0.377	< 0.001	-0.822	< 0.001	-0.081	0.006	-0.063	0.032	—	—	—	—	—	—	—	—	—	—
BMI [kg/m²]	0.276	< 0.001	0.215	0.007	-0.617	< 0.001	0.003	0.909	0.013	0.661	—	—	—	—	—	—	—	—	—	—
Z-score BMI* [SD]	-0.052	0.186	0.106	0.477	-0.050	0.202	-0.025	0.524	-0.036	0.353	0.000	0.998	-0.043	0.270	-0.243	< 0.001	-0.080	0.041	-0.108	0.006
Sedentarism [Yes: 1; No: 0]	-0.119	< 0.001	0.022	0.150	-0.038	0.226	-0.043	0.176	-0.032	0.305	-0.147	< 0.001	0.006	0.857	0.069	0.029	-0.043	0.180	-0.034	0.282
Hypertension [Yes: 1; No: 0]	0.067	0.023	0.043	0.958	-0.220	< 0.001	0.019	0.511	0.016	0.589	-0.017	0.564	0.101	0.001	0.081	0.007	-0.027	0.369	-0.025	0.392
Current smoke [Yes: 1; No: 0]	0.090	0.004	0.002	< 0.001	-0.092	0.003	0.010	0.736	0.011	0.724	-0.006	0.854	-0.044	0.156	0.041	0.183	0.033	0.293	0.031	0.323
Dyslipidemia [Yes: 1; No: 0]	0.033	0.261	-0.104	0.055	-0.321	< 0.001	0.088	0.003	0.076	0.010	-0.108	< 0.001	-0.086	0.004	-0.031	0.304	0.051	0.085	0.042	0.156
Diabetes [Yes: 1; No: 0]	0.006	0.969	-0.281	0.340	-0.471	0.001	0.182	0.220	0.246	0.096	-0.233	0.133	-0.463	0.002	-0.464	0.002	0.161	0.303	0.238	0.124
Family history of premature CVD [Yes: 1; No: 0]	0.070	0.021	-0.029	0.002	-0.152	< 0.001	0.040	0.180	0.038	0.213	0.030	0.328	0.013	0.665	0.007	0.826	0.025	0.410	0.025	0.414
Pharmacological treatment for hypertension [Yes: 1; No: 0]	0.013	0.673	-0.094	< 0.001	-0.258	< 0.001	0.108	< 0.001	0.081	0.009	-0.098	0.002	0.002	0.950	0.091	0.003	0.067	0.032	0.042	0.178
Pharmacological treatment for dyslipedemia [Yes: 1; No: 0]	0.032	0.301	-0.143	0.418	-0.288	< 0.001	0.144	< 0.001	0.122	< 0.001	-0.111	< 0.001	-0.136	< 0.001	-0.066	0.035	0.120	< 0.001	0.101	0.001
Pharmacological treatment for diabetes [Yes: 1; No: 0]	-0.048	0.122	-0.025	< 0.001	-0.149	< 0.001	0.031	0.321	0.017	0.585	-0.120	< 0.001	-0.012	0.706	0.013	0.680	0.005	0.883	-0.008	0.805
Total cholesterol [mg/dL]	-0.152	0.003	-0.205	< 0.001	-0.127	0.013	0.110	0.030	0.074	0.146	-0.164	0.001	-0.139	0.007	-0.096	0.063	0.091	0.077	0.057	0.268
HDL cholesterol [mg/dL]	-0.138	0.008	-0.184	0.003	-0.020	0.699	-0.038	0.468	-0.011	0.825	0.005	0.930	0.091	0.084	-0.054	0.305	-0.089	0.091	-0.043	0.418
LDL cholesterol [mg/dL]	-0.120	0.024	-0.156	0.823	-0.071	0.185	0.100	0.060	0.043	0.416	-0.137	0.011	-0.129	0.016	-0.085	0.115	0.078	0.145	0.024	0.660
Triglycerides [mg/dL]	-0.009	0.873	0.012	0.100	-0.116	0.031	0.076	0.156	0.067	0.210	-0.099	0.069	-0.095	0.082	-0.020	0.710	0.084	0.124	0.070	0.200
Glycemia [mg/dL]	-0.069	0.259	-0.101	< 0.001	-0.204	0.001	0.056	0.365	0.061	0.319	-0.149	0.016	-0.108	0.082	-0.084	0.177	0.030	0.624	0.039	0.536
Signal quality (continuous variable)	0.008	0.784	-0.296	< 0.001	0.007	0.815	1.000	—	0.877	< 0.001	0.091	0.002	-0.272	< 0.001	-0.101	0.001	0.873	—	0.873	< 0.001
Signal quality (categorical variable)	0.009	0.751	-0.269	< 0.001	-0.018	0.543	0.877	< 0.001	1.00	—	0.078	0.009	-0.255	< 0.001	-0.125	< 0.001	-0.016	< 0.001	-0.034	—
pSBP [mmHg]	0.252	< 0.001	0.267	< 0.001	-0.403	< 0.001	-0.025	0.397	-0.026	0.371	-0.013	0.656	0.208	< 0.001	0.087	0.003	0.050	0.581	-0.023	0.436
pMBP (calculated; form factor: 0.33) [mmHg]	0.187	< 0.001	0.138	0.159	-0.450	< 0.001	0.043	0.149	0.023	0.432	-0.108	< 0.001	0.108	< 0.001	0.051	0.088	0.091	0.090	0.024	0.420
pDBP [mmHg]	0.129	< 0.001	0.042	< 0.001	-0.430	< 0.001	0.084	0.004	0.052	0.076	-0.152	< 0.001	0.028	0.351	0.027	0.367	-0.112	0.002	0.051	0.084
pPP [mmHg]	0.213	< 0.001	0.340	0.614	-0.080	0.007	-0.0137	< 0.001	-0.101	0.001	0.131	< 0.001	0.241	< 0.001	0.088	0.003	-0.270	< 0.001	-0.082	0.006
Heart rate [beats/min]	-0.773	< 0.001	-0.015	< 0.001	0.547	< 0.001	-0.196	< 0.001	-0.187	< 0.001	-0.714	< 0.001	0.177	< 0.001	0.293	< 0.001	0.186	< 0.001	-0.254	< 0.001
aSBP [mmHg]	0.520	< 0.001	0.192	0.200	-0.584	< 0.001	0.114	< 0.001	0.101	0.001	0.271	< 0.001	0.047	0.117	-0.066	0.027	0.124	< 0.001	0.160	< 0.001
aDBP [mmHg]	0.147	< 0.001	0.038	< 0.001	-0.430	< 0.001	0.110	< 0.001	0.071	0.016	-0.129	< 0.001	0.013	0.666	0.023	0.446	0.101	< 0.001	0.075	0.012
aPP [mmHg]	0.580	< 0.001	0.230	< 0.001	-0.392	< 0.001	0.050	0.094	0.070	0.018	0.423	< 0.001	0.042	0.159	-0.093	0.002	0.099	0.001	0.115	< 0.001
P1 [mmHg]	0.572	< 0.001	0.401	< 0.001	-0.496	< 0.001	0.038	0.203	0.029	0.326	0.299	< 0.001	0.272	< 0.001	0.103	0.001	0.185	0.001	0.075	0.011
P2 [mmHg]	0.520	< 0.001	0.192	< 0.001	-0.584	< 0.001	0.113	< 0.001	0.100	0.001	0.271	< 0.001	0.047	0.118	-0.066	0.027	0.250	< 0.001	0.159	< 0.001
AP [mmHg]	0.099	0.001	-0.422	< 0.001	-0.464	< 0.001	0.234	< 0.001	0.218	< 0.001	0.032	0.289	-0.467	< 0.001	-0.385	< 0.001	0.298	< 0.001	0.235	< 0.001
AIx [%]	-0.185	< 0.001	-0.625	< 0.001	-0.354	< 0.001	0.279	< 0.001	0.251	< 0.001	-0.207	< 0.001	-0.629	< 0.001	-0.436	< 0.001	0.091	0.002	0.272	< 0.001
AIx@75 [%]	-0.699	< 0.001	-0.601	< 0.001	0.057	0.056	0.136	< 0.001	0.113	< 0.001	-0.674	< 0.001	-0.451	< 0.001	-0.189	< 0.001	0.179	< 0.001	0.076	0.011
Pb [mmHg]	0.604	< 0.001	0.153	0.011	-0.456	< 0.001	0.126	< 0.001	0.131	< 0.001	0.456	< 0.001	-0.022	0.468	-0.135	< 0.001	0.185	< 0.001	0.176	< 0.001
Pf [mmHg]	0.519	< 0.001	0.234	< 0.001	-0.310	< 0.001	0.025	0.406	0.048	0.102	0.366	< 0.001	0.034	0.255	-0.083	0.005	0.077	0.009	0.094	0.002
RC [%]	0.369	< 0.001	-0.076	< 0.001	-0.447	< 0.001	0.244	< 0.001	0.214	< 0.001	0.302	0.003	-0.090	0.002	-0.140	< 0.001	0.276	< 0.001	0.241	< 0.001
PWV [m/s]	0.227	< 0.001	-0.116	< 0.001	-0.539	0.009	0.077	0.009	0.069	0.020	0.088	0.003	-0.056	0.059	-0.120	< 0.001	0.024	0.411	0.029	0.336
SVR [s·mmHg/mL]	-0.306	< 0.001	-0.715	< 0.001	-0.377	< 0.001	0.279	< 0.001	0.242	< 0.001	-0.425	< 0.001	-0.760	< 0.001	-0.500	< 0.001	0.269	< 0.001	0.235	< 0.001

*For subjects < 18 years. A p < 0.05 (red text) was considered statistically significant; CVD — atherosclerosis-related cardiovascular disease; Signal quality: 1 (excellent), 2 (good), 3 (minimum acceptable); R — Pearson coefficient; other abbreviations — see Table 1

Table 3. Pulse contour analysis-derived stroke volume, cardiac output and cardiac index data: explanatory variables (multiple linear regression models).

Dependent variable [Unit]	Model		Unstandardized coefficients		Standardized coefficients	P	95%-CI for β		VIF	R	Adjusted R²	SE of the estimate	Change statistics	
			β	SE	β		Lower bound	Upper bound					R² change	P (F change)
Stroke volume [mL/beat]														
	1	(Constant)	118.631	3.604		< 0.001	111.528	125.734		0.627	0.390	9.817	0.393	8.336E-26
		Heart rate [beats/min]	-0.629	0.053	-0.627	< 0.001	-0.733	-0.526	1.000					
	2	(Constant)	119.584	3.181		< 0.001	113.315	125.854		0.728	0.526	8.659	0.136	6.848E-14
		Heart rate [beats/min]	-0.577	0.047	-0.575	< 0.001	-0.669	-0.485	1.020					
		Sex [female: 1; male: 0]	-9.384	1.172	-0.374	< 0.001	-11.694	-7.074	1.020					
	3	(Constant)	129.487	4.340		< 0.001	120.933	138.041		0.743	0.546	8.473	0.021	0.001
		Heart rate [beats/min]	-0.654	0.051	-0.652	< 0.001	-0.755	-0.552	1.288					
		Sex [female: 1; male: 0]	-8.651	1.169	-0.344	< 0.001	-10.955	-6.348	1.059					
		Age [years]	-0.100	0.031	-0.167	0.001	-0.160	-0.040	1.278					
	4	(Constant)	94.483	10.338		< 0.001	74.108	114.858		0.761	0.571	8.237	0.026	0.0002
		Heart rate [beats/min]	-0.622	0.051	-0.620	< 0.001	-0.722	-0.521	1.327					
		Sex [female: 1; male: 0]	-5.941	1.351	-0.236	< 0.001	-8.604	-3.279	1.497					
		Age [years]	-0.129	0.031	-0.216	< 0.001	-0.190	-0.069	1.367					
		Body height [cm]	20.011	5.395	0.207	< 0.001	9.377	30.644	1.610					
	5	(Constant)	101.820	10.571		< 0.001	80.984	122.655		0.769	0.582	8.127	0.013	0.008
		Heart rate [beats/min]	-0.654	0.052	-0.652	< 0.001	-0.755	-0.552	1.406					
		Sex [female: 1; male: 0]	-5.980	1.333	-0.238	< 0.001	-8.607	-3.353	1.497					
		Age [years]	-0.132	0.030	-0.221	< 0.001	-0.192	-0.072	1.369					
		Body height [cm]	19.389	5.328	0.200	< 0.001	8.888	29.891	1.613					
		Signal quality (categorical variable)	-2.806	1.063	-0.118	0.009	-4.902	-0.710	1.065					
Cardiac output [L/min]														
	1	(Constant)	3.438	0.250		< 0.001	2.945	3.931		0.401	0.157	0.681	0.160	4.923E-10
		Heart rate [beats/min]	0.024	0.004	0.401	< 0.001	0.017	0.031	1.000					
	2	(Constant)	3.497	0.227		< 0.001	3.050	3.944		0.559	0.306	0.618	0.151	3.940E-11
		Heart rate [beats/min]	0.027	0.003	0.456	< 0.001	0.020	0.034	1.020					
		Sex [female: 1; male: 0]	-0.582	0.084	-0.393	< 0.001	-0.747	-0.417	1.020					
	3	(Constant)	4.321	0.319		< 0.001	3.693	4.950		0.592	0.341	0.602	0.038	0.0004
		Heart rate [beats/min]	0.023	0.003	0.392	< 0.001	0.016	0.030	1.130					
		Sex [female: 1; male: 0]	-0.592	0.082	-0.400	< 0.001	-0.753	-0.432	1.021					
		Signal quality (categorical variable)	-0.380	0.106	-0.206	< 0.001	-0.588	-0.171	1.114					
	4	(Constant)	3.111	0.507		< 0.001	2.112	4.110		0.614	0.365	0.591	0.026	0.0026
		Heart rate [beats/min]	0.026	0.004	0.443	< 0.001	0.019	0.033	1.229					
		Sex [female: 1; male: 0]	-0.471	0.089	-0.318	< 0.001	-0.647	-0.295	1.275					
		Signal quality (categorical variable)	-0.364	0.104	-0.198	0.001	-0.569	-0.159	1.117					
		BSA [m²]	0.511	0.168	0.191	0.003	0.179	0.842	1.386					

Table 3 (cont.). Pulse contour analysis-derived stroke volume, cardiac output and cardiac index data: explanatory variables (multiple linear regression models).

Dependent variable [Unit]	Model		Unstandardized coefficients		Standardized coefficients	P	95%-CI for β		VIF	R	Adjusted R²	SE of the estimate	Change statistics	
			β	SE	β		Lower bound	Upper bound					R² change	P (F change)
	5	(Constant)	3.561	0.503		< 0.001	2.569	4.553		0.647	0.405	0.571	0.042	9.670E-05
		Heart rate [beats/min]	0.021	0.004	0.347	< 0.001	0.013	0.028	1.446					
		Sex [female: 1; male: 0]	-0.365	0.091	-0.246	< 0.001	-0.544	-0.187	1.397					
		Signal quality (categorical variable)	-0.379	0.101	-0.206	< 0.001	-0.578	-0.181	1.119					
		BSA [m²]	0.696	0.169	0.261	< 0.001	0.363	1.030	1.500					
		Age [years]	-0.009	0.002	-0.242	< 0.001	-0.013	-0.004	1.387					
Cardiac index [L·min/m²]	1	(Constant)	5.313	0.214		< 0.001	4.891	5.735		0.625	0.387	0.480	0.390	3.163E-25
		BSA [m²]	-1.383	0.117	-0.625	< 0.001	-1.614	-1.152	1.000					
	2	(Constant)	3.391	0.289		< 0.001	2.821	3.962		0.739	0.542	0.415	0.155	1.253E-15
		BSA [m²]	-1.082	0.107	-0.489	< 0.001	-1.293	-0.871	1.119					
		Heart rate [beats/min]	0.020	0.002	0.418	< 0.001	0.016	0.025	1.119					
	3	(Constant)	4.135	0.294		< 0.001	3.556	4.714		0.784	0.608	0.3841	0.067	3.823E-09
		BSA [m²]	-1.389	0.111	-0.627	< 0.001	-1.607	-1.170	1.403					
		Heart rate [beats/min]	0.020	0.002	0.412	< 0.001	0.016	0.025	1.119					
		Sex [female: 1; male: 0]	-0.360	0.059	-0.294	< 0.001	-0.476	-0.245	1.278					
	4	(Constant)	4.403	0.292		< 0.001	3.828	4.978		0.801	0.634	0.371	0.026	8.050-05
		BSA [m²]	-1.265	0.111	-0.571	< 0.001	-1.484	-1.045	1.519					
		Heart rate [beats/min]	0.017	0.002	0.340	< 0.001	0.012	0.021	1.315					
		Sex [female: 1; male: 0]	-0.289	0.059	-0.236	< 0.001	-0.406	-0.172	1.401					
		Age [years]	-0.006	0.001	-0.193	< 0.001	-0.008	-0.003	1.380					
	5	(Constant)	4.687	0.306		< 0.001	4.084	5.289		0.808	0.644	0.365	0.012	0.0068
		BSA [m²]	-1.259	0.110	-0.569	< 0.001	-1.476	-1.042	1.520					
		Heart rate [beats/min]	0.015	0.002	0.310	< 0.001	0.011	0.020	1.388					
		Sex [female: 1; male: 0]	-0.286	0.058	-0.234	< 0.001	-0.402	-0.171	1.402					
		Age [years]	-0.006	0.001	-0.201	< 0.001	-0.009	-0.003	1.385					
		Signal quality (categorical variable)	-0.131	0.048	-0.114	0.007	-0.226	-0.037	1.063					

95% CI — 95% confidence interval; VIF — variance inflation factor; SV, CO, CI were obtained using the pulse contour analysis (PCA) algorithm. A p value < 0.05 (red text) was considered statistically significant; other abbreviations — see Tables 1 and 2
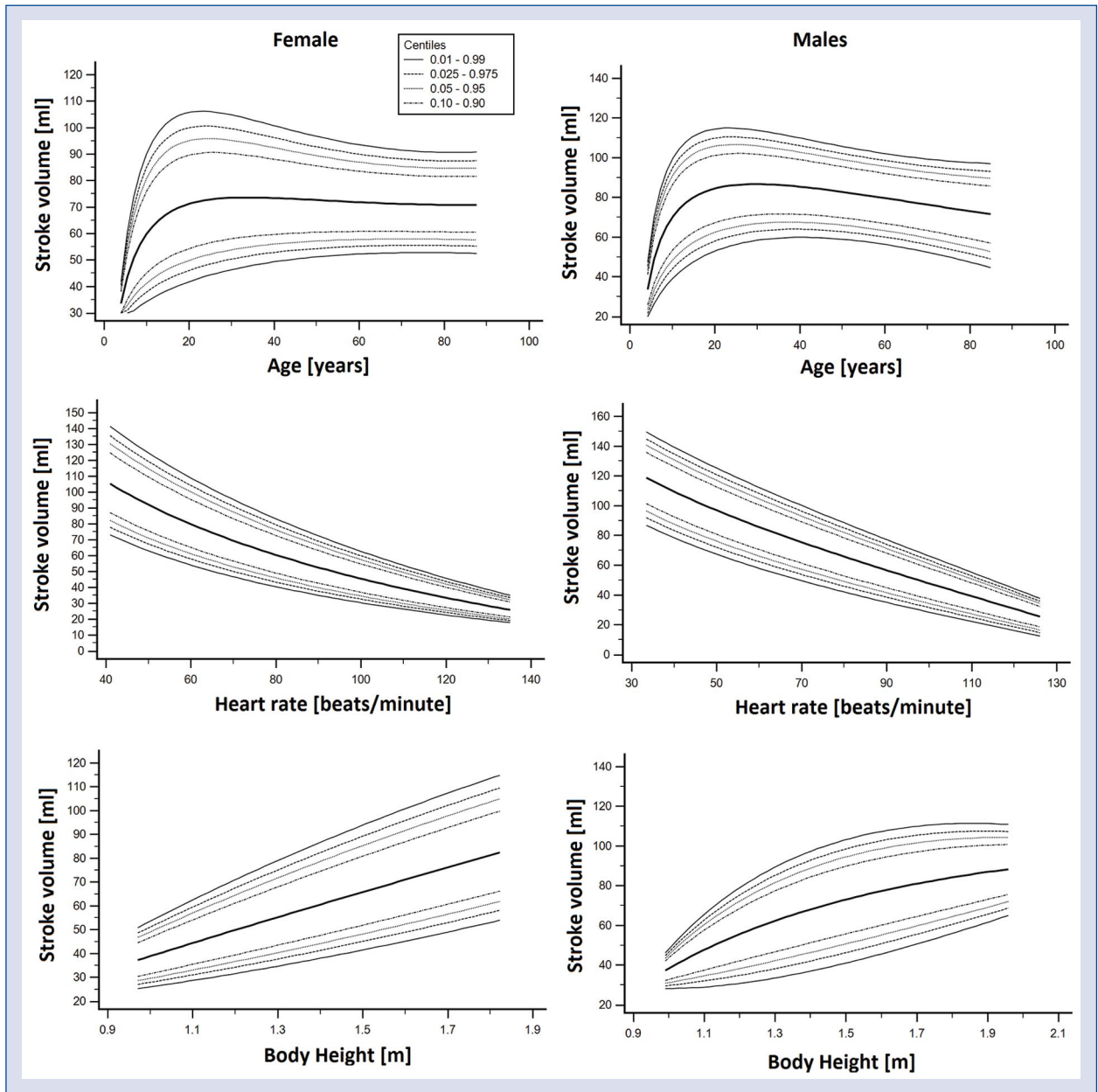
Figure 1. Age-specific, heart rate-specific and body height-specific percentiles of left ventricle stroke volume in females and males.

age, HR and BSA. **Supplementary Tables S13–S18** show sex-specific RIs for CI considering age, HR and BSA.

Discussion

The work's main findings were:

— First, in the construction of RIs for PCA-derived SV, CO and CI, not only were the age and anthropometric variables of the subjects taken into account, but also their sex and HR. The importance of the different explanatory variables varied depending on the parameter for which the RIs were constructed (SV, CO or CI) (Tables 2, 3).

— Second, this study represents the first study in which RIs and percentiles for PCA-derived SV, CO and CI are defined for children, adolescents, adults and elderly subjects (as a continuum throughout life; 3–88 years old) (Figs. 1–3; **Suppl. Tables S1–S18**).

— Third, when SV levels were analyzed it a steep rise in SV was observed during the first two decades, followed by a slow decline over the
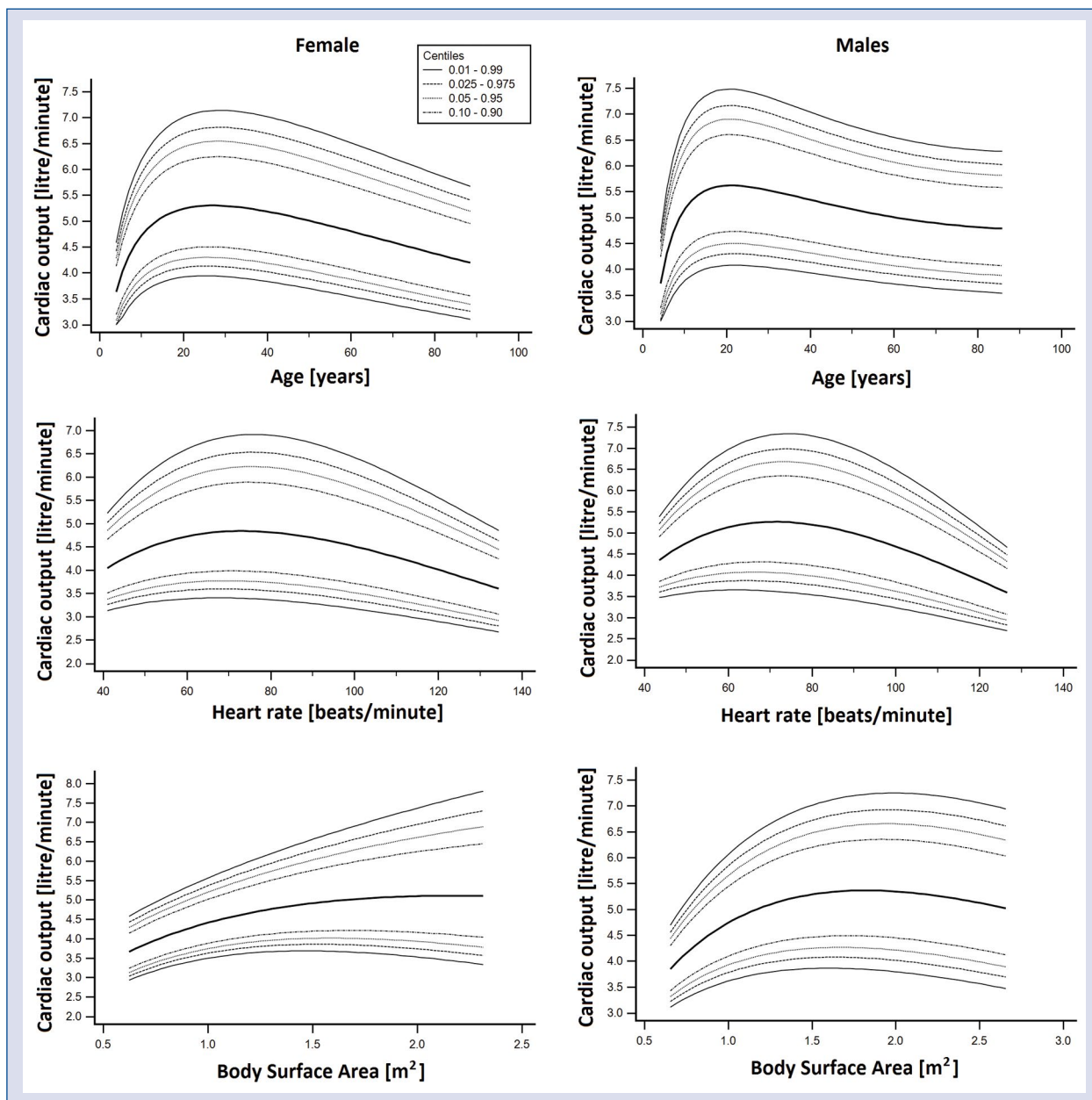
Figure 2. Age-specific, heart rate-specific and body surface area-specific percentiles of left ventricle cardiac output in females and males.

rest of their lives; additionally, the higher the HR, the lower the SV, while the higher the height, the higher the expected SV values (Fig. 1). There was a rapid increase in CO in the first two decades of life, followed by a fall throughout adult life (Fig. 2). Initially CO increases as HR increases, until HR reaches ~70–80 beats/min, then CO begins to fall in association with increases in HR; additionally, CO increases as the BSA increases (Fig. 2). CI values showed an important fall during the first two decades and then they remained

practically unchanged over the rest of their lives (Fig. 3). CI increases in association with increases in HR, while lower CI values were observed in association with higher BSA values (Fig. 3).

The need to express SV, CO and/or CI values considering the age and/or anthropometric characteristics is widely known and accepted. However, it is of note that RIs constructed for a population including subjects from childhood to old age are scarce; in most works the age-groups included people of very different ages (i.e. 20 years apart)
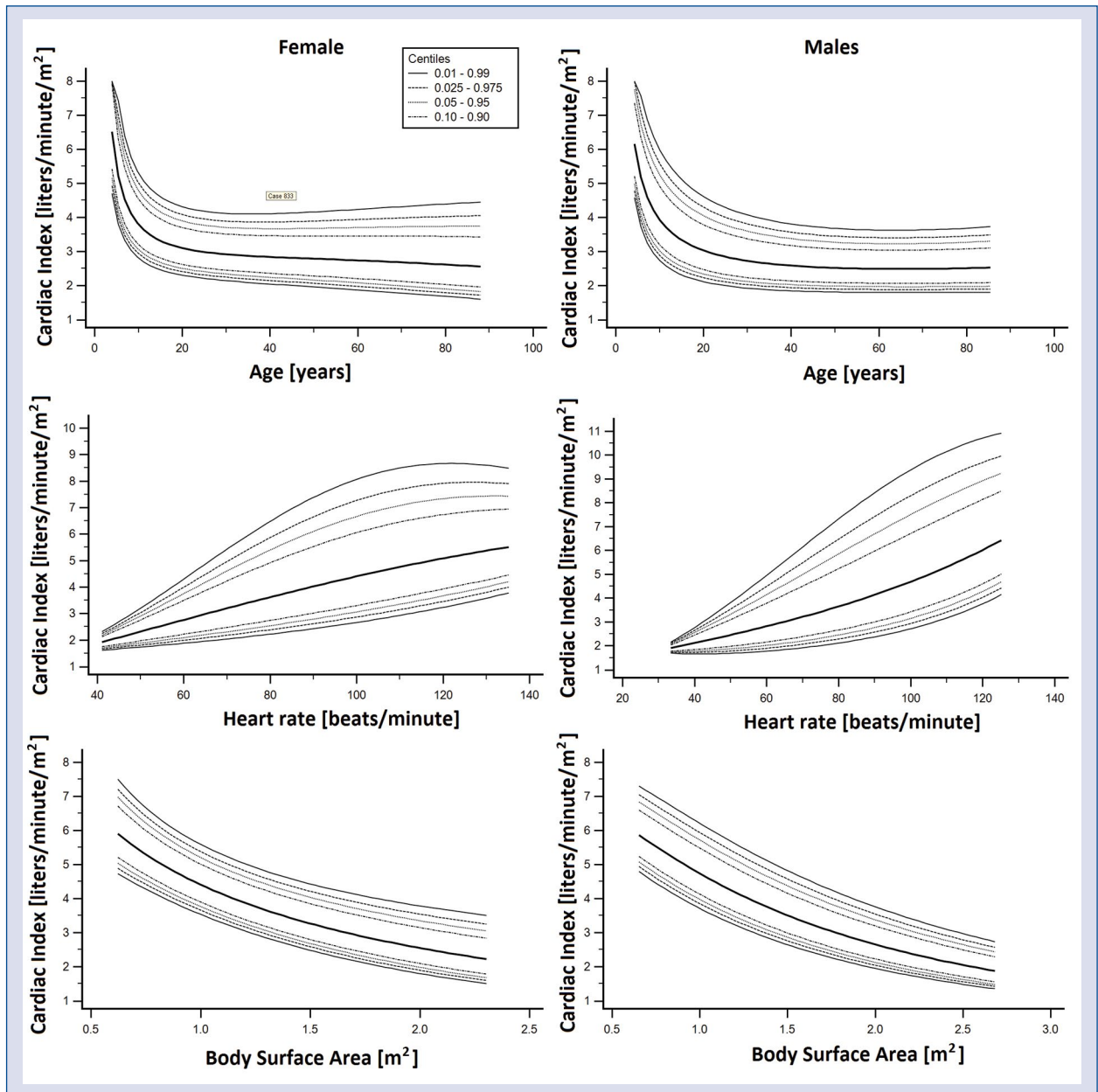
Figure 3. Age-specific, heart rate-specific and body surface area-specific percentiles of left ventricle cardiac index in females and males.

[30]; only adults were considered [5, 30, 31]; subjects aged 60–65 and older were assigned to a single group [5, 30] and/or non-uniform age ranges were considered (i.e. 0–2.9, 3–5.9, 6–11.9, 12–17.9, 18–29.9, 30–59.9, and ≥ 60 years old) [32]. The above does not allow for an adequate analysis of the age impact on hemodynamic characteristic and their variations. In addition, it does not allow for the use of accurate cut-off points in clinical practice (i.e. a 31 year old would be given reference values for a group ranging from 30 to 50.9 years old) [32].

The need to define RIs for males and females separately is not universally accepted and could even be considered controversial. There are works in which it was considered necessary to define sex-specific RIs, others in which the issue was not analyzed or was evaluated inaccurately, and finally, there are works that considered negligible the sex-related differences in the RIs of hemodynamic variables [16, 32–34]. In relation to the latter, sex-specific RIs were not defined; even when sex-related differences in hemodynamic
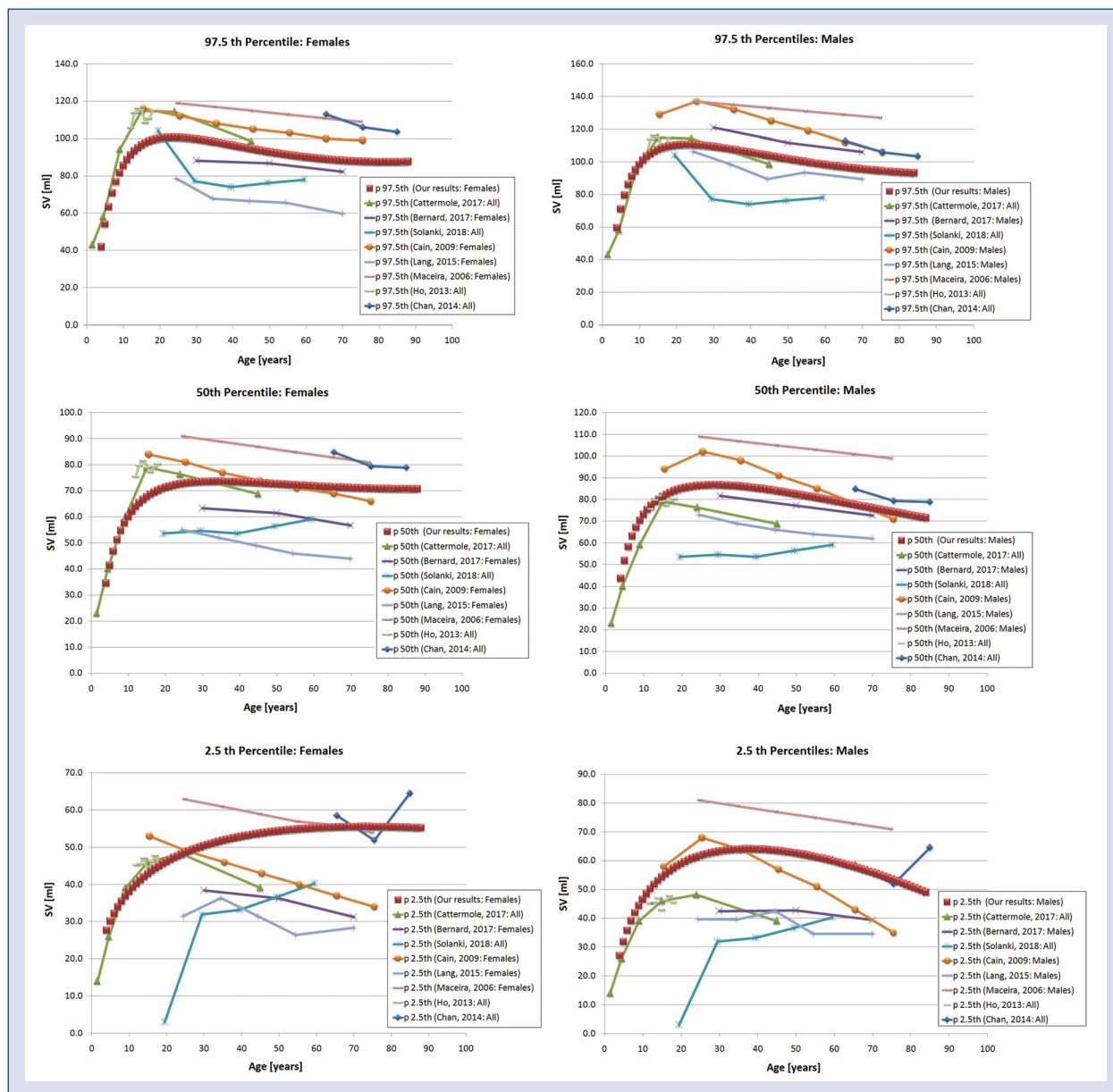
Figure 4. Age-specific percentiles (97.5th, 50th and 2.5th) of left ventricular stroke volume obtained in the present population and those reported from other authors [5, 16, 30, 31, 32, 33, 34, 35].

parameters remained statistically significant after controlling for anthropometric parameters [32]. Results herein, reinforce that the RIs in males differ for females, even after adjusting for height, weight and/or BSA (Table 3); highlighting the need for sex-specific RIs.

Finally, it is of note that oscillometric-derived signal quality was associated with SV, CO and CI values (Table 3). On average, a variation in the signal quality equal to the unit, could independently explain variations in SV, CO and CI equal to 2.8 mL/ beat, 0.38 L/min and 0.13 L/min/m², respectively.

Therefore, at least in theory, further work would be necessary to identify the specific wave characteristics required and/or the minimum quality value of an aortic waveform that would allow accurate CO values to be obtained using PCA.

Related with our second and third main result, when RIs for SV were analyzed taking into account age-related variations, a steep rise in SV was observed during the first two decades, followed by a slow decline during the rest of life (Fig. 1). In addition, the higher the HR, the lower the SV, while the greater the height, the higher the expected SV
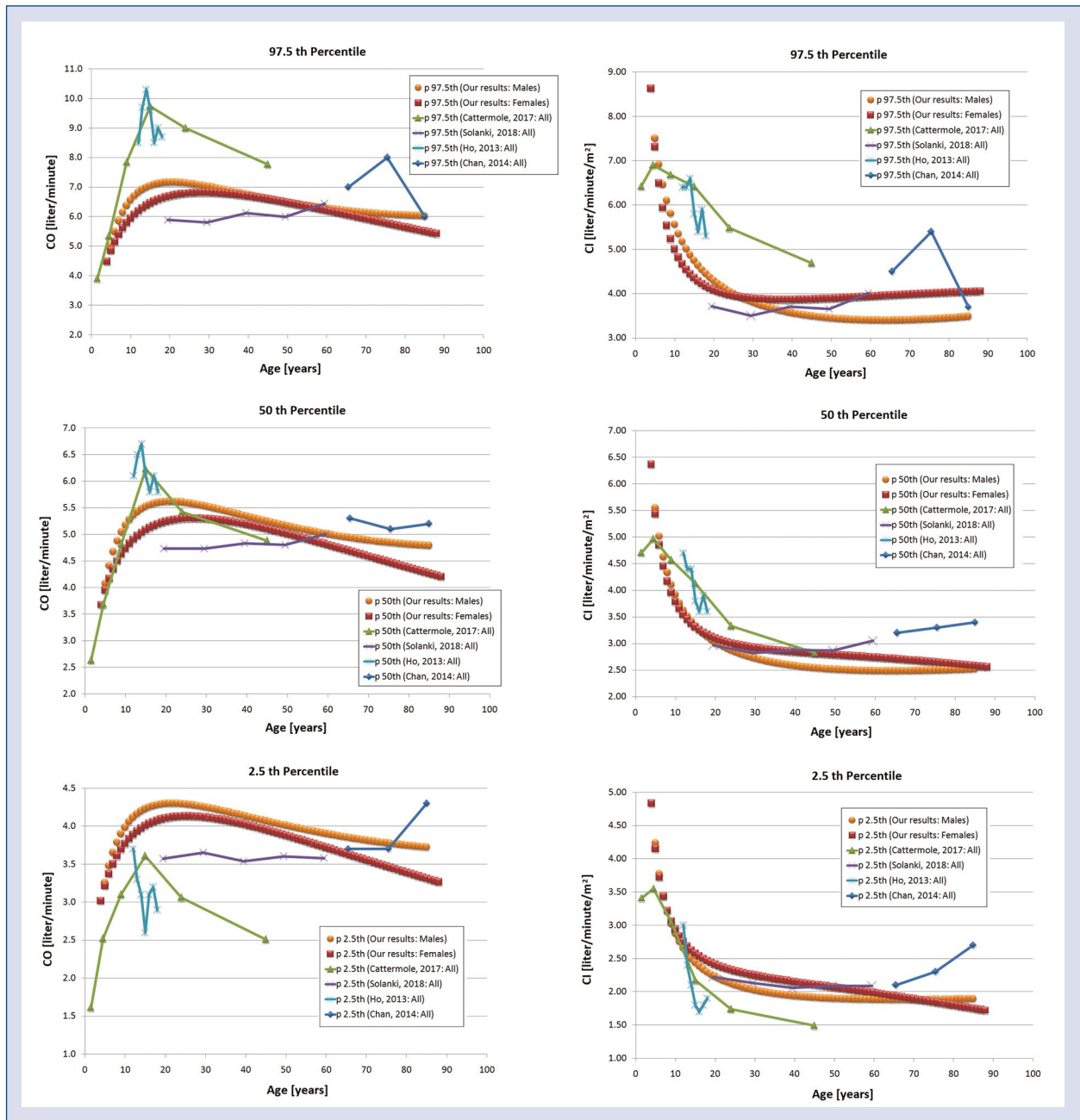
Figure 5. Age-specific percentiles (97.5[th], 50th and 2.5[th]) of left ventricular cardiac output and cardiac index obtained in the present population and those reported from other authors [16, 32, 33, 34].

(Fig. 1). According to available research, until now there have been no reference values defined based on simultaneous or joint analysis of children, adolescents, adults or elderly subjects from a population. Since most available data correspond to values for pediatric or adult subjects it was not possible to perform direct comparisons with the present data. Therefore, a comparative analysis, from available works, an average was taken and SD values were obtained for the different ages. Then, assuming

normal distribution, the 97.5[th] (mean +1.96 SD), 50th (mean) and 2.5[th] (mean –1.96 SD) percentiles were calculated (Figs. 4, 5). Being aware of the described limitation, it could be said that similar trends were observed among other studies.

Cattermole et al. [32] in a population based, cross-sectional, observational study performed in healthy Chinese subjects (n = 2218, age mean/range: 16.4/0.5–89 years old, 52% females), including data previously published by Ho et al. in 2013

(n = 590, age: 12–18 years old, 49% boys) and Chan et al. [34] in 2014 (n = 165, age groups: 61–70, 71–80, > 80 years old, 48.5% males), reported reference ranges for SV, CO and CI data obtained non-invasively (transcutaneous continuous Doppler) [32–34]. Despite methodological differences, including the non-uniformity of ranges used in the determination of age-subgroups and the lack of consideration of sex-related differences, in agreement with the present study the authors found a rapid increase in SV reaching its peak in their 20 s followed by a slow fall from the beginning of the third decade of life (Fig. 4). Time profiles and percentiles 2.5th, 50th and 97.5th reported by Cattermole et al. [32] are similar to those presented here.

Cattermole et al. [32] is almost the only study that can be fully compared with the present results (i.e. it included a large number of subjects within a wide age range). However, they studied: (1) a small number of subjects (e.g. n = 96 [31, 35]), (2) considered few age-groups and/or wide age intervals in the same group (i.e. 20–40, 40–60, ≥ 60) [30], (3) defined sex-specific analysis as unnecessary despite the sex-related differences observed [16] and/or (4) included subjects with mild chronic illness [34], also evidenced an SV tendency which decreases with age, within the heterogeneity of the reported values. The tendency of SV (percentile 50th) to decrease with age was evidenced regardless of the measurement method used: three-dimensional-echocardiography [30], PCA [16], magnetic resonance [31, 35], transcutaneous continuous-wave Doppler [32–34], biplane-echocardiography (Fig. 4) [5]. The rates of SV change with age (slope of association between SV 50th-percentile and age) were not very different when compared to results of other authors among themselves to the present data.

The analysis of age-related RIs for CO showed there was a rapid increase in CO levels over the first two decades of life, followed by a fall throughout adult life (in both, males and females) (Fig. 2). Initially CO increases as HR increases, until HR reaches ~70–80 beats/min, then CO begins to fall in association with increases in HR; CO increases as the BSA increases (Fig. 2).

Temporal profiles for CO were similar to those reported by Cattermole et al. (2017) [32]. The authors found an increase in CO, until 20 years of age. Thereafter, an age-related reduction in CO was observed. Cattermole et al. [32] values for the 50th-percentile and those from the present work almost overlap. In turn, Solanki et al. [16] and Chan et al. [34] reported average values (50th-percentile)

for CO in adults and old age subjects similar to those found in the current data (Fig. 5).

Cardiac index values showed an important fall during the first two decades and then they remained practically unchanged (Fig. 3). CI values were associated with HR and BSA. CI increases in association with increases in HR, while lower CI values were observed in association with higher BSA values (Fig. 3). The described findings are in agreement with those reported by other authors (Fig. 5). In this regard, Cattermole et al. (2017) [32] and Ho et al. (2013) [33] described age-associated variations in CI, and their 50th-percentile curves were similar to the present ones. The present curves and those reported by Solanki et al. (2018) [16] and Chan et al. (2014) [34] for the 50th-percentile in adults are comparable.

Jointly analyzing the described results, it could be stated that CO rises steadily and reaches a peak in the 15–20 (teenage) years of life. Thereafter, it gradually declines. However, when considering CO adjusted for BSA (that it is to say CI), maximum (peak) would be observed < 6 years old, corresponding to a weight of 10–15 kg [32]. The variations in CO and CI could be related to and explained by the oxygen requirements of the tissues during those periods of life (i.e. those of maximum growth). High absolute CO levels in teenagers probably corresponds to accelerated growth and elevated oxygen consumption. From late teens onwards there is little or no growth, but a steadily declining level of physical activity was observed [32]. Overall, SV rises steadily until late teens then tends to decline gradually over the years, but when viewed against height (present data) or weight (Cattermole et al. data [32]), it shows a more linear positive relationship (Figs. 1, 4).

Conclusions

Sex, age, HR, and body height (for SV) or BSA (for CO and CI) are independent factors that explain PCA-derived hemodynamic values. Consequently, when constructing RIs of SV, CO and CI, it is necessary to discriminate using these variables.

This study provides the largest database concerning RIs and percentile curves of left ventricle SV(PCA), CO(PCA) and CI(PCA), obtained in children, adolescents and adults (3–88 years of age) from Latin-America (Uruguay), expressing results according to sex (males and females), age (year-to-year), HR (beats/minute), body height (in cm) and BSA (m²).

Ethics

All procedures were in accordance with the ethical standards of the institutional and/or the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual included in the study.

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