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Original article

Nomograms for two-dimensional echocardiography derived valvular and arterial dimensions in Caucasian children

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ABSTRACT

Background: Despite recent advances, current pediatric echocardiographic nomograms for valvular and arterial dimensions remain limited.
Methods: We prospectively studied healthy Caucasian Italian children by two-dimensional (2D) echocardiography. Echocardiographic measurements for 18 valvular and arterial dimensions were performed and models were generated testing for linear, logarithmic, exponential, and square root relationships. Heteroscedasticity was accounted for by White or Breusch–Pagan test. Age, weight, height, heart rate, and body surface area (BSA) were used as independent variables in different analyses to predict the mean values of each measurement. Structured *Z*-scores were then computed.
Results: In all, 1151 subjects (age 0 days to 17 years; 45% females; BSA 0.12–2.12 m^2) were studied. The Haycock formula was used when presenting data as predicted values (mean ± 2 SDs) for a given BSA and within equations relating echocardiographic measurements to BSA. The predicted values and *Z*-score boundaries for all measurements are presented.
Conclusions: We report echocardiographic nomograms for valvular and arterial dimensions derived from a large population of children. Integration of these data with those of previous reports would allow for a comprehensive coverage of pediatric 2D echocardiographic nomograms for measurement of 2D cardiac structures.

Introduction

Echocardiography is the front-line modality for the diagnosis and management of children with congenital and acquired cardiac disease, and quantification is an essential aspect of this modality [1–3]. In the pediatric age group, echocardiographic measurements need to be normalized according to age and somatic growth [1–5]. The availability of a robust range of normality is essential for accurate evaluation of disease severity [1–5]. Despite this, as we and others have underscored [6–12], most available nomograms have multiple numerical and methodological limitations [2,3,5]. Multiple efforts have been initiated both in Europe and in North America [6,13] for creation of more reliable nomograms. Our group recently reported echocardiographic nomograms for left ventricular, valvular, and arterial dimensions in neonates and infants up to 3 years of age, and bi-ventricular and bi-atrial dimensions for the entire pediatric age (0–18 years) [6]. These reports however lacked data for valvular and major vessels dimensions (i.e. aorta, aortic arch, and pulmonary arteries) in children aged 3–18 years. Although nomograms of vessel dimensions are of great relevance in the evaluation of several forms of heart disease, they are either limited (for example, for the aortic arch and pulmonary artery) [7,10,14] or very limited (for example, for the ascending aorta) [11,12,14]. For valvular

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dimensions, echocardiographic nomograms do exist but present significant limitations, affecting their accuracy and reproducibility [2,6].

The primary aim of this investigation was to establish pediatric nomograms for two-dimensional (2D) echocardiographic valvular and arterial measurements derived from a wide population of healthy neonates, infants and children. The secondary aims were (1) to identify the best body size parameter to normalize cardiac measurements and (2) to determine the effects of confounding factors such as gender and prematurity, and evaluate intra-observer variability of these measurements.

Materials and methods

Inclusion and exclusion criteria

These data are derived from healthy children partly presented in two recent investigations that evaluated other measurements [6,8]. The inclusion and exclusion criteria have been reported elsewhere [6,8]. Briefly, consecutive healthy Caucasian children evaluated from February 2012 to June 2015 in the outpatient pediatric cardiology department at the Fondazione G. Monasterio CNR-Regione Toscana of Massa for congenital heart disease (CHD) screening were prospectively recruited.

Only those with technically adequate echocardiographic examinations were enrolled in the study. The presence of intra-cardiac defects that represent normal circulatory physiology such as a patent ductus arteriosus with small left-to-right shunting in the first 3 days of life, or a patent foramen ovale, was considered normal [6,7]. Premature neonates were included only if they had an APGAR score $\geq$8, did not require ventilatory support, and had good clinical status [6,7].

All subjects with clinical, electrocardiographic, or echocardiographic evidence of congenital or acquired heart disease were excluded. Other exclusion criteria consisted of patients with known or suspected neuro-muscular disease, genetic syndromes, or chromosomal abnormalities; body mass index (BMI) $\geq$95th percentile for children $\geq$2 years old [15,16], or weight-for-length *Z*-score $\geq$2 based on the World Health Organization (WHO) Child Growth Standards for children <2 years old [15,16]; pulmonary hypertension; systemic hypertension (for children >4 years of age), connective tissue disease; or family history of genetic cardiac disease (such as Marfan syndrome or cardiomyopathy) [6,8,15,16]. All non-Caucasian subjects were also excluded to avoid racial variability bias.

All patients underwent a complete 2D, color flow Doppler, and tissue Doppler examination and images were digitally stored for subsequent offline analysis.

Approval for this study was obtained from the Local Ethics Committee. Parents or legal guardians of all the children were informed and accepted to participate in the study by signing a written consent.

Echocardiographic examination

Echocardiograms were performed using Philips iE33 systems (Philips Medical Systems, Bothell, WA, USA). Offline measurements were performed on a commercially available computer workstation (EnConcert, Philips Medical Systems, Andover, MA, USA) according to guidelines [1]. The measurements, the view from which they were obtained, and the point in the cardiac cycle are displayed in Table 1. For any given parameter, measurements were only made if excellent and unambiguous views were available. Thus, not all parameters were measured in all patients (Table 2).

Statistical methods

Statistical methods have been described in previous works [6,8,17–23] and will be briefly summarized. To examine the relationship between parameters of body size, heart rate, age, and each of the echocardiographic variables, multiple models using linear, logarithmic, exponential, and square root equations were tested [17–23]. Among the models that satisfied the assumption of homoscedasticity, the model with the highest R^2 value was considered to provide the best fit. The presence or absence of heteroscedasticity, a statistical term used to describe the behavior of variance and normality of the residuals, was tested by the White test and the Breusch–Pagan test as described previously [6,8,22,23]. To test the normality of residuals, the Shapiro–Wilk and Lilliefors (Kolmogorov–Smirnov) tests were used. Age, weight, height, heart rate (HR), and body surface area (BSA) [19] were used as independent variables in different regression analyses to predict the mean values of each echocardiographic measurement. The Haycock formula was used to calculate BSA [19]. Outliers to be

Table 1
Two-dimensional echocardiographic anatomical measurements.

Measurement	View	Description
1. Inferior vena cava	Sub-costal long axis	Maximal systolic dimension at the level of the diaphragm
2. Mitral valve annulus	Apical 4 chamber	Distance between the hinge points during diastole
3. Tricuspid valve annulus	Apical 4 chamber	Distance between the hinge points during diastole
4. Aortic valve annulus	Para-sternal long axis	Maximal distance between hinge points during systole
5. Sinuses of Valsalva	Para-sternal long axis	Maximum systolic dimension
6. Sino-tubular junction	Para-sternal long axis	Maximum systolic dimension
7. Transverse arch after the origin of innominate artery	Supra-sternal long axis	Maximum systolic dimension between the innominate and left carotid artery
8. Transverse arch after the origin of left carotid artery	Supra-sternal long axis	Maximum systolic dimension between the left carotid arteries and the left subclavian artery
9. Transverse arch after the origin of left subclavian artery	Supra-sternal long axis	Maximum systolic dimension immediately after the left subclavian artery
10. Aortic isthmus	Supra-sternal long axis	Maximum systolic dimension at the narrowest point beyond left subclavian artery
11. Distal aortic arch	Supra-sternal long axis	Maximum systolic dimension immediately beyond aortic isthmus
12. Aorta at diaphragm	Sub-costal long axis	Maximal systolic dimension at the level of the diaphragm
13. Superior vena cava	Supra-sternal long axis	Maximal systolic dimension
14. Pulmonary valve annulus	Para-sternal long axis	Distance between hinge points during systole
15. Main pulmonary artery	Para-sternal short axis	Maximal systolic dimension
16. Right pulmonary artery	Para-sternal short axis	Maximal systolic dimension immediately beyond the bifurcation
17. Left pulmonary artery	Para-sternal short axis	Maximal systolic dimension immediately beyond the bifurcation

Table 2
Number of valid measurements.

Measurements	N valid
IVC	1062
Tricuspid annulus	1093
Mitral annulus	1066
Aortic annulus	1102
Sinuses of Valsalva	1104
Junction	1088
Asc Ao	1074
Arch IA LCA	1096
Arch LCA-LSA	1102
Arch after LSA	1062
Isthmus	971
Thorac Ao	957
Abdominal Ao	1003
Pulmonary annulus	794
MPA	1085
LPA	1088
RPA	1101

Ao, aorta; Asc Ao, ascending aorta; IA, innominate artery; IVC, inferior vena cava; LCA, left carotid artery; LSA, left subclavian artery; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

Table 3
Distribution of BSA calculated with the Haycock formula.

BSA	*N*	%
[0.1–0.15)	7	0.6
[0.15–0.2)	88	7.6
[0.2–0.25)	139	12.1
[0.25–0.3)	86	7.5
[0.3–0.35)	53	4.6
[0.35–0.4)	67	5.8
[0.4–0.45)	61	5.3
[0.45–0.5)	43	3.7
[0.5–0.6)	67	5.8
[0.6–0.7)	78	6.8
[0.7–0.8)	83	7.2
[0.8–0.9)	66	5.7
[0.9–1.0)	61	5.3
[1.0–1.1)	53	4.6
[1.1–1.2)	47	4.1
[1.2–1.3)	31	2.7
[1.3–1.4)	26	2.3
[1.4–1.5)	33	2.9
[1.5–1.6)	27	2.3
[1.6–2.1)	35	3.0
Total	1151	100

BSA, body surface area.

excluded from analysis were identified visually, and using the Leverage values and the Studentized error residuals, the observations were omitted in the final analysis if they significantly deviated from the models.

The effects of confounding factors such as gender, prematurity, and type of delivery were also evaluated, as previously described [6,8]. Inter-observer and intra-observer agreements were calculated by overall agreement (percentage of observed-exact agreement) and was tested using repeated measures of ANOVA in 30 subjects. Two independent experienced pediatric cardiologists (M.C., N.A.) performed measurements. The *Z*-score, a standardized value that indicates by how many standard deviations a value is above or below the mean in a normally distributed population, has been recommended for normalization [4]. We computed *Z*-scores by dividing the residual values by the modeled standard error of the residual value. Values of $p < 0.05$ were considered statistically significant. As reported previously [6,8], the sample size necessary to obtain nomograms with sufficient statistical power [17–19] dividing the population into 6 major age stages (Group 1, neonates: 0–30 days; Group 2, infancy: 31 days to 12 months; Group 3, toddlers: 13 months to 2 years; Group 4, early childhood: 2–5 years; Group 5, middle childhood: 6–11 years; Group 6, early adolescence 12–17 years) is at least 840 patients [6,8]. The Statistical Package for Social Sciences (SPSS) Release 13.0 (Chicago, IL, USA) and Stata Version 10 for Windows (Stata Corp, 2001, College Station, TX, USA) were used for analyses.

Results

Subjects

In all, 1151 children were enrolled. Mean age of the study population was 48.9 ± 54.4 months (median 23 months, interquartile interval 2.1–86.7 months, range 0–17 years). Body weight

Table 4
Coefficients for regression equations relating echocardiographic measurements and body surface area, the standard error of the estimate, the determination coefficient. Normality test: Shapiro–Wilk and Lilliefors (Kolmogorov–Smirnov). Heteroscedasticity test (White test and Breusch–Pagan test). BSA Haycock. $(\ln[y] = a + b * \ln[x])$; *Z* value = $(\ln[\text{Measurement}] - (\text{Intercept} + B * \ln[\text{BSA}]))/\sqrt{\text{MSE}}$.

Measurement	Intercept	*B*	SEE ($\sqrt{}$MSE)	R^2	SW	KS	BP	W
IVC	2.406	0.826	0.240	0.849	0.000	0.008	0.993	0.702
Tricuspid annulus	3.187	0.466	0.140	0.904	0.085	0.200	0.313	0.681
Mitral annulus	3.161	0.471	0.087	0.931	0.456	0.200	0.037	0.425
Aortic annulus	2.750	0.515	0.088	0.942	0.166	0.200	0.678	0.553
Sinuses of Valsalva	3.051	0.481	0.092	0.927	0.415	0.200	0.160	0.081
Junction	2.797	0.512	0.098	0.928	0.184	0.200	0.138	0.467
Asc Ao	2.949	0.486	0.096	0.924	0.692	0.200	0.623	0.825
Arch IA LCA	2.742	0.515	0.121	0.895	0.241	0.200	0.638	0.886
Arch LCA-LSA	2.572	0.521	0.124	0.893	0.643	0.200	0.461	0.761
Arch after LSA	2.472	0.515	0.127	0.884	0.350	0.200	0.451	0.674
Isthmus	2.356	0.550	0.146	0.871	0.064	0.200	0.448	0.303
Thorac Ao	2.518	0.498	0.130	0.875	0.410	0.200	0.464	0.741
Abdominal Ao	2.352	0.477	0.122	0.874	0.060	0.200	0.000	0.000
Pulmonary annulus	2.908	0.538	0.113	0.911	0.175	0.200	0.010	0.069
MPA	2.945	0.489	0.112	0.899	0.407	0.200	0.673	0.075
LPA	2.383	0.569	0.159	0.856	0.087	0.029	0.003	0.059
RPA	2.397	0.558	0.145	0.873	0.155	0.054	0.049	0.058

Ao, aorta; Asc Ao, ascending aorta; BSA, body surface area; BP, Breusch–Pagan; IA, innominate artery; IVC, inferior vena cava; LCA, left carotid artery; LSA, left subclavian artery; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery; SEE, standard error of estimate; MSE, mean square error; KS, Kolmogorov–Smirnov; SW, Shapiro–Wilk; W, White.

ranged from 1.3 to 88 kg (median 12.0 kg; inter-quartile interval 4.9–26.0 kg); height ranged from 40.8 to 181 cm (median 86 cm; inter-quartile interval 57–124 cm); and BSA ranged from 0.12 to 2.12 m^2 (median 0.54 m^2; inter-quartile interval 0.28–0.94 m^2). The distribution for classes of BSA is shown in Table 3. Among neonates, 8.3% had been born premature and 11% had cesarean delivery. The population we report include subjects already evaluated in previous works [6,8].

Preliminary and final models

The measurements were first modeled with HR, age, weight, height, and BSA [6,15]. For all measurements, linear, logarithmic, exponential, and square root models were evaluated for best fit, and tests for heteroscedasticity were applied. As previously reported [6,8], BSA calculated by Haycock provided the best fit. The best-fit models for each measurement were the exponential ($\ln[y] = a + b * \ln[x]$) models because they satisfied the assumption of homoscedasticity and normality of residuals and showed the highest R^2 score (Table 4).

The predicted values and *Z*-score boundaries for all measurements are presented in Tables 5A and 5B, and Fig. 1(A)–(E).

Confounders

The influence of gender, and in neonates, prematurity and the type of delivery on measured parameters were evaluated by multiple linear regression models incorporating those factors as covariates along with BSA, HR, and age. A small but significant effect of gender was found in the model for half of the measurements, while an effect for the type of delivery was found

Table 5A
Predicted values (mean ± 2SD) of measured echocardiography variables expressed by body surface area (BSA) (Haycock).

	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
	1.02	1.43	1.82	2.18	2.54	2.88	3.22	3.55	3.87
IVC	**1.66**	**2.31**	**2.93**	**3.53**	**4.10**	**4.66**	**5.20**	**5.73**	**6.26**
	2.68	3.74	4.74	5.70	6.63	7.53	8.41	9.27	10.11
	6.26	7.56	8.65	9.59	10.44	11.22	11.94	12.62	13.25
Tricuspid annulus	**8.28**	**10.00**	**11.44**	**12.69**	**13.82**	**14.85**	**15.80**	**16.69**	**17.53**
	10.96	13.24	15.13	16.79	18.28	19.64	20.91	22.08	23.20
	6.70	8.11	9.29	10.32	11.25	12.09	12.88	13.61	14.30
Mitral annulus	**7.98**	**9.65**	**11.06**	**12.28**	**13.38**	**14.39**	**15.32**	**16.20**	**17.02**
	9.49	11.49	13.16	14.62	15.93	17.12	18.24	19.28	20.26
	4.01	4.94	5.73	6.42	7.06	7.64	8.18	8.70	9.18
Aortic annulus	**4.78**	**5.89**	**6.83**	**7.66**	**8.41**	**9.11**	**9.76**	**10.37**	**10.95**
	5.70	7.02	8.14	9.13	10.03	10.86	11.64	12.36	13.05
	5.81	7.06	8.11	9.03	9.85	10.61	11.32	11.98	12.60
Sinuses of Valsalva	**6.98**	**8.49**	**9.75**	**10.85**	**11.84**	**12.76**	**13.60**	**14.40**	**15.14**
	8.39	10.20	11.71	13.04	14.24	15.33	16.35	17.30	18.20
	4.15	5.10	5.91	6.63	7.28	7.87	8.43	8.95	9.45
Junction	**5.04**	**6.21**	**7.19**	**8.06**	**8.85**	**9.58**	**10.26**	**10.89**	**11.50**
	6.14	7.55	8.75	9.81	10.77	11.65	12.48	13.25	13.99
	5.14	6.27	7.21	8.03	8.77	9.46	10.09	10.69	11.25
Asc Ao	**6.23**	**7.59**	**8.73**	**9.73**	**10.63**	**11.46**	**12.23**	**12.95**	**13.63**
	7.55	9.20	10.58	11.79	12.88	13.88	14.82	15.69	16.51
	3.72	4.59	5.32	5.97	6.55	7.09	7.60	8.07	8.53
Arch IA LCA	**4.74**	**5.84**	**6.77**	**7.60**	**8.35**	**9.04**	**9.68**	**10.29**	**10.86**
	6.04	7.44	8.63	9.68	10.63	11.51	12.33	13.10	13.83
	3.08	3.80	4.42	4.96	5.46	5.91	6.34	6.74	7.12
Arch LCA-LSA	**3.94**	**4.87**	**5.66**	**6.36**	**6.99**	**7.58**	**8.12**	**8.64**	**9.12**
	5.05	6.24	7.25	8.15	8.96	9.71	10.41	11.07	11.69
	2.81	3.46	4.01	4.50	4.94	5.35	5.73	6.09	6.43
Arch after LSA	**3.62**	**4.46**	**5.17**	**5.80**	**6.37**	**6.90**	**7.39**	**7.85**	**8.29**
	4.67	5.75	6.67	7.48	8.21	8.89	9.53	10.12	10.69
	2.22	2.77	3.25	3.67	4.06	4.42	4.76	5.08	5.38
Isthmus	**2.97**	**3.72**	**4.35**	**4.92**	**5.44**	**5.92**	**6.37**	**6.80**	**7.20**
	3.98	4.98	5.83	6.59	7.28	7.93	8.53	9.10	9.65
	3.04	3.72	4.29	4.80	5.25	5.67	6.06	6.43	6.77
Thorac Ao	**3.94**	**4.82**	**5.57**	**6.22**	**6.81**	**7.35**	**7.86**	**8.33**	**8.78**
	5.11	6.25	7.22	8.07	8.83	9.54	10.19	10.81	11.39
	2.74	3.33	3.82	4.25	4.64	4.99	5.32	5.62	5.91
Abdominal Ao	**3.50**	**4.25**	**4.88**	**5.42**	**5.92**	**6.37**	**6.79**	**7.18**	**7.55**
	4.47	5.43	6.22	6.92	7.55	8.13	8.66	9.16	9.63
	4.23	5.27	6.15	6.93	7.65	8.31	8.93	9.51	10.07
Pulmonary annulus	**5.31**	**6.60**	**7.71**	**8.69**	**9.59**	**10.41**	**11.19**	**11.92**	**12.62**
	6.65	8.28	9.66	10.89	12.02	13.06	14.03	14.95	15.82
	4.93	6.01	6.92	7.71	8.43	9.09	9.71	10.28	10.83
MPA	**6.17**	**7.52**	**8.65**	**9.65**	**10.55**	**11.38**	**12.15**	**12.87**	**13.55**
	7.71	9.41	10.83	12.07	13.20	14.23	15.19	16.10	16.95
	2.13	2.68	3.16	3.58	3.97	4.34	4.68	5.01	5.32
LPA	**2.92**	**3.68**	**4.34**	**4.92**	**5.46**	**5.96**	**6.43**	**6.88**	**7.31**
	4.02	5.06	5.96	6.77	7.51	8.20	8.84	9.46	10.04
	2.28	2.85	3.35	3.79	4.20	4.58	4.93	5.27	5.59
RPA	**3.04**	**3.81**	**4.48**	**5.07**	**5.61**	**6.12**	**6.59**	**7.04**	**7.46**
	4.06	5.10	5.98	6.78	7.50	8.18	8.81	9.41	9.98

The estimates values are in bold, the values above are −2SD and the values below are +2SD.
Ao, aorta; Asc Ao, ascending aorta; IA, innominate artery; IVC, inferior vena cava; LCA, left carotid artery; LSA, left subclavian artery; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

Table 5B
Predicted values (mean ± 2SD) of measured echocardiography variables expressed by body surface area (BSA) (Haycock).

	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7
	4.50	5.11	5.71	6.29	6.86	7.42	7.98	8.52	9.06	9.59	10.12	10.64
IVC	**7.27**	**8.26**	**9.22**	**10.17**	**11.09**	**12.00**	**12.89**	**13.77**	**14.64**	**15.50**	**16.35**	**17.19**
	11.75	13.35	14.90	16.43	17.92	19.39	20.83	22.26	23.66	25.05	26.42	27.78
	14.42	15.50	16.49	17.42	18.30	19.13	19.92	20.68	21.41	22.11	22.78	23.44
Tricuspid annulus	**19.09**	**20.51**	**21.82**	**23.06**	**24.22**	**25.32**	**26.36**	**27.36**	**28.33**	**29.25**	**30.15**	**31.01**
	25.25	27.13	28.88	30.51	32.04	33.50	34.88	36.21	37.48	38.70	39.89	41.03
	15.59	16.76	17.85	18.87	19.83	20.74	21.60	22.43	23.23	24.00	24.74	25.46
Mitral annulus	**18.55**	**19.95**	**21.24**	**22.45**	**23.59**	**24.68**	**25.71**	**26.70**	**27.65**	**28.56**	**29.44**	**30.29**
	22.07	23.74	25.28	26.72	28.08	29.37	30.60	31.77	32.90	33.99	35.04	36.05
	10.08	10.92	11.69	12.43	13.12	13.78	14.41	15.02	15.60	16.16	16.71	17.24
Aortic annulus	**12.02**	**13.02**	**13.94**	**14.82**	**15.64**	**16.43**	**17.18**	**17.91**	**18.60**	**19.28**	**19.93**	**20.56**
	14.34	15.52	16.63	17.67	18.65	19.59	20.49	21.35	22.18	22.98	23.76	24.51
	13.75	14.81	15.79	16.72	17.58	18.41	19.20	19.95	20.67	21.37	22.04	22.70
Sinuses of Valsalva	**16.53**	**17.80**	**18.99**	**20.09**	**21.14**	**22.13**	**23.07**	**23.98**	**24.85**	**25.69**	**26.50**	**27.28**
	19.87	21.40	22.82	24.15	25.41	26.60	27.74	28.82	29.87	30.88	31.85	32.79
	10.38	11.23	12.02	12.77	13.48	14.15	14.80	15.41	16.01	16.59	17.14	17.68
Junction	**12.62**	**13.66**	**14.63**	**15.53**	**16.40**	**17.22**	**18.00**	**18.75**	**19.48**	**20.18**	**20.86**	**21.51**
	15.36	16.62	17.79	18.90	19.95	20.94	21.90	22.81	23.70	24.55	25.37	26.17
	12.29	13.25	14.13	14.97	15.75	16.50	17.21	17.89	18.55	19.18	19.79	20.39
Asc Ao	**14.89**	**16.05**	**17.13**	**18.13**	**19.09**	**19.99**	**20.86**	**21.68**	**22.48**	**23.24**	**23.98**	**24.70**
	18.04	19.45	20.75	21.97	23.13	24.22	25.27	26.27	27.24	28.16	29.06	29.93
	9.36	10.14	10.86	11.54	12.18	12.80	13.38	13.94	14.49	15.01	15.52	16.01
Arch IA LCA	**11.93**	**12.91**	**13.83**	**14.70**	**15.52**	**16.30**	**17.05**	**17.76**	**18.45**	**19.12**	**19.77**	**20.39**
	15.19	16.45	17.62	18.72	19.77	20.76	21.71	22.63	23.51	24.36	25.18	25.98
	7.83	8.48	9.10	9.67	10.22	10.74	11.23	11.71	12.17	12.62	13.05	13.47
Arch LCA-LSA	**10.03**	**10.87**	**11.66**	**12.39**	**13.09**	**13.76**	**14.40**	**15.01**	**15.60**	**16.17**	**16.72**	**17.26**
	12.86	13.93	14.94	15.88	16.78	17.63	18.45	19.23	19.99	20.72	21.43	22.12
	7.06	7.65	8.19	8.70	9.19	9.65	10.09	10.52	10.93	11.32	11.71	12.08
Arch after LSA	**9.11**	**9.86**	**10.56**	**11.22**	**11.85**	**12.44**	**13.01**	**13.56**	**14.09**	**14.60**	**15.09**	**15.57**
	11.74	12.71	13.61	14.47	15.27	16.04	16.78	17.48	18.16	18.82	19.45	20.07
	5.95	6.47	6.97	7.43	7.88	8.30	8.71	9.10	9.48	9.85	10.20	10.55
Isthmus	**7.96**	**8.67**	**9.33**	**9.95**	**10.55**	**11.12**	**11.66**	**12.19**	**12.69**	**13.18**	**13.66**	**14.12**
	10.67	11.61	12.49	13.33	14.13	14.89	15.62	16.32	17.00	17.65	18.29	18.91
	7.42	8.01	8.56	9.08	9.56	10.03	10.47	10.90	11.31	11.70	12.09	12.46
Thorac Ao	**9.62**	**10.39**	**11.10**	**11.77**	**12.40**	**13.01**	**13.58**	**14.14**	**14.67**	**15.18**	**15.67**	**16.16**
	12.47	13.47	14.39	15.26	16.09	16.87	17.62	18.33	19.02	19.69	20.33	20.95
	6.45	6.94	7.40	7.83	8.23	8.61	8.98	9.33	9.66	9.99	10.30	10.60
Abdominal Ao	**8.23**	**8.86**	**9.45**	**9.99**	**10.51**	**11.00**	**11.46**	**11.91**	**12.34**	**12.75**	**13.15**	**13.53**
	10.51	11.31	12.06	12.75	13.41	14.03	14.63	15.20	15.74	16.27	16.78	17.27
	11.10	12.06	12.96	13.81	14.61	15.38	16.12	16.83	17.51	18.18	18.82	19.44
Pulmonary annulus	**13.92**	**15.12**	**16.25**	**17.31**	**18.32**	**19.28**	**20.21**	**21.10**	**21.96**	**22.79**	**23.59**	**24.37**
	17.45	18.96	20.37	21.70	22.97	24.17	25.33	26.45	27.52	28.56	29.57	30.55
	11.84	12.76	13.62	14.43	15.20	15.92	16.61	17.28	17.91	18.53	19.12	19.70
MPA	**14.81**	**15.97**	**17.05**	**18.06**	**19.01**	**19.92**	**20.78**	**21.61**	**22.41**	**23.18**	**23.92**	**24.64**
	18.53	19.98	21.33	22.59	23.78	24.92	26.00	27.04	28.04	29.00	29.93	30.83
	5.90	6.44	6.95	7.43	7.89	8.32	8.75	9.15	9.55	9.93	10.30	10.66
LPA	**8.10**	**8.85**	**9.55**	**10.21**	**10.84**	**11.44**	**12.02**	**12.58**	**13.12**	**13.65**	**14.16**	**14.66**
	11.14	12.16	13.12	14.03	14.89	15.72	16.52	17.29	18.04	18.76	19.46	20.14
	6.18	6.74	7.26	7.75	8.22	8.67	9.10	9.52	9.92	10.31	10.69	11.06
RPA	**8.26**	**9.01**	**9.70**	**10.36**	**10.99**	**11.59**	**12.17**	**12.72**	**13.26**	**13.78**	**14.29**	**14.78**
	11.04	12.04	12.97	13.85	14.69	15.49	16.26	17.00	17.72	18.42	19.09	19.75

The estimates values are in bold, the values above are −2SD and the values below are +2SD.
Ao, aorta; Asc Ao, ascending aorta; IA, innominate artery; IVC, inferior vena cava; LCA, left carotid artery; LSA, left subclavian artery; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

in only one of the measurements (Table 6 panels A and B). However, because the effects were small and were not found for all measurements, gender and type of delivery were not included in the final models.

Inter-observer and intra-observer agreements

The inter-observer and intra-observer agreements were tested by repeated measures of ANOVA, and no significant differences were seen for any of the measurements (Table 7).

Discussion

Currently available pediatric nomograms present limitations [2–6], and scarce data for cardiac vessel dimensions is a major one. For example, limited data [7,10,14] are available for measurements, including ascending aorta and aortic arch at multiple levels, which are frequently necessary in daily practice. Moreover, various pediatric echocardiographic nomograms for pulmonary arteries, aortic annulus, aortic root, and atrioventricular valves have been reported [7,11,14] but they have methodological and numerical limitations [3–5]. Heterogeneity in the nomograms introduces a significant bias in the estimation of disease severity [2–6]. For a given subject and a given measurement, *Z*-scores generated by different nomograms may be widely discordant, and this may lead to errors and confusion [3–5]. We have previously reported normative echocardiographic data for various echocardiographic measures in neonates, infants, and children up to 3 years of age derived from a large cohort of healthy subjects [6,8]. Data for cardiac valves and

vessels [6] however were incomplete in those reports, and did not encompass the entire pediatric population. In particular, the age interval 3–18 years was not evaluated. The nomograms by Pettersen et al. [7] offer good coverage of most of the cardiac structures over the entire pediatric age (782 healthy children 0–18 years). However, that work [7] does not report normative data for some important structures evaluated in the present investigation, including the ascending aorta, the aortic arch at multiple levels, and the inferior vena cava.

The nomograms reported here offer several advantages compared to previous reports. First, we used a rigorous statistical approach, the relevance and advantages of which has been widely explained [1–6] and tested [6,8]. The coefficient of determination (R^2) relating echocardiographic measurements and BSA were all above 0.85, demonstrating high reproducibility and optimal fit of the proposed models. Secondly, a series of potentially relevant covariates were evaluated in this investigation, most of which have not been evaluated in prior studies [2–6]. Thirdly, these results in combination with our previous reports [6,8], including a recent paper reporting *Z*-scores for chamber dimensions and area (calculated on 1091 of the 1151 subjects of the present study), offer comprehensive normative data for 2D echocardiographic measurements in Caucasian European children. Our data are complementary to others reported in the literature [6–8,14], and could serve as a valuable tool for echocardiographic classification of CHD severity [4].

Strengths and limitations

The present study has several strengths. These data are derived from a homogeneous cohort of healthy children including a wide population of healthy neonates and infants. The study had prospective cohort design and robust statistical methodology. Careful attention was paid to potentially relevant confounders. A few limitations are also acknowledged. This investigation lacked data from different ethnic backgrounds. However, this eliminated bias of differing racial compositions, and would potentially allow comparisons with populations of other races and ethnicities. It is also important to remark that when individual cardiac structures are analyzed, our ranges of normality are similar to values reported by Pettersen et al. [7] that have been calculated on a multi-racial American population of healthy children. Thus the present nomograms may be reasonably adopted for children of different races and ethnicities.

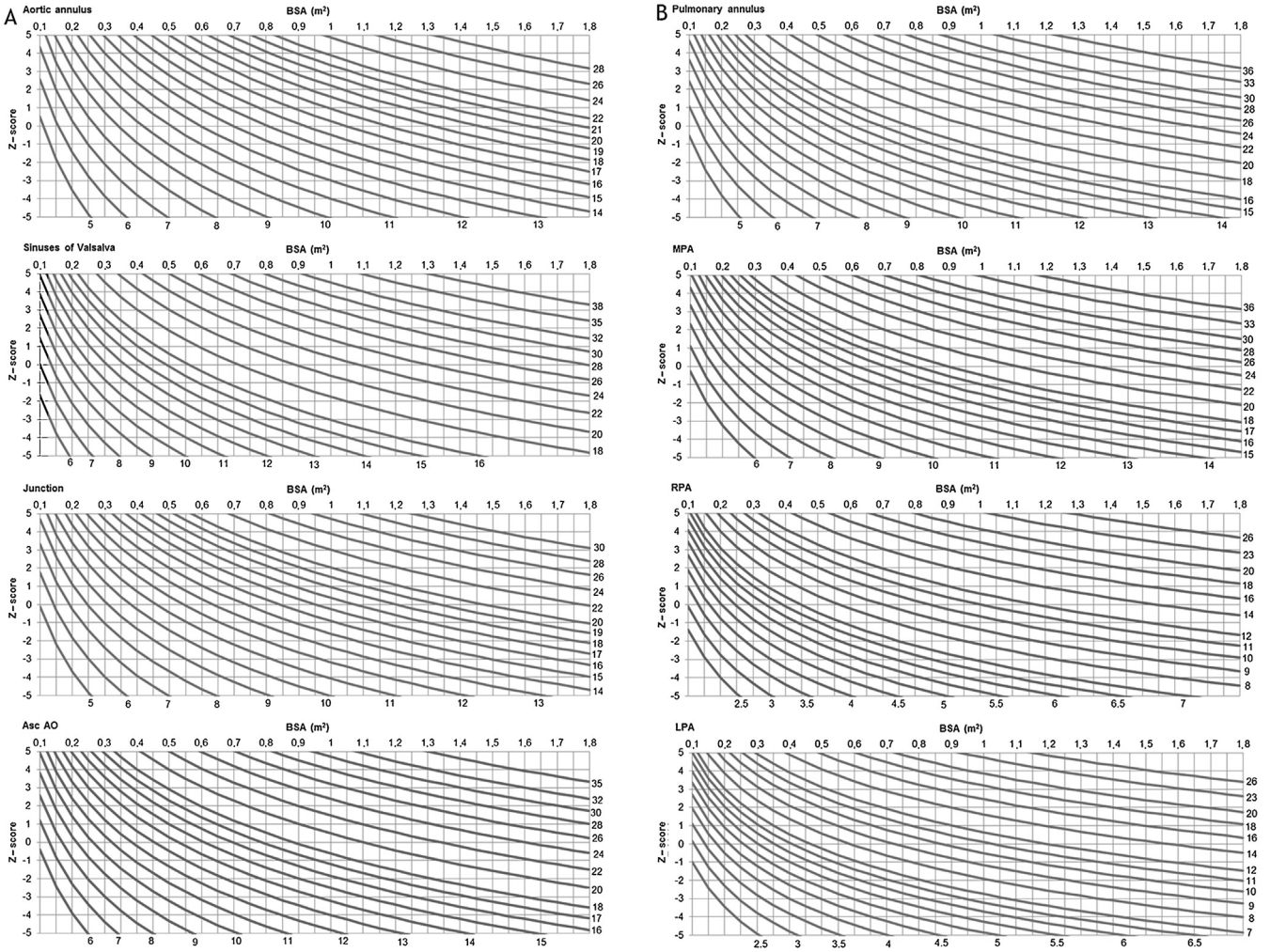

Fig. 1. (A) *Z*-score charts for aortic measurements at multiple levels according to body surface area (BSA) calculated by Haycock. Ascending aorta (Asc AO). (B) *Z*-score charts for pulmonary annulus and pulmonary arteries measurements according to BSA calculated by Haycock. Main pulmonary artery (MPA), right pulmonary artery (RPA), and left pulmonary artery (LPA). (C) *Z*-score charts for mitral and tricuspid valve measurements according to BSA calculated by Haycock. (D) *Z*-score charts for inferior vena cava (IVC), abdominal and thoracic aorta (AO) measurements according to BSA calculated by Haycock. (E) *Z*-score charts for aortic arch measurements at multiple levels according to BSA calculated by Haycock. Innominate artery (IA), left carotid artery (LCA), and left subclavian artery (LSA).

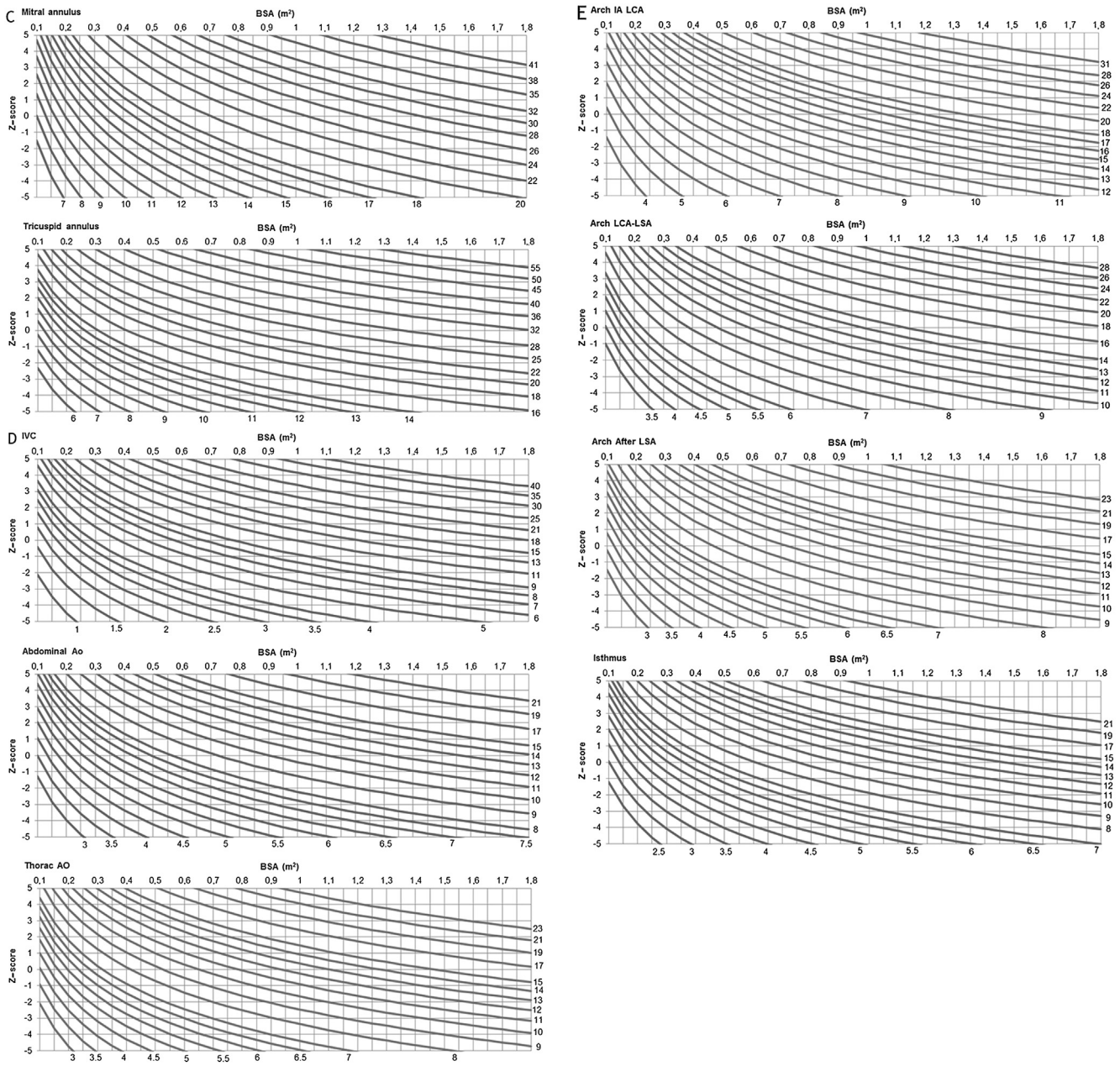

Fig. 1. (*Continued*).

Table 6A
Coefficients for regression equations relating echocardiographic measurements to body surface area of Haycock and gender. Measurement = intercept + B_1 * BSA + B_2 * gender(male).

Measurement	B_2	p value
Tricuspid annulus	0.030	<0.001
Mitral annulus	0.013	0.014
Aortic annulus	0.029	<0.001
Sinuses of Valsalva	0.043	<0.001
Junction	0.027	<0.001
Asc Ao	0.025	<0.001
Arch LCA-LSA	0.015	0.041
Thorac Ao	0.029	0.001
Abdominal Ao	0.032	<0.001
Pulmonary annulus	0.039	<0.001
MPA	0.023	0.001
LPA	0.020	0.040

Table 6B
Coefficients for regression equations relating echocardiographic measurements to body surface area of Haycock, gender, cesarean section and prematurity. Measurement = intercept + B_1 * BSA + B_2 * gender + B_3 * cesarean + B_4 * premature.

Measurement	B_3	B_4	p value
LPA	–	0.055	0.022

Ao, aorta; Asc Ao, ascending aorta; IA, innominate artery; IVC, inferior vena cava; LCA, left carotid artery; LSA, left subclavian artery; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

Table 7
Inter- and intra-observer analyses calculated on 30 subjects.

Measurements	*p* value Inter	*p* value Intra
IVC	0.405	0.898
Tricuspid annulus	0.613	0.834
Mitral annulus	0.536	0.899
Aortic annulus	0.437	0.891
Sinuses of Valsalva	0.367	0.855
Junction	0.634	0.829
Asc Ao	0.301	0.922
Arch IA LCA	0.424	0.995
Arch LCA-LSA	0.337	0.843
Arch after LSA	0.398	0.848
Isthmus	0.553	0.841
Thorac Ao	0.524	0.881
Abdominal Ao	0.635	0.857
Pulmonary annulus	0.641	0.848
MPA	0.429	0.849
LPA	0.369	0.847
RPA	0.393	0.916

Ao, aorta; Asc Ao, ascending aorta; IA, innominate artery; IVC, inferior vena cava; LCA, left carotid artery; LSA, left subclavian artery; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

Conclusions

We report 2D echocardiographic normative data for cardiac valvular and great vessels dimensions from a wide and homogeneous cohort of healthy neonates, infants, and children. This investigation addresses limitations of previous nomograms. Integrating these data with existing literature would allow accurate and comprehensive measurement of cardiac structures in children by 2D echocardiography. Further studies are required to reinforce these data, and to evaluate other parameters including functional and three-dimensional (3D) echocardiographic measurements, as well as non-Caucasian races and ethnicities.

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Conflict of interest

The authors declare that there is no conflict of interest.

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