

ORIGINAL ARTICLE

Reference values (Z-score) of inlet and trabecular portion diameters of the right ventricle: First description in Spanish healthy children[☆]



Luisa García-Cuenllas Álvarez^{a,*}, Federico Gutiérrez-Larraya Aguado^b, Enrique Maroto Álvaro^c, Ana Rodríguez-López Domingo^d, Pedro Luis Sánchez Fernández^e, Luis García-Guereta Silva^b, Félix Lorente Toledano^f

^a *Cardiología Pediátrica, Servicio de Pediatría, Hospital Sant Joan de Déu, Barcelona, Spain*

^b *Servicio de Pediatría, Cardiología Pediátrica, Hospital Universitario La Paz, Madrid, Spain*

^c *Cardiología Pediátrica, Servicio de Pediatría, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

^d *Servicio de Cardiología, Hospital Hospiten, Santa Cruz de Tenerife, Spain*

^e *Servicio de Cardiología, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain*

^f *Cardiología Pediátrica, Servicio de Pediatría, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain*

Received 22 March 2019; accepted 5 May 2019

Available online 20 February 2020

KEYWORDS

Reference values;
Z-score;
Echocardiography;
Right ventricle;
Children;
Paediatrics

Abstract

Introduction and objectives: Right ventricle (RV) measurements are crucial for certain congenital heart diseases and various cardiovascular conditions. Echocardiographic RV diameters are especially useful for its assessment. Paediatric echocardiographic data standardisation in normal subjects is complex, scarce, and heterogeneous. The aim of this study was to establish reliable and reproducible echocardiographic reference values (Z-score) of RV diameters in a healthy Spanish paediatric cohort.

Methods: A multicentre study was conducted on 661 healthy subjects (age range 0–18 years, 43.5% female). Several regression models were tested to examine the relationship between RV diameters and biometric variables. Heteroscedasticity and residual associations (Shapiro–Wilk and Breusch–Pagan tests) and confounding factors (gender, age, inter/intraobserver agreement) were considered for an unbiased standardisation.

Results: Structured Z-scores were computed for each RV diameter. Predicted mean value for each diameter was determined according to age, weight, height, and different body surface area. The Haycock formula provided the best fit for basal, midcavity, and longitudinal diameters (R^2 0.81, 0.82, 0.9). Confounders were not significant, and therefore not included in final models (inter/intraobserver agreement > 0.9).

[☆] Please cite this article as: Álvarez LG-C, et al. Valores de referencia (Z-score) de diámetros de porción de entrada y trabecular del ventrículo derecho: primera descripción en población pediátrica española sana. An Pediatr (Barc). 2020;92:147–155.

* Corresponding author.

E-mail addresses: luisa.cuenllas@gmail.com, lulugca@hotmail.com (L. García-Cuenllas Álvarez).

PALABRAS CLAVE

Valores de referencia;
Z-score;
Ecocardiografía;
Ventrículo derecho;
Pediatria

Conclusions: This study reports reference values for echocardiographic RV diameters from a Spanish healthy paediatric cohort using a rigorous statistical design. These Z-scores partly cover a gap in current paediatric cardiology and represent a relevant diagnostic tool for clinical practice, as well as a useful guide to decision making at any paediatric stage.

© 2020 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Valores de referencia (Z-score) de diámetros de porción de entrada y trabecular del ventrículo derecho: primera descripción en población pediátrica española sana

Resumen

Introducción y objetivos: La cuantificación del tamaño del ventrículo derecho (VD) es crucial en determinadas cardiopatías congénitas. Para su evaluación se recomiendan distintas técnicas de imagen, siendo más accesible la medición de diámetros ventriculares mediante ecocardiografía. En pediatría la normalización de parámetros ecocardiográficos es compleja, escasa y heterogénea. El objetivo de este estudio consistió en establecer Z-score de diámetros de VD fiables y reproducibles capaces de predecir valores de referencia en población pediátrica sana española.

Métodos: Estudio multicéntrico prospectivo de 661 pacientes sanos (edades 0–18 años, 43.5% mujeres). Los diámetros ecocardiográficos del VD se relacionaron con variables biométricas mediante distintas ecuaciones de regresión. Para su estandarización se analizaron factores de confusión (sexo, edad y variabilidad inter/intraobservador), heterocedasticidad y residuos (test Saphiro–Wilk y Breusch–Pagan).

Resultados: Se obtuvieron curvas de normalidad (Z-score) para cada diámetro del VD que permitieron predecir el valor medio de cada diámetro en función de la edad, peso, talla y distintas superficies corporales. La superficie corporal según fórmula de Haycock ofreció un excelente ajuste para los distintos diámetros basal, medial y longitudinal (R^2 0.81, 0.82, 0.9). Los factores de confusión no aportaron cambios significativos, por lo que no fueron incluidos en los modelos finales (variabilidad inter e intraobservador, CCI > 0.9).

Conclusiones: Se brindan valores de referencia de diámetros VD de población pediátrica sana. Las curvas de Z-score ofrecidas cubren una importante carencia en cardiología pediátrica y son aplicables a todos los grupos de edad para evaluar el tamaño del VD, de gran interés clínico en la práctica diaria.

© 2020 Asociación Española de Pediatría. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

In cardiology, many decisions regarding medical, catheter-based or open surgery interventions are made based on the size of cardiac structures. The follow-up of children that have or have not undergone correction of congenital heart defects may also depend on how heart growth and development deviates from what is expected. The detection of pathological changes in heart structures requires a precise definition of what is normal.

In paediatrics, the normal heart size varies based on various biometric determinants intrinsic to development and is affected by multiple confounding factors. Although guidelines for the assessment of the right ventricle (RV) in adults have been published recently,¹ there are currently no guidelines for the echocardiographic evaluation of the RV in paediatrics, and therefore the development of validated and reliable reference values is essential.² Establishing the size of the normal RV in the healthy paediatric population

would allow the optimal evaluation of patients with abnormalities, which would have an important impact on diagnosis and prognosis.

Our study focused in the measurement of the right ventricular diameter of healthy children to establish normal ranges (z-score distributions) useful for the detection of abnormal RVs with an easy and reproducible approach.

Methods

We conducted a multicentre, prospective, cross-sectional observational study in 661 healthy children recruited over 4 years in different paediatric cardiology clinics. We estimated that we would need 88 patients or more per age group to obtain representative data. We calculated this sample size for a 95% confidence level and a margin of error of 0.106 assuming a standard deviation of 0.5.

We classified children into age groups applying the age bands established by the World Health Organization (WHO):

newborn (0–28 days), infant (29 days to 24 months), young child (25 months to 5 years) child (6–10 years), adolescents (11–18 years).

Inclusion criteria

Healthy white children seeking care for a functional murmur or other reasons and without evidence of congenital or acquired structural abnormalities in the electrocardiogram (ECG) or echocardiographic examination. We considered a small, clinically insignificant ductus arteriosus in the first 3 days post birth and patent foramen ovale normal.

Exclusion criteria

We excluded patients with chest wall deformities, neuromuscular disease, syndromes or chromosomal disorders, high blood pressure, pulmonary hypertension, a family history of genetic disease (such as Marfan syndrome), age 19 years or greater or preterm birth.

Echocardiographic evaluation

Two ultrasound systems were used: the Phillips iE33 (Phillips Medical Systems; Bothell, Washington, USA) and the Hitachi Aloka Pro Sound Alpha 7 (Aloka Medical Ltd). The images were captured with multifrequency linear transducers (8 MHz transducers for newborns and similarly aged patients and 5 MHz transducers for patients of greater age and weight). Three cardiac cycles were recorded, and each measurement was taken twice (at different heart beats), with subsequent calculation of the mean of both values. Three experienced echocardiographers measured the basal, mid-cavity and longitudinal RV diameters in the 4-chamber apical view following a standardised protocol and guidelines for the measurement of the RV^{3,4} (Fig. 1); the observed interrater variability is described below. The images were obtained at the end of the diastole (right before the closure of the tricuspid valve, coinciding with the onset of the QRS complex) including the trabeculations (measuring up to the endocardial border) simultaneously with ECG recording. The analysis of the images was performed in the ultrasound system or with the clinical workstation post-processing software EchoPAC version 6.3.6 (GE Medical Systems). We did not find any significant differences based on the system used for image acquisition or for post-processing analysis. We only included patients with images of good quality and an appropriate echocardiographic window (visualization of endocardium and entire RV free wall).

Definitions and reference values

We defined normal RV diameter as a diameter corresponding to a z-score between -2 and $+2$. We used body surface area (BSA) formulas developed by de Haycock, DuBois, Mosteller, Boyd, Gehan and Meban to normalise RV diameters.^{5–10}

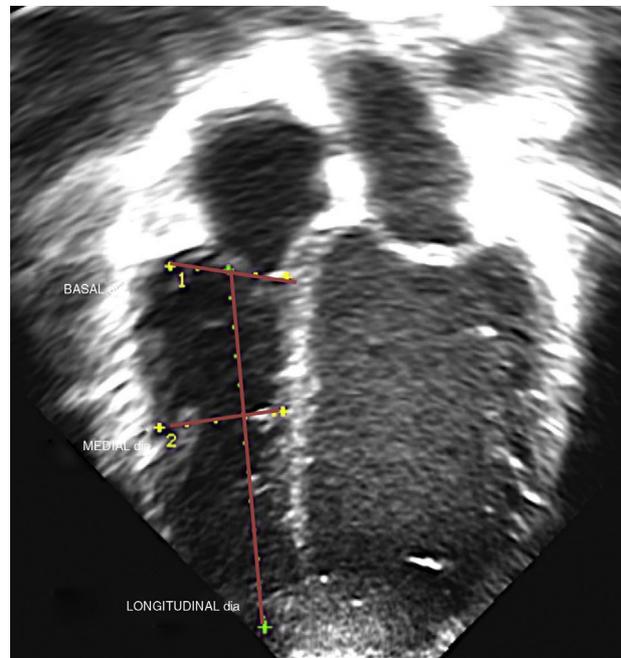


Figure 1 Example of standardised measurement of basal, mid-cavity and longitudinal diameters in the apical 4-chamber view.

Statistical analysis

We normalised the different diameters using parametric normalization models (z-score distribution) adjusted for age and biometric variables (weight, height and body surface area). We fitted different regression models (lineal, logarithmic, exponential, square root and cubic) to analyse the association of the parameters under study. For each regression model, we analysed the residuals using graphic methods, a test of normality (Shapiro–Wilk) and a test of heteroskedasticity (Breusch–Pagan test). We defined statistical significance as a *p*-value of 0.05 (two-tailed).

Of the models that met the assumptions, we selected the one that was simplest and offered the best fit (R^2) to develop the z-score curves. The z-score is a standardised value that expresses the number of standard deviations by which a specific value is above or below the mean of a normal population.

We used multivariate models and stratified analyses to assess the effect of sex as a confounder. We assessed interrater and intrarater agreement in 20 subjects and calculated the intraclass correlation coefficient (ICC) by means of repeated measures and mixed model analysis of variance.

Results

Study sample

Table 1 presents the demographic characteristics of the sample. Table 2 presents the right ventricular diameters by age group.

Table 1 Characteristics of the sample, expressed as mean \pm standard deviation or as absolute frequency (percentage).

Characteristics	Total	Newborns	Infants	Young children	Children	Adolescents
<i>n</i>	611	89	105	114	171	132
Age (years)	6.1 \pm 4.9	0.014 \pm 0.02	1.1 \pm 0.86	4.44 \pm 0.86	8.1 \pm 1.6	13.2 \pm 1.4
Sex (F/M)	266 (43.5%)/345 (56.5%)	41 (46%)/48 (54%)	48 (45.7%)/57 (54.3%)	50 (43.8%)/64 (56.2%)	68 (39.8%)/103 (60.2%)	59 (44.7%)/73 (55.3%)
Weight (kg)	25 \pm 18.4	3.17 \pm 0.4	9.1 \pm 3.6	18.5 \pm 4	29.8 \pm 9.4	51.76 \pm 11.3
Height (cm)	110.6 \pm 38.6	50 \pm 2.2	73.6 \pm 14	107.1 \pm 8.6	129.6 \pm 11.4	159.2 \pm 9
BSA (m ² . Haycock)	0.9 \pm 0.5	0.21 \pm 0.02	0.43 \pm 0.13	0.74 \pm 0.11	1.03 \pm 0.2	1.51 \pm 0.2

BSA, body surface area; F, female; M, male.

Table 2 Distribution of right ventricular diameters by age group.

RV diameters		Total	Newborns	Infants	Young children	Children	Adolescents
Basal (mm)	Mean \pm SD	22.2 \pm 7	12 \pm 2.1	16.4 \pm 3.1	21.9 \pm 3.3	25.6 \pm 4.4	29.5 \pm 4.3
	Median (IQR)	22.3 (17.2–27)	11.8 (10.9–12.8)	16.8 (13.5–18.4)	22 (19.7–24.1)	25 (22.1–28.3)	29.4 (27–32)
	Range	8.1–44.5	8.1–21	10.9–26.3	14.1–29.1	17.6–41.3	19–44.5
Mid-cavity (mm)	Mean \pm SD	20.1 \pm 6.3	11 \pm 1.8	14.9 \pm 2.9	19.8 \pm 2.7	23.1 \pm 3.5	26.7 \pm 4.6
	Median (IQR)	20.1 (15.5–24.5)	10.8 (10–11.7)	15.1 (12.5–17)	20 (18.1–21.7)	23 (20.4–25.1)	27 (23.6–30)
	Range	7.4–42	7.4–18	8.3–23	13–26	15–33.8	15.2–42
Longitudinal (mm)	Mean \pm SD	49 \pm 14.9	25.1 \pm 3.2	37.5 \pm 5.9	49.1 \pm 5	55.3 \pm 6.9	66.2 \pm 8.5
	Median (IQR)	50.7 (38.4–59)	24.8 (22.9–27.4)	37.7 (32.1–41.2)	49.5 (46–52.4)	55 (50.8–59.1)	65.8 (60.3–73)
	Range	17.5–87.9	17.5–33	27.7–51.6	36.5–65.8	36.6–77.2	44–87.9

IQR, interquartile range; RV, right ventricle; SD, standard deviation.

Selection of the optimal biometric parameter and regression model

Of the models that fulfilled the normal distribution of residuals and homogeneity of variance assumptions, we selected the one with the highest coefficient of determination, finding very small differences between the BSA and other biometric parameters used for indexing (Table 3). We selected the BSA calculated with the Haycock formula^{1,4,11,12} as the most suitable biometric parameter for normalization of RV diameters (R^2 values of 0.81, 0.82 and 0.9 for the different diameters), followed by weight, height and lastly age.

Table 3 Coefficient of determination for the association between right ventricular diameters and the main biometric variables.

R^2	Haycock BSA	Weight	Height	Age
Basal diameter	0.81	0.8	0.82	0.8
Mid-cavity diameter	0.82	0.81	0.82	0.8
Longitudinal diameter	0.9	0.9	0.89	0.9

BSA, body surface area.

The regression equations that best fitted the different diameters and the BSA corresponded to nonlinear models.

For the association of the basal diameter and the BSA using the Haycock formula, we used square root transformation:

$\ln(y) = a + b \times \sqrt{x}$, so that $z = (\ln[\text{measured value}] - [a + b \times \sqrt{SC}]) / \sqrt{SEM}$, where SEM stands for the standard error of the mean.

Exponential equations provided the best fit for the mid-cavity and longitudinal diameters:

$\ln(y) = a + b \times \ln(x)$, so that $z = (\ln[\text{measured value}] - [a + b \times \ln(\text{BSA})]) / \sqrt{SEM}$

These equations satisfied the assumptions of homoskedasticity and normality of residuals with excellent R^2 values (Table 4), allowing a more homogeneous variance across the full BSA range.

Parametric normalization: z-score curves

We proceed to present the z-score curves for the different RV diameters indexed by BSA (Haycock formula) accompanied by the regression equation, normalised residual plot and homoskedasticity (Fig. 2). The z-score of a given RV diameter can be identified by finding the diameter value in the z-score curves or consulting Table 5.

Table 4 Regression equations associating right ventricular diameters with body surface area (Haycock formula). Shapiro-Wilk test for normality. Breusch-Pagan test for heteroskedasticity. Standard error of estimate. Coefficient of determination.

	Coefficients		$\sqrt{\text{SEM}}$	R^2	Normal residuals	Heteroskedasticity
	Constant (a)	Haycock (b)			Shapiro-Wilk	Breusch-Pagan
$\ln(y) = a + b \times \sqrt{x}$, with $z = (\ln[\text{measured value}] - [a + b \times \sqrt{\text{BSA}}]) / \sqrt{\text{SEM}}$						
Basal	2.02	1.16	0.15	0.81	0.427	0.179
$\ln(y) = a + b \times \ln(x)$, with $z = (\ln[\text{measured value}] - [a + b \times \ln(\text{BSA})]) / \sqrt{\text{SEM}}$						
Mid-cavity	3.11	0.46	0.15	0.82	0.172	0.859
Longitudinal	4.01	0.48	0.11	0.9	<0.01	0.282

BSA, body surface area; SEM, standard error of the mean.

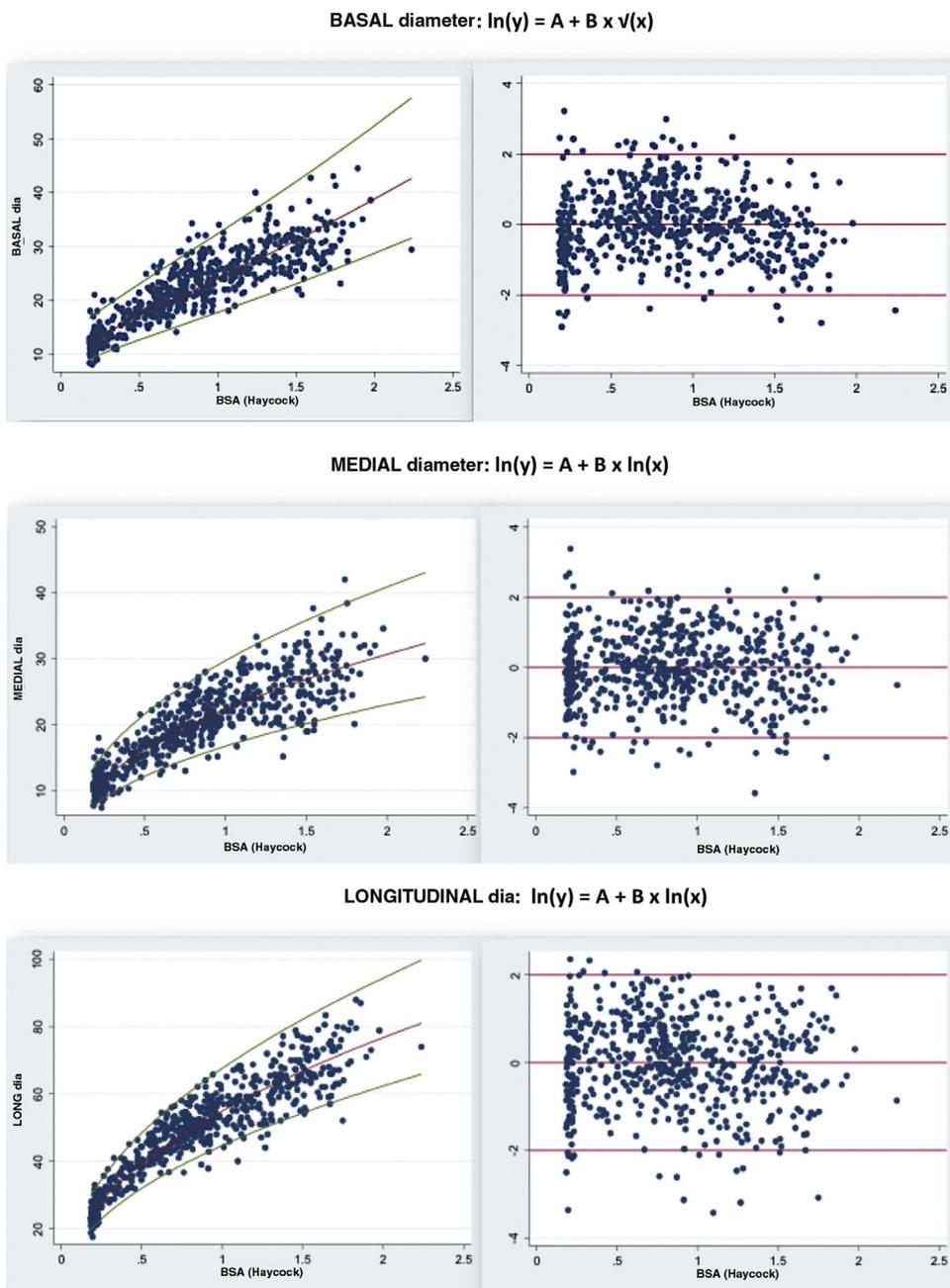


Figure 2 Right: z-score curves for the different right ventricular diameters indexed by body surface area (Haycock formula). Left: regression model, standardised residuals and homoskedasticity.

Table 5 Right ventricular values normalised by body surface area (Haycock formula) corresponding to z-scores of 0, +2 and -2.

		Basal diameter			Mid-cavity diameter			Longitudinal diameter		
Model	Equation	$\ln(y) = a + b \times \sqrt{(x)}$			$\ln(y) = a + b \times \ln(x)$			$\ln(y) = a + b \times \ln(x)$		
	Coefficients	Constant (a)	2.02		Constant (a)	3.11		Constant (a)	4.01	
		Haycock (b)	1.16		Haycock (b)	0.46		Haycock (b)	0.48	
	$\sqrt{\text{SEM}}$	0.15			0.15			0.11		
z-score	BSA Haycock	-2	0	2	-2	0	2	-2	0	2
0.10		8.1	10.9	14.7	5.8	7.8	10.5	14.7	18.3	22.8
0.20		9.4	12.7	17.1	7.9	10.7	14.4	20.4	25.5	31.7
0.30		10.5	14.2	19.2	9.5	12.9	17.4	24.8	30.9	38.6
0.40		11.6	15.7	21.2	10.9	14.7	19.9	28.5	35.5	44.3
0.50		12.7	17.1	23.1	12.1	16.3	22.0	31.7	39.5	49.3
0.60		13.7	18.5	25.0	13.1	17.7	23.9	34.6	43.2	53.8
0.70		14.7	19.9	26.9	14.1	19.0	25.7	37.3	46.5	57.9
0.80		15.8	21.3	28.7	15.0	20.2	27.3	39.8	49.5	61.7
0.90		16.8	22.7	30.6	15.8	21.4	28.8	42.1	52.4	65.3
1.00		17.8	24.0	32.5	16.6	22.4	30.3	44.3	55.1	68.7
1.10		18.9	25.4	34.4	17.4	23.4	31.6	46.3	57.7	71.9
1.20		19.9	26.9	36.3	18.1	24.4	32.9	48.3	60.2	75.0
1.30		21.0	28.3	38.2	18.7	25.3	34.1	50.2	62.5	77.9
1.40		22.0	29.7	40.1	19.4	26.2	35.3	52.0	64.8	80.8
1.50		23.1	31.2	42.1	20.0	27.0	36.5	53.8	67.0	83.5
1.60		24.2	32.7	44.1	20.6	27.8	37.6	55.5	69.1	86.1
1.70		25.3	34.2	46.2	21.2	28.6	38.6	57.1	71.1	88.7
1.80		26.5	35.7	48.2	21.8	29.4	39.7	58.7	73.1	91.1

BSA, body surface area; SEM, standard error of the mean.

Analysis of confounders

We fitted multivariate models that included sex as a confounder. We found a statistically significant ($P < .05$) but negligible effect. Afterwards, we performed an analysis stratified by age group in which we also included sex. This yielded estimates that were nearly equal, so we decided not to correct the different models for sex.

We analysed the effect of age on the different ventricular diameters, and found high R^2 values (0.79, 0.8, 0.9) demonstrating a strong association between these variables.

In the neonatal group, we assessed the association between ventricular diameters and weight. The highest R^2 was 5.7%, and the assumption of the normal distribution of residuals was not met. We also assessed the association between ventricular diameters and the Meban BSA formula. When we fitted different models to establish this association, we found that the best coefficient of determination was 4% and the assumption of the normality of residuals was not met.

In the adolescent group we analysed the association between ventricular diameters and height. The best model that met the assumptions corresponded to an R^2 of 14%.

Inter- and intrarater reliability

We assessed reliability in 20 patients and found a high level of agreement for all measures ($\text{ICC} > 0.9$). The highest inter-rater variability corresponded to the mid-cavity diameter.

Comparison with the literature

We present z-score curves based on data from the population of healthy white children in Spain. Other authors have also developed z-score curves in the paediatric population. We thought it would be interesting to compare our z-score curves with those published by Koestenberger et al.¹³ and Cantinotti et al.,¹¹ graphically and through calculation of the coefficient of agreement.

Cantinotti et al. normalised values using the Haycock BSA formula and published their regression models. Fig. 3 provides a graphical comparison of the z-score curves obtained in our study with those obtained by Cantinotti et al. We found good agreement in the mid-cavity and longitudinal diameters (concordance indices of 0.9 and 0.76) and an underestimation of the basal diameter (concordance index of 0.36).

Koestenberger et al. indexed RV measures by BSA (Mosteller formula) and age. Their article did not include the equations of the regression models, so we were unable to calculate concordance indices. We made a subjective, visual comparison of the z-score curves obtained in our study with those obtained by Koestenberger et al. and considered that there was greater agreement in the mid-cavity and longitudinal diameters, and once again underestimation of the basal diameter z-scores.

Given the discrepancy we had observed in the basal diameter values, we compared the values obtained by Cantinotti et al. with those obtained by Koestenberger et al. normalising the RV diameters by BSA. Once again, we found a good

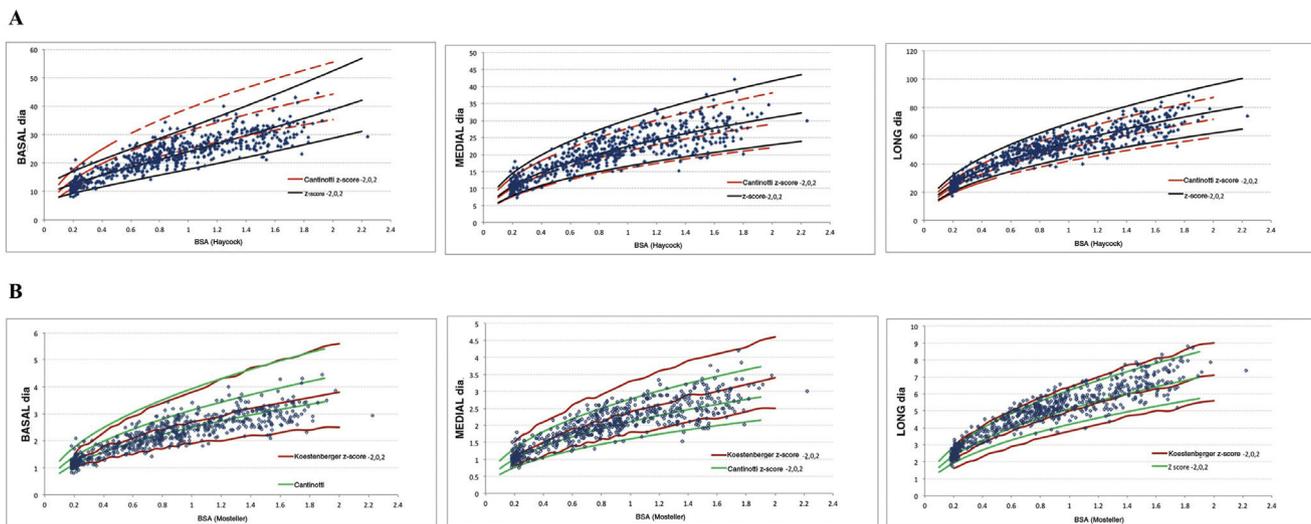


Figure 3 Comparison of z-score curves for right ventricle diameters obtained by different authors.

correlation in the mid-cavity and longitudinal diameters but found disagreement in the basal diameters.

Discussion

The assessment of the RV with imaging techniques is essential, as many medical and surgical management decisions are made based on the dimensions of this chamber. Our study focused on the use of 2D echocardiography because it is a simple, inexpensive and widely available technique. The dimensions of the RV at the inlet and in the trabecular zone are optimal measures due to their repeatability, easy measurement in the apical 4-chamber view and an ample body of evidence supporting their use. However, we must not forget the RV outlet, which is significantly dilated in some congenital heart diseases.

The need to standardise echocardiographic parameters in paediatric cardiology stems from another obvious need, which is to establish reference values. Once *normal* is known and defined, it will be possible to detect the pathological. Despite these essential needs, expressed in the main echocardiography guidelines,^{4,14} efforts to standardise measurements of heart structures in the paediatric population have yet to bear fruit. Reference value ranges have been proposed for most structures,¹⁵ but there are no specific guidelines for the evaluation of the RV in the paediatric population, and the available guidelines for its evaluation in adults^{2,3} cannot be applied to children because the measurements are not indexed by any biometric parameter (such as body surface area).

Several authors¹² have demonstrated that despite advances in methodology, the normalization of echocardiographic measures in paediatrics has not been properly validated and is thus not reliable.^{11,13}

Our study fulfils the required criteria for normalization of echocardiographic measures described in the literature^{12,16,17} as follows:

- 1 We collected RV dimensions following a uniform protocol that adhered to current guidelines.
- 2 The cohort under study was homogeneous, with similar sizes for each age group and all participants being white, which makes it possible to obtain normal values for a specific population (Spanish and/or white) and to make comparisons with populations of similar characteristics and difference race.
- 3 We selected the most suitable biometric parameter for the normalization of right ventricular diameters (BSA calculated with Haycock formula), followed by weight, height and age.

The normalization of echocardiographic parameters in paediatrics is challenging due to allometry (the influence of bodily growth on the heart chambers) and other confounders. This results in substantial variability and disagreement in the measurements of a given parameter that has an impact on clinical decision-making. To address this problem, echocardiographic values are adjusted based on biometric variables (weight, height or BSA), as this allows to take into account the change in cardiac dimensions that occurs in growing children. However, there is still disagreement as to which is the most suitable biometric variable to use for this purpose. Several authors propose that, overall, the body surface area is the best indicator of somatic growth, performing better than weight or height alone in the paediatric population.^{1,18} In our study, the best fit also corresponded to the BSA (although followed closely by weight) with a lesser influence of height or age.

The BSA is not a perfect parameter, as depending on the formula used in its calculation different normalised values will be obtained from the same measurement, with a degree of variation that will depend on the magnitude of the weight or height of the patient. Considering this issue, in our study we analysed the differences in the values obtained using different BSA formulas and found an R^2 greater than 0.99 for their association, which suggests that any BSA formula could be used for normalising RV diameter values.

4 None of the variables followed a normal distribution, which extended to the residual distribution and was associated with heteroskedasticity. To counteract these phenomena, we applied specific statistical methods^{15–17} and parametric methods: development of z-score charts for the association of RV diameters (dependent variable) and body surface area (independent variable) using regression equations capable of estimating the theoretical mean of the RV diameter for a given BSA.

The use of z-scores is essential in paediatrics for estimating the distribution of measured values through the range of body sizes in the normal population, thus allowing the identification of abnormal dimensions. Their use is endorsed and recommended by the United States echocardiography guidelines as the best parametric normalization method for the purpose of establishing reference values. However, z-scores are not absolutely accurate and should always be interpreted taking into account the clinical context of the patient.¹⁹

5 We fitted linear and nonlinear regression models. We selected nonlinear models (exponential and square root) because they were simpler and allowed a correct fit (visual and statistical) throughout the sample.

To prevent heteroskedasticity and obtain results that could be extrapolated to the general population, we used logarithmic and square root transformation in the regression equations, which we subsequently assessed with the Breusch–Pagan test. We then used the Shapiro–Wilk test to select models with a normality of the error distribution and a high predictive power.

6 We analysed confounding factors and found no significant changes in the results.

The confounding factors we analysed in our sample were age, sex and inter- and intrarater reliability. We fitted multivariate regression models and used analysis of variance to assess the effect of these factors on ventricular diameters.

In our study, we found a strong association of age with RV diameters as evinced by high R^2 values nearing the values achieved with the BSA, suggesting a strong association between both variables. There is evidence that specific analysis is necessary in the extreme age groups (newborns and adolescents), subsets of the population in which the use of the BSA for indexing is more controversial. Ahn et al.^{20–22} claim that weight provides a better fit in newborns and Motz et al.^{23,24} propose the use of height in adolescents, and therefore we analysed the fit for these two variables. We found that the coefficients of determination were significantly lower and that the assumption of the normal distribution of residuals was not met. It is possible that the disagreement with our findings is due to these authors analysing different variables in their studies.

We found a significant effect of sex, but negligible, and therefore sex was not included in the definitive models. Many articles provide evidence on the effect of sex on cardiac dimensions in adults,^{25–27} whereas in paediatrics, Cantinotti et al. reported findings similar to ours.^{1,11,12} It is possible that sex becomes relevant with increasing age,²⁸

which would explain the discrepancies found between the results in paediatric and adult studies.

Lastly, the inter-rater and intrarater reliability analysis yielded a high ICC (0.89–0.98), which supports the reproducibility of the study.

7 We compared the obtained z-score curves with those published in the literature.

Our results exhibited a high degree of agreement with those published by Koestenberger¹³ and Cantinotti¹² for the mid-cavity and longitudinal diameters indexed by BSA, but not for the basal diameter. Upon noticing this discrepancy, we compared these two sources with each other, and once again found a good correlation between the mid-cavity and longitudinal diameters and disagreement in the basal diameters. It may be worth considering whether age could be the optimal parameter to normalise the basal diameter (or a different parameter other than the BSA) or that there may be factors associated with the measurement of this diameter that interfere with the estimation of its dimension, such as the variability in the basal diameter associated with the apical 4-chamber view. On the other hand, the disagreement found in z-score distributions supports the development of local standards.

Conclusions

By obtaining a representative sample and applying robust statistical methods and a standardised imaging protocol, we were able to develop accurate and reliable ventricular diameter z-score curves.

We have established reference values, which are scarce in the current literature, to allow accuracy and precision in the echocardiographic measurement of the RV, which is extremely useful in clinical practice.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

I thank every author involved in this publication. Without their help and guidance, my dissertation and this project would not have been possible.

References

1. Lang R, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39.
2. Cantinotti M, Scalese M, Molinaro S, Murzi B, Passino C. Limitations of current echocardiographic nomograms for left ventricular, valvular and arterial dimensions in children: a critical review. *J Am Soc Echocardiogr.* 2012;25:142–82.
3. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic

- assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713.
4. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the pediatric measurements writing group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010;23:465–95.
 5. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr*. 1978;93:62–6.
 6. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med*. 1916;17:863–71.
 7. Mosteller RD. Simplified calculation of body-surface area. *New Engl J Med*. 1987;317:1098.
 8. Boyd E. The growth of the surface area of the human body. Minneapolis: University of Minnesota Press; 1935.
 9. Gehan EA, George SL. Estimation of human body surface area from height and weight. *Cancer Chemother Rep*. 1970;54:225–35.
 10. Meban C. The surface area and volume of human fetus. *J Anat*. 1983;137:271.
 11. Cantinotti M, Scalese M, Murzi B, Assanta N, Spadoni I, De Lucia V, et al. Echocardiographic Nomograms for chamber diameters and areas in caucasian children. *J Am Soc Echocardiogr*. 2014;27:1279–92.
 12. Cantinotti M, Scalese M, Murzi B, Assanta N, Spadoni I, Festa PL, et al. Echocardiographic Nomograms for Ventricular, Valvular and Arterial Dimensions in Caucasian Children with a Special Focus on Neonates, Infants and Toddlers. *J Am Soc Echocardiogr*. 2014;27:179–91.
 13. Koestenberger M, Nagel B, Ravekes W, Avian A, Burmas A, Grangl G, et al. Reference Values and Calculation of z-Scores of Echocardiographic Measurements of the Normal Pediatric Right Ventricle. *Am J Cardiol*. 2014;114:1590–2159.
 14. Lemmer CE, Engel ME, Satanfliet JC, Mayosi BM. Reference intervals for the echocardiographic measurements of the right heart in children and adolescents: a systematic review. *Cardiovascular Ultrasound*. 2014;12:1–17.
 15. Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, et al. Relationship of Echocardiographic Z Scores Adjusted for Body Surface Area to Age, Sex, Race, and Ethnicity The Pediatric Heart Network Normal Echocardiogram Database. *Circ Cardiovasc Imaging*. 2017;10:1–23.
 16. Mawad W, Drolet C, Dahdah N, Dallaire F. A review and critique of the statistical methods used to generate reference values in pediatric echocardiography. *J Am Soc Echocardiogr*. 2013;26:29–37.
 17. Colan SD. The why and how of Z scores. *J Am Soc Echocardiogr*. 2013;26:38–40.
 18. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. *J Appl Physiol*. 2005;99:445–57.
 19. Cantinotti M, Kutty S, Franchi E, Paterni M, Scalese M, Iervasi G, et al. Pediatric echocardiographic nomograms: What has been done and what still needs to be done. *Trends Cardiovasc Med*. 2017;27:336–49.
 20. Ahn Y. Formula and scale for body surface area estimation in high-risk infants. *Coll Antropol*. 2010;34:1273–80.
 21. Ahn Y, Garruto RM. Estimation of body surface area in newborns. *Acta Paediatrica*. 2008;97:366–70.
 22. Levy P, Dioneda B, Holland MR, Sekarski TJ, Lee CK, Mathur A, et al. Right Ventricular Function in Preterm and Term Neonates: Reference Values for Right Ventricle Areas and Fractional Area of Change. *J Am Soc Echocardiogr*. 2015;28:559–69.
 23. Jain A, Mohamed A, El-Khuffash A, Connelly KA, Dallaire F, Jankov RP, et al. A Comprehensive Echocardiographic Protocol for Assessing Neonatal Right Ventricular Dimensions and Function in the Transitional Period: Normative Data and Z scores. *J Am Soc Echocardiogr*. 2014;27:1293–304.
 24. Motz R, Schumacher M, Nurnberg J, Viemann M, Graffmüller S, Fiedler K, et al. Echocardiographic Measurements of Cardiac Dimensions Correlate Better With Body Length Than With Body Weight or Body Surface Area. *Pediatr Cardiol*. 2014;35:1327–36.
 25. D'Oronzio U, Senn O, Biaggi P, Grunner C, Jenni R, Tanner FC, et al. Right heart assessment by echocardiography: gender and body size matters. *J Am Soc Echocardiogr*. 2012;25:1251–8.
 26. Pfaffenberger S, Bartko P, Graf A, Pernicka E, Babayev J, Lolice E, et al. Size Matters! Impact of Age, Sex, Height, and Weight on the Normal Heart Size. *Circ Cardiovasc Imaging*. 2013;6:1073–9.
 27. Willis J, Augustine D, Shah R, Stevens C, Easaw J. Right ventricular normal measurements: time to index? *J Am Soc Echocardiogr*. 2012;25:1259–67.
 28. Dallaire F, Bigras JL, Prsa M, Dahdah N. Bias related to body mass index in pediatric echocardiographic Z scores. *Pediatr Cardiol*. 2015;36:667–76.