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ORIGINAL PAPER

How should we determine normal echocardiographic right ventricle function reference values in pediatrics?

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Abstract

Several models have been used to establish pediatric Z-scores for echocardiographic right ventricle (RV) variables. This study aimed to determine the most appropriate mathematical model for RV function reference values in pediatrics. Prospective cross-sectional study among 314 healthy children ages 2 days to 18 years (46% female, 88 infants, 26 neonates, 226 children). RV parameters (S′, E′, A′ waves, TEI index, TAPSE) were modelized with four explanatory variables: age, height, weight and body surface area. Four mathematical models were applied: a linear model, a polynomial model of degree 2, a linear regression model by spline with free knot, and a polynomial regression model of degree 2 by spline with a free knot. The choice of the best method used the adjusted coefficient of determination (aR^2). The modelization of RV variables did not follow a linear model. A single explanatory variable could not determine all Z-scores, as specific and independent variables were required for each parameter. The quadratic spline model best adjusted the modelization of RV variables. The S′ wave was best modelized by the spline model with the weight (knot at 6.86 kg). The E′ wave was best modelized by the spline model with the age (knot at 0.29 years). The A′ wave was best modelized by the model with the height (knot at 81 cm). The TAPSE was best modelized by the spline model with the weight (knot at 9.04 kg). The spline regression models best applies to echocardiographic RV reference values in pediatrics.

Keywords Heart ventricles · Echocardiography · Child · Pediatrics · Diagnosis imaging · Mathematics

Introduction

In the context of medical and surgical advances in pediatric cardiology, increased attention has been recently given to heart diseases involving the right ventricle (RV) [1]. The care of these young patients includes complex surgical reconstruction of the right outflow tract, balloon or stenting in the pulmonary arteries and advance pharmaceutical therapies for pulmonary arterial hypertension. As a result, echocardiographic assessment of RV function has become essential in pediatric cardiology. However, this evaluation is based on the existence of reliable normal values for each RV index, taking into account the growth from the neonate to the teenager.

Several mathematic models have been used to establish pediatric Z-scores for the main RV function variables: tricuspid annular plane systolic excursion (TAPSE) [2–4], pulsed wave tissue Doppler imaging (TDI) of the tricuspid annulus [5, 6], and index of myocardial performance (TEI index) [6–10]. Most authors have used linear regression models. However, the relevance of a linear model might raise questions when considering the non-linear child's growth between birth and adulthood, along with the significant physiological change defining RV hemodynamic. Wang et al. recently stated that a cubic polynomial model best described the RV norms in 515 children [11]. Other

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more flexible mathematical models such as spline functions have been applied to medicine in oxidation curves or normal values for spirometry, but to our knowledge, not in echocardiography [12–14].

The aim of our study was to determine whether a non-linear mathematical model could improve the quality of Z-scores for RV function reference values in normal children.

Method

Study design and patients

This prospective cross-sectional study was carried out over 6 months in a tertiary care pediatric cardiology department. We screened children aged 0–18 years referred to the outpatient pediatric cardiology consultation for murmur, chest pain, palpitations or sport certificate. Only those with normal physical examination, electrocardiogram and echocardiogram were eligible for the study. Children with any chronic disease or under any treatment were not included. This study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles, after approval of the CCTIRS Ethics Committee (national advisory committee for data processing in health research). Informed consent was obtained from all parents or legal guardians.

Echocardiographic measurements

Echocardiographic examinations were performed using an IE-33 ultrasound (Philips Healthcare). The study of RV function can be evaluated using several imaging and functional modalities reflecting RV systolic and diastolic function. The most commonly used echocardiographic indices of RV systolic function are TAPSE, which reflect the extent of contraction, myocardial velocity indices such as the tricuspid annular plane maximal systolic velocity and hemodynamic indices such as interval indices (TEI index), which reflect both systolic and diastolic parameters.

Doppler echocardiography parameters were collected according to international guidelines [15, 16]. Three consecutive cycles were averaged for every parameter. Following RV function variables were collected in the four-chamber view: TDI E′, A′ and S waves, TDI TEI Index of myocardial performance and TAPSE [2, 5, 17]. The myocardial systolic and diastolic velocities were obtained by placing a TDI sample volume at the lateral tricuspid annulus. We calculated the TEI index derived from TDI. We divided the isovolumic time [assessed as the time between tricuspid valve closure (end of A′) and opening (start of E′) minus the ejection time (duration of S′)] by the ejection time. TAPSE was measured using M-mode from the tricuspid lateral annulus. Two left ventricle data were informed to control the normality of the population: the left ventricle ejection fraction (LVEF), measured with the Teichholz formula, and the wall stress (WS). LVEF using the Teichholz formula was obtained in a long axis view, left ventricular measurements were made with the M-mode beam positioned just beyond the mitral leaflet tips in diastole, perpendicular to the long axis of the left ventricle. Both ventricular diameters (systolic and diastolic) were measured from the leading edge to leading edge of each interface, and LVEF by Teichholz is then calculated using the ultrasound software. The WS assessed the tension within the wall of the left ventricle [18]. It was determined by the pressure in the ventricle using cuff blood pressure at the time of echocardiography, the internal radius of the ventricle by M-mode, and the thickness of the wall. The blood pressure was measured when the child was calm, using a manual sphygmomanometer with adapted pediatric cuffs.

Statistical analysis

The characteristics of the children included in the study were described with proportions for categorical variables and with means and standard deviation (SD) values for continuous variables. The comparison parameters between ultrasound equipment were performed using student t-test. In order to identify the best model for the Z-Score construction, each RV parameters (S′, E′, A′ waves, TEI index, TAPSE) was modelized with four explanatory variables: age, height, weight and body surface area. Four different mathematical models were successively applied: (1) a linear model, (2) a polynomial model of degree 2, (3) a linear regression model by spline with free knot (a single knot whose location has been identified using the method presented by Molinari et al. [13]), and (4) a polynomial regression model of degree 2 by spline with a free knot (modelization with a single knot). The use of a spline regression model, allows modeling a variable by a line or a curve presenting a sudden change of slope at a point named “knot”. The choice of the best explanatory variable and the best modelization method was made on the basis of the adjusted coefficient of determination (aR^2), which takes into account the number of explanatory terms in a model relative to the sample size, and avoids the choice of an over-fitted model. The results of the chosen model were then plotted by estimating the evolution of each RV parameter’s mean with its confidence interval at 95% and prediction intervals at 1 SD and 2 SD (Z-scores).

Statistical significance was set at 0.05 and analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

Table 1 Population

	Total	Female	Male	p Value
Patients (N, %)	314 (100%)	144 (46%)	170 (54%)	
Age (years ± SD)	6.1 ± 5.1	5.9 ± 5	6.3 ± 5.25	0.76
Weight (kg ± SD)	23.1 ± 17.2	23 ± 17.5	23.2 ± 16.9	0.88
Height (cm ± SD)	108.2 ± 38.9	107.7 ± 37.9	108 ± 39.8	0.87
BSA (m^2 ± SD)	0.81 ± 0.45	0.81 ± 0.44	0.81 ± 0.44	0.88
LVEF (% ± SD)	69.9 ± 6.43	70.2 ± 7	69.6 ± 5.8	0.41
WS (g/cm^2 ± SD)	49.1 ± 21.2	48.9 ± 21.2	49.1 ± 21.2	0.41

SD standard deviation, *BSA* body surface area, *LVEF* left ventricle ejection fraction, *WS* wall stress

Table 2 RV variables

	N	Mean ± SD	Range	Missing data (%)
TAPSE (mm)	292	18.7 ± 4.9	6.6–33	7
S′ (cm/s)	299	12 ± 2.2	6–21.1	5
E′ (cm/s)	298	13.7 ± 3.8	3.45–26.6	5.1
A′ (cm/s)	286	10.1 ± 3.7	3.9–38	9
TEI index	275	0.41 ± 0.11	0.08–0.95	12.5

Results

Population

Within the 24-month study period, 6407 children were referred to the pediatric cardiology outpatient consultation. We included 314 normal children aged 2 days to 18 years (46% female, 88 infants under 1 year old, 26 neonates, 226 children). One family refused to participate. No demographic differences were observed between male and female (Table 1).

RV variables

The five RV variables (mean values and ranges) measured in the present study were presented in Table 2. The modelization of these echocardiographic RV variables over all ages did not follow a linear model, according to all four explanatory variables (age, height, weight and body surface area), with the lowest adjusted coefficients of determination (aR^2) in those four variables (Table 3). The quadratic spline model best adjusted the modelization of all RV variables, but with little difference with the linear spline model. No model accurately explained the TEI index in any of the four explanatory variables. The S′ wave was best modelized by the quadratic spline model with the weight (Fig. 1a). The knot at 6.86 kg corresponded to the curves' break (Fig. 1b). The E′ wave was best modelized by the quadratic spline model with the

Table 3 Modelization of RV variables

	RV variable	S′		E′		A′		TEI index		TAPSE	
		Knot	aR^{2*}	Knot	aR^{2*}	Knot	aR^{2*}	Knot	aR^2	Knot	aR^{2*}
	Mathematical model										
Age (years)	Linear		0.12		0.10		0.13		0.01		0.55
	Quadratic polynomial		0.13		0.12		0.14		0.01		0.60
	Linear spline	0.11	0.25	0.29	0.25	8.27	0.14	3.79	0.01	0.37	0.68
	Quadratic spline	0.28	0.24	0.29	0.27	8.27	0.15	7.7	0.00	0.46	0.69
Height (cm)	Linear		0.15		0.14		0.12		0.01		0.64
	Quadratic polynomial		0.18		0.18		0.12		0.01		0.67
	Linear spline	58	0.23	56	0.26	57	0.15	115	0.01	68	0.69
	Quadratic spline	64	0.22	62	0.25	81	0.16	154	0.00	80	0.69
Weight (kg)	Linear		0.11		0.10		0.09		0.01		0.49
	Quadratic polynomial		0.18		0.15		0.11		0.01		0.64
	Linear spline	5.84	0.24	4.54	0.27	4.42	0.11	6.39	0.01	9.16	0.66
	Quadratic spline	6.86	0.25	6.18	0.27	5.94	0.14	6.39	0.02	9.04	0.70
BSA (kg/m^2)	Linear		0.14		0.13		0.10		0.01		0.57
	Quadratic polynomial		0.19		0.17		0.11		0.01		0.67
	Linear spline	0.31	0.24	0.29	0.26	0.27	0.13	0.77	0.01	0.42	0.68
	Quadratic spline	0.38	0.24	0.35	0.26	0.34	0.15	0.78	0.00	0.41	0.69

BSA body surface area, *RV* right ventricle, aR^2 adjusted coefficient of determination

*All aR^2 (except for TEI index) are significantly different from 0 (p value < 0.0001)

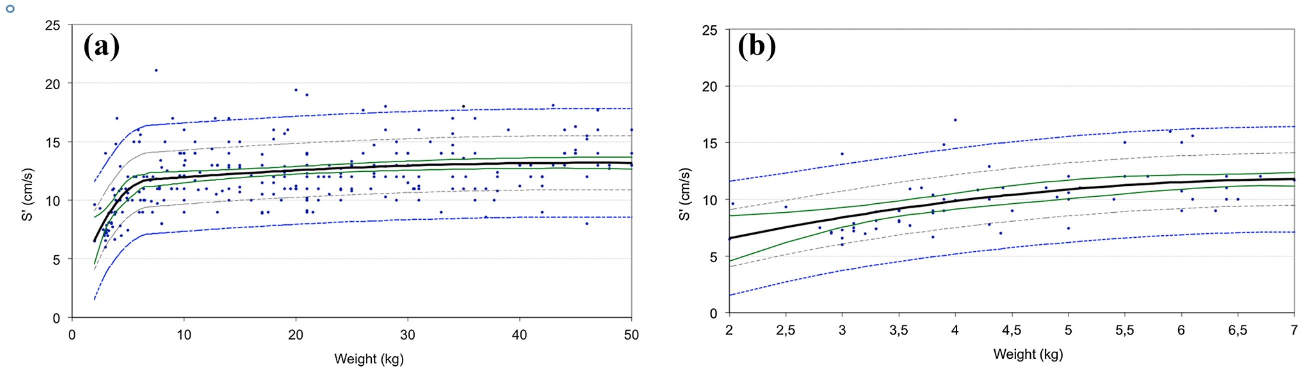

Fig. 1 **a** Modelization of S′ wave with quadratic spline model (all weight ranges). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval. **b** Modelization of S′ wave with quadratic spline model (2–7 kg). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval

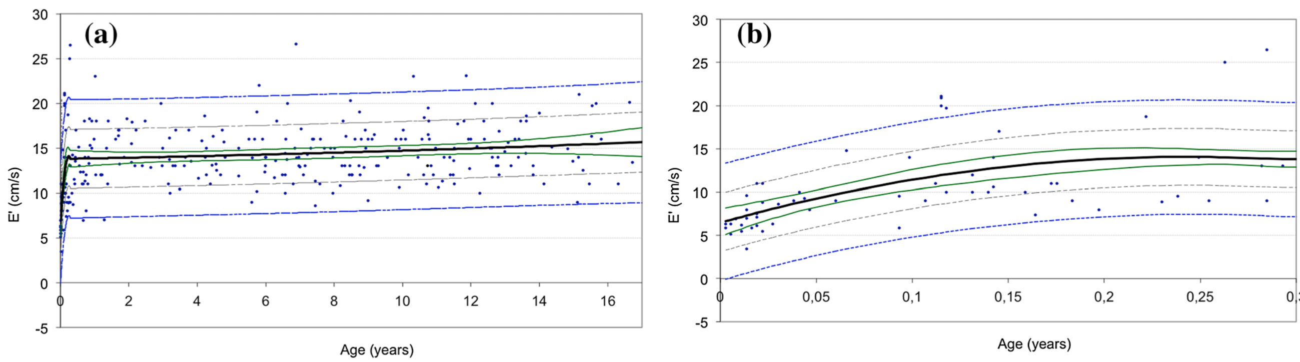

Fig. 2 **a** Modelization of E′ wave with quadratic spline model (all ages). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval. **b** Modelization of E′ wave with quadratic spline model (0–0.3 years). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval

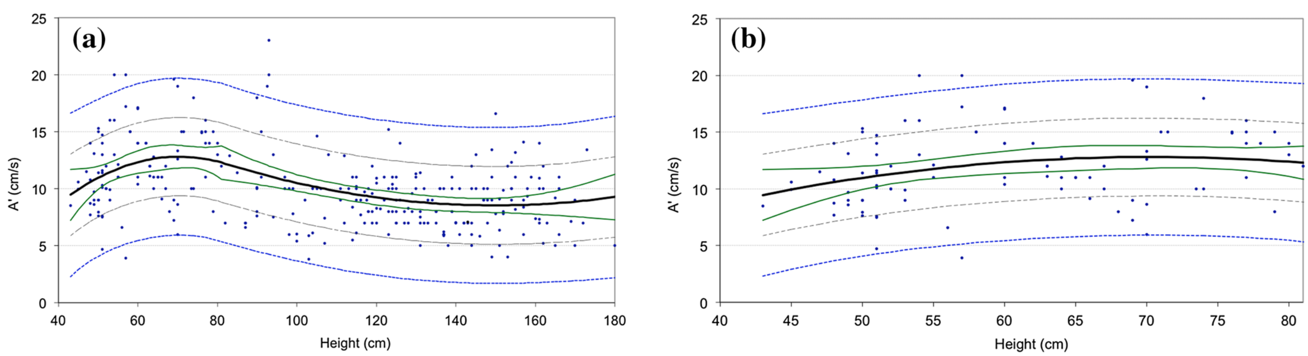

Fig. 3 **a** Modelization of A′ wave with quadratic spline model (all height ranges). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval. **b** Modelization of A′ wave with quadratic spline model (40–80 cm). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval

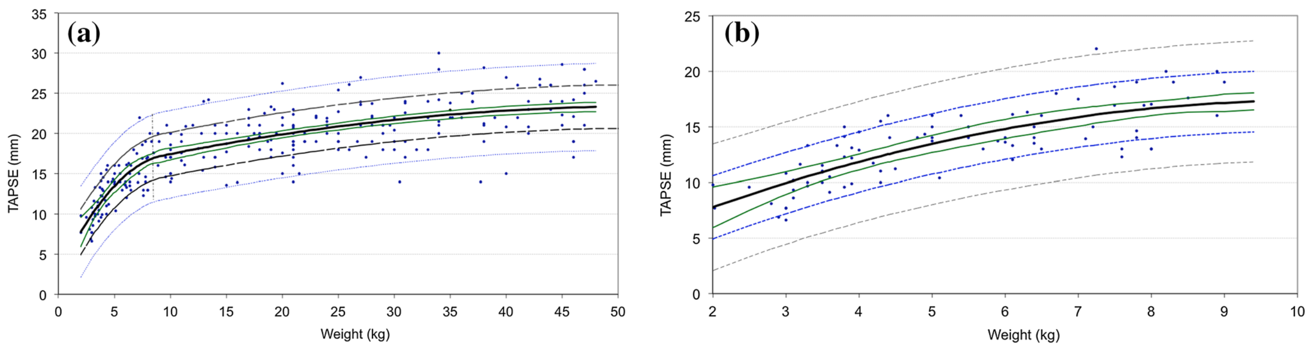

Fig. 4 **a** Modelization of TAPSE with quadratic spline model (all weight ranges). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval. **b** Modelization of TAPSE with quadratic spline model (2–10 kg). The green bands correspond to the 95% confidence interval, the black dotted bands correspond to the 1SD prediction interval, and the blue dotted bands correspond to the 1SD prediction interval

age (Fig. 2a). The knot at 0.29 years corresponded to the curve's break (Fig. 2b). The A′ wave was best modelized by the quadratic model with the height (Fig. 3a). The knot at 81 cm corresponded to the break of the curve (Fig. 3b). The TAPSE was best modelized by the quadratic spline model with the weight (Fig. 4a). The knot at 9.04 kg corresponded to the curve's break (Fig. 4b).

Discussion

This study of a large cohort of 314 children presented four mathematical models to define RV Z-scores in normal children. Among these models, the use of spline regression models appeared to improve the quality of the mathematical modeling for most echocardiographic RV parameters. The choice of a single-node spline method was made on the basis of the graphical representation of our data, which clearly showed a single break in the curve for several parameters (S′, E′ and TAPSE). Moreover, we focused on the curve breaks values, which could be clinically relevant. The single-node spline method that we used, developed by Molinari et al., provided a way to statistically determine the best value of this breakpoint [12, 13]. Modeling using splines with two or more nodes (set a priori and not by the model) did not provide this type of information.

Despite recent advances, echocardiographic RV parameters nomograms are limited in the pediatric population. Indeed, there are several methodological issues including the lack of standardization, the different types of body size measurements used for normalization, and the various ways to express normalized data [19, 20]. Moreover, if reference values seem to be reproducible in older children, they vary significantly in neonates and infants [21].

By evaluating the main parameters used to evaluate RV function in pediatric population, our data showed that linear or quadratic polynomial models were not appropriate. Our results suggested that spline regression models with one knot were better mathematical models to modelize RV parameters. Our data also supported that RV parameters evolution was not linear during childhood but presented several curves' breaks. Moreover, these curves' breaks did not relate to a single anthropometric variable. As opposed to other authors who commonly associated echocardiographic measurement to only one variable (body surface area, weight or height) to calculate Z-scores, we pointed out that specific and independent variables were required for each parameter. Indeed, the best independent variable used to predict the mean value of the S wave and the TAPSE was the weight, whereas it was the age for the E wave and the height for the A wave. These findings show that all anthropometric variables should be considered in the pediatric population. Nevertheless, no variable or mathematical model was related to the TEI index.

Using linear regression model based on a single variable to determine Z-scores and norms in the pediatric population might lead to major and systematic biases for certain age groups, especially neonates and infants. This might have pejorative consequences if used in acquired or congenital heart diseases.

New mathematical models to determine norms in children have been also studied by Wang and al. These authors provided reference values for RV echocardiographic parameters using a cubic polynomial relationship with BSA and for coronary artery using a cubic regression in a large cohort of Chinese children [22, 23]. Our study highlighted that this type of model was actually more pertinent than a linear regression for norm construction. However, the adequacy of modeling can still be improved by using spline models.

Spline regression models have recently generated some interest in adult cardiology and could probably apply to various situations in the field of pediatric cardiology. Indeed, in a study among adults with asymptomatic primary mitral regurgitation and preserved ejection fraction, Mentias et al. showed with a quadratic spline analysis, that the risk of death progressively increased as resting left ventricle global longitudinal strain worsened [24]. Similarly, Rabkin et al. measured the association between age and QT interval and found that the cubic spline had significant increases in adjusted-R^2 compared to linear model in male adults [25]. Recently, Zhou et al. used a spline-automated method to identify the best-quality coronary arterial segment from multiple-phase coronary CT angiography acquisitions [26].

Study limitations

With a sample size of 312 children, aR^2 for S′, E′, A′ and TEI index were below 0.3. Missing data represented 5–12% of variables collected but this range is relatively small for a pediatric study as patient's cooperation might be limited. Even if there is no "magic number", generally an $aR^2 > 0.6$ is considered as statistically reliable and only aR^2 for TAPSE was > 0.6 in our results [27].

The sample size required for pediatric nomograms has been indicated in previous publications and should ideally be at least of 600 subjects [28, 29]. However, this study did not intend to define new Z-scores, but mostly aimed to criticize linear models regularly used in cardiovascular imaging studies and define a more accurate mathematical model to use in pediatric cardiology.

Conclusions

Because of several curve breaks during childhood, linear model might not be relevant to define normal echocardiographic values in infants and children. Our data suggested that the spline regression models represented more appropriate mathematical models to assess right ventricular function than linear or quadratic polynomial ones, and might be used to determine normal values in pediatrics. The spline models should probably be tested in future pediatric cardiovascular imaging studies.

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Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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