Echocardiographic Nomograms for Ventricular, Valvular and Arterial Dimensions in Caucasian Children with a Special Focus on Neonates, Infants and Toddlers

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Background: A quantitative echocardiographic assessment is often essential for the management of congenital heart disease, especially in the first months of life. Despite this, pediatric echocardiographic nomograms are limited and heterogeneous, particularly for neonates and infants. The aim of this study was to establish reliable echocardiographic nomograms in a broad population of healthy Caucasian children.

Methods: Two-dimensional and M-mode measurements of 22 cardiovascular structures were performed. Models using linear, logarithmic, exponential, and square root relationships were tested. Heteroscedasticity was tested using the White and Breusch-Pagan tests. Age, weight, height, and body surface area (BSA; calculated using seven different formulas) were used as the independent variables in different analyses to predict the mean value of each echocardiographic measurement. Structured *Z* scores were then computed.

Results: A total of 445 consecutive Caucasian Italian healthy subjects (age range, 0 days to 36 months; 49% female subjects) with BSAs ranging from 0.12 to 0.67 m^2 were prospectively enrolled. The calculation of BSA using the Haycock formula provided the best results, while other formulas either underestimated (DuBois, Mosteller, Dreyer, and Meban) or overestimated (Boyd and Gehan) BSA. The Haycock formula has been used when presenting data as predicted values (mean $\pm$ 2 SDs) for a given BSA and within equations relating echocardiographic measurements to BSA. For all the measurements, there was no significant intraobserver or interobserver variability.

Conclusions: The investigators report new, reliable echocardiographic *Z* scores derived from a large population of Caucasian neonates, infants, and toddlers calculated using a rigorous statistical design. These nomograms represent a valid diagnostic tool for echocardiographic quantification in this age group. (J Am Soc Echocardiogr 2014;27:179-91.)

Keywords: Echocardiography, Children, Nomograms

Echocardiography represents the primary imaging modality used in the diagnosis and management of congenital heart disease (CHD).[1-5] A quantitative assessment of cardiac chambers, valves, and vessels is critical in the evaluation of CHD severity to plan the most appropriate medical and/or interventional treatment, especially in neonates.[4]

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Despite advances in the methodologies to normalize pediatric echocardiographic measurements, nomograms continue to present a few important limitations,[6-17] including small sample sizes, poor or inconsistent differentiation by age groups, and a paucity of data for neonates.[2,5,17]

The heterogeneity of available nomograms results in discordant reference values and introduces bias in individual clinical decisions that are based on specific nomograms.[12] For instance, a mitral valve annular diameter of 11 mm in a male child with a body surface area (BSA) of 0.3 m^2 corresponds to a range of *Z* scores from -1.63, which represents a value at the lower limit of normal,[10,12] to -4.84, which represents significant hypoplasia.[7,12]

Furthermore, data for some structures (the pulmonary arteries, the aortic arch) are limited,[9,10] especially in neonates.[1]

Several methodologic issues remain undefined, mainly related to the difficulty with adjusting measurement values for the effects of body size.[1-4] In particular, it is still controversial which body

Abbreviations

BSA = Body surface area

CHD = Congenital heart disease

size measurement should be used for normalization and how normalized data should be expressed.[1-4]

Moreover, little attention has been given to confounding factors such as gender and intraobserver and interobserver variability, which likely contribute to variable results.[2]

The primary aim of the present work was to establish reliable echocardiographic nomograms in a population of healthy children, with a special emphasis on neonates and infants. This age range has been poorly represented in previous nomograms and is especially important because critical management decisions for patients with CHD occur during the first few weeks and months of life.

The secondary aims were to identify the best body size parameter (i.e., weight, age, or BSA calculated using various formulas)[18-26] for normalization of measurements, especially in neonates, and to determine the effects of confounding factors such as gender, prematurity, type of delivery, and intraobserver variability on echocardiographic measurements.

METHODS

Subject Enrollment

All consecutive Caucasian neonates, infants, and toddlers (age range, 0 days to 36 months) evaluated in the outpatient of the Pediatric Cardiology Department for screening for CHD at Fondazione G. Monasterio CNR-Regione Toscana of Massa eligible for inclusion in the study were prospectively enrolled.

Our department provides an outpatient service reserved for neonatologists from nearby hospitals and pediatricians in our territory to refer children with suspicion for congenital cardiac defects for full cardiologic examinations. The evaluation routinely consists of physical examination plus electrocardiography and echocardiography. No supplemental examinations were performed for the present study.

In addition to routine clinical activity, we digitally stored all the echocardiographic images, which were subsequently analyzed.

Most patients were evaluated for the presence of cardiac murmurs. Immaturity and suspicion of left-to-right shunt on fetal echocardiography were other common reasons that led the pediatricians to request full cardiologic assessments.

Approval for this study was obtained from the local ethics committee. Parents or legal guardians of all children were informed and consented to participation to the study by signing a written consent form.

Inclusion Criteria

Only children with technically adequate echocardiographic evaluations were enrolled in the study.

The presence of innocent defects such as a patent ductus arteriosus with small or less left-to-right shunting seen in the first 3 days of life or a patent foramen ovale was considered normal.[10] Premature neonates were included only if they had Apgar scores ≥8, did not require ventilatory support, and had good clinical status.

Exclusion Criteria

All subjects with clinical, electrocardiographic, or echocardiographic evidence of congenital or acquired heart disease were excluded. Other exclusion criteria included patients with known or suspected neuromuscular disease, genetic syndromes, or chromosomal abnormalities; body mass index ≥95th percentile for children ≥2 years old[27] or weight-for-length Z score ≥2 on the basis of the World Health Organization child growth standards for children <2 years old[27,28]; pulmonary hypertension; connective tissue disease; or family history of genetic cardiac disease (such as Marfan syndrome or cardiomyopathy).[10] All non-Caucasian subjects were also excluded to avoid racial variability bias.

Echocardiographic Examination

Echocardiographic studies were performed using a Philips iE33 system (Philips Medical Systems, Bothell, WA). Two-dimensional and M-mode measurements of 22 cardiovascular structures were performed in the study population. All echocardiographic data used for this analysis were digitally recorded, allowing offline measurements with automatic calibration using a computer workstation (EnConcert; Philips Medical Systems, Andover, MA).

Measurements of the sizes of cardiovascular structures as well as calculations of functional parameters were performed according to recent guidelines.[4] Aortic and pulmonary arterial dimensions and semilunar valve diameters were measured in peak systole. Atrioventricular valve diameters were measured in diastole at the point of maximal valve excursion. Valve dimensions were measured from hinge point to hinge point, and arterial dimensions were measured from inner edge to inner edge. The measurements as well as the view and timing during the cardiac cycle in which they were obtained are listed in Table 1.

For any given structure, measurements were made only if excellent and unambiguous views were available. Thus, not all structures were measured in all patients.

Statistical Analysis

Models using linear ($y = a + bx$), logarithmic ($y = a + b \times \ln[x]$, $\ln[y] = a + bx$), exponential ($\ln[y] = a + b \times \ln[x]$), and square root ($y = a + b \times \sqrt{x}$, $\sqrt{y} = a + bx$, $\sqrt{y} = a + b \times \sqrt{x}$) equations were tested to examine the relationships between parameters of body size and each of the echocardiographic variables. Among the models that satisfy 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 of the residuals, was then tested by the White test[29] and the Breusch-Pagan test.[30] If the variance of the residuals is constant, the data are said to be homoscedastic. To test the normality of residuals, the Shapiro-Wilk[31] and Lilliefors (Kolmogorov-Smirnov)[32] tests were used. The graphical analysis of standardized residuals was also observed (i.e., if the distribution of standardized residuals is normal, 95% of the values must be between −1.96 and +1.96). Age, weight, height, and BSA[9,18-26] were used as the independent variables in seven different regression analyses to predict the mean values of each echocardiographic measurement.

To evaluate the potential differences between methods for calculating BSA, BSA was calculated according to seven published methods:

- Du Bois and Du Bois[18]: $\text{height}^{0.725} \times \text{weight}^{0.425} \times 0.007184$
- Dreyer and Ray[21]: $\text{weight}^{0.6666} \times 0.1$
- Boyd[22]: $0.0003207 \times (1{,}000 \times \text{weight})^{[0.7285 - 0.0188 \times \log(1{,}000 \times \text{weight})]} \times \text{height}^{0.3}$
- Haycock *et al.*[19]: $\text{weight}^{0.5378} \times \text{height}^{0.3964} \times 0.024265$
- Mosteller[20]: $\sqrt{[(\text{height} \times \text{weight})/3{,}600]}$