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Echocardiographic reference ranges in older children and adolescents in sub-Saharan Africa

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ABSTRACT

Background: Echocardiographic reference ranges are important to identify abnormalities of cardiac dimensions. Reference ranges for children in sub-Saharan Africa have not been established. The aim of this study was to establish echocardiographic z-score references for Black children in sub-Saharan Africa.
Methods: 282 healthy subjects aged 6–16 years (143 [51%] males) with no known history of cardiac disease were enrolled in the study in Harare, Zimbabwe between 2014 and 2016. Standard M-mode echocardiography was performed and nine cardiac chamber dimensions were obtained. Two non-linear statistical models (gamma weighted model and cubic polynomial model) were tested on the data and the best fitting model was used to calculate z-scores of these cardiac chamber measures. The reference ranges are presented on scatter plots against BSA.
Results: Normative data for the following cardiac measures were obtained and z-scores calculated: right ventricular diameter at end diastole (RVEDD); left ventricular diameter at end diastole (LVEDD) and systole (LVESD); interventricular septal wall thickness at end diastole (IVSd) and systole (IVSs); left ventricular posterior wall thickness at end diastole (LVPWd) and systole (LVPWs); left atrium diameter at end systole (LA) and tricuspid annular plane systolic excursion (TAPSE). Girls had higher values for BMI and heart rate than boys ($p = 0.048$ and $p = 0.001$, respectively). Mean interventricular septal and left ventricular posterior walls thickness was higher than published normal values in predominantly Caucasian populations.
Conclusion: These are the first echocardiographic reference ranges for children from sub Saharan Africa and will allow accurate assessment of cardiac dimensions in clinical practice.

1. Introduction

Transthoracic echocardiography enables non-invasive assessment of cardiac size and function and is an essential tool for cardiac evaluation in children and adults. As cardiac chamber dimensions can change with somatic growth in childhood and adolescence, it is important to normalise echocardiographic measurements to body size. Several echocardiographic references have been published for children and adolescents from various regions including Europe, Asia and North America [1–5]. However, no echocardiography references have been established for children and adolescents in sub Saharan Africa, and echocardiographic studies from this region have utilised published references for normative data mostly derived from predominantly white populations [4,6]. Racial differences in cardiac dimensions have been reported from previously published nomograms with Black race children found to have significantly larger cardiac dimensions than White race children [7]. In addition, the standards of growth for a

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population may be influenced by environmental, social and economic factors of that region. This necessitates development of regional echocardiographic references. The aim of this study was to establish echocardiographic z-score references in Black African children.

2. Methods

The study was conducted at the Harare Children's Hospital, Zimbabwe, between August 2014 and December 2016. Children aged between 6 and 16 years who were HIV-uninfected were invited to participate in the study. Participants were recruited from seven primary care clinics in Harare that were offering HIV-testing to all attendees regardless of the reason for presentation as part of a project evaluating HIV testing services. The study was also advertised at the hospital to the general public. Those who tested HIV-negative were given a flyer with information about the study and asked for consent to be contacted for possible inclusion in the study. Participants were included if they had no known congenital and/or acquired cardiac disease, no cardiac symptoms, a normal electrocardiogram (ECG) and no evidence of structural or functional heart disease on echocardiography. The age, height and weight were obtained and body surface area (BSA) was calculated using Dubois and Dubois method [8].

Ethical approval was obtained from Harare Central Hospital Ethics Committee, Medical Research Council of Zimbabwe, London School of Hygiene and Tropical Medicine Ethics Committee and Biomedical Research and Training Institute Institutional Review Board. Written informed consent from guardians and assent from participants were obtained prior to enrolment in all cases.

2.1. Echocardiographic examination

Echocardiography was performed using a Mindray DC N6 multipurpose ultrasound machine (Mindray, Shenzhen, China) by a trained and experienced paediatric echocardiographer (EM). 2D guided M-mode echocardiography was performed on all children using a standard protocol, according to published guidelines [9]. No sedation was required prior to the examination. Participants were scanned in the left lateral or supine position to obtain an optimum image quality. Images were acquired using a transducer with frequencies ranging from 3.5 MHz to 7.0 MHz and simultaneous 3-lead ECG monitoring and were saved in DICOM format for subsequent off-line analysis.

The following cardiac measures were obtained over three cardiac cycles: right ventricular diameter at end diastole (RVEDD); left ventricular diameter at end diastole (LVEDD) and end systole (LVESD); interventricular septal wall diameter at end diastole (IVSd) and end systole (IVSs); left ventricular posterior wall thickness at end diastole (LVPWd) and end systole (LVPWs); left atrium diameter at end systole (LA); and tricuspid annular plane systolic excursion (TAPSE). End diastole was defined as the start of the QRS-wave on the ECG tracing, or preferably described as the frame in the cardiac cycle in which LV dimension is largest and systole as the frame prior to mitral valve opening in which LV dimension is smallest, as previously described [10]. Measurements were performed in the parasternal long axis (PLAX) or parasternal short axis (PSAX) views using the leading edge to leading edge method [11]. TAPSE was measured in apical 4-chamber view. Measurements were only made on technically adequate images, thus not all measurements were obtained in every patient (Table 1). Repeated measurements were performed on 20 randomly selected echocardiograms by the same rater (EM) and a further 28 (10%) of all the echocardiograms were randomly selected and re-measured by an independent rater (MSP).

2.2. Statistical analysis

Data were analyzed using STATA version 12 software (StataCorp, Texas, USA). Continuous variables are presented as mean ± standard deviation (SD) for normally-distributed data or median and interquartile range (IQR) for non-normally-distributed data. To compute the z-scores, two regression models were tested on the data to optimise goodness of fit for the various cardiac measures and the selected independent variable, BSA. The two models were a gamma function weighted model [$y = \alpha x^{\beta} \times e^{-\lambda x}$] proposed by Nevill et al. [12] and a cubic polynomial model [$y = ax^3 + bx^2 + cx + d$] used by Petterson et al. [5] The final best model was selected based on several characteristics: first, by visual inspection of the goodness of fit of data plotted on a graph; secondly, the association between the residual and/or z-score plots against the BSA were assessed and no significant association should be observed if there is an adequate fit; thirdly, residual values were assessed for normal distribution; fourthly, the tails of distributions were assessed to ensure that individuals falling outside of the reference ranges (i.e. individuals with z-scores > + 2 or <−2) were <2.28% [13] to ensure that no bias was introduced and finally the model with the smallest Akaike information criterion (AIC) value was selected. Intra-rater and inter-rater reliability was calculated using Intra-class correlation coefficient (ICC). A value of $p < 0.05$ was considered statistically significant.

Table 1
Clinical and echocardiographic characteristics of participants.

Variable	Overall N = 282	Males N = 143	Females N = 139	*P*-value
Age (y)	10.7 (3.0)	10.7 (3.1)	10.7 (2.9)	0.922
6–9 years	*107 (38)**	*55 (38)**	*52 (37)**	
10–13 years	*107 (38)**	*51 (36)**	*56 (40)**	
14–16 years	*68 (24)**	*37 (26)**	*31 (22)**	
Height (cm)	140.3 (16.2)	140.4 (17.5)	140.2 (14.8)	0.920
Weight (kg)	35.6 (13.2)	34.3 (12)	37 (14.3)	0.008
BSA (m^2)	1.18 (0.3)	1.16 (0.3)	1.19 (0.3)	0.421
BMI (kg/m^2)	17.4 (3.1)	16.8 (2.0)	18.1 (3.9)	**0.001****
Systolic BP (mmHg)	112.7 (12.9)	112 (13.0)	113 (12.9)	0.571
Diastolic BP (mmHg)	74 (9.6)	73 (9.0)	74.7 (9.7)	0.205
Heart rate (bpm)	81.7 (13.0)	80.2 (12.0)	83.3 (13.7)	**0.048****
RV diastole (mm)	14.9 (2.0)	14.9 (2.0)	14.9 (2.0)	0.969
LV diastole (mm)	39.2 (4.1)	39.7 (4.0)	38.7 (4.1)	**0.036****
LV systole (mm)	26.8 (3.1)	27 (3.1)	26.5 (3.2)	0.170
IVS diastole (mm)	7.5 (1.3)	7.6 (1.3)	7.5 (1.3)	0.303
IVS systole (mm)	9.9 (1.7)	10 (1.8)	9.8 (1.6)	0.473
LVPW diastole (mm)	7.3 (1.1)	7.4 (1.1)	7.2 (1.1)	0.253
LVPW systole (mm)	9.8 (1.7)	9.8 (1.7)	9.7 (2.9)	0.511
Left atrium (mm)	25.6 (3.4)	25.7 (3.3)	25.5 (3.5)	0.579
***TAPSE (mm)	20.7 (2.3)	20.7 (2.1)	20.8 (2.4)	0.873

*Results are **mean ± SD**.*
BSA, body surface area; BMI, body mass index; BP, blood pressure; RV, right ventricle; LV, left ventricle; IVS, interventricular septum; LVPW, left ventricular posterior wall; TAPSE, tricuspid annular plane systolic excursion.
* *N(%).*
** *Significant at p ≤ 0.05.*
*** *N = 237.*

3. Results

A total of 282 children were enrolled in the study, of whom 143 (51%) were male. All participants were in sinus rhythm. The baseline demographic and clinical characteristics are shown in Table 1, stratified by gender. Girls had higher values for BMI and heart rate than boys ($p = 0.048$ and $p = 0.001$, respectively) whereas boys had higher LVEDD dimensions ($p = 0.036$).

Both the gamma function weighted and the cubic polynomial models had comparable visual goodness-of-fit of the data on plotted graphs and no significant association was observed between residuals and BSA. However, the gamma weighted model was selected because of the higher R^2 values and smaller AIC values compared to the cubic polynomial model. In addition, the cubic polynomial did not have enough observations in the tail of the distribution. The regression analysis coefficients of the gamma weighted model are presented in Table 2. These include alpha, beta, lambda, root mean squared error (RMSE) and

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