Normative Left Ventricular M-Mode Echocardiographic Values in Preterm Infants up to 2 kg

Swati Choudhry, MD, Amber Salter, PhD, Tyler W. Cunningham, MD, Philip T. Levy, MD, Hoang H. Nguyen, MD, Michael Wallendorf, PhD, Gautam K. Singh, PhD, and Mark C. Johnson, MD, *St. Louis, Missouri; and Morristown, New Jersey*

Background: There is a paucity of normative echocardiographic data in preterm infants. The objectives of this study were to (1) derive left ventricular (LV) M-mode reference values and (2) compare the performance of alternative methods of indexing LV dimensions and LV mass (LVM) in preterm infants. The authors propose that indexing LV measures to weight in preterm infants is a practical approach given the variability associated with tape-measure length measurement in infants.

Methods: In this retrospective study, LV M-mode echocardiographic measurements of end-diastolic interventricular septal thickness, end-diastolic LV posterior wall thickness, LV end-diastolic and end-systolic dimensions, LVM, and relative wall thickness were remeasured in 503 hospitalized preterm infants ≤2 kg (372 from a retrospective sample and 131 prospectively enrolled). Measures for all variables did not differ between retrospective and prospective samples, so results were pooled. LV dimensions and LVM indexed for weight, length, and body surface area sex-specific centile curves and corresponding *Z* scores were generated using Cole's lambda-mu-sigma method. Threshold limits (10th and 80th percentiles) were used to generate the normative range for relative wall thickness.

Results: Sex-specific centile curves using LVM, end-diastolic interventricular septal thickness, end-diastolic LV posterior wall thickness, LV end-diastolic dimension, and LV end-systolic dimension indexed to weight were similar to the curves generated using length and body surface area. The mean normal range for relative wall thickness was 0.33 (10th percentile, 0.26; 80th percentile, 0.38).

Conclusions: From this large cohort of preterm infants, LV M-mode dimension and LVM centile curves indexed to weight were developed as a practical method to assess LV morphology in preterm infants. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Echocardiography, Reference values, M-mode, Preterm, Left ventricle

INTRODUCTION

Two dimensionally guided M-mode echocardiography is commonly used to obtain measures of left ventricular (LV) chamber size and wall thickness as well as derived values of LV mass (LVM) and relative wall thickness (RWT) in children and adults. Because LV hypertrophy (LVH) is known to be associated with adverse cardiac events in adults, increased attention is being paid to the identification of early stages of LVH during childhood.[1-5] Elevated LVM, derived from M-mode echocardiography, is of particular interest because it is often used to define LVH.[6] M-mode echocardiography offers the advantage of quick acquisition in irritable preterm infants with sedation risks. Appropriate normalization of LV measures is especially critical in young infants because of the enormous variability in body size and altered body proportions with variable gestational age and growth.[7] Numerous methods have been proposed to normalize cardiac dimensions to body size, including simple division by height, weight, or body surface area (BSA) or more complex allometric relationships of these body measures.[7-13] LVM indexed to height ($g/m^{2.7}$or $g/m^{2.16}$) has gained wide acceptance but may not be an ideal method for standardizing LVM to body size in infants.[4-7,14] Furthermore indexing to length or body surface may not be optimal in preterm infants, because of the inaccuracy of the commonly used tape-measure technique for length measurement in neonates.[15,16] More

From the Department of Pediatrics (S.C., T.W.C., P.T.L., H.H.N., G.K.S., M.C.J.) and the Department of Biostatistics (A.S., M.W.), Washington University School of Medicine, St. Louis, Missouri; and the Department of Pediatrics, Goryeb Children's Hospital, Morristown, New Jersey (P.T.L.).

This work was supported in part by a grant from the Premature and Respiratory Outcomes Program of the National Institutes of Health (grants U01 HL101794 and HL1014650).

Reprint requests: Mark C. Johnson, MD, Department of Pediatrics, Washington University School of Medicine, One Children's Place, Campus Box 8116-NWT, St. Louis, MO 63132 ((E-mail: *johnson_m@wustl.edu*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2017.04.010

Abbreviations

BSA = Body surface area

ICC = Intraclass correlation coefficient

IVSd = End-diastolic interventricular septal thickness

LBM = Lean body mass

LMS = Lambda-mu-sigma

LV = Left ventricular

LVEDD = Left ventricular end-diastolic dimension

LVESD = Left ventricular end-systolic dimension

LVH = Left ventricular hypertrophy

LVM = Left ventricular mass

LVPWd = End-diastolic left ventricular posterior wall thickness

PDA = Patent ductus arteriosus

RWT = Relative wall thickness

recently, centile curves used for pediatric growth charts by the National Center for Health Statistics have been demonstrated to be useful for evaluating LVM in children.[7,17-20]

Improved survival of extremely premature babies has further led to the recognition of LVH in preterm infants.[21] Studies of former preterm infants at 5 and 7 years of age found decreased LV chamber size and increased ventricular septal thickness but did not track cardiac abnormalities from the nursery.[22,23] The paucity of normative echocardiographic data in preterm infants limits the identification of patients that might be at risk for persistent cardiac abnormalities. Biased or imprecise cardiac growth curves can lead to inappropriate clinical or management decisions.[8,24-30] In this study, we sought to derive LV M-mode reference values with centile curves and to compare the performance of alternative methods of indexing LV measures in preterm infants (length, weight, and BSA).

METHODS

Study Design

For the purpose of this retrospective study, LV M-mode echocardiographic remeasurements were made in two cohorts of preterm infants: (1) a prospective cohort of 131 preterm infants (born at <29 weeks' gestational age) recruited between August 2011 and November 2013, and (2) a retrospective database-generated cohort of 372 preterm infants from January 1, 2005, through December 31, 2014. The institutional review board of Washington University School of Medicine approved the study. All subject guardians in the prospective sample provided written informed consent.

Retrospective Study Population. Last 10-year echocardiographic and clinical databases for St. Louis Children's Hospital were retrospectively reviewed. All preterm infants ≤2 kg born from 2005 to 2014 with technically adequate echocardiographic evaluations (defined as echocardiograms with measurable M-mode) performed at St. Louis Children's Hospital were eligible for inclusion. Exclusion criteria were (1) congenital heart disease, including moderate or large atrial-level shunt; (2) moderate or large patent ductus arteriosus (PDA); (3) known genetic cardiomyopathy, including hypertrophic cardiomyopathy, genetic syndromes (such as Noonan syndrome and Pompe disease), neuromuscular disease, chromosomal abnormalities, diagnosis of pulmonary hypertension (diagnosed on the basis of clinical chart review or echocardiographic interpretation), connective tissue disease, and clinical or radiologic diagnosis of kidney disease; (4) incomplete medical records; and (5) enrollment in the prospective sample (described later). Patients with moderate or large shunts on prior echocardiographic studies were eligible if ≥1 month elapsed until the time of the study echocardiographic examination.

Prospective Study Population. Additionally, 131 preterm infants were prospectively enrolled from among infants participating in the Prematurity and Respiratory Outcomes Program, a seven-center initiative sponsored by the National Heart, Lung, and Blood Institute (ClinicalTrials.gov identifier NCT01435187).[31] All infants in the prospective sample were enrolled at St. Louis Children's Hospital neonatal intensive care unit between August 2011 and November 2013. All prospective subjects had structurally normal hearts; none had a family history of genetic cardiomyopathy, genetic syndromes, or known chromosomal abnormality. All prospectively enrolled subjects were reevaluated 1 year later to validate that they remained free of any recognizable systemic disorder, including hypertension. All patients enrolled in the prospective study routinely underwent echocardiograms per the Prematurity and Respiratory Outcomes Program study protocol.[31]

All subjects with initial echocardiographic readings of moderate or large shunts were excluded without review. If the initial reading of shunt size was small to moderate, a senior echocardiographer (M.C.J.) reviewed the studies to exclude any with moderate or larger shunts. PDA was graded as small if the ratio of the smallest ductal diameter to ostium of the left pulmonary artery was <0.5.[32] Atrial shunts were qualitatively graded as small if there was no right ventricular or right atrial enlargement and the color flow Doppler diameter of the shunt was <20% of the length of the atrial septum.

Body Size Parameters

Measurements for weight and length were based on neonatal intensive care clinical records with daily weight and weekly tape-measured length while the infant was supine with stretched legs. The most recent length and weight measurements on the day echocardiography was performed were collected. We used the Haycock formula to calculate BSA: weight$^{0.5378}$ × height$^{0.3964}$ × 0.024265.[33]

Echocardiography

All echocardiographic studies were performed on commercially available cardiac ultrasound scanners according to the guidelines of the American Society of Echocardiography.[28] All of the 503 echocardiograms were remeasured offline for the purposes of the present study by S.C. M.C.J. remeasured 100 studies in a blinded fashion and was allowed to choose the M-mode image for measurement for interobserver variability determination. Measurements were made by two-dimensional guided M-mode echocardiography using the parasternal short-axis view at the level of the papillary muscles. End-diastole was defined as the time of maximum LV dimension. Electronic calipers were used to measure end-diastolic interventricular septal thickness (IVSd), end-diastolic LV posterior wall thickness (LVPWd), LV end-diastolic dimension (LVEDD), and LV end-systolic dimension (LVESD). Measurements were repeated over three consecutive cardiac cycles and averaged. LVM was estimated using the Devereux equation: LVM (g) = $0.8\{1.04[(LVEDD + LVPWd + IVSd)^3 - (LVEDD)^3]\} + 0.6$.[34] RWT was calculated using two formulas: (1) RWT = 2(LVPWd)/LVEDD and (2) RWT = (LVPWd + IVSd)/LVEDD.[35,36]