Reference Ranges of Left Ventricular Strain Measures by Two-Dimensional Speckle-Tracking Echocardiography in Children: A Systematic Review and Meta-Analysis

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Background: Establishment of the range of reference values and associated variations of two-dimensional speckle-tracking echocardiography (2DSTE)–derived left ventricular (LV) strain is a prerequisite for its routine clinical adoption in pediatrics. The aims of this study were to perform a meta-analysis of normal ranges of LV global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) measurements derived by 2DSTE in children and to identify confounding factors that may contribute to variance in reported measures.

Methods: A systematic review was launched in MEDLINE, Embase, Scopus, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library. Search hedges were created to cover the concepts of pediatrics, STE, and left-heart ventricle. Two investigators independently identified and included studies if they reported 2DSTE-derived LV GLS, GCS, or GRS. The weighted mean was estimated by using random effects models with 95% CIs, heterogeneity was assessed using the Cochran *Q* statistic and the inconsistency index (I^2), and publication bias was evaluated using the Egger test. Effects of demographic (age), clinical, and vendor variables were assessed in a metaregression.

Results: The search identified 2,325 children from 43 data sets. The reported normal mean values of GLS among the studies varied from −16.7% to −23.6% (mean, −20.2%; 95% CI, −19.5% to −20.8%), GCS varied from −12.9% to −31.4% (mean, −22.3%; 95% CI, −19.9% to −24.6%), and GRS varied from 33.9% to 54.5% (mean, 45.2%; 95% CI, 38.3% to 51.7%). Twenty-six studies reported longitudinal strain only from the apical four-chamber view, with a mean of −20.4% (95% CI, −19.8% to −21.7%). Twenty-three studies reported circumferential strain (mean, −20.3%; 95% CI, −19.4% to −21.2%) and radial strain (mean, 46.7%; 95% CI, 42.3% to 51.1%) from the short-axis view at the midventricular level. A significant apex-to-base segmental longitudinal strain gradient ($P < .01$) was observed in the LV free wall. There was significant between-study heterogeneity and inconsistency ($I^2 > 94\%$ and $P < .001$ for each strain measure), which was not explained by age, gender, body surface area, blood pressure, heart rate, frame rate, frame rate/heart rate ratio, tissue-tracking methodology, location of reported strain value along the strain curve, ultrasound equipment, or software. The metaregression showed that these effects were not significant determinants of variations among normal ranges of strain values. There was no evidence of publication bias ($P = .40$).

Conclusions: This study defines reference values of 2DSTE-derived LV strain in children on the basis of a meta-analysis. In healthy children, mean LV GLS was –20.2% (95% CI, −19.5% to −20.8%), mean GCS was −22.3% (95% CI, −19.9% to −24.6%), and mean GRS was 45.2% (95% CI, 38.3% to 51.7%). LV segmental longitudinal strain has a stable apex-to-base gradient that is preserved throughout maturation. Although variations among different reference ranges in this meta-analysis were not dependent on differences in demographic, clinical, or vendor parameters, age- and vendor-specific referenced ranges were established as well. (J Am Soc Echocardiogr 2015;■:■-■.)

Keywords: Left ventricle, Cardiac function, Global strain, Speckle-tracking echocardiography, Children

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Abbreviations

BSA = Body surface area

CS = Circumferential strain

ESS = End-systolic strain

FR = Frame rate

GCS = Global circumferential strain

GLS = Global longitudinal strain

GLSr = Global longitudinal strain rate

GRS = Global radial strain

HR = Heart rate

LS = Longitudinal strain

LV = Left ventricular

RS = Radial strain

RV = Right ventricular

SLS = Segmental longitudinal strain

2DSTE = Two-dimensional speckle-tracking echocardiography

Left ventricular (LV) function is an important prognostic determinant of cardiopulmonary pathologies in children.[1-3] The LV myocardium has a complex architecture and consists of circumferential fibers in the midwall layer and longitudinal fibers in the endocardial and epicardial layers.[4,5] This results in inhomogeneous and complex contraction patterns, as the myofiber orientation changes continuously from a right-handed helix in subendocardium to a left-handed helix in subepicardium.[4-6] LV deformation comprises radial thickening, circumferential shortening, and longitudinal shortening, and myocardial strain describes this deformation under an applied force.[2,6] Specifically, two-dimensional speckle-tracking echocardiography (2DSTE) is an angle-independent method for myocardial strain measurement that has been used to estimate deformation measures and quantitatively characterize LV function in children.[7-71]

Clinical application of cardiac strain by 2DSTE to measure LV function in children requires knowledge of the range of normal values.[72] The use of strain imaging to assess LV systolic and diastolic function in healthy children and children with specific cardiac conditions has recently produced measures of normal global and segmental longitudinal strain (LS), circumferential strain (CS), and radial strain (RS) and strain rate.[7-71] Measurements of myocardial strain imaging are subject to "physiologic variation" depending on patient demographics (age, gender, race), clinical factors (heart rate [HR], blood pressure, weight or body surface area [BSA]), and equipment and image technique variables (ultrasound and vendor-customized software, probe size, tissue-tracking methodology, location of reported strain value along the strain curve, frame rate [FR], and FR/HR ratio).[1,73,74] Similar to Yingchoncharoen *et al.*'s[1] meta-analysis of the normal ranges of LV strain in adults, and our own meta-analysis of the normal ranges of right ventricular (RV) strain in children, we sought to define a range of normal LV strain measures by using a compilation of all studies that reported values for cohorts of normal or control children.[73] These reference values and associated variations of the deformation measures need to be "firmly established before routine clinical adoption" of LV strain measurements can be implemented in children.[1,72,73]

The objectives of this study were to perform a meta-analysis of the normal ranges of LV global LS (GLS), global CS (GCS), and global RS (GRS) measurements derived by 2DSTE in children and identify factors that may contribute to differences in reported measures.

METHODS

Search Strategy/Search Protocol

L.H.Y., A.H., and S.Y., the medical librarians at Washington University School of Medicine (St. Louis, Missouri), trained in systematic reviews, created search hedges to cover the concepts of pediatrics and children, speckle-tracking echocardiography, and the left-heart ventricle using terms harvested from standard term indices and on-topic articles (Appendix 1). To exclude animals, L.H.Y. used the human filter for PubMed recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* and then used that as a model created by S.Y. to create similar filters for the other searched databases.[75] The search strategy was launched in MEDLINE, Embase, Scopus, the Cumulative Index of Nursing and Allied Health Literature, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Searches were completed by November 2015. The reference lists of all selected reports were screened to identify additional studies.

Study Selection/Eligibility Criteria

Studies were included if they reported using strain derived by 2DSTE to measure LV function in healthy pediatric normal or control subjects. Studies that exclusively included children <21 years of age were considered eligible for the meta-analysis. The systematic review incorporated observational studies that used pediatric control groups with normal results on echocardiography (who were recruited for specific studies) or if healthy children were the primary objective.[7-71] Studies were excluded if they were review articles or abstracts only, without full text.

LV GLS and global longitudinal strain rate (GLSr) from a 17- or 18-segment model (calculated from segmental averaging of the three apical views [apical four-, three-, and two-chamber]) were included in this meta-analysis. GCS and GRS, calculated from segmental averaging of the short-axis views at the apical, midventricular, and basal levels, were also included in the meta-analysis. In addition, we also evaluated the LV free wall LS measures and included segmental LS (SLS) at the apical, midventricular, and basal levels of the LV free wall from segmental averaging of the three apical views. Clinically, LS is also reported from the weighted average of the six segments from the apical four-chamber view, and CS and RS are reported from weighted averages of the six segments from the midventricular level at the papillary muscle.[74,76] We therefore stratified our meta-analysis by the different methods, "global" strain (GLS, GCS, and GRS) and "six-segment method" (LS, CS, and RS), of reporting LV strain and incorporated the publications that reported these different methods in the meta-analysis to account for the different techniques used among studies.

Data Collection

Each eligible article meeting the inclusion criteria was reviewed by two independent reviewers (P.T.L and A.M.), and the following data were extracted and entered into an electronic database: (1) study: first and last authors and year of publication; (2) demographics: number of control subjects, age, and gender; (3) clinical: HR, BSA, or body metabolic index; and (4) echocardiographic parameters: vendor-customized ultrasound and model, vendor-customized software and version, probe frequency, FR, FR/HR ratio,[77] tissue-tracking methodology, (endomyocardial, epicardium to endocardium), and reported location of the strain value along the stain curve (systolic strain, end-systolic strain, or postsystolic strain).[74] All the authors of the eligible studies were contacted by e-mail to notify them of the meta-analysis and obtain any missing information not reported in their individual studies.