Normal Values and Growth-Related Changes of Left Ventricular Volumes, Stress, and Strain in Healthy Children Measured by 3-Dimensional Echocardiography

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Normal pediatric values of three-dimensional (3D) left ventricular (LV) volumes and strain are not well established; moreover, no reports exist of the stress-strain relation and the heart rate-corrected velocity of circumferential fiber shortening (VCFc) based upon 3D imaging in children. Three-dimensional LV datasets were obtained in pediatric patients (≤18 years of age) with structurally normal hearts. Ventricular volumes and strain components (longitudinal, GLS; circumferential, GCS; and 3D strain, 3DS) were analyzed using a commercial 3D speckle-tracking analysis package. LV mid-wall global average end-systolic fiber stress was calculated from 3D LV volumes. A total of 238 patients were included in the analysis with a median age of 13.1 years (range 0.4 to 17.9 years). Regression equations were derived for 3D volume parameters, permitting body surface area-based Z score calculation. Overall, 3DS values were more negative than GLS and GCS (mean ± SD = −33.8 ± 2.8; −27.8 ± 2.9; and −21.7 ± 3.1, respectively); only GLS varied significantly with age (r = 0.22; p <0.001). Both global average end-systolic fiber stress and 3D VCFc increased significantly with age (p <0.001 for both). Stress-adjusted 3DS and VCFc both varied with age (p <0.001 for both), consistent with increased contractility. In conclusion, 3D echocardiography may be used to calculate LV stress, strain, and volumes in pediatric patients with strong reproducibility. Among strain parameters, significant age-related changes were seen only in GLS. Both indexes of contractility investigated (3DS and VCFc indexed to wall stress) improved with age. Future studies of the 3D echocardiography stress-strain relation may yield new insights into maturational changes in myocardial contractility. **(Am J Cardiol ■■;■■:■■–■■)**

The measurement of left ventricular (LV) volumes and function is among the most frequent and important tasks performed in any clinical echocardiography laboratory. Techniques used to make these measurements have evolved considerably over the course of the last several decades, reflecting improvements both in transducer technology and microprocessor speed. Recent advances in ultrasound technology have made three-dimensional echocardiography (3DE) imaging feasible, practical, and routinely available in most clinical echocardiography laboratories. Multiple studies have shown a high concordance between LV volume calculations made by 3DE and those made by cardiac magnetic resonance, commonly accepted as the gold standard for volumetric measurements.[1–3] In addition to the measurement of ventricular volumes, 3DE provides a means of obtaining multiple strain components. Although strain has been shown to be an important measure of myocardial function, it is strongly load-dependent, varying with both preload and afterload. The LV end-systolic wall stress-heart rate-corrected velocity of circumferential fiber shortening (VCFc) relation is a load-independent measure of myocardial contractility.[4] This index, however, has typically been calculated based on one-dimensional measurements (e.g., fractional shortening).[4] Therefore, the aims of our study were to generate regression equations for three-dimensional (3D) LV volumes based upon a largest pediatric cohort, to identify values of 3D strain components in this group and to report age-related changes in these values, and to describe age-related changes in indexes of contractility, including the novel parameter of 3D-VCFc indexed for wall stress.

Methods

Three-dimensional LV datasets were obtained as part of routine clinical care in outpatient or inpatient (newborn) echocardiographic examinations in patients beginning in January 2014. Typical indications for echocardiography

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included murmur, dizziness or syncope, family history of congenital heart disease (such as bicuspid aortic valve), and chest pain. Inclusion criteria included age ≤18 years and body surface area (BSA) >0.2 m^2 (average size for a normal newborn), with echocardiographic evidence of a structurally normal heart. Exclusion criteria included cardiac abnormalities other than a patent foramen ovale or trivial branch pulmonary artery stenosis (maximum instantaneous gradient <15 mm Hg within the first 2 months of life); arrhythmia (other than rare atrial or ventricular premature beats); acquired heart disease (e.g., cardiomyopathy and Kawasaki disease); co-morbidities with a potential impact on ventricular size or function such as hypertension, renal failure, and anemia; family history of cardiomyopathy (first-degree relative); more than trivial stenosis or mild regurgitation of any heart valve; bradycardia or tachycardia (heart rate Z score relative to age <–2 or >2); connective tissue disorder; patent ductus arteriosus other than trivial; dilated aorta (Z score >2.5); obesity or underweight (body mass index Z <2 or >2); hypertension (systolic blood pressure or diastolic blood pressure >95% at the time of the echocardiogram); and two-dimensional (2D)-based LV mass, volume, or ejection fraction (EF) Z score <–2.5 or >2.5. Studies were also excluded if there were significant concerns regarding image quality.

Demographic information including gender, height, and weight was recorded from the patient's clinical note at the time of the echocardiogram. Two-dimensional imaging data (end-systolic and end-diastolic volume) were recorded from the clinical echocardiogram reports; of note, 2D volumes in our laboratory are calculated based upon the $\frac{5}{6}\,area \times length$ method.[5] Blood pressures (systolic, diastolic, and mean) from the same visit were recorded as well. This study was performed according to a protocol approved by the Committee for Clinical Investigation at Boston Children's Hospital.

Images were acquired using the Philips IE33 and Epiq platforms using X3/5/7 probes (Philips Healthcare, Best, The Netherlands), with care taken to include the entire LV. Full-volume acquisitions were obtained over 4 consecutive beats (screenshot of a typical 4 beat acquisition provided in Figure 1). Volumes were excluded if image quality was judged to be inadequate (frame rate too low, significant stitch artifact, or portions of the LV not included in the acquisition). For patients in whom multiple 3D LV volumes had been acquired, the volume judged to have the highest image quality was chosen for analysis. Three-dimensional LV volumes and strain components (3D global, 3DS; circumferential, GCS; and longitudinal, GLS) were analyzed using a commercial 3D speckle-tracking analysis package (4D LV Analysis 3.1; Tomtec Imaging Systems, Unterschleissheim, Germany). Strain values are reported in their raw form; for example, more negative numbers reflect greater changes in deformation.

LV wall stress was calculated using the formula for global average end-systolic fiber stress (ESFSga) as described by Regen[6]:

$$\left(\frac{ESFSga = 1.5 \times (ESVmw/EDVmw) \times P}{Ln(EDVepi) - Ln(EDV)}\right)$$

where ESVmw = end-systolic mid-wall volume; EDVmw = end-diastolic mid-wall volume; P = end-systolic pressure; EDVepi = epicardial end-diastolic volume; EDV = endocardial end-diastolic volume. All mass and volume measurements were obtained by 3DE methods. The end-systolic pressure was estimated from the mean automated blood pressure, as has been validated in prior publications.[7–9] Epicardial EDV was calculated using the formula: Epicardial LVEDV = (LV mass/1.03) + Endocardial LVEDV.

Velocity of circumferential fiber shortening is a one-dimensional measure of contractility that is equal to shortening fraction (SF) divided by ejection time, typically calculated from M-mode echocardiography. In this study, we calculated the novel parameter 3D velocity of circumferential fiber by substituting 3DS (a 3D dimensional fraction reflective of fiber shortening) for SF and dividing by ejection time. This parameter was then rate-corrected as:

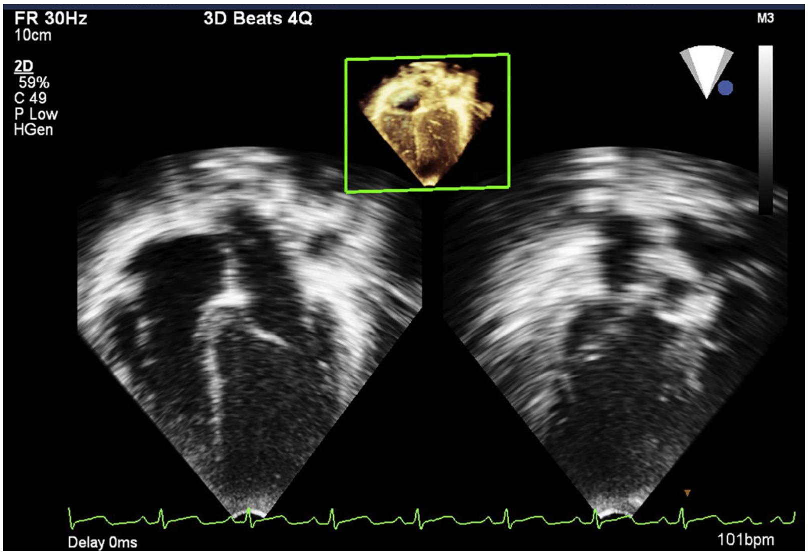

Figure 1. Three-dimensional LV volume acquisition. An image from an apical 4-chamber 3D full-volume acquisition using the Philips iE33 platform. Full-volume acquisitions were obtained over 4 consecutive beats.