Feasibility and Reproducibility of Echocardiographic Measures in Children with Muscular Dystrophies

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Background: Cardiac disease is a major cause of death in patients with muscular dystrophies. The use of feasible and reproducible echocardiographic measures of cardiac function is critical to advance the field of therapeutics for dystrophic cardiomyopathy.

Methods: Participants aged 8 to 18 years with genetically confirmed Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, or limb-girdle muscular dystrophy were enrolled at five centers, and standardized echocardiographic examinations were performed. Measures of systolic and diastolic function and speckle-tracking echocardiography–derived cardiac strain were reviewed independently by two central readers. Furthermore, echocardiographic measures from participants with DMD were compared with those from retrospective age-matched control subjects from a single site to assess measures of myocardial function.

Results: Forty-eight participants (mean age, 13.3 ± 2.7 years) were enrolled. Shortening fraction had a greater interobserver correlation (intraclass correlation coefficient [ICC] = 0.63) compared with ejection fraction (ICC = 0.49). One reader could measure ejection fraction in only 53% of participants. Myocardial performance index measured by pulse-wave Doppler and Doppler tissue imaging showed similar ICCs (0.55 and 0.54). Speckle-tracking echocardiography showed a high ICC (0.96). Focusing on participants with DMD (n = 33), significantly increased mitral A-wave velocities, lower E/A ratios, and lower Doppler tissue imaging mitral lateral E′ velocities were observed compared with age-matched control subjects. Speckle-tracking echocardiography demonstrated subclinical myocardial dysfunction with decreased average circumferential and longitudinal strain in three distinct subgroups: participants with DMD with normal shortening fractions, participants with DMD aged < 13 years, and participants with DMD with myocardial performance index scores < 0.40 compared with control subjects.

Conclusions: In a muscular dystrophy cohort, assessment of cardiac function is feasible and reproducible using shortening fraction, diastolic measures, and myocardial performance index. Cardiac strain measures identified early myocardial disease in patients with DMD. (J Am Soc Echocardiogr 2015;28:999-1008.)

Keywords: Muscular dystrophy, Echocardiography, Cardiac strain, Cardiomyopathy

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Abbreviations

BMD = Becker muscular dystrophy

CINRG = Cooperative International Neuromuscular Research Group

CS = Circumferential strain

DMD = Duchenne muscular dystrophy

DTI = Doppler tissue imaging

EF% = Percentage ejection fraction

ET = Ejection time

ICC = Intraclass correlation coefficient

IVCT = Isovolumic contraction time

IVRT = Isovolumic relaxation time

LGMD = Limb-girdle muscular dystrophy

LS = Longitudinal strain

MD = Muscular dystrophy

MPI = Myocardial performance index

PWD = Pulse-wave Doppler

SF% = Percentage shortening fraction

STE = Speckle-tracking echocardiography

Cardiomyopathy causes significant morbidity and mortality in multiple forms of muscular dystrophy (MD) affecting children, including Duchenne MD (DMD), Becker MD (BMD), and subtypes of autosomal-recessive limb-girdle MD (LGMD).[1] The prevalence of cardiomyopathy increases with age and is currently underdiagnosed in patients with DMD.[2,3] Therefore, it is increasingly important to study cardiac disease in muscular dystrophies to determine the best diagnostic and treatment modalities.

Adequately powered pharmaceutical studies for the treatment of MD require the collection of reproducible data across multiple clinical sites because of the rarity of these diseases. Several studies have researched cardiac end points, but comparisons across studies are hindered by different study designs and functional measures, which include percentage shortening fraction (SF%), percentage ejection fraction (EF%), mitral inflow velocities, myocardial performance index (MPI), and myocardial strain.[4-25] These measures are also affected by technical limitations in patients with MD, including scoliosis, barrel chest deformities with lung hyperinflation, and limited mobility.

The purpose of this study was to assess the feasibility and reproducibility of noninvasive echocardiography-based functional cardiac measures in a multicenter cohort of participants with MD and determine which measures can detect early subclinical changes in myocardial function. The Cooperative International Neuromuscular Research Group (CINRG) is a coalition of academic clinical centers dedicated to MD research. CINRG has validated skeletal muscle functional measures for multisite DMD studies.[26] The results of this study will help direct the selection of cardiac measurements for future clinical trials and enhance consistency within the field of cardiomyopathies in patients with MD.

METHODS

This was a multicenter, prospective study investigating different echocardiographic parameters with participants enrolling at five institutions in the CINRG network, all also part of the Clinical and Translational Science Award network (http://www.ctsacentral.org). The study was approved by the institutional review board at each institution. Written informed consent and assent were obtained from all participants and their parents or legal guardians. The study was registered with ClinicalTrials.gov (identifier NCT01066455). Participants had confirmed genetic diagnoses of DMD, BMD, or an autosomal-recessive subtype of LGMD (LGMD2C, LGMD2D, LGMD2E, LGMD2F, or LGMD2I). Participants were excluded if they had histories of congenital cardiac defects or other cardiac diseases unrelated to MD. Retrospective control subjects for participants with DMD were patients referred to the cardiology clinic at one of the five participating CINRG clinical sites (Children's National Health System) for cardiac murmur or chest pain and were determined to have normal results on cardiac evaluation with normal conventional echocardiographic parameters. Race and ethnicity were self-reported and not required for control subjects.

Methods to Determine the Feasibility and Reproducibility of Noninvasive Echocardiography-Based Functional Cardiac Measures

A central sonographer traveled to each participating CINRG site to review and train the site personnel on the use of a centralized protocol using standard imaging planes and recording three-beat loops saved in Digital Imaging and Communications in Medicine format. Echocardiographic studies were performed with participants in the supine position on an examination table or seated in a power wheelchair if transfer to an examination table was not possible. These digital loops were interpreted by two pediatric cardiologists and one pediatric cardiology fellow. There were two readers at the Washington site (C.F.S. and S.J.G. [fellow]) and one reader at the Pittsburgh site (F.M.M.).

All measurements and calculations, including SF%, EF% using the single-plane modified Simpson protocol, wall stress, velocity of circumferential shortening, rate-corrected velocity of circumferential shortening, MPI (which includes measures of ejection time [ET], isovolumic contraction time [IVCT], and isovolumic relaxation time [IVRT]) using both pulse-wave Doppler (PWD) and Doppler tissue imaging (DTI), mitral inflow, and left ventricular peak E-wave velocities, were made according to standards of the American Society of Echocardiography.[27] Each reader (C.F.S. and F.M.M.) measured two-dimensional and Doppler values over three cardiac cycles (or the maximum feasible when imaging was of limited quality), and the average was used for analysis. To assess intraobserver variability, 47 echocardiograms were reassessed by the same observer (C.F.S.) after a period of ≥2 weeks. Interobserver variability was assessed by having a different reader (F.M.M.) perform all the measures on the conventional echocardiographic images independently.

Methods to Determine Early Subclinical Myocardial Changes

Cardiac strain was measured using speckle-tracking echocardiography (STE) on the subset of participants with DMD from all five participating CINRG centers and historical control subjects from a single institution (Children's National Health System), using proprietary software (Syngo Velocity Vector Imaging; Siemens Medical Solutions USA Inc, Mountain View, CA). Speckle-tracking echocardiographic analysis was performed by two readers (C.F.S. and S.J.G.). For STE, endocardial tracings of the left ventricle were manually performed in the apical four-chamber view (for longitudinal measurements) and the parasternal short-axis view at the level of the midpapillary muscles (for circumferential measurements). A single cardiac beat with the best-appearing image quality was used. Tracking was