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Cardiac Imaging and Biomarkers for Assessing Myocardial Fibrosis in Children with Hypertrophic Cardiomyopathy

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Declaration of Interests:

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Abstract

Background: Myocardial fibrosis, as diagnosed on cardiac magnetic resonance imaging (cMRI) by late gadolinium enhancement (LGE), is associated with adverse outcomes in adults with hypertrophic cardiomyopathy (HCM), but its prevalence and magnitude in children with HCM have not been established. We investigated: 1) the prevalence and extent of myocardial fibrosis as detected by LGE cMRI; 2) the agreement between echocardiographic and cMRI measurements of cardiac structure; and 3) whether serum concentrations of N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) and cardiac troponin-T are associated with cMRI measurements.

Methods: A cross-section of children with HCM from 9 tertiary-care pediatric heart centers in the U.S. and Canada were enrolled in this prospective NHLBI study of cardiac biomarkers in pediatric cardiomyopathy (ClinicalTrials.gov Identifier: NCT01873976). The median age of the 67 participants was 13.8 years (range 1-18 years). Core laboratories analyzed echocardiographic and cMRI measurements, and serum biomarker concentrations.

Results: In 52 children with non-obstructive HCM undergoing cMRI, overall low levels of myocardial fibrosis with LGE >2% of left ventricular (LV) mass were detected in 37 (71%) (median %LGE, 9.0%; IQR: 6.0%, 13.0%; range, 0% to 57%). Echocardiographic and cMRI measurements of LV dimensions, LV mass, and interventricular septal thickness showed good agreement using the Bland-Altman method. NT-proBNP concentrations were strongly and positively associated with LV mass and interventricular septal thickness ($P<0.001$), but not LGE.

Conclusions: Low levels of myocardial fibrosis are common in pediatric patients with HCM seen at referral centers. Longitudinal studies of myocardial fibrosis and serum biomarkers are warranted to determine their predictive value for adverse outcomes in pediatric patients with HCM.

Keywords

Pediatric hypertrophic cardiomyopathy; cardiac magnetic resonance imaging; late gadolinium enhancement; myocardial fibrosis; myocardial stress; left ventricular mass

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is characterized by hypertrophy of the left ventricular (LV) myocardium without dilation of the LV or evidence of other cardiac or systemic diseases capable of causing LV hypertrophy. (1,2) Isolated HCM in children may be

idiopathic or the result of a known disease-causing mutation and can also occur in the context of various genetic or metabolic syndromes. The disease increases the risk of heart failure (HF), ventricular arrhythmias, and sudden cardiac death (SCD). (2) The incidence of SCD in children and adolescents with HCM is about 6 cases per 100,000 population annually. (3-6)

In adults with HCM, risk factors for SCD and criteria for consideration of primary implantable cardioverter defibrillator (ICD) placement include a maximal interventricular septal thickness >30 mm, a history of non-sustained ventricular tachycardia, unexplained syncope, LV systolic dysfunction, LV apical aneurysm, and/or a family history of SCD secondary to HCM. (2) In addition, extensive myocardial fibrosis, as assessed by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (cMRI), has been adopted as a supportive criterion for defibrillator placement as primary prevention in adults because myocardial fibrosis may be a substrate for arrhythmias and HF. (7-12) Accordingly, several studies have tested serum cardiac and collagen metabolism biomarkers that may relate to myocardial fibrosis, as well as N-terminal-proB-type natriuretic peptide (NT-proBNP) and cardiac troponin-T, in patients with HCM to establish their value in detecting and monitoring myocardial fibrosis, myocardial stress and injury. (13-15)

Recent data suggest that many of the classical risk factors accepted in adult patients are important in children, but there is still no consensus on the importance of LGE on cMRI as a risk factor in children with HCM. Among 1,085 children with HCM enrolled in the NHLBI-supported Pediatric Cardiomyopathy Registry between 1990 and 2006, identified risk factors for death or transplant were age at diagnosis of <1-year, HF, or a mixed cardiomyopathy phenotype (HCM with dilated or restrictive features), diminished LV fractional shortening, and increased LV posterior wall thickness in diastole measured by echocardiography. (5) That study was conducted before the availability of LGE imaging. The importance of prevalence and degree of myocardial fibrosis in children with HCM are not well established. A primary *a priori* aim of the NHLBI-funded Cardiac Biomarkers in Pediatric Cardiomyopathy prospective study (ClinicalTrials.gov Identifier: NCT01873976) from the NHLBI-sponsored Pediatric Cardiomyopathy Registry (ClinicalTrials.gov Identifier: NCT00005391) was to determine the prevalence of myocardial fibrosis as assessed by LGE in children with HCM, to determine whether echocardiographic and cMRI measurements for interventricular septal thickness and LV dimensions agree, and whether serum concentrations of NT-proBNP and cardiac troponin-T are associated with cMRI measurements of LV hypertrophy, mass, or myocardial fibrosis. This paper addresses this primary study aim.

METHODS

Study Design

In this cross-sectional study, we enrolled children with HCM seen at 9 tertiary pediatric heart centers in the U.S. and Canada (Clinical Trial Registration: NCT01873976). Eligibility was based on strict echocardiographic or cMRI criteria, as described by Everitt *et al.* (16) Briefly, patients were eligible for enrollment if 1) they were alive and <21 years old, 2) had been diagnosed with idiopathic or familial HCM or HCM from a known-disease causing

mutation, and 3) had undergone cMRI imaging within 2 months of enrollment and had a blood specimen and echocardiogram acquired within 6 months of the cMRI. Children were excluded if they had syndromes associated with cardiomyopathy (e.g., Noonan syndrome or phenocopies, glycogen storage disease, metabolic disease, mitochondrial disease); a history of rheumatic fever; a history of radiation treatment, chemotherapy treatment, iron overload, uremia, or other potential toxic exposures; a history of congenital heart disease, ischemic coronary artery disease, or Kawasaki disease; a history of autoimmune disease or immunodeficiency; or a history of systemic or pulmonary hypertension or pulmonary vascular disease. (16) Infants of mothers with diabetes were also excluded.

The Institutional Review Boards at all centers participating in the study approved the protocol, with informed consent obtained from parents or legal guardians and assent from participants when appropriate.

Clinical Data Collection

Study data were abstracted from the electronic health record at each site by a specially trained data collection team. Data were entered into the study database through a web-based system designed by the study's data coordinating center at the New England Research Institutes, Inc. (HealthCore, Inc.) in Watertown, MA. Data elements included demographics, age at HCM diagnosis, cardiac medications used at enrollment, results of clinical genetic testing, and surgical history.

Cardiac Magnetic Resonance Image Acquisition and Measurements

Results of cMRI were collected and analyzed in the core MRI laboratory at Washington University School of Medicine in St. Louis, MO. (16) All scans were performed on 1.5 T-conventional, whole-body standard medical MRI scanners with phased-array coils. The cardiac protocol included scout scans for localization; horizontal and vertical long- and short-axis; and multiphase, gated cine imaging using a steady-state free-precession (SSFP) sequence for function and anatomy at the highest optimal flip angle. In addition, LGE, phase-sensitive, inversion-recovery, and gradient-echo images were obtained after intravenous administration of a gadolinium-based contrast agent, (gadopentetic acid [Magnevist], gadoversetamide [OptiMARK], gadodiamide [Omniscan], gadoterate meglumine [Dotarem], or gadobenate dimeglumine [MultiHance]).

Gadolinium-enhanced images were acquired 7 to 10 minutes after administering the intravenous gadolinium bolus. Inversion times were between 200 and 350 ms, set to null signal from the normal myocardium. All long-axis images were acquired at a 6-mm slice thickness. Short-axis images were, in general, acquired at a 6-mm slice thickness (0 gap) in children <6 years old, and at an 8-mm slice thickness (0 gap) in children >6 years old. All cMRI images were de-identified and interpreted at a core laboratory by a single trained cardiac radiologist (PKW). Only the age of the child was known at the time of interpretation. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), interventricular septal thickness, LV mass, and %LGE were measured using Medis QMass software (Leiden, Netherlands). Late gadolinium enhancement in the myocardium was defined as 6 standard deviations above the signal in the normal

myocardium. (17, 18) No adjustment or erasure was made of identification of high myocardial signal potentially caused by artifact.

Echocardiographic Image Acquisition and Measurements

Echocardiograms were acquired at each study site according to the study's echocardiographic imaging protocol, which consisted of complete two-dimensional, transthoracic echocardiographic and Doppler evaluations, a complete assessment of any anatomic abnormalities, valve dysfunction, and intracardiac thrombi, and standard short- and long-axis views of the LV to assess regional wall motion. (16)

The study sites provided age, height, weight, and blood pressure data. Echocardiograms were uploaded in the DICOM (Digital Imaging and Communications in Medicine) format using a commercial, HIPAA-compliant image transfer service (AMBRA, Inc) to the study's core echocardiography laboratory at Boston Children's Hospital. Images were de-identified during import to the core lab server, and all analyses were performed by a single trained cardiologist (FIL) using custom core-lab designed software that archived all measurements as a non-destructive overlay and the derivation of all calculated variables, as specified by the American Society of Echocardiography guidelines. (19) Body surface area (BSA) was calculated according to the formula of Haycock et al., and Z-scores were calculated relative to age or BSA as described elsewhere. (20, 21) The cardiologist measuring the echocardiograms was blinded to the cMRI results.

Serum Biomarker Concentrations

Serum concentrations of NT-proBNP and cardiac troponin-T were measured. Blood was drawn within 2 months of the cMRI study. Samples were sent by express mail to the Study Biological Specimen Repository (Wayne State University, Detroit, MI). Blood samples were processed centrally and stored at −80°C until batch analysis occurred at the Diabetes Research Institute Immunoassay and Chemistry CLIA-approved Core Laboratory (University of Miami Miller School of Medicine, Miami, FL).

Statistical Methods

All data were analyzed by the Data Coordinating Center at the New England Research Institutes with SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). Normally distributed data are summarized with means and standard deviations, and skewed data are summarized with medians and interquartile ranges. Distributions were examined using histograms and Q-Q plots, and log-transformation was used to achieve normal distributions. Pearson correlation analysis was used to determine relationships between cMRI parameters, age at diagnosis, and disease duration. Within this analysis, LV mass index was developed using a scaling factor of 1.33, as per previously published pediatric analysis of structural measurements adjusting for growth. (21, 22)

Bland-Altman analysis was used to determine the agreement between echocardiographic and cMRI measurements. Values near the line of equality or within the confidence interval of the mean difference indicate good agreement and minimal bias. Associations between cMRI and biomarker measures were assessed with multivariable linear regression models, adjusted

for age at diagnosis, time since diagnosis, race, and ethnicity. Linearity was assessed with residual plots. Alpha was set at 0.05, and all tests were twotailed. List-wise deletion or complete-case analysis was used by removing observations with missing values.

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RESULTS

Patient Characteristics

The median age of the 67 participants was 12.1 years (range, birth to 18 years) at the time of HCM diagnosis, and 13.8 years (range, 1 to 18 years) at study enrollment. Children were predominantly boys (78%) and White (82%; Table 1). Most patients (57%) were on a beta-blocker at time of enrollment and 10% were on a calcium channel blocker.

Cardiac Imaging Measurements

Of the 67 participants with cMRI scans, 63 (94%) had images suitable for measuring LV wall-thickness and chamber volumes and function; 52 (78%) had LGE images suitable for calculating the extent of myocardial fibrosis. Reasons for excluding cMRI images from further analysis were lack of or incomplete LGE imaging, artifacts caused by excess respiratory motion, and/or poor reduction of background signal (nulling) of the normal myocardium on LGE images to accentuate areas of abnormal tissue. Cardiac MRIs were obtained at clinical discretion, typically with consideration of ICD placement and/or heart transplantation.

In our cohort, 48 of 52 (92%) children had detectable LGE, and 37 of 52 (71%) had %LGE greater than 2% of the LV mass. Median %LGE was 9.0% (IQR: 6.0%, 13.0%) with a range of 0% to 57% (Table 2). Children <5 years old had the highest %LGE with a median %LGE of 11.5% (IQR: 9.0%, 13.0%). Children between 11 and 15 years old had the lowest %LGE, with a median %LGE of 8.0% (IQR: 5.0%, 14.0%). Overall, when we excluded LGE <2%, similar levels of myocardial fibrosis were measured across all age groups.

Further analysis of LV mass and interventricular septal thickness adjusted for BSA showed a greater interventricular septal thickness in children <5 years old (median, 18.4 mm/m2; IQR: 11.5 mm/m2, 24.9 mm/m2). Interventricular septal thickness and LV mass adjusted for BSA were strongly correlated ($r = 0.70$, $P<0.001$, Table 3). Neither interventricular septal thickness nor LV mass adjusted for BSA had any significant correlation with %LGE (or %LGE >2%), duration of disease, or age at diagnosis. Across all age groups, only 2 children had LGE solely at right/left ventricular hingepoints, also associated with thickened myocardium in this region. These were not present in patients with < 2% LGE.

Fifty-five children had evaluable cMRI images and corresponding echocardiographic images acquired within the defined time window. Median time between the cMRI and the echocardiogram was 29 days (IQR: 1 day, 56 days). Bland-Altman analysis indicated good agreement between echocardiographic and cMRI measurements of cardiac structure (LVEDV, LVESV, LV mass, and interventricular septal thickness) within the 95% confidence interval (Figure 1; Supplemental Table). No patient had LV outflow tract obstruction (peak gradient of > 30 mm Hg) as assessed by cMRI or echocardiography at rest.

Association of Serum Biomarker Concentrations with Cardiac Imaging Measurements

None of the serum biomarkers were significantly associated with %LGE (Table 4). The serum concentration of NT-proBNP was associated (P<0.001) with cMRI measures of LV mass and interventricular septal thickness, and serum cardiac troponin-T concentrations were marginally associated with LV mass adjusted for BSA (P=0.05). A 1%-increase in the average concentration of NT-proBNP (pg/mL) was associated with an increase of 0.20% in the average LV mass (P<0.001) and with a 0.19% increase in the average interventricular septal thickness (P<0.001). A 1%-increase in serum cardiac troponin-T (ng/mL) was marginally associated with an increase of 0.18% in the average LV mass (P=0.05).

DISCUSSION

In this study, we found a high prevalence of myocardial fibrosis overall as detected by LGE in children with HCM, particularly in children <5 years old. Additionally, while the interventricular septal thickness and LV mass adjusted for BSA were strongly correlated, neither of these parameters had a significant correlation with %LGE, duration of disease (the clinical HCM phenotype), or age at HCM diagnosis. We also found that echocardiography and cMRI show good agreement in measurements of LV dimensions and interventricular septal thickness. Increases in serum NT-proBNP and cardiac troponin-T concentrations were associated with increasing LV mass. Increased concentrations of serum NT-proBNP were also associated with increases in interventricular septal thickness.

Myocardial Fibrosis

In our cohort, LGE was detected in most children (48/52, 92%) with 34 of 52 children (71%) having >2% LGE of LV mass. Cardiac MRI has the advantage over echocardiography of detecting myocardial fibrosis through LGE, and histologic analyses have confirmed a strong relationship between myocardial fibrosis and %LGE. (23) As suggested in the literature, we used a signal intensity value of 6 SDs above that in the normal myocardium on the most visibly normal slice as the threshold of LGE. (17) However, possible artifacts (a high signal secondary to a motion artifact, for instance) might be included objectively as LGE in an otherwise normal examination, especially at the LV apex. (24, 25)

Few studies have reported the prevalence of myocardial fibrosis in children with HCM Using cMRI, Chaowu *et al.* found myocardial fibrosis in 52 (73%) of 71 children with HCM, although they did not report %LGE data. (26) In their analysis 2 years later, 11 of the 71 children with HCM had received a cardioverter defibrillator or had undergone heart transplantation, and children with any level of LGE had more adverse outcomes than those

without any LGE (P=0.03). El Saiedi *el al.,* also demonstrated similar levels of myocardial fibrosis in their cohort of 40 children with HCM with 82% of children having detectable LGE with average 9.7±9% LGE of LV mass. (27) Another recent study by Raja *et al.,* found myocardial fibrosis in 70 of 155 (46%) children with HCM, with a median %LGE of 3.3% of LV mass (IQR: 0.8%, 7.1%). (28) After a median of 2.5 years, the median %LGE increased from 2.9% (IQR, 0.8%, 3.2%) to 4.3% (IQR: 2.9%, 6.8%; P=0.02). These cohorts, as well as our cohort, illustrate the presence of LGE in children <5 years of age. Such a high prevalence of myocardial fibrosis in children this young with non-obstructive HCM is surprising, given that the duration of disease is shorter in children than in adults. However, our analysis also illustrates that %LGE is not strongly correlated with age at diagnosis or the duration of a clinically detected HCM phenotype. Our study, as well as the other studies discussed, may reflect a selection bias as well for young children with clinically advanced disease who warrant sedation for cardiac MRI and, therefore, LGE assessment.

Overall, as discussed, our study demonstrates presence of myocardial fibrosis like other pediatric cohorts as described. As low levels of LGE (<2%) may also convey background artifact, we also examined our parameters relative to LGE >2% of LV mass. (24, 25) As such, we still identified a large prevalence of myocardial fibrosis in our cohort (71%) but no major differences were seen in further analyses using only children with LGE >2% of %LGE relative to cardiac MRI parameters or serum biomarkers (NT-proBNP and cardiac troponin-T). At this time, we are not aware of other published pediatric cohort analyses to which our results between LGE <2% of LV mass and LGE >2% of LV mass can be compared. Additionally, LGE was solely present at the right/left ventricular hingepoints in only 2 patients. In both patients the myocardium was also thickened and LGE was >2%. As such, this LGE appears to be more related to fibrosis found in HCM rather than mild fibrosis associated with right ventricular strain.

The 2020 AHA/ACC Guidelines for Hypertrophic Cardiomyopathy have updated recommendations for ICD placement with consideration for extensive LGE on cMRI (>15% LGE of LV mass) in adults, in addition to other previously described risk factors. (2) Similar to adult analyses, pediatric cohorts of HCM are under investigation for risk factors for SCD. In particular, the HCM Risk-Kids study by Norrish *et al.,* developed a risk prediction model for SCD in children with HCM with variables including unexplained syncope, interventricular septal thickness, left atrial diameter, LV outflow tract gradient, and non-sustained ventricular tachycardia. (29) Using this model, a newer investigation by Grosse-Wortmann *et al.*, demonstrated LGE to be an independent risk factor for SCD in their analysis of 720 pediatric patients with HCM. (30)

In addition to defining myocardial fibrosis as %LGE measured with cMRI, alternative methods are being explored in adults for measuring myocardial fibrosis in patients with marked nephropathy to avoid the side effects of gadolinium. Native T1 mapping and diffusion-weighted cMRI have both detected myocardial fibrosis. (31, 32) Multiple cMRI methods, including feature-tracking of standard cine images, have the potential to characterize myocardial strain, which decreases as myocardial hypertrophy and myocardial fibrosis increase. (33, 34) Finally, new data suggest that myocardial T2* values are associated with an increased interventricular septum and LV mass indexed by body

surface area in a subset of patients with LGE, providing another potential cMRI imaging biomarker for risk stratification. (35) These studies offer promising alternatives for assessing myocardial fibrosis in patients with HCM without the use of contrast agents.

Because of the retrospective nature of this study five different gadolinium-based magnetic resonance imaging contrast agents were used across participating centers. Although, theoretically, the varying contrast agents used could provide some small differences in %LGE, all agents are commonly used in the practice of LGE cMRI and demonstrate similar washout after 5-10 minutes. (36) All agents used, except for gadobenate dimeglumine (MultiHance), have similar relaxivities. (37) The relaxivity or signal of gadobenate dimeglumine is approximately 1.5 times that of the others. (37) In practice, however, all are treated the same in terms of analysis and predictive value. Some prefer to use agents other than gadobenate dimeglumine because of its prolonged half-life in the blood pool secondary to a small intravascular component, and the possibility that small subendocardial infarctions might be missed because of similar signal to the blood pool; however, that was not a concern in this study. (38)

Echocardiography versus Cardiac Magnetic Resonance Imaging

Transthoracic echocardiography remains the most common imaging modality for routinely monitoring patients with HCM. Although cardiac measurements are typically less costly and easier to obtain with echocardiography than with cMRI, they might not be as accurate. A recent study of 19 children with HCM found that measurements made on echocardiograms over-estimated LV wall thickness when compared to those made on cMRI images in certain segments, such as the LV basal anterolateral and apical segments, and underestimated measurements of the mid-ventricular inferior and inferoseptal segments. (39) Some studies in adults have also found discrepancies between echocardiographic and cMRI measurements of interventricular septal thickness and have related these discrepancies to poor acoustic windows, focal LV hypertrophy, LV trabeculations, and the inclusion of the right ventricular myocardium, papillary muscle, and apical septal bundle in the images. (40)

In this study, we found good agreement between echocardiographic and cMRI measurements using the Bland-Altman method, with most data near the line of unity and within the 95% Cl. In particular, interventricular septal thickness between echocardiographic and cMRI measures reveals on average no significant difference between the two imaging modalities. However, as noted earlier, cMRI measures are thought to be more accurate with regards to the interventricular septal thickness. (39, 40). Given these results, cMRI may provide additional clarity in the interventricular septal thickness measurement when considering ICD placement based upon the accepted threshold of 30 mm interventricular septal thickness (or massive LVH by Z-score). (2) Recent guidelines question reliance on absolute interventricular thickness (30 mm) as an indication for pediatric implantable cardioverter-defibrillator placement; rather using age-related septal thickness Z-scores may be preferable (2). In investigating the range of interventricular thickness in this pediatric cohort by echocardiogram, median septal thickness measured 17.0 mm (IQR: 14.0 mm, 22.0 mm) with a median Z-score of+10.4 (IQR: +5.3, +18.1), consistent with significant age-related hypertrophy (Supplemental Table). As noted in Figure 1D, there is good

agreement overall between echocardiographic and cMRI measures for septal thickness (Mean difference -0.2 mm; 95% CI: -11.7 mm, 11.4 mm). Given this distribution, we further examined interventricular septal thickness by echocardiogram ≥ 20 mm (Figure 1E). As Figure 1E illustrates, our cohort has 23 children with an interventricular septal thickness >20 mm by echocardiogram with the mean of differences of 2.1 mm (95% CI: -5.6 mm, 9.8 mm). As such, when interventricular septal thickness is <20 mm by echocardiogram, it is more likely to correlate with interventricular septal thickness by cMRI and echocardiogram may be sufficient for the routine surveillance of LV dimensions and interventricular septal thickness.

Associations of Serum Biomarkers with Cardiac Magnetic Resonance Imaging

We found that NT-proBNP concentrations were associated with interventricular septal thickness and LV mass and that serum cardiac troponin-T concentrations were also associated with LV mass, as measured by cMRI. Concentrations of serum NT-proBNP can predict HF in patients with HCM and, in children with HCM, NT-proBNP concentrations previously have been correlated with non-invasive measurements of disease severity and may increase with increased filling pressures in the heart. (41-43) Similarly, serum cardiac troponin-T concentrations have been used to evaluate myocardial injury, especially in adults with HF. (44-46) Recent analysis of an NHLBI supported registry of adults with HCM found that serum concentrations of B-type natriuretic peptide (BNP) and highly sensitive cardiac troponin-T were significantly associated with LGE as measured on cMRI. (47) Studies of the association between imaging characteristics and biomarkers may clarify the usefulness of these biomarkers for disease surveillance in pediatric HCM.

Strengths and Limitations of the Study

Strengths of the study include the prospective identification of eligible cases and the central measurement of cMRIs, echocardiograms, and select serum biomarkers (NT-proBNP and cardiac troponin-T). Children were selected with clinical eligibility criteria and may not be representative of all children with HCM. Children included in this study are from major tertiary pediatric heart centers in the U.S. and Canada. Additionally, because many children under 5 years of age require sedation for cMRI, our results likely reflect more severe cases in which cMRI was clinically warranted at the discretion of providers. Because adolescents generally do not require sedation for cMRI, they notably comprise the largest subset of our analysis. Given our study design, we also were not able to relate our data to genetic information and therefore could not make genotype-phenotype correlations. Additionally, we have insufficient data for left atrial dimensions, which is also a key variable in assessment of children with HCM. Our study also is not designed to correlate cMRI data with risk for arrhythmia or ICD placement as most devices were placed for primary prevention. Finally, as this is not a longitudinal study, we lack sufficient data with regard to outcomes for the parameters studied.

Conclusions

In children with HCM, cMRI measurements of %LGE detected a high prevalence but overall low levels of myocardial fibrosis. Echocardiography and cMRI provided similar measurements of cardiac structure, LV mass, and interventricular septal thickness,

suggesting that cMRI need not be used to confirm interventricular septal thickness alone, unless further myocardial characterization and measurement of the extent of myocardial fibrosis are required. Finally, increases in serum NT-proBNP and cardiac troponin-T concentrations may reflect increases in LV mass and interventricular septal thickness; however, no biomarkers were associated with the presence or absence, or the level of myocardial fibrosis.

Recently published HCM guidelines (48) have discouraged serial evaluations of HCM in children < 12 years of age. However, the possibility of attenuation of HCM with therapies instituted early in the course of HCM has been demonstrated in the VANISH trial and in prior work in which we have been part of in genotype positive-phenotype negative children with hypertrophic cardiomyopathy (49,50). Longitudinal studies of the rates of change in myocardial fibrosis, LV mass and dimensions, and serum NT-proBNP and cardiac troponin-T concentrations and the rates of SCD or heart transplantation are warranted to determine the predictive value of each of these variables as well as evaluating the impact of future attenuating therapies on the natural history of HCM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

BNP	B-type natriuretic peptide
BSA	body surface area
CLIA	Clinical Laboratory Improvement Amendments
cMRI	cardiac magnetic resonance imaging
HF	heart failure
HCM	hypertrophic cardiomyopathy
IQR	interquartile range
ICD	implantable cardioverter defibrillator
LGE	late gadolinium enhancement
LV	left ventricle
LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume

NHLBI	National Heart, Lung, and Blood Institute
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
SCD	sudden cardiac death

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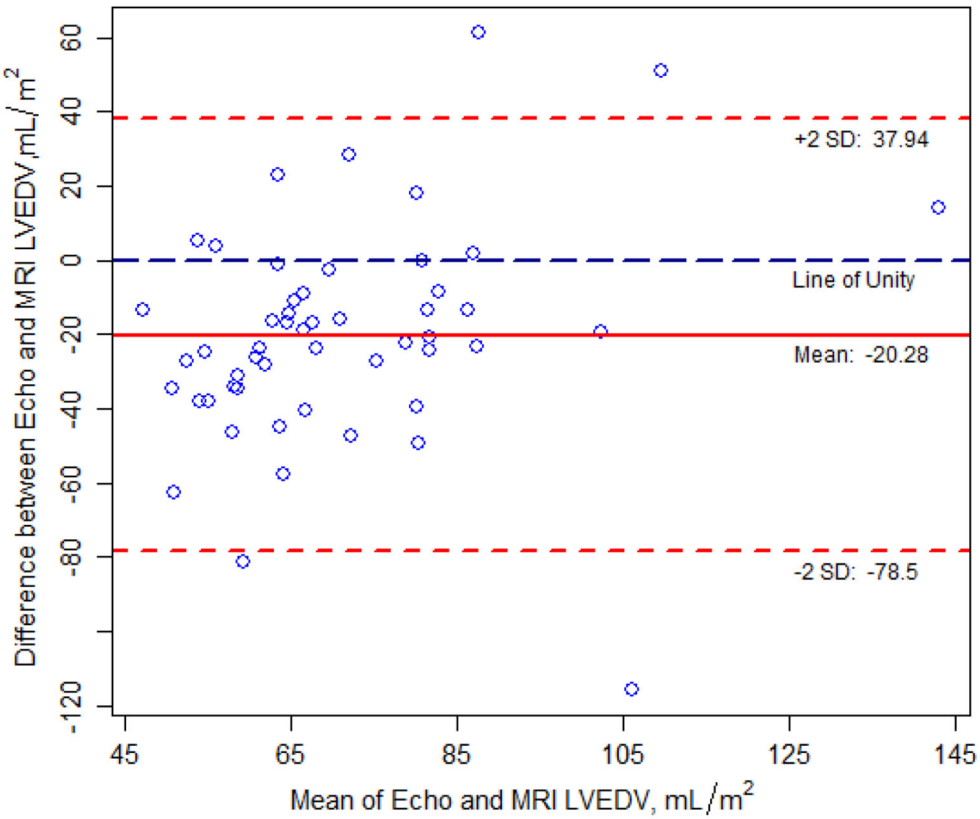
A)



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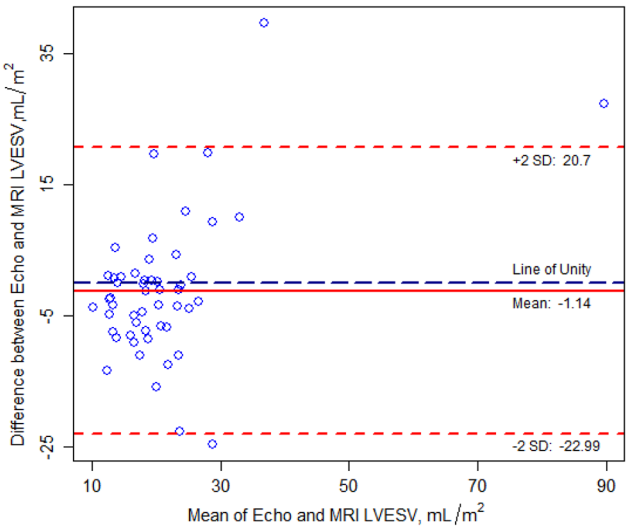

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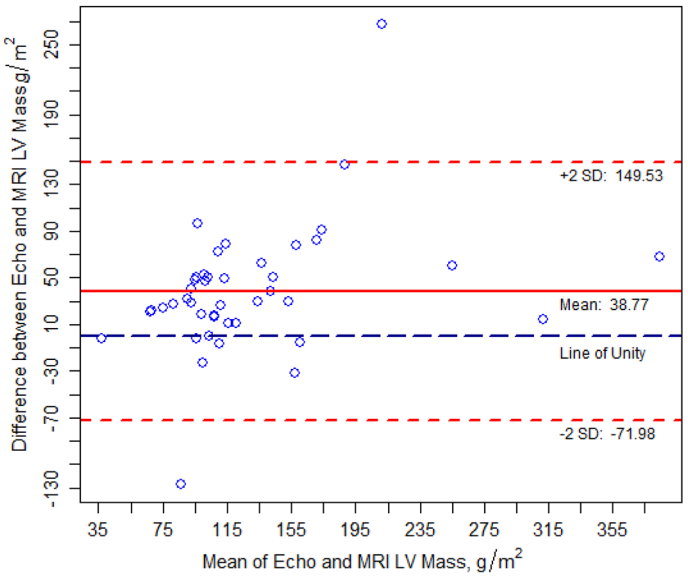

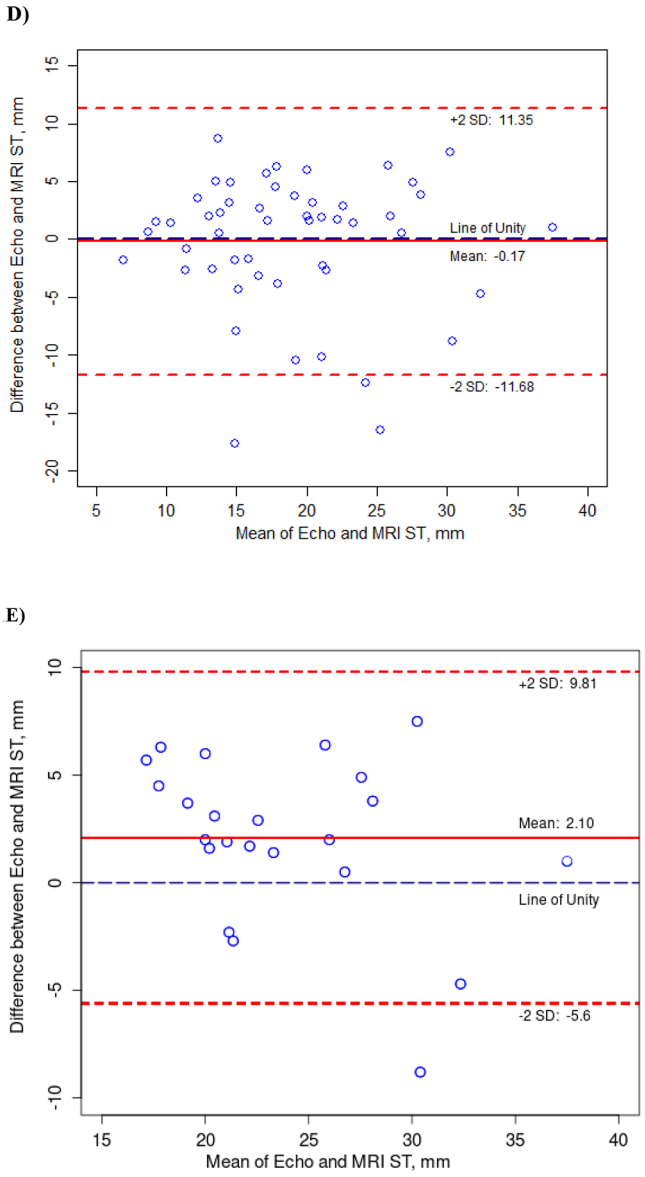

Figure 1.

Agreement Between Cardiac Measurements from Transthoracic Echocardiograms and Cardiac Magnetic Resonance Images (cMRI) in Children with Hypertrophic Cardiomyopathy, as Determined with the Bland-Altman Method.

All measurements were adjusted for BSA except interventricular septal thickness. A) Left ventricular end-diastolic volume (LVEDV), B) Left ventricular end-systolic volume (LVESV), C) Left ventricular (LV) mass, D) Interventricular septal thickness (ST), E) Interventricular septal thickness (ST) >20 mm by echocardiogram.

Table 1.

Characteristics of 67 Children with Hypertrophic Cardiomyopathy in a Study to Determine the Prevalence of Myocardial Fibrosis with Late Gadolinium-Enhancement

Patient Characteristic	Values
Age at Enrollment, median (IQR), years	13.8 (11.1 to 15.3)
Age at Diagnosis, median (IQR), years	12.1 (8.8 to 14.3)
Males, N (%)	52 (78)
Ethnicity, N (%)	
Not Hispanic	63 (94)
Hispanic	4 (6)
Race, N (%)	
White	55 (82)
Black or African American	6 (9)
American Indian or Alaskan Native	1 (1.5)
Asian	1 (1.5)
Multi-racial	3 (4.5)
Unknown	1 (1.5)
Cardiac medications at enrollment, N (%)	
Beta-Blocker	38 (57)
Calcium-Channel Blocker	7 (10)

Table 2.

Percent of Late Gadolinium Enhancement Detected in Children with Hypertrophic Cardiomyopathy

Age group, years	%LGE		%LGE >2%		LV Mass adjusted for BSA, gni/m^2		LV Mass to LVEDV (gm/ml)		LV Mass to LVESV (gm/ml)		Interventricular septal thickness adjusted for BSA, mm/m^2	
	N	Median (25%, 75%)	N	Median (25%, 75%)	N	Median (25%, 75%)	N	Median (25%, 75%)	N	Median (25%, 75%)	N	Median (25%, 75%)
Overall	5	6.0 (2.0,	3	9.0	5	94.3	5	1.3	5	4.9	63	11.6 (6.8,16.2)
Birth to 5	6	11.5 (9.0,13.0)	6	11.5(9.0,13.0)	6	94.3(78.0,138.3)	6	1.3(1.1,1.4)	6	5.4(2.7,6.8)	10	18.4 (11.5,24.9)
6 to 10	13	7.0 (3.0, 8.0)	10	7.0(6.0,9.0)	13	81.2(74.9,89.2)	13	1.2(0.9,1.3)	13	5.0(3.4,6.5)	14	13.7 (12.0,16.2)
11 to 15	28	4.5 (1.0, 9.5)	18	8.0(5.0,14.0)	28	104.3(68.7,121.9)	27	1.4(0.9,1.6)	27	4.6(3.0,7.8)	33	10.2 (6.6,13.5)
16+	5	7.0 (1.0,11.0)	3	11.0(7.0,14.0)	5	77.6(74.9,114.8)	5	1.3(0.9,1.4)	5	4.2(2.8,5.2)	6	7.6 (5.6,10.2)

Abbreviations: BSA, body surface area; LV, left ventricle; LVEDV, left ventricular end- diastolic volume; LVESV, left ventricular end-systolic volume; %LGE, percent late gadolinium enhancement.

Table 3.

Pearson Correlation (Correlation *P*-value) Between Cardiac Parameters, Age at Diagnosis and Disease Duration (Defined as the Time from Date of Diagnosis to Date of Cardiac Magnetic Resonance Imaging).

	%LGE	Interventricular Septal Thickness (mm)	LV Mass / BSA ($gm/m^{2,66}$)	LV Mass / $BSA^{1,33*}$ ($gm/m^{2,66}$)	LV Mass /LVEDV (gm/ml)	LV Mass /LVESV (gm/ml)	Age at Diagnosis	Disease Duration (years)
%LGE	1.0							
Interventricular Septal Thickness (mm)	0.02 (0.87)	1.0						
LV Mass / BSA (gm/m^2)	0.27 (0.05)	0.730 (<0.001)	1.0					
LV Mass / $BSA^{1,33*}$ (gm/m^2)	0.28 (0.05)	0.70 (<0.001)	0.98 (<0.001)	1.0				
LV Mass/LVEDV < 2% LGE. (gm/ml)	0.16 (0.26)	0.76 (<.0001)	0.91 (<.0001)	0.91 (<.0001)	1.0			
LV Mass/LVESV (gm/ml)	0.05 (0.72)	0.67 (<.0001)	0.66 (<.0001)	0.67 (<.0001)	0.74 1.0 (<.00 01)	1.0		
Age at Diagnosis (years)	- 0.13 (0.34)	0.08 (0.55)	0.02 (0.88)	-0.10 (0.47)	0.004 (0.98)	-0.03 (0.83)	1.0	
Disease Duration	0.06 (0.6)	-0.07 (0.58)	0.04 (0.76)	0.04 (0.76)	-0.07 (0.64)	-0.08 (0.6)	−0.64 *(<0.001)	1.0

*Scaling factor 1.33 used per pediatric analysis of structural measurements adjusting for growth (21, 22)

Abbreviations: BSA, body surface area; LV, left ventricle; LVEDV, left ventricular end- diastolic volume; LVESV, left ventricular end-systolic volume; %LGE, percent late gadolinium enhancement.

Table 4.

Association between Serum Biomarker Concentrations and Cardiac Dimensions as Measured by Cardiac Magnetic Resonance Imaging, Adjusted for Age at Diagnosis, Time Since Diagnosis, Race, and Ethnicity[*†]

	Log of %LGE			Log of LV Mass (BSA-adjusted)			Log of LV Mass/ LVEDV			Log of LV Mass / LVESV			Log Interventricular Septal Thickness		
Serum Biomarker	**N**	**β (SE)**	**P-value**	**N**	**β (SE)**	**P-value**	**N**	**β (SE)**	**P-value**	**N**	**β (SE)**	**P-value**	**N**	**β (SE)**	**P-value**
NT-proBNp, pg/mL	44	0.09(0.09)	0.31	48	0.20(0.03)	**<0.001**	47	0.21(0.03)	**<0.001**	47(0.04)	0.16	0.001	59	0.19(0.02)	**<0.001**
Cardiac troponin-T, ng/mL	44	0.03(0.20)	0.90	48	0.18(0.09)	0.05	47	0.12(0.09)	0.21	47	0.13(0.11)	0.22	59	0.03(0.08)	0.69

Abbreviations: LGE, late gadolinium enhancement; LV, left ventricle; BSA, body surface area; NT-proBNP, N-terminalpro B-type natriuretic peptide.

[*] Four patients with 0% LGE of LV mass were excluded because zero cannot be log-transformed.

[†] Four patients with LAMP2 mutations were excluded from the association analysis.