Early Changes in Apical Rotation in Genotype Positive Children with Hypertrophic Cardiomyopathy Mutations without Hypertrophic Changes on Two-Dimensional Imaging

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Background: Hypertrophic cardiomyopathy (HCM) is the most common form of inherited cardiomyopathy. Echocardiography is the mainstay of screening and disease surveillance, and genetic testing has identified a carrier population without hypertrophy. The aim of this study was to investigate whether changes in left ventricular (LV) function are detectable before the advent of hypertrophy.

Methods: Fourteen children with genotype-positive, phenotype-negative HCM were identified (12 male; median age, 9.14 years; range, 1.91–15.9 years; median weight, 34.6 kg; range, 15–92.1 kg) and compared with age-matched and sex-matched healthy controls. All children underwent full echocardiographic studies using an extensive functional protocol, including two-dimensional dimensions, Doppler tissue imaging, and two-dimensional speckle-tracking echocardiography.

Results: There were no differences in LV wall thickness, chamber dimensions, length, and shortening fraction between the groups. Doppler tissue imaging in children with HCM demonstrated mildly reduced septal velocities, notably A′ (5.9 cm/sec [range, 4–8.9 cm/sec] vs 6.7 cm/sec [range, 5.2–9.5 cm/sec]; $P = .009$). Circumferential and longitudinal strain was similar between groups. Mean apical circumferential deformation was increased in the HCM group ($-24.6 \pm 3.8\%$ vs $-22.2 \pm 2.5\%$, $P = .04$). There were significant increases in basal and apical rotation and LV twist in children with HCM, most marked at the apex ($11.7 \pm 4.4^\circ$ vs $5.3 \pm 2.5^\circ$, $P = .0001$). On receiver operating characteristic curve analysis, apical rotation $> 7^\circ$ conferred 83% sensitivity and 82% specificity for predicting HCM (area under the curve, 0.919; $P = .0001$).

Conclusions: Increased LV rotation and twist are present in children with genotype-positive, phenotype-negative HCM. Apical rotation on speckle-tracking echocardiography provides good sensitivity and specificity for the prediction of gene-positive HCM and may be a clinically useful early marker of HCM before the onset of hypertrophy. (J Am Soc Echocardiogr 2014;27:215-21.)

Keywords: Hypertrophic cardiomyopathy, Speckle-tracking echocardiography, Strain, Early detection

Hypertrophic cardiomyopathy (HCM) is a common inherited genetic cardiovascular disease. The definition of the characteristic phenotype is one of left ventricular (LV) hypertrophy unexplained by either abnormal loading conditions or systemic disease.[1] Typically the diagnosis has been made after the demonstration of LV hypertrophy > 15 mm in adults or >2 standard deviations above the mean for children on two-dimensional (2D) echocardiography in either symptomatic patients or as part of screening echocardiography. The prevalence is estimated to be 0.2%, equating to 1 in 500 in the general population, with an equal global distribution.[1,2] Inheritance is in an autosomal-dominant pattern with variable penetrance and expression, with typical phenotypic features usually presenting in the second to third decade of life. However, patients with HCM demonstrate a wide spectrum of disease, with the onset of clinical features possible from early childhood.[3] The presentation and clinical course vary widely from an asymptomatic benign finding to sudden cardiac death as the initial event. The estimated incidence of sudden cardiac death due to HCM in childhood is 1% to 2%.[4,5]

The advent of commercially available genetic testing has led to the identification of genotype-positive, phenotype-negative (G+P−) population. Recent guidelines have advocated the use of genetic testing in index cases and in first-degree relatives of index cases with identified mutations.[1] At this time, it is possible to identify a pathogenic mutation in 60% to 70% of index cases with positive family histories.[6] Mutations have been identified in genes encoding for sarcomere proteins and sarcomere-associated proteins, with a single mutation capable of

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Abbreviations

G+P− = Genotype-positive, phenotype-negative

HCM = Hypertrophic cardiomyopathy

LV = Left ventricular

ROC = Receiver operating characteristic

STE = Speckle-tracking echocardiography

2D = Two-dimensional

producing HCM, but when multiple mutations occur, potentially a more severe phenotype is seen.[7,8]

Although the availability and indications for genetic testing are increasing in the HCM population, echocardiography remains the mainstay of diagnosis and disease surveillance.[9] Given the potential for early presentation and potential clinical implications, the early identification of at-risk patients is important. Previous studies have used Doppler tissue imaging to try to identify G+P− patients.[10,11] We sought to determine if it was possible to identify G+P− patients using 2D speckle-tracking echocardiography (STE). STE is a relatively new, angle-independent technique using speckles in grayscale B-mode images to track myocardial deformation, validated against sonomicrometry and magnetic resonance imaging.[12-14]

METHODS

Study Population

A total of 14 first-degree relatives of patients with HCM with known genetic mutations were identified from our outpatient population. The inclusion criterion was a known genetic mutation with no evidence of LV hypertrophy on 2D echocardiographic imaging. This was defined as LV septal and LV posterior wall thickness Z scores < 2.0. The study subjects were matched 1:2 with normal control patients (healthy volunteers) from our normal control database. Control patients were scanned according to the same functional protocol. The study was approved by our institutional research ethics board.

Echocardiography

Echocardiographic studies were performed using either the Vivid 7 and E9 ($n = 12$; GE Healthcare, Milwaukee, WI) or the iE33 ($n = 2$; Philips Medical Systems, Andover, MA) ultrasound system. All studies were performed at rest in the left lateral position. A standardized clinical functional assessment was undertaken with 2D, M-mode, spectral Doppler, and tissue Doppler images obtained. Particular attention was paid to ensuring optimized short-axis 2D imaging at the level of the mitral valve (base), midventricle, and apex and an apical four-chamber view for strain analysis, in keeping with manufacturers' recommendations regarding frame rate. A single observer (J.F.) analyzed the echocardiographic data offline. Chamber dimensions and septal and posterior wall thickness were measured from M-mode short-axis acquisitions, and LV volumes and ejection fraction were calculated using the modified Simpson's method in accordance with standard protocols.[15] Spectral Doppler was used to quantify transmitral inflow with peak E and A waves and aortic outflow peak velocity and duration. These values were used to calculate the E/A ratio and myocardial performance index. Pulsed-wave Doppler tissue imaging acquired from an apical four-chamber view was measured for E′, A′, and S′ velocities just below the level of the mitral valve for both the ventricular septum and the LV lateral wall. Postprocessing was performed using dedicated software (EchoPAC version 6.0.1; GE Vingmed Ultrasound AS, Horten, Norway).

Terminology and Strain Analysis

Only images acquired on the Vivid 7 or E9 ultrasound system were used for subsequent strain analysis. All strain analysis was undertaken using a manufacturer-specific postprocessing system (EchoPAC). Two-dimensional STE was performed for both circumferential and longitudinal deformation. Strain analysis was performed at three levels for circumferential strain (basal, midventricular, and apical) and from an apical four-chamber view for longitudinal strain. The endocardium was manually traced at end-systole, with the range of interest adjusted to incorporate the entire myocardium. Once visual inspection of tracking was accepted, a six-segment model in keeping with standard nomenclature at each level was calculated.[16] Peak strain was defined as the maximal deformation of a segment in systole and is represented as a percentage of the original size. Values for peak strain as indicated by the software were accepted only if adequate tracking was obtained as judged by visual inspection. Global or mean strain is the average of the segments at each level and was calculated only if adequate tracking was obtained in a minimum of four segments. Rotation is the clockwise or counterclockwise movement of the heart along the long axis of the left ventricle as seen in the short axis when viewed from the apex. Peak rotation was calculated at both the base and the apex and measured in degrees. LV twist was defined as the peak net difference in rotation at a simultaneous time point between the base and apex of the left ventricle and measured in degrees.[17] Examples of circumferential strain curves and rotational profiles are depicted in Figure 1.

Statistical Analysis

Data are expressed as mean ± SD, ranges, and percentages as appropriate. Standard 2D echocardiographic parameters, tissue Doppler, and speckle-tracking echocardiographic values were compared using unpaired t tests, with P values $< .05$ accepted as indicating statistical significance. Receiver operating characteristic (ROC) curves were plotted to determine optimal cutoff values for apical rotation to predict genotype-positive individuals. Interobserver variability was calculated for 10 randomly selected patients across both the G+P− and control groups using Bland-Altman statistics for all strain and rotational parameters. Two observers blinded to the others' results performed strain measurements, and each observer selected a single best cardiac cycle for analysis from a designated three-beat loop. Variability measures are reported as mean ± SD, and the coefficient of variability was calculated as the standard deviation of the difference of the samples divided by the mean of the paired samples. Because of the small patient groups, further analysis was undertaken to include the absolute difference, expressed as a percentage of the mean of repeated measurements. Intraclass correlation coefficients were also calculated (proportion of variability in the observations that is due to differences between each pair of observations) to validate the reproducibility and reliability of measures. All statistical analyses were performed using GraphPad InStat version 3.01 (GraphPad Software, San Diego, CA).

RESULTS

Clinical Characteristics and 2D Imaging

Fourteen patients were identified from 9 families with four different sarcomeric mutations: MYBPC3 ($n = 6$), MYH7 ($n = 5$), MYHC ($n = 2$), and TPM1 ($n = 1$). The 14 patients with HCM were control matched for age, sex, and weight with 28 healthy volunteers taken