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SUBCLINICAL ECHOCARDIOGRAPHIC ABNORMALITIES IN PHENOTYPE-NEGATIVE CARRIERS OF *MYBPC3* GENE MUTATION FOR HYERTROPHIC CARDIOMYOPATHY

Sabe De, MD[1], **Allen G. Borowski, RDCS**[2], **Heng Wang, MD PhD**[3,4], **Leah Nye, NP**[2,3], **Baozhong Xin, PhD**[3], **James D. Thomas, MD**[2], and **W.H. Wilson Tang, MD**[2,4]

[1]Division of Cardiology, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

[2]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio

[3]*Das Deutsch Center* (DDC) Clinic for Special Needs Children, Middlefield, Ohio

[4]Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio

Abstract

Background—Early diastolic myocardial tissue Doppler (TD) velocities have reported to be reduced in mutation-positive patients with HCM in some studies even in the absence of left ventricular hypertrophy (LVH). Strain is a sensitive tool in detecting early systolic abnormalities in patients with hypertrophic cardiomyopathy (HCM). Our goal is to examine novel echocardiographic characteristics of phenotype-negative carriers for a known sarcomeric gene mutation for HCM.

Methods—We evaluated 41 consecutive subjects with a known myosin binding protein C3 (*MYBPC3*) mutation (c.3330+2T>G). Subjects who were mutation-positive without LVH (G+/LVH−, n=35) were compared to healthy controls (n=30) regarding tissue Doppler and segmental longitudinal strain measures.

Results—The G+/LVH− group was similar to the normal controls with respect to chamber size, LV mass index, and most diastolic filling parameters, including tissue Doppler derived Ea. Global longitudinal strain was similar for both groups (20.3 ± 2.1 vs. 19.8 ± 1.8; p=0.36) although regional segment analysis showed a notable reduction in the basal septum (16.8 ± 3.1 vs. 19.0 ± 4.0%, p=0.02) and increase in the basal posterior (22.5 ± 5.2 vs. 17.9 ± 5.2, p=0.001) as well as mid posterior (21.8 ± 4.7 vs. 18.2 ± 3.0, p=0.001) walls.

Conclusions—In our cohort of phenotype-negative carriers of a specific *MYBPC3* mutation, there were minimal differences in conventional 2-dimensional, Doppler, and speckle-tracking derived parameters of systolic and diastolic function compared to that of normal subjects. The

Corresponding Author: W.H. Wilson Tang, MD Heart and Vascular Institute, Cleveland Clinic 9500 Euclid Avenue, Desk J3-4, Cleveland, Ohio 44195. Phone: (216) 444-2121 / Fax: (216) 445-6165 / tangw@ccf.org .

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presence of regional alterations in strain indicative of the presence of underlying subclinical disease requires further validation.

Keywords

hypertrophic cardiomyopathy; genetic heart disease; echocardiography; longitudinal strain

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a disease characterized by left ventricular hypertrophy (LVH) with septal predominance and several associated phenotypes[1]. Molecular genetic studies have identified over a hundred mutations that give rise to hypertrophy involving sarcomeric proteins[2, 3]. Mutations identified in the myosin-binding protein C3 (*MYBPC3*) gene account for 15% of all familial HCM cases[4]. As the clinical spectrum of phenotypes associated with HCM is increasing, it is becoming recognized that LVH may be absent in mutation carriers. *MYBPC3* carriers demonstrate age related penetrance with hypertrophy occurring later in life than those with mutations involving cardiac beta-myosin heavy chain[4].

Echocardiography remains a useful tool in the screening of family members of HCM[5, 6]. As a non-invasive test, echocardiography allows assessment of hypertrophy, valvular abnormalities, and diastolic dysfunction that may correlate with symptoms of syncope or breathlessness in some patients. Animal and human studies with sarcomeric gene mutations have demonstrated tissue Doppler (TD) imaging abnormalities in the absence of LVH, mostly characterized by reductions in early myocardial velocities[7-10]. However, this has been challenged by recent studies that observed preserved Ea velocities in some *MYBPC3* mutation carriers, although these heterogeneous case series were small in sample sizes[11].

Speckle tracking-derived longitudinal strain is a newer novel technology that assesses myocardial deformation using long axis images obtained by echocardiography[12]. Despite labor-intensive measurements in the current configuration, it offers several advantages over TD imaging particularly in the assessment of regional abnormalities and in the reduction of angle dependent errors of measurement. To date, several studies have demonstrated that early abnormalities in systolic function in patients with hypertrophied ventricles can be detected by strain analysis[10, 12, 13], which may directly reflect underlying myocardial abnormalities. Herein, we aim to characterize the cardiac phenotypes of heterozygous carriers of the *MYBPC3* gene (c.3320+2T>G), and particularly to assess the ability of TD imaging and longitudinal strain to distinguish these carriers from normal controls as well as to explore the heterogeneity of regional dysfunction in early forms of this inherited condition.

METHODS

Study Population

This is a prospective cohort outreach study evaluating subjects with an HCM-affected family member at the Geauga Amish community at the *Das Deutsch Center* Clinic for Special Needs Children in Middlefield, Ohio. A known *MYBPC3* mutation (c.3330+2T>G) has been identified in this large Amish community based on homozygous mutation found in a number of children[14], and family members without known cardiac diseases. All subjects provided informed consent approved by their local Institutional Review Board to undergo *MYBPC3* gene testing for the specific mutation. All mutation carriers identified by genetic testing then underwent further evaluation including physical exams, 12-lead electrocardiograms, and transthoracic echocardiograms to identify underlying cardiac

abnormalities. “Phenotype-negative” was defined as no clinical signs and symptoms consistent with obstructive HCM.

A separate control group of normals was assembled, age- and gender-matched based on the patient cohort. Healthy volunteers were recruited as controls after informed consent, and their echocardiographic examination reviewed by staff cardiologist to be deemed normal examination by standard measurements including TD parameters. All patients and controls had recorded height, weight, gender, blood pressure, and heart rate, and they had previously been scanned using a Vivid 7 machine with frame rates >50 fps so that appropriate longitudinal strain measurements could be made. The Cleveland Clinic Institutional Review Board approved this study whereby echocardiographic data from both cohorts were analyzed offline.

Echocardiography

All patients underwent standard transthoracic echocardiograms (Vivid i, GE Vingmed Ultrasound AS, Horten, Norway) using an ultrasound machine with a 3.5 MHz probe and digital storage capacity. Data was analyzed offline by a single observer who was blinded to patient factors. Standard views were taken and chamber dimensions were assessed using M-mode or 2D measurements based on current guidelines[15]. Left ventricular (LV) ejection fraction was calculated using the modified Simpson’s method[15]. LV mass and mass index were calculated based on established criteria. Mitral valve inflow using spectral Doppler displays were used to determine peak early (E) and late (A) trans-mitral filling velocities, E/A ratio, and deceleration time (DT) of E wave. Pulmonary vein flow was assessed for peak systolic velocity (S), peak diastolic velocity (D), atrial flow reversal velocity, and the duration of atrial flow reversal (Adur). Tissue Doppler imaging was used to measure septal and lateral mitral annular velocities, including those in systole (Sa), early (Ea), and late (Aa) diastole. Diastolic function was graded as stage I, II, or III based on the latest American Society of Echocardiography guideline recommendations[16].

Longitudinal strain analysis (ε) was performed offline using dedicated software (EchoPac PC version BT06; GE Healthcare, Milwaukee, WI). Images were able to be analyzed in all patients with adequate frame rates (>50 fps). Two dimensional longitudinal strain was assessed in the apical 4, 2-, and 3- chamber views at 6 segments in each view[17]. For each apical view, sample points were placed along the endocardium at end systolic frames. The software package automatically constructed a region of interest along the length of the LV wall, after which individual speckles were tracked to generate strain curves. Global longitudinal strain was calculated as the average value of the total 18 segments. Measurements were made without knowledge of gene mutation carrier status.

Statistical Analysis

All data is expressed as mean and standard deviation or number and percentage. Mean measurements were compared by paired t-tests, with significance set at $p<0.05$. All statistics were done using JMP Statistical software for Macintosh (Version 7.0, SAS Institute Inc, Cary, North Carolina).

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RESULTS

Baseline characteristics

A total of 41 consecutive mutation carriers for the specific *MYBPC3* mutation were identified as part of the screening study. Of these, 6 were felt to have possible phenotype expression, with 4 having echocardiographic features of HCM and 2 having concentric LVH. The phenotypes identified in these subjects present with classic septal hypertrophy as described in the Supplementary Files. The remaining 35 patients were identified as genotype-positive/phenotype-negative ("G+/LVH−"'). Comparing subjects in the G+/LVH− and control groups, mean age (30 ±14 and 35 ±12 years, respective) and gender (51% and 47% males, respectively) were similar. They also had similar body mass indices (24.8 ± 5.9 vs 23.9 ± 3.0 kg/m^2), and all blood pressures and heart rates were within normal limits. All subjects were noted to be in sinus rhythm with no evidence of LVH or conduction block by 12-lead electrocardiogram. Nonspecific T-wave abnormalities were evident in 12 G+/LVH− subjects, while 11 showed an RSR' or incomplete right bundle branch block patterns in lead V_1.

2D Echocardiographic and Doppler Indices

Subjects in both groups had similar LV dimensions, mass, and left atrial areas (Table 1). All subjects have preserved LV ejection fraction, even though G+/LVH− subjects demonstrated statistically significant higher LV ejection fraction compared to normal control subjects. No subject had evidence of significant valvular lesions, systolic anterior motion (SAM) of the mitral valve, papillary muscle abnormalities, pulmonary hypertension estimated by tricuspid regurgitant velocities, gradients across any valve or left ventricular outflow tract (LVOT). For G+/LVH− subjects, septal thicknesses ranged from 7 to 12 mm and posterior wall thicknesses ranged from 7 to 12 mm with the criteria for LVH based on current ASE guidelines. LV mass was further indexed to height^2.7 for 10 pediatric aged patients (0-18years) to further ensure that none had echocardiographic evidence of LVH.

Based on the latest guidelines, diastolic function was normal in all control patients and 89% of G+/LVH− subjects, while 4 G+/LVH− subjects showed evidence of Grade I diastolic dysfunction. Mean Doppler variables based on mitral valve inflow and pulmonary vein flow were similar in both groups with the only difference being noted the A-wave amplitude across the mitral valve (Table 1). Mean TDI septal Sa, Ea, and Aa velocities were comparable between G+/LVH− subjects and normal controls. In contrast, there was a statistically significantly higher lateral annular Sa and a trend towards higher lateral annular Ea in G+/LVH− subjects compared to controls, but no difference were noted in Aa between the groups (Table 1). When averaging septal and lateral Sa and Ea, there were no difference between G+/LVH− subjects and normal controls.

Longitudinal Strain

Table 2 illustrates the longitudinal strain patterns between G+/LVH− subjects and normal controls. There was no significant difference noted in mean global longitudinal strain between the two groups. Overall, the mean of segments taken in the apical 3-chamber view was higher in the mutation positive group compared to normal controls. For mutation positive patients, the segment associated with the lowest value of all 18 segments was the basal septum (Figure 1), whereas the basal and mid posterior wall demonstrated increased strain compared to normal controls, all statistically significantly different.

DISCUSSION

This is the first study to our knowledge to not only carefully examine typical systolic and diastolic echocardiographic markers of cardiac performance in a large group of asymptomatic carriers with the same *MYBPC3* mutation, but also to utilize novel speckle tracking techniques that examine the tissue deformation and regional abnormalities to further delineate the presence of early subclinical disease. We observed that in the absence of cardiac hypertrophy, TDI indices were relatively preserved in our specific cohort of mutation carriers. These findings suggested that prior reports of diminished TDI indices in HCM mutation carriers may not universally apply to *all* sarcomeric mutations, or may imply that TDI indices may vary depending on the different stages of disease progression. In other words, the absence of TDI abnormalities does not exclude the presence of underlying sarcomeric gene mutation. Another important observation is that despite similar degrees of global longitudinal strain compared to healthy controls, we observed a consistent decrease in longitudinal strain at the basal septum accompanied by a consistent increase in longitudinal strain at the basal and mid segment of the posterior wall in our cohort of *MYBPC3* mutation carriers. These findings demonstrate the presence of early subclinical regional (but not global) deformities in this particular cohort of phenotype-negative *MYBPC3* mutation carriers, and provide potential clues to localization of the fundamental defects leading to the development of the HCM phenotype.

Clinicians have relied heavily on echocardiographic screening as the primary modality in identifying affected individuals with clinically significant HCM[5]. Despite relatively preserved cardiac structure and LV systolic function being observed in many affected but asymptomatic HCM mutation carriers, the sarcomeric gene mutation itself is believed to contribute to a fundamental global myocardial defect. Such subclinical abnormalities can therefore lead to progressive diastolic dysfunction or microvascular dysfunction, thereby producing pathologic findings of fibrosis and myofibril disarray. This hypothesis is supported by previous observations whereby septal and lateral Ea measurements at the mitral annulus were significantly reduced in G+/LVH− subjects when compared to non-affected individuals (some also affected by various forms of *MYBPC3* mutations)[7, 9]. However, such findings were not replicated in our cohort, nor identified in other contemporary series[11]. Even with the use of speckle-tracking techniques to determine global longitudinal strain, the overall G+/LVH− population demonstrated similar global strain levels than that of normal controls. There may be several explanations for this discrepancy. First, a referral bias in those undergoing genetic testing at tertiary medical centers in other reports may favor individuals with more “malignant” mutations, and hence with genotype-positive individuals having more prominent phenotypes. Second, most reports have combined different mutations in their analysis, whereas our study population all shared the same *MYBPC3* gene mutation. We also cannot exclude that the specific mutation affected this particular Amish population may have a more benign clinical manifestation, even though homogenous mutations are generally lethal in early life and some individuals have echocardiographic characteristics (see Supplemental Files)[14]. It is therefore important to emphasize that TDI abnormalities observed in prior reports may represent only a proportion of sarcomeric gene mutation carriers, and absence of TDI abnormalities (or with lack of abnormal global longitudinal strain) do not preclude the presence of underlying sarcomeric gene mutations even in a young adult population.

Our study cohort did not identify any overt hypertrophic phenotypes in the majority of *MYBPC3* mutation carriers. In particular, we identified lower percentages of echocardiographic abnormalities than reported in previous studies[11], with only 6 of the initial 42 individuals screened (15%) showing any evidence of cardiac hypertrophy. While it is believed that 60% of patients with the *MYBPC3* mutation will eventually develop some

form of hypertrophy, there are many environmental and genetic factors that may contribute to incomplete penetrance of the gene mutation. Nevertheless in our G+/LVH− cohort, 11% showed unexplained stage I diastolic dysfunction, and an incomplete right bundle branch block or RSR' was observed in 30% of subjects. Meanwhile in our G+/LVH−, TDI-derived Sa and Ea velocities were well above published normal values[16] as well as above those observed in our healthy controls. Instead of implying preclinical diastolic dysfunction in this population, our observations may suggest that *MYBPC3* mutation carriers in our cohort exhibit "supra-normal" myocardial contractile function, with regards to annular motion both in systole and diastole. This may paradoxically precede (or may even be independent of) the development of left ventricular hypertrophy and overt diastolic dysfunction, and consistent with the notion that compensatory mechanisms to sarcomeric mutations may play a role in the development of asymmetric hypertrophy.

Speckle tracking overcomes difficulties in angle dependence, and provides information on strain, a more direct measurement of myocardial deformation[12]. Prior strain studies have shown the presence of reduced septal strain being more pronounced in the mid-septum[17], and reductions in global strain were observed in patients with overt HCM[18]. This is to our knowledge the first report to assess longitudinal strain for regional myocardial abnormalities in a homogenous asymptomatic carrier population with a single *MYBPC3* mutation. Assessment of regional strain identified a significantly lower strain at the basal septum (despite being within the reported "normal range"[18]), and a significantly higher strain in the basal and mid posterior wall. These regional deformities occur in the approximate location where hypertrophy may most commonly manifest. It is interesting to note that the six patients identified with abnormal phenotypes showed marked reduced global strain, with an average value of 17.5 ±1.2%, with the lowest strain also noted at the basal septum (group mean 11.3 ±4.5%), also predominantly at the site of regional hypertrophy. The precise mechanism of *MYBPC3* mutation leading to a regional abnormality of longitudinal strain remains unclear. Whether regions experiencing higher longitudinal strain occur as a cause or effect of adjacent basal septal deformity (with lower strain) remains to be determined and such observations may not be applicable to a broad heterogeneous HCM population. Even thought the absolute values of these measurements were different, true differences between the two groups may not be apparent in larger populations or in different mutation carriers. Further investigations are warranted to better explain why a genetic mutation implicated in all sarcomeric apparatus may lead to a regional hypertrophy and pathologic changes.

CONCLUSIONS

We observed minimal differences between phenotype-negative subjects with the *MYBPC3* gene mutation without LVH and normal controls based on conventional 2D echocardiographic and tissue Doppler indices as well as with global longitudinal strain measurements. Our data do not support prior reports regarding the presence of subclinical echocardiography abnormalities found in phenotype-negative subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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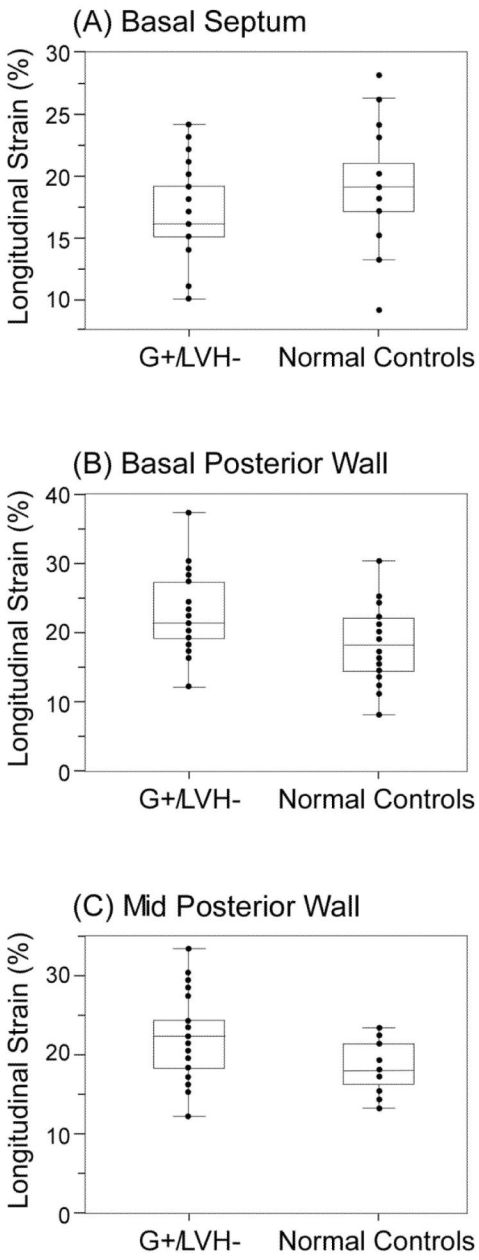

Figure 1.

Segments associated with regional differences in longitudinal strain (A) Basal septum (p=0.02) (B) Basal posterior (p=0.001) and (C) Mid posterior (p=0.001) walls.
Abbreviation: G+/LVH−: gene mutation positive, no left ventricular hypertrophy

Table 1

Standard Echocardiographic and Doppler Indices between Genotype-positive/phenotype-negative and normal control subjects

	G+/LVH− (n=35)	Normal Controls (n=30)	p-value
Cardiac Structure and Function			
Septal wall thickness (cm)	1.0 ± 0.2	0.9 ± 0.1	NS
Posterior wall thickness (cm)	0.9 ± 0.2	0.9 ± 0.1	NS
LV mass (g)	143 ± 50	146 ± 41	NS
LV mass index (g/m^2)	80 ± 19	80 ± 18	NS
LV ejection fraction (%)	61 ± 4	58 ± 4	p<0.05
Doppler Indices			
Mitral valve E wave (cm/s)	84 ± 15	77 ± 13	NS
Mitral valve A wave (cm/s)	58 ± 18	45 ± 12	p<0.05
Mitral valve E/A ratio	1.6 ± 0.6	1.8 ± 0.5	NS
Deceleration time (ms)	185 ± 38	186 ± 24	NS
Pulmonary vein S wave (cm/s)	51 ± 15	49 ± 10	NS
Pulmonary vein D wave (cm/s)	56 ± 16	52 ± 12	NS
PV A wave (cm/s)	25 ± 10	27 ± 5	NS
PV Adur (cm)	115 ± 18	105 ± 17	NS
Mitral Annular Tissue Doppler Velocities			
Lateral Wall (cm/s)			
Sa	10.2 ± 2	9.1 ± 2.1	p<0.05
Ea	16.4 ± 4.9	14.1 ± 3.0	NS
Aa	8.8 ± 3.0	8.1 ± 1.4	NS
Septal Wall (cm/s)			
Sa	7.9 ± 1.2	8.0 ± 1.6	NS
Ea	11.7 ± 3.2	11.0 ± 2.6	NS
Aa	7.5 ± 2.2	8.1 ± 1.4	NS
Averaged (cm/s)			
Sa	9.0 ± 1.3	8.5 ± 1.6	NS
Ea	13.9 ± 3.8	12.0 ± 2.7	NS

Abbreviations: E: early rapid filling wave, A: filling wave due to atrial contraction, S: systolic peak velocity, D: diastolic peak velocity, PV A: pulmonary vein atrial flow reversal velocity, PV Adur: duration of pulmonary vein atrial flow reversal, Sa: systolic annular velocities, Ea: early diastolic annular velocities, Aa: late diastolic annular velocities

Table 2

Longitudinal Strain Assessment of Individual Segments Based Comprising Apical 2-, 3-, and 4- Views by Echocardiography

	G+/LVH− (n=35)	Normal Controls (n=30)	p value
Apical 4-chamber			
Basal Septum (%)	16.8 ± 3.1	19.0 ± 4.0	0.02
Mid Septum (%)	20.5 ± 4.3	21.5 ± 3.4	NS
Apical Septum (%)	23.1 ± 6.2	23.1 ± 4.2	NS
Basal Lateral (%)	21.3 ± 3.7	21.5 ± 6.9	NS
Mid Lateral (%)	19.8 ± 3.6	18.8 ± 4.0	NS
Apical Lateral (%)	19.2 ± 5.1	19.0 ± 8.5	NS
Apical 2-chamber			
Basal Inferior (%)	21.1 ± 4.5	20.1 ± 6.6	NS
Mid Inferior (%)	22.0 ± 3.6	20.5 ± 3.9	NS
Apical Inferior (%)	22.6 ± 4.8	23.2 ± 4.7	NS
Basal Anterior (%)	18.9 ± 4.8	19.0 ± 9.3	NS
Mid Anterior (%)	20.4 ± 3.2	18.7 ± 5.3	NS
Apical Anterior (%)	18.7 ± 6.1	19.2 ± 6.4	NS
Apical 3-chamber			
Basal Posterior (%)	22.5 ± 5.2	17.9 ± 5.2	0.002
Mid Posterior (%)	21.8 ± 4.7	18.2 ± 3.0	0.001
Apical Posterior (%)	20.6 ± 5.3	20.1 ± 5.1	NS
Basal Antero-septum (%)	17.8 ± 5.4	17.2 ± 4.6	NS
Mid Antero-septum (%)	21.3 ± 3.9	20.2 ± 3.7	NS
Apical Antero-septum (%)	20.6 ± 5.3	22.3 ± 6.1	NS
Global Strain (%)	20.3 ± 2.1	19.8 ± 1.8	NS