



Left ventricular strain and myocardial work in apical hypertrophic cardiomyopathy

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Background: Apical hypertrophic cardiomyopathy (ApHCM) is recognized for its associated cardiovascular morbidity. Herein we describe left ventricular (LV) function and mechanics over long-term follow-up in ApHCM.

Methods: A retrospective study of 98 consecutive ApHCM patients was performed (mean age: 64±15 years, 46% female) using 2D and speckle-tracking echocardiography. LV function and mechanics were characterized by global longitudinal strain (GLS), segmental strain, and myocardial work indices. Myocardial work was calculated by integrating longitudinal strain and blood pressure as estimated by the brachial artery cuff pressure, to generate an LV pressure-strain loop with adjusted ejection and isovolumetric periods. Composite complications were defined as all-cause mortality, sudden death, myocardial infarction, and/or stroke.

Results: Mean LV ejection fraction measured 67%±11% and GLS was -11.7%±3.9%. Global work index (GWI) was 1,073±349 mmHg%, constructive work was 1,379±449 mmHg%, wasted work was 233±164 mmHg%, and work efficiency was 82%±8%. In 72 patients with follow-up echocardiography, at a median of 3.9 years there was progressive impairment in GLS (-11.9% *vs.* -10.7%; *P*=0.006), GWI (1,105 *vs.* 989 mmHg%; *P*=0.02), and global constructive work (1,432 *vs.* 1,312 mmHg%; *P*=0.03), without change in wasted work or work efficiency. Atrial fibrillation (β =0.37; *P*<0.001), mitral annular *e'* velocity (β =-0.32; *P*=0.001), and glomerular filtration rate (β =-0.2; *P*=0.03) were independently associated with follow-up GLS; atrial fibrillation (β =-0.27; *P*=0.01) and glomerular filtration rate (β =0.23; *P*=0.04) were also associated with follow-up GWI. Global wasted work >186 mmHg% was predictive of composite complications (AUC =0.7, 95% CI: 0.53–0.82, sensitivity 93%, specificity 41%).

Conclusions: ApHCM is associated with preserved LV ejection fraction but abnormal LV GLS and work indices, with progressive impairment. Important clinical and echocardiographic measures are independently predictive of long-term follow-up LV GLS, GWI and adverse events.

Keywords: Heart failure; apical hypertrophic cardiomyopathy (ApHCM); myocardial work; speckle-tracking; strain echocardiography

Submitted Feb 08, 2023. Accepted for publication May 12, 2023. Published online May 23, 2023.

doi: 10.21037/jtd-23-202

View this article at: <https://dx.doi.org/10.21037/jtd-23-202>

Introduction

Hypertrophic cardiomyopathy is a heterogeneous genetic disorder with a variable phenotypic expression, and an estimated prevalence of 1:200 to 500 individuals (1,2). Apical hypertrophic cardiomyopathy (ApHCM) variant accounts for 10–25% of all cases, is more commonly seen in males, and may be sporadic or inherited due to myofibrillar gene mutations (3,4). Initially described in 1970's Japan and thought to have a more indolent clinical course than other HCM morphologies, contemporary studies have attributed a significant morbidity to ApHCM (4–8). Patients presenting with late-onset ApHCM, have co-existing cardiovascular risk factors, and those with left ventricular (LV) apical aneurysms or wall motion abnormalities appear to be at increased risk (6,7).

Global longitudinal strain (GLS) is a sensitive marker of subclinical myocardial dysfunction and an important predictor of adverse outcomes across HCM phenotypes (9–12). Complementary to GLS has been the development of non-invasive myocardial work estimation, which takes into account LV afterload when assessing GLS to produce LV pressure-strain loops, and has itself been shown to

correlate with outcomes, diastology, and degree of fibrosis in non-obstructive HCM (13–16). Importantly, ApHCM patients have not been represented in large proportions in the aforementioned studies, and longitudinal data remain limited. The aim of the present study was to assess LV strain and myocardial work over long-term follow-up in ApHCM using 2D speckle-tracking echocardiography, and to assess for associations between these indices and clinical outcomes. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-202/rc>).

Methods

Patient selection and definitions

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Mount Sinai Medical Center Institutional Review Board (No. FWA00000176) and individual consent for this retrospective analysis was waived. We retrospectively analyzed the institutional Echocardiography digital database and identified 98 consecutive patients with ApHCM referred for echocardiography between January 2005 and January 2021. The database includes both inpatient and outpatient echocardiograms. Review of the institutional electronic health records was performed to assess patient demographics, clinical risk factors and co-morbidities, and laboratory values. Composite complications were defined as the occurrence of all-cause mortality, sudden cardiac death, myocardial infarction and/or stroke at follow-up.

A diagnosis of ApHCM was the main inclusion criteria. ApHCM was defined as left ventricular wall thickness ≥ 15 mm distal to the insertion points of the papillary muscles, that is not explained solely by loading conditions (17). Two subtypes of ApHCM include those with apical aneurysm or midventricular obstructive cavity obliteration, respectively (18). Apical aneurysm was defined as discrete and thinned apical segments with dyskinetic contraction and a distinct neck (19,20). Midventricular obstructive cavity obliteration was defined as systolic intra-cavitary LV obliteration and obstruction due to hypertrophied myocardium extending from the apex to include mid-segments (18). Obstruction was defined as a peak instantaneous intra-cavitary pressure gradient of ≥ 30 mmHg at rest or with provocation. Patients who had any of the following conditions were excluded: (I) untreated or uncontrolled hypertension; (II) hypertensive heart

Highlight box

Key findings

- Apical hypertrophic cardiomyopathy (ApHCM) is associated with preserved left ventricular (LV) ejection fraction but progressively abnormal longitudinal strain and work indices.
- Important clinical and echocardiographic measures are independently predictive of long-term follow-up LV global longitudinal strain (GLS), global work index (GWI), and adverse events.

What is known and what is new?

- ApHCM variant has been poorly represented in prior studies on longitudinal strain mechanics in hypertrophic cardiomyopathy.
- LV strain mechanics and energetics are moderately impaired in ApHCM, with further reduction occurring over long-term follow-up, particularly in the mid and apical segments.
- Atrial fibrillation, average mitral annular e' velocity, and glomerular filtration rate are predictors of follow-up GLS and GWI.
- Global wasted work >186 mmHg% is a predictor of composite complications.

What is the implication, and what should change now?

- Contemporary studies suggest significant morbidity with ApHCM, and the pre-sent study provides supportive quantifiable data. Larger studies and longer-term follow-up are needed to confirm our findings.

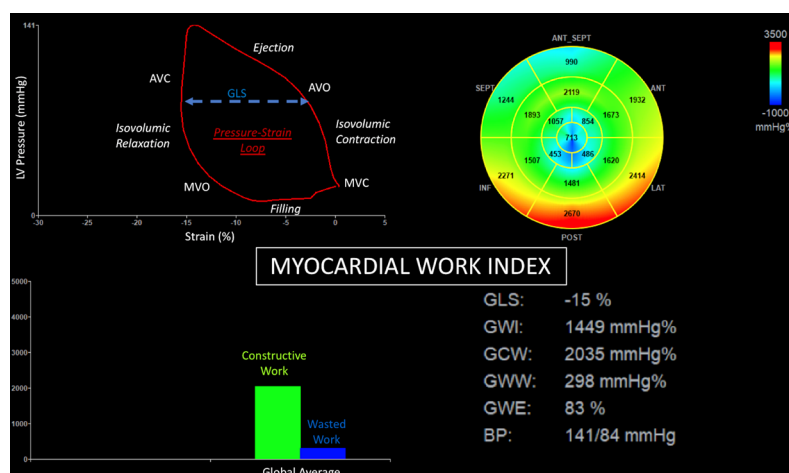


Figure 1 Example of myocardial work analysis in a patient with apical hypertrophic cardiomyopathy. Top left shows a pressure-strain loop from a patient with apical hypertrophic cardiomyopathy. The area within the loop represents the GWI, and the blue dashed line represents GLS. The top right bullseye map shows segmental GLS with the apical segments most impaired. The bottom left is a bar graph representation of GCW versus GWW. AVC, aortic valve closure; AVO, aortic valve opening; BP, blood pressure; GCW, global constructive work; GLS, global longitudinal strain; GWI, global work index; GWW, global wasted work; LV, left ventricle; MVC, mitral valve closure; MVO, mitral valve opening.

disease; (III) infiltrative cardiomyopathy; (IV) phenocopy conditions (i.e., Andersen-Fabry disease, Danon disease, Friedrich's ataxia).

2D and speckle-tracking echocardiography

All transthoracic echocardiograms were performed using a GE cardiovascular ultrasound system (General Electric Healthcare, Waukesha, WI, USA). The assessment of cardiac geometry and function was performed in accordance with the American Society of Echocardiography chamber quantification guidelines, and LV diastology in accordance with the diastolic function guidelines (21,22). Specifically, the LV internal diastolic and systolic diameters, and maximal septal and posterior wall thickness were assessed in the parasternal long-axis view. Maximal apical wall thickness was measured in the three standard apical views and in a cross-sectional parasternal short-axis view distal to the papillary muscle insertions. In terms of diastolic assessment, the peak transmitral E-wave velocity was measured to reflect the left atrial to LV pressure gradient, the average mitral annular e' velocity to reflect LV relaxation, and the E/e' velocity ratio as a surrogate of LV filling pressure. The mitral valve anatomy and function was assessed in a multi-parametric manner according to the native valvular regurgitation guidelines (23).

Cardiac mechanics were analyzed using the two-dimensional speckle tracking technique via the GE EchoPAC Automated Function Imaging and Q-Analysis software (General Electric Healthcare, Waukesha, WI, USA) according to inter-societal consensus statements on cardiac mechanics quantitation (24,25). Peak full-wall GLS measurements were obtained in the apical four, three and two chamber views, and averaged. Peak systolic strain at the basal, mid, and apical levels was measured and averaged separately in assessing segmental LV longitudinal strain in these individual territories. Myocardial work was calculated by integrating longitudinal strain and blood pressure as estimated by the brachial artery cuff pressure, to generate an LV pressure-strain loop with adjusted ejection and isovolumetric periods. The four myocardial work parameters measured were defined as follows: (I) global work index (GWI), the area of the LV pressure-strain loop between mitral valve opening and closure representing the total LV work performed during systolic ejection and isovolumic relaxation; (II) global constructive work, segmental shortening during systole plus lengthening during isovolumic relaxation; (III) global wasted work, segmental lengthening during systole plus shortening during isovolumic relaxation; and (IV) cardiac efficiency, calculated by the equation: constructive work/(constructive work + wasted work) $\times$ 100 (Figure 1) (13).

Table 1 Demographics and clinical characteristics of patients with apical hypertrophic cardiomyopathy

Variables	Value [N=98]
Age, years	64±15
Female	45 [46]
Heart rate (beats/minute)	72±15
Systolic blood pressure (mmHg)	130±17
Diastolic blood pressure (mmHg)	74±11
Glomerular filtration rate (mL/min/1.73 m ²)	72±25
African-American	17 [17]
Smoking	27 [28]
Family history of HCM	3 [3]
HCM signs and symptoms	
Angina	40 [41]
Dyspnea	25 [26]
Palpitations	21 [21]
Syncope	11 [11]
Sudden cardiac death	0
Non-sustained ventricular tachycardia	9 [9]
Electrocardiogram T-wave inversions	73 [75]
Hypertension	78 [80]
Dyslipidemia	46 [47]
Diabetes mellitus	23 [24]

Table 1 (continued)**Table 1** (continued)

Variables	Value [N=98]
Coronary artery disease	24 [25]
Congestive heart failure	13 [13]
New York Heart Association functional class III/IV	7 [7]
Cerebrovascular accident	14 [14]
Atrial fibrillation/flutter	30 [31]
Implantable cardioverter defibrillator	4 [4]
History of septal myectomy	1 [1]
History of coronary artery bypass graft surgery	2 [2]
History of mitral valve replacement	1 [1]
Medications	
Aspirin	48 [49]
ACEi/angiotensin receptor blocker	40 [41]
Beta-blocker	58 [59]
Calcium-channel blocker	27 [28]
Direct oral anticoagulant	19 [19]
Diuretics	24 [25]
Disopyramide	1 [1]
P2Y12-inhibitor	15 [15]
Warfarin	3 [3]

Categorical variables are expressed as n [%], and continuous variables as mean ± standard deviation. ACEi, angiotensin converting enzyme inhibitor; HCM, hypertrophic cardiomyopathy; P2Y12, adenosine diphosphate chemoreceptor.

Statistical analysis

Data was analyzed using IBM SPSS Statistics version 21 (IBM Corporation, Armonk, NY). Categorical variables were expressed as number (frequency percentage), while continuous variables were expressed as mean ± standard deviation or median (interquartile range) dependent upon their Gaussian distribution. In the event of missing at random continuous variables, a multiple imputation model using multivariate linear regression was applied (26). Continuous variables with a normal distribution were compared using a paired *t*-test for repeated measures. Hierarchical multivariable linear regression analysis tested for correlations between baseline clinical and echocardiographic measures and follow-up GLS; step one included the constant and baseline GLS, and step

two incorporated exploratory variables whose univariate correlations with follow-up GLS were statistically significant. The same hierarchical multivariable linear regression modeling was performed for GWI. The range estimates and expected treatment effects are expressed as unstandardized and standardized beta coefficients, with a 95% confidence interval. The receiver operating characteristic was applied to GLS and GWI to assess their utility in predicting adverse events at follow-up. A *P* value <0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics

The mean age was 64±15 years, 46% were female, and 3%

Table 2 Baseline and follow-up 2-dimensional echocardiography in patients with apical hypertrophic cardiomyopathy

Variables	Entire cohort (N=98)	Patients with Follow-up		
		Baseline (N=72)	Follow-up (N=72)	P value
Left ventricular structure and function				
LV ejection fraction (%)	67±11	68±11	64±12	0.008
LV internal diastolic diameter index (mm/m²)	24±3	24±4	24±4	0.85
LV internal systolic diameter index (mm/m²)	15±4	15±4	15±4	0.26
LV mass index (g/m²)	126±37	126±38	127±37	0.81
Septal wall thickness (mm)	15±4	15±4	15±4	0.5
Posterior wall thickness (mm)	12±2	12±2	12±2	0.66
Apical wall thickness (mm)	19±3	18±3	19±3	0.08
Relative wall thickness	0.53±0.11	0.53±0.11	0.53±0.13	0.91
Left ventricular diastology				
Peak transmitral E-wave velocity (m/s)	0.76±0.21	0.78±0.22	0.8±0.21	0.35
Average mitral annular e' velocity (m/s)	0.06±0.02	0.06±0.02	0.05±0.02	0.007
Average E/e' ratio	13±4	13±5	15±7	0.003
Right ventricular structure and function				
Right ventricular basal diameter (mm)	33±5	33±5	34±6	0.26
Tricuspid annular plane systole excursion (mm)	17±4	17±3	15±4	<0.001
Right ventricular systolic pressure (mmHg)	32±12	35±13	36±16	0.8
Left atrial volume index (mL/m²)	37±16	36±12	38±13	0.13

Data are expressed as mean ± standard deviation.

had a family history of HCM. Common cardiovascular co-morbidities included hypertension in 80%, coronary artery disease in 25%, diabetes mellitus in 24%, and congestive heart failure in 13%, of which 54% had New York Heart Association functional class III/IV symptoms. Angina, dyspnea, and syncope were present in 41%, 26%, and 11%, respectively. Electrocardiogram T-wave inversions were observed in 75% (Table 1).

2D and speckle-tracking echocardiography

Mean LV ejection fraction measured 67%±11%, end-diastolic diameter index was 24±3 mm/m², maximum apical wall thickness was 19±3 mm, and E/e' ratio was 13±4. An apical aneurysm was present in 9%. Midventricular obstructive cavity obliteration was present in 3% with provocative maneuvers only. Longitudinal strain and myocardial work parameters were impaired and included an LV GLS measuring -11.7%±3.9%,

GWI of 1,073±349 mmHg%, global constructive work of 1,379±449 mmHg%, global wasted work of 233±164 mmHg%, and global work efficiency of 82%±8%. There was a decreasing systolic longitudinal strain gradient from basal (-13.4%±5.1%) to mid (-11.8%±4.8%) and apical LV (-8.5%±7.3%).

Systolic anterior motion of the mitral valve or chordal apparatus was present in 11 (11%) patients, with moderate or greater mitral regurgitation observed in 8 (8%). No patient had evidence of LV outflow tract obstruction. In assessment of the right ventricle, the mean tricuspid annular plane systolic excursion measured 17±4 mm, the basal diameter was 33±5 mm, and the pulmonary artery systolic pressure was 32±12 mmHg (Table 2).

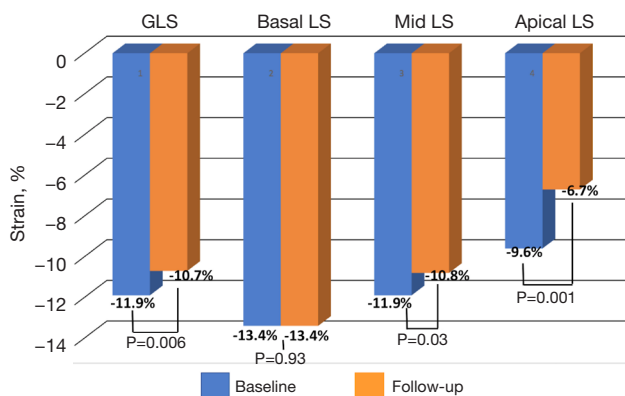
Follow-up echocardiography

A total of 72 patients had baseline and follow-up echocardiography available for analysis at a median follow-

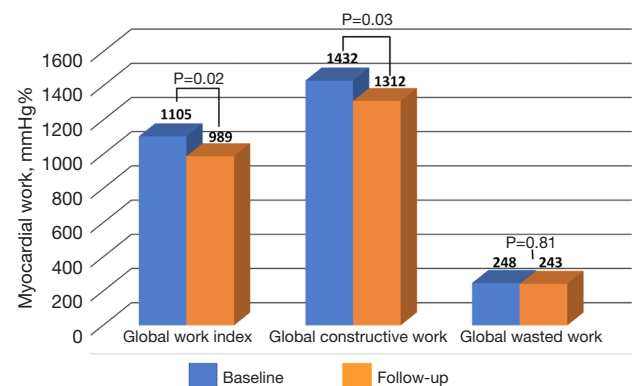
Table 3 Baseline and follow-up speckle-tracking echocardiographic assessment of left ventricular mechanics in patients with apical hypertrophic cardiomyopathy

Left ventricular mechanics	Entire cohort (N=98)	Patients with follow-up		
		Baseline (N=72)	Follow-up (N=72)	P value
Global longitudinal strain (%)	-11.7±3.9	-11.9±4	-10.7±3.3	0.006
Peak systolic basal longitudinal strain (%)	-13.4±5.1	-13.4±5.2	-13.4±5.2	0.93
Peak systolic mid longitudinal strain (%)	-11.8±4.8	-11.9±4.9	-10.8±4.3	0.03
Peak systolic apical longitudinal strain (%)	-8.5±7.3	-9.6±7.1	-6.7±4.9	0.001
Global work index (mmHg%)	1,073±349	1,105±362	989±343	0.02
Global constructive work (mmHg%)	1,379±449	1,432±472	1,312±372	0.03
Global wasted work (mmHg%)	233±164	248±170	243±115	0.81
Global work efficiency (%)	82±8	82±8	81±8	0.1
Basal work efficiency (%)	88±9	88±9	88±7	0.84
Mid work efficiency (%)	85±10	85±10	85±8	0.68
Apical work efficiency (%)	71±15	73±14	70±15	0.08

Data are expressed as mean ± standard deviation.

**Figure 2** Bar graph depiction of baseline versus follow-up longitudinal strain indices in patients with apical hypertrophic cardiomyopathy. GLS, global longitudinal strain; LS, peak systolic longitudinal strain.

up of 3.9 years [interquartile range (IQR), 1.6–9.2]. There was no difference in characteristics between the follow-up group and the total cohort. When compared with baseline, there was a decrease in the LV ejection fraction ($68\% \pm 11\%$ vs. $64\% \pm 12\%$, $P=0.008$), and progressive impairment in GLS ($-11.9\% \pm 4\%$ vs. $-10.7\% \pm 3.3\%$, $P=0.006$), GWI ($1,105 \pm 362$ vs. 989 ± 343 mmHg%, $P=0.02$), and global constructive work ($1,432 \pm 472$ vs. $1,312 \pm 372$ mmHg%, $P=0.03$), with no change in global wasted work or work efficiency. There was no change in peak systolic longitudinal

**Figure 3** Bar graph depiction of baseline versus follow-up myocardial work indices in patients with apical hypertrophic cardiomyopathy.

strain in the LV basal segments, however, significant worsening was observed in the mid ($-11.9\% \pm 4.9\%$ vs. $-10.8\% \pm 4.3\%$, $P=0.03$) and apical segments ($-9.6\% \pm 7.1\%$ vs. $-6.7\% \pm 4.9\%$, $P=0.001$). A decrease in the average mitral annular e' velocity was observed (0.06 ± 0.02 vs. 0.05 ± 0.02 m/s, $P=0.007$), with a converse increase in the E/e' ratio (13 ± 5 vs. 15 ± 7 , $P=0.003$). Finally, there was a decrease over follow-up in tricuspid annular plane systolic excursion (TAPSE, 17 ± 3 vs. 15 ± 4 , $P<0.001$), while the right ventricular systolic pressure remained stable (Table 3; Figures 2,3).

Table 4 Hierarchical multivariable linear regression analysis assessing for correlations between baseline clinical and echocardiographic measures and follow-up GLS

Variables	Unstandardized B	95% confidence interval for B		Standardized β	P value
		Lower	Upper		
Step 1					
Constant	−5.8	−8	−3.7		<0.001
GLS (%)	0.41	0.24	0.58	0.5	<0.001
Step 2					
Constant	−2.7	−5.6	0.15		0.06
GLS (%)	0.28	0.13	0.44	0.35	<0.001
Atrial fibrillation	2.6	1.3	3.9	0.37	<0.001
Average mitral annular e' velocity (m/s)	−58.8	−92.2	−25.5	−0.32	0.001
Glomerular filtration rate (mL/min/1.73 m ²)	−0.03	−0.05	−0.003	−0.2	0.03

Step 1: initial model including only baseline Global Longitudinal Strain. Step 2: full model with significant variables. Congestive heart failure, septal wall thickness, and left ventricular mass index were univariate correlates that were excluded from the full model due to statistical non-significance. $r=0.5$, $r^2=0.24$ for step 1; $r=0.71$, $r^2=0.5$ for step 2 ($P<0.001$). Negative B/ β coefficients indicate negative associations. GLS, global longitudinal strain.

Table 5 Hierarchical multivariable linear regression analysis assessing for correlations between baseline clinical and echocardiographic measures and follow-up Global Work Index

and follow-up Global Work Index					
Variables	Unstandardized B	95% confidence interval for B		Standardized β	P value
		Lower	Upper		
Step 1					
Constant	622	376	868		<0.001
Global work index (mmHg%)	0.33	0.12	0.54	0.35	0.003
Step 2					
Constant	563	256	870		<0.001
Global work index (mmHg%)	0.25	0.05	0.45	0.27	0.02
Atrial fibrillation	-197.4	-352.1	-42.6	-0.27	0.01
Glomerular filtration rate (mL/min/1.73 m ²)	3	0.17	5.8	0.23	0.04

Step 1: initial model including only baseline Global Work Index. Step 2: full model with significant variables. Congestive heart failure was a univariate correlate that was excluded from the full model due to statistical non-significance. $r=0.35$, $r^2=0.11$ for step 1; $r=0.51$, $r^2=0.26$ for step 2 ($P<0.001$). Negative B/ β coefficients indicate negative associations.

In hierarchical multivariable linear regression analysis, the presence of atrial fibrillation ($\beta=0.37$, $P<0.001$), and measures of average mitral annular e' velocity ($\beta=-0.32$, $P=0.001$) and glomerular filtration rate ($\beta=-0.2$, $P=0.03$) were significant predictors of follow-up GLS, independent of baseline GLS ($\beta=0.35$, $P<0.001$) (Model fit: $r=0.71$, $P<0.001$) (Table 4). Similarly, the presence of atrial fibrillation ($\beta=-0.27$, $P=0.01$) and glomerular filtration

rate ($\beta=0.23$, $P=0.04$) were also independent predictors of follow-up GWI, independent of baseline GWI ($\beta=0.27$, $P=0.02$) (Model fit: $r=0.51$, $P<0.001$) (Table 5).

Clinical outcomes

A total of 5 (5%) all-cause mortality were observed, and 14 (14%) patients had at least one heart failure hospital

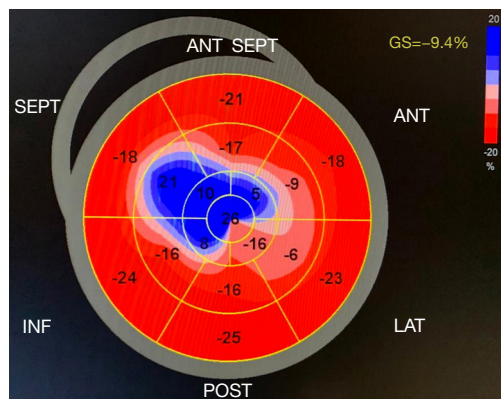


Figure 4 Bullseye plot depicting the basal left ventricular sparing pattern in a patient with apical hypertrophic cardiomyopathy. Note the base-to-apex decreasing peak systolic strain with a ‘sparing’ pattern of the base. There is systolic dyskinesia of the apex, denoted by the blue color of these segments. ANT, anterior; ANT SEPT, anteroseptum; GS, global longitudinal strain; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.

admission. Of the patients who died, 4 of 5 had a preserved left ventricular ejection fraction (LVEF) $\geq 55\%$, while all had an abnormal GLS $> -16\%$. Adverse cardiovascular outcomes included 2 (2%) sudden cardiac deaths, 6 (6%) myocardial infarctions, and 7 (7%) cerebrovascular accidents. Composite complications occurred in 14 (14%) patients. Global wasted work was a fair predictor of composite complications, with a cutoff value of >186 mmHg% having an area under the curve, sensitivity, and specificity of 0.7 (95% CI: 0.53–0.82), 93%, and 41%, respectively. Finally, cardiac surgery was infrequent, and included 1 (1%) coronary artery bypass grafting, 2 (2%) aortic valve replacements, and 1 (1%) septal myectomy in a patient with combined apical and septal hypertrophy.

Discussion

In the present study of patients with ApHCM who underwent 2D and speckle-tracking echocardiography, the following findings are summarized: (I) mean age was 64 years, the majority of patients were male, few patients had a family history of HCM, and the LV ejection fraction and size were normal; (II) LV longitudinal strain mechanics and energetics were moderately impaired, with further reduction in GLS and myocardial work indices over long-term follow-up, particularly in the mid and apical segments; (III) the LV diastolic parameters of mean annular e' velocity

and E/e' ratio were also impaired and worsened over follow-up; (IV) the presence of atrial fibrillation, average mitral annular velocity, and glomerular filtration rate were significant predictors of follow-up GLS and GWI; and (V) global wasted work >186 mmHg% was a fair predictor of follow-up composite complications.

Despite a normal or hyperdynamic LV ejection fraction in the majority of patients of HCM, it is well established that the myocardial fiber disarray and interstitial fibrosis that characterize the disease significantly impact LV function and energetics (2,27). LV ejection fraction may be overestimated by contribution from mid-wall contraction and in the setting of a small and hypertrophied chamber, and thus, is generally regarded as a suboptimal global marker of LV function. Conversely, GLS is a measure of global longitudinal myocardial shortening and lengthening, and full-wall assessment takes into account subendocardial, mid-wall, and subepicardial function. The inclusion of subendocardial fiber assessment is paramount as they are most at-risk to repetitive injury and may be impaired despite a normal LV ejection fraction. This is particularly useful in subclinical early-stage disease processes or in phenotypes such as HCM (9,10). In the present study, although all regional LV GLS was impaired at baseline, the basal segments were most preserved and did not further deteriorate at follow-up. This LV basal ‘sparing’ pattern may be a useful marker to identify ApHCM patients, however, this hypothesis must be further assessed in additional larger cohorts and in comparison with other cardiomyopathies (Figure 4).

In patients with non-obstructive HCM, GLS has proven useful in risk assessment for adverse cardiovascular events and survival. In a group of 296 patients with non-obstructive HCM and preserved LV ejection fraction, a GLS $> -16\%$ was associated with a 5-fold increase in heart failure compared with normal GLS, and increased to 12.5-fold if the LV ejection fraction was preserved at the lower end of normal between 50% to 59% (28). Additionally, a GLS $> -10\%$ has been shown to portend a 4-fold increase in ventricular tachyarrhythmias, heart failure, cardiac transplantation, and death (11). Within these studies, ApHCM represented a small proportion of patients and few studies have detailed their LV strain mechanics. In this context, our observations of a markedly decreased GLS at baseline with progressive impairment and worsening LV filling pressure at long-term follow-up is a concerning trend in the natural history of ApHCM.

Assessment of myocardial work indices accounts for not

only impaired LV deformation, but also the hemodynamic stress imparted by systemic afterload, for a comprehensive non-invasive analysis of myocardial energetics (13). In a study of 110 patients with non-obstructive HCM, when compared with an age and sex-matched control group, the HCM patients had a significantly lower global work index, constructive work, and work efficiency, with a higher degree of wasted work (29). Of note, only 11 (10%) of patients had ApHCM phenotype. In the present study, ApHCM patients had similarly impaired work indices, with a progressive relative decrease of 11% in global work index and 8% in constructive work at long-term follow-up, respectively. Global wasted work > 186 mmHg% at baseline was identified as a predictor of follow-up composite complications, which is more than double the normal value in healthy hearts, and represents quantification of metabolic burden and myocardial energy waste (13).

The common clinical phenotypic presentation of ApHCM is that of symptomatic heart failure with preserved ejection fraction resulting from chronic microvascular ischemia, myocardial fibrosis, and increased LV filling pressures (18). Patients experience adverse events and recurrent hospitalizations for dyspnea, angina, and tachyarrhythmias, which incur a significant medical and cost burden. Specifically, atrial fibrillation is associated with a 2-fold increase in mortality amongst patients with ApHCM, while an E/e' ratio >15 has been demonstrated to be an important threshold for decreased event-free survival (6,7). In patients with differing HCM morphologies, chronic kidney disease appears to increase the risk of sudden death and worsens underlying arrhythmic substrates (30). Thus, the present findings of a negative association between atrial fibrillation and decreased mitral annular velocity and glomerular filtration rate with GLS and GWI highlight important co-morbidities that may be therapeutically targeted.

There are limitations to the present study that should be considered. Firstly, this was a retrospective analysis and the sample size is relatively small, which confers a selection bias and limits statistical power. Secondly, ApHCM patients referred for echocardiography are likely to be symptomatic which may affect both imaging findings and clinical outcomes. Nevertheless, the echocardiography database includes inpatient and outpatient referral studies, and is representative of a general community cohort. Thirdly, while clinical long-term follow-up was 100% complete, not all patients had a follow-up echocardiogram available for detailed analysis. Although this is a form of attrition

bias and an uncontrollable confounder, it is important to note that no significant differences existed in baseline echocardiographic or clinical characteristics between the entire cohort and those who were analyzed with baseline and follow-up echocardiograms. Fourthly, in certain cases GLS analysis may be difficult to perform in HCM due to the abnormal LV geometry inherent to the disease. This can affect inter- and intra-observer accuracy and reproducibility. Fifthly, adjudication of myocardial infarction did not differentiate between a type I (atherothrombotic coronary artery disease) and type II (oxygen supply and demand mismatch) event. While both are associated with adverse outcomes in the general population, the risk profiles of these patients differ and its translation to the HCM population is not well recognized. Sixthly, cerebrovascular accidents were defined as either ischemic or hemorrhagic, and the distinct prevalence of each subtype was not adjudicated. Although the overall event rate was low, the difference in prognosis is acknowledged as a potential confounder. Seventhly, we observed a reduction in TAPSE at follow-up, which is a surrogate marker for worsening RV systolic function. RV involvement is known to adversely impact clinical outcomes in HCM; however, it is unknown in the present cohort if the observed RV dysfunction was due to deterioration in left-sided function or primary RV myopathy, and requires further investigation (31). Eighthly, contrast echocardiography was not universally performed for all patients, and thus, the prevalence of apical aneurysm may be underestimated. Finally, HCM is a heterogeneous disorder in terms of phenotypic expression, and as such, the current findings are not generalizable to morphologies other than ApHCM, or in those with obstructive physiology. Larger studies and longer-term follow-up are important to confirm our data.

Conclusions

In conclusion, ApHCM is associated with preserved LV ejection fraction but abnormal longitudinal strain mechanics and work indices, with progressive impairment over long-term follow-up. The presence of atrial fibrillation, degree of early LV myocardial relaxation, and glomerular filtration rate are independently associated with follow-up GLS and GWI. A global wasted work >186 mmHg% at baseline is predictive of follow-up composite complications in this group.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-202/rc>

Data Sharing Statement: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-202/dss>

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-202/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-202/coif>). CGM serves as an unpaid editorial board member of *Journal of Thoracic Disease* from February 2023 to January 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Mount Sinai Medical Center Institutional Review Board (No. FWA00000176) and individual consent for this retrospective analysis was waived.

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Cite this article as: Mihos CG, Horvath SA, Fernandez R, Escolar E. Left ventricular strain and myocardial work in apical hypertrophic cardiomyopathy. *J Thorac Dis* 2023;15(6):3197-3207. doi: 10.21037/jtd-23-202