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ORIGINAL ARTICLE

Mechano-energetic efficiency in patients with hypertrophic cardiomyopathy with and without sarcomeric mutations

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Abstract

Hypertrophic cardiomyopathy (HCM) is mainly caused by sarcomeric mutations which may affect myocardial mechano-energetic efficiency (MEE). We investigated the effects of sarcomeric mutations on MEE. A non-invasive pressure/volume (P/V) analysis was performed. We included 49 genetically screened HCM patients. MEEi was calculated as the ratio between stroke volume and heart rate normalized by LV mass. Fifty-seven percent (57%) HCM patients carried a sarcomeric mutation. Patients with and without sarcomeric mutations had similar LV ejection fraction, heart rate, LV mass, and LV outflow gradient. Younger age at diagnosis, family history of HCM, and lower MEEi were associated with presence of sarcomeric mutation ($p = 0.017$; $p = 0.001$ and $p = 0.0001$, respectively). Lower MEEi in HCM with sarcomeric mutation is not related to significant differences on filling pressure as shown on P/V analysis. Sarcomeric mutations determine a reduction of the LV pump performance as estimated by MEEi in HCM. Lower MEEi may predict a positive genetic analysis.

Keywords Hypertrophic cardiomyopathy · Sarcomeric HCM · Non-sarcomeric HCM · Mechano-energetic

Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disease characterized by asymmetric left ventricular (LV) hypertrophy, unexplained by other cardiac or systemic diseases [1, 2]. Mutations in genes encoding sarcomere proteins are the main cause of HCM. Despite the progress in genetic screening, the causal mutation remains unidentified in up to 60% of HCM patients [3, 4]. In addition, the current knowledge of the pathophysiological mechanisms that lead to the development of HCM phenotype is still limited [5, 6]. Several evidences suggest that energy depletion, i.e., inadequate utilization of adenosine triphosphate (ATP) by the myocardium, could be the stimulus for the cardiac phenotype development [7, 8]. Hence, we hypothesized that LV mechano-energetic efficiency (MEE) could be reduced in HCM. MEE of a system is defined as the ratio of the external work performed by the system over the total energy consumption. In cardiac physiology, the LV external work during a single beat is represented by the stroke work (SW), while the total energy consumption corresponds to myocardial oxygen consumption (MVO2) [9], both measurable non-invasively and indirectly by echocardiography [10]. It has been shown that MEE is reduced in sarcomeric mutation carriers and in overt HCM, with no significant differences between patient harboring mutation in genes encoding for myosin heavy chain 7 (*MYH7*), myosin binding protein C3 (*MYBPC3*), or cardiac troponin T (*cTnT*) [11]. However, there are no studies aiming to understand if the presence of LV hypertrophy per se affects the LV MEE in the presence or not of a sarcomeric mutation. Thus, the aim of our study was to assess the MEE by echocardiography in HCM patients with (Sarc-HCM) and without (noSarc-HCM) sarcomeric mutations.

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Felice Borrelli and Raffaella Lombardi contributed equally to the study.

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Then, considering the result of MEE analysis, and in order to have a better understanding on what could determine that finding, we decided to analyze pressure/volume (P/V) loops in both groups since this analysis can provide useful information on LV performance [12, 13].

Methods

Population

Patients with a diagnosis of HCM were prospectively enrolled between October 2020 and February 2022 from the Outpatient Clinic for the Study and Treatment of Hypertrophic Cardiomyopathies, of the Department of Advanced Biomedical Sciences of the "Federico II" University of Naples. The protocol was approved by the internal ethic committee, and informed consent was obtained from each patient or from the legal guardian or parent of patients younger than 18 years, according to the Helsinki Declaration [14]. The patient underwent complete cardiological evaluation, including clinical-anamnestic evaluation, electrocardiogram, and transthoracic echocardiography. Patients aged between 16 and 74 years, in sinus rhythm, with normal ejection fraction ($\geq$ 50%), MWT > 15 mm, and with available genetic testing were included. Patients with a suboptimal echocardiographic window and moderate to severe mitral valve regurgitation were excluded. Patients without causal sarcomeric mutation and patients from families in which we did not observe a male-to-male genetic transmission were screened to exclude Fabry disease. Amyloidosis was excluded, through negative results of serum free light chains, urine and serum immunofixation tests, and negative diphosphonate scintigraphy, in the presence of at least one red flag, like prior carpal tunnel syndrome, pericardial effusion, and low ECG voltages [15]. Patients with variant of uncertain significance in sarcomeric genes were excluded (1 patient). Among the total HCM population, 49 patients were selected based on the inclusion and exclusion criteria.

Genetic screening

A whole-blood sample was collected in EDTA, and genomic DNA extraction was performed on the Maxwell 16 instrument (Promega, Madison, Wisconsin, USA) according to the user manual. DNA concentration, purity, and integrity of each sample were measured using NanoDrop One spectrophotometer (ThermoFisher Scientific, USA) and TapeStation 4200 (Agilent, USA) respectively. Targeted next-generation sequencing (NGS) was performed by using a custom-made panel including 60 genes known to be associated with cardiomyopathies [16]. HaloPlex technology (Agilent, Santa Clara, California, USA) was used for libraries preparation. The obtained enriched and indexed libraries were sequenced using the MiSeq (Illumina, San Diego, California, USA) instrument (2 × 250 PE). The Alyssa software (Agilent, Santa Clara, California, USA) was used to perform sequence data analysis. Variants were classified according to the current American College of Medical Genetics recommendations [17, 18]. Variants that passed internal quality and frequency filters were confirmed by direct Sanger sequencing.

Echocardiography

2D Doppler echocardiography was performed as previously reported [19]. Briefly, MWT was measured form LV short axis views at mitral, mid, and apical levels; LV outflow gradient was evaluated by M-mode [20] and by continuous Doppler echocardiography both, at rest and during Valsalva maneuver [21]; mitral regurgitation was identified by color Doppler echocardiography; LV ejection fraction (EF) was measured by the method of disk from 4 and 2 chamber apical views. The stroke volume (SV) was calculated as the differences between LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively). The heart rate (HR) was the one recorded at the time of the apical views' acquisition.

MEE analysis

To calculate the LV MEE, we estimated the stroke work (SW) as the product of the systolic blood pressure (BP) for the SV (mmHg × mL). MVO2 was estimated using the "double product" (DP) of systolic BP × HR [22]. MEE was calculated in mL/s by the following formula [23]:

$$MEE = \frac{SW}{DP} \approx \frac{mmHg \times mL}{mmHg \times bpm} = \frac{mL}{bpm \times 60^{-1}} = \frac{mL}{s}$$

Because of the reported close dependence of MEE on LV mass, we normalized the MEE to the LV mass (in grams) to estimate the energetic expenditure per unit of myocardial mass (MEEi in mL/s/g) [24, 25]. As in HCM LV hypertrophy is often asymmetric, LV mass cannot be calculated by the autopsy validated formula [26], which assumes that hypertrophy is symmetrically distributed. For this reason, we calculated the LV mass by applying a cardiac magnetic resonance (CMR) validated echocardiographic method, as previously published by our group, as LV diastolic epicardial volume minus LVEDV in 4 and 2 chamber views multiplied by 1.05 [27].

P/V analysis

The left ventricle pressure-volume (P/V) relationship has always been considered as a useful method to highlight the cardiac chamber function since it has been measured using

invasive conductance catheter methods. Recently, different non-invasive techniques have been developed making the P/V loops construction easier. The P/V loops were built starting from five coordinates on the PV plane estimated using a previously validated, feasible, and non-invasive method derived from brachial pressure and standard transthoracic two dimensional-Doppler echocardiographic measurements [28]. The five coordinates were:

- *Point A* (end-systolic P/V after isovolumic relaxation time)
- *Point B* (end-diastolic P/V)
- *Point C* (end of isometric contraction)
- *Point D* (peak-systolic LV pressure)
- *Point E* (end-systolic P/V before isovolumic relaxation time)

Considering the presence of dynamic LV outflow tract obstruction, the peak-systolic LV pressure was estimated as SBP + LVOT max gradient: the addiction of max LVOT gradient was empirically introduced in our study to adapt the existing method to patient with hypertrophic and obstructive cardiomyopathy.

By using this method, a mean LV echo P/V loop, represented as an irregular pentagonal shaped area, was obtained for both Sarc-HCM and noSarc-HCM.

Statistics

Data were analyzed using SPSS (version 25.0; SPSS, Chicago, IL) and expressed as mean ± 1SD. *T* test was used to compare baseline characteristics of patients with or without sarcomeric mutations. The χ^2 distribution was used to compare categorical variables, with the Monte Carlo simulation to obtain exact *p* values. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by using multivariate regression analysis to identify predictors of sarcomeric mutation. MEEi was used as continuous variable and was dichotomized in normal or reduced using the cut-offs recently suggested by Ferrara F et al. [29] (low if < 0.41 in men and < 0.45 mL/s*g^{-1} in women, respectively). A *p* value < 0.05 was considered statistically significant.

Results

A pathogenic sarcomeric mutation was identified in 28 patients (Sarc-HCM, 57% of the HCM study-population): 14 carried a mutation in MYBPC3, 10 in MYH7, and 3 in Cardiac Troponin T (TNNT2), whereas 1 patient carried two mutations, one in MYBPC3 and another in MYH7. Mutations and their classification as suggested by ACMG [30, 31] are reported in Table 1.

In the remaining patients (noSarc-HCM), a causal mutation was not identified, thus representing non-Mendelian HCM with a more complex etiology (Supplemental Table).

No other P/LP/VUS variants were detected in the remaining analyzed genes, except benign known polymorphisms (not annotated).

Table 2 reports the genetic and clinical characteristics of the Sarc-HCM and noSarc-HCM groups. Sarc-HCMs were younger at diagnosis and had higher prevalence of family history of HCM and of sudden death and of implantable cardioverter defibrillator ($p = 0.017$; $p = 0.001$; $p = 0.001$; $p = 0.0001$, respectively); moreover, the prescription of renin angiotensin-aldosterone system drugs was less common in the HCM-Sarc as compared with the NoSarc HCM group ($p = 0.004$).

The echocardiographic variables of the 2 groups are reported in Table 3. HR, left atrial volume, LVEF, and LV mass were not statistically different between the two groups. In Sarc-HCM, MWT was greater whereas LVEDV and LV SV were lower than in noSarc-HCM- ($p = 0.003$; $p = 0.033$; $p = 0.007$, respectively). Remarkably, MEEi was significantly lower in Sarc-HCM patients ($p = 0.0001$) (Table 2; Fig. 1).

To identify the variable which could predict the presence of sarcomeric mutation, multivariate analysis was run using the variables which were significantly different at the univariate analysis, including age at diagnosis, MWT, family history of HCM, and abnormal MEEi based on the cut-offs indicated in the "Methods" section. Family history of sudden death was not run due to high collinearity with family history of HCM. Family history of HCM (OR 25.752; CI 2.581–256.981), abnormal MEEi (OR 16.784; CI 1.830–153.911), and younger age at diagnosis (OR 0.914; CI 0.846–0.986) strongly and independently predicted the presence of a sarcomeric mutation ($p = 0.01$) (Table 3).

The PV loop analysis (Fig. 2) showed that both groups have similar filling pressure and LVESV, differing for the smaller stroke volume and LVEDV found in the Sarc-HCM one.

Discussion

In this study, we demonstrate that the presence of a sarcomeric mutation is associated with reduced MEEi in patients with overt HCM. Moreover, we show that low MEEi is an independent predictor of the presence of a sarcomeric mutation together with family history of HCM and younger age at diagnosis. The enhanced cardiac contractility, typical of HCM, has been advocated as responsible for stimulating parallel replication of sarcomeres and hypertrophy [32]. Nevertheless, despite normal or supernormal LV EF, several studies in various HCM models suggest a reduced

Table 1 Sarcomeric HCM mutations

Pt	Gene	Reference sequences	DNA	Effects on protein	Class of variant	ACMG Classification	ACMG level of evidence	gnomAD allele frequency	dbSNP
1	*MYBPC3*	NM_000256.3	c.1484 G>A	p.Arg495Gln	Missense	LP	PM2 PM5 PM1 PP3 PP5	0,00002408	rs200411226
2	*MYH7*	NM_000257.4	c.1615 A>C	p.Met539Leu	Missense	LP	PM1 PP2 PM2 PM5 PP3 PP5	N/A	rs730880930
3	*MYH7*	NM_000257.4	c.1615 A>C	p.Met539Leu	Missense	LP	PM1 PP2 PM2 PM5 PP3 PP5	N/A	rs730880930
4	*MYH7*	NM_000257.4	c.1615 A>C	p.Met539Leu	Missense	LP	PM1 PP2 PM2 PM5 PP3 PP5	N/A	rs730880930
5	*MYH7*	NM_000257.4	c.1615 A>C	p.Met539Leu	Missense	LP	PM2 PM5 PM1 PP3 PP2 PP5	N/A	rs730880930
6	*MYH7*	NM_000257.4	c.1615 A>C	p.Met539Leu	Missense	LP	PM2 PM5 PM1 PP3 PP2 PP5	N/A	rs730880930
7	*MYH7*	NM_000257.4	c.1615 A>C	p.Met539Leu	Missense	LP	PM1 PP2 PM2 PM5 PP3 PP5	N/A	rs730880930
8	*MYBPC3*	NM_000256.3	c.1790 G>A	p. Arg597Gln	Missense	LP	PM2 PM5 PP3 PP5	0,00002996	rs727503195
9	*MYH7*	NM_000257.4	c.2167 C>T	p.Arg723Cys	Missense	P	PP1 PM2 PM5 PM1 PM6 PS4 PP3 PP2 PP5	0,00001194	rs121913630
10	*MYH7*	NM_000257.4	c.2167 C>T	p.Arg723Cys	Missense	P	PP1 PM2 PM5 PM1 PM6 PS4 PP3 PP2 PP5	0,00001194	rs121913630
11	*MYBPC3*	NM_000256.3	c.2309-2 A>G		Splice altering	LP	PVS1 PM2 PP5	N/A	rs111729952
12	*MYBPC3*	NM_000256.3	c.2309-2 A>G		Splice altering	LP	PVS1 PM2 PP5	N/A	rs111729952
13	*MYH7*	NM_000257.4	c.2555 T>C	p.Met852Thr	Missense	LP	PP3 PM2 PM5 PM1 PP2 PP5	0,00003187	rs397516157
14	*TNNT2*	NM_001276345.2	c.283G>A	p.Val95Met	Missense	LP	PM1 PM2 PP3 PP2 PP5	N/A	
15	*TNNT2*	NM_001276345.2	c.283G>A	p.Val95Met	Missense	LP	PM1 PM2 PP3 PP2 PP5	N/A	
16	*TNNT2*	NM_001276345.2	c.283G>A	p.Val95Met	Missense	LP	PM1 PM2 PP3 PP2 PP5	N/A	
17	*MYH7*	NM_000257.4	c.3134 G>A	p.Arg1045His	Missense	P	PP3 PM2 PM5 PP2 PP5	0,00003536	rs397516178
18	*MYBPC3*	NM_000256.3	c.3192dupC	p.Lys1065GlnfsTer12	Frameshift	P	PVS1 PM2 PP5	N/A	rs397516007

Table 1 (continued)

Pt	Gene	Reference sequences	DNA	Effects on protein	Class of variant	ACMG Classification	ACMG level of evidence	gnomAD allele frequency	dbSNP
19	*MYBPC3*	NM_000256.3	c.3192dupC	p.Lys1065GlnfsTer12	Frameshift	P	PVS1 PM2 PP5	N/A	rs397516007
20	*MYBPC3*	NM_000256.3	c.3192dupC	p.Lys1065GlnfsTer12	Frameshift	P	PVS1 PM2 PP5	N/A	rs397516007
21	*MYBPC3*	NM_000256.3	c.3192dupC	p.Lys1065GlnfsTer12	Frameshift	P	PVS1 PM2 PP5	N/A	rs397516007
22	*MYBPC3*	NM_000256.3	c.3627+2T>A		Splice altering	LP	PVS1 PM2	0,000004049	rs1299079662
23	*MYBPC3*	NM_000256.3	c.3627+2T>A		Splice altering	LP	PVS1 PM2	0,000004049	rs1299079662
24	*MYBPC3*	NM_000256.3	c.3775 C>T	p. Gln1259Ter	Nonsense	LP	PVS1 PM2 PP5	N/A	rs730880605
24	*MYBPC3*	NM_000256.3	c.3775 C>T	p. Gln1259Ter	Nonsense	LP	PVS1 PM2 PP5	N/A	rs730880605
26	*MYBPC3*	NM_000256.3	c.1790G>A	p.Arg595Gln	Missense	LP	PP3 PM2 PM5 PP5	0,00002996	rs727503195
27	*MYBPC3*	NM_000256.3	c.506-2 A>C		Splice altering	P	PVS1 PM2 PP5	N/A	rs397516057
28	*MYBPC3*	NM_000256.3	c.3775 C>T	p. Gln1259Ter	Nonsense	LP	PVS1 PM2 PP5	N/A	rs730880605
	MYH7	NM_000257.4	c.4066 G>A	p.Glu1356Lys	Missense	P	PP1 PM2 PM1 PS4 PP3 PP2 PP5	N/A	rs727503246

ACMG American College of Medical Genetics and Genomics, *dbSNP* single nucleotide polymorphism database, *gnomAD* genome aggregation consortium database, *Pt* patient

Table 2 Clinical characteristic of HCM patient with and without sarcomeric mutation

Variable	HCM-Sarc (no. 28)	HCM-NoSarc (no. 21)	*p*
Age at evaluation (years)	46 ± 15	54 ± 15	0.084
Age at diagnosis (years)	35 ± 16	47 ± 16	0.017
Female sex (%)	32	19	0.304
Body mass index (kg/m^2)	22 ± 2	22 ± 3	0.756
NYHA functional class	1.5 ± 0.5	1.6 ± 0.6	0.453
Family history of HCM (%)	86	40	0.001
Family history of sudden death (%)	64	16	0.001
ICD (%)	54	5	0.0001
History of atrial fibrillation (%)	18	14	0.738
Systolic arterial pressure (mmHg)	129 ± 17	129 ± 16	0.941
Diastolic arterial pressure (mmHg)	76 ± 16	77 ± 8	0.874
Beta-blockers (%)	54	57	0.804
Anti-RAAS (%)	20	59	0.004
Calcium-antagonist (%)	14	5	0.299
Diuretics (%)	21	30	0.499
MYBPC3 gene mutation	15	Unidentified	
MYH7 gene mutation	11	Unidentified	
TNNT2 gene mutation	3	Unidentified	

Anti-RAAS anti renin-angiotensin-aldosterone system, *HCM* hypertrophic cardiomyopathy, *HCM-Sarc* patients with sarcomeric mutation, *HCM-NoSarc* patients without sarcomeric mutation, *ICD* implantable cardioverted defibrillator, *NYHA* New York Heart Association

Table 3 Echocardiographic characteristics of patient with and without sarcomeric mutation

Variable	HCM-Sarc (no. 28)	HCM-NoSarc (no. 21)	*p*
Heart rate (bpm)	64 ± 11	62 ± 9	0.351
Left atrial volume index (ml/m2)	39 ± 19	34 ± 12	0.297
E/E prime	10 ± 3	11 ± 4	0.271
Maximal wall thickness (mm)	23 ± 5	19 ± 4	0.003
LV outflow tract gradient (mmHg)	14 ± 20	13 ± 18	0.914
LV end-diastolic volume (ml)	82 ± 24	99 ± 24	0.033
LV end-systolic volume (ml)	30 ± 12	32 ± 11	0.507
LV ejection fraction (%)	64 ± 7	67 ± 7	0.111
LV mass (g)	154 ± 48	152 ± 55	0.695
Stroke volume (ml)	53 ± 15	67 ± 17	0.007
MEEi (ml/sec*g^{-1})	0.33 ± 0.09	0.45 ± 0.11	0.0001
Abnormal MEEi (%)	79	38	0.0001

LV left ventricular, *MEEi* indexed mechano-energetic-efficiency

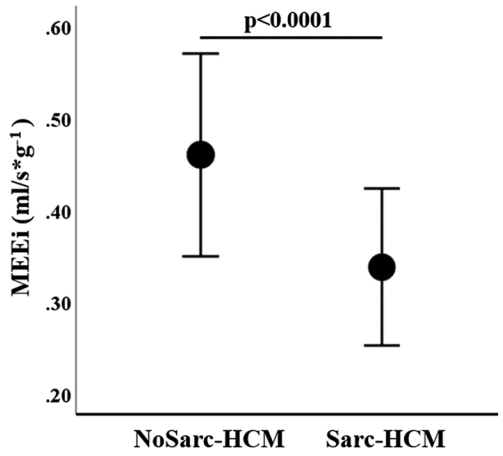

Fig. 1 MEEi (indexed mechano-energetic-efficiency) in patients with HCM without (noSarc-HCM) and with (Sarc-HCM) sarcomeric mutations

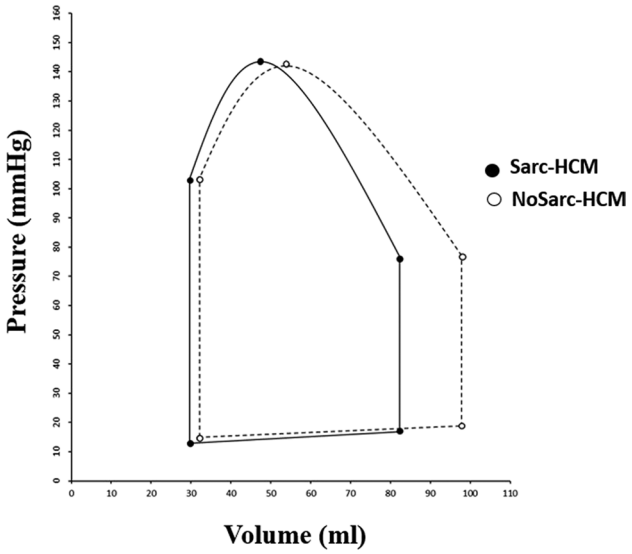

Fig. 2 P/V loops in in patients with HCM without (noSarc-HCM) and with (Sarc-HCM) sarcomeric mutations

sarcomeric contraction [32] due to the incorporation of the mutant protein which exerts a dominant negative effect [33]. The primary defect induced by the mutation on sarcomeric function activates secondary effects such as activation of stress-related genes and fetal genes which lead to compensatory hypertrophy and interstitial fibrosis [34]. Another hypothesis, named "energy depletion," suggests that an inefficient sarcomeric adenosine triphosphate (ATP) utilization leads to increased energy demand [35].

Studies evaluating myocardial bioenergetics in HCM patients carrying sarcomeric mutations have shown that patients with sarcomeric HCM present with bioenergetic deficit, which is independent to the presence of LV hypertrophy, suggesting that bioenergetics in HCM are altered because of the presence of the mutation itself [11, 36]. By using [11C]-acetate positron emission tomography and CMR imaging, Güçlü et al. demonstrated that MEE was significantly reduced in genotype-positive/phenotype-negative carriers as compared with normal subjects, and it was further decreased in overt obstructive HCM. This study suggests that the development of hypertrophy could add an additive negative effect on MEEi. To better understand this point, we decided to investigate the MEEi in patients with overt HCM, by comparing carriers of sarcomeric mutation and HCM patients in which no sarcomeric mutation had been identified.

Individuals with a negative HCM gene-panel test are usually referred to as "sarcomere-negative" HCM (noSarc-HCM in our study) and represent an important portion of patients with HCM, clinically distinct from sarcomeric HCM [37]. Epidemiological associations of NoSarc-HCM with comorbidities [38] suggest that these patients have a complex,

polygenic trait with distinct clinical implications and risk to develop the disease in the relatives [39]. Thus, NoSarc-HCM could represent a good model to test if reduction of MEEi is due to hypertrophy or to the presence of a sarcomeric mutation. In our study, the LV mass was not different between Sarc-HCM and NoSarc-HCM while MEEi resulted to be significantly reduced in patients with Sarc-HCM as compared to noSarc-HCM suggesting that although LV performance at the chamber level is preserved, at cardiomyocytes, the mechanical efficiency is rather reduced (Fig. 1).

According to the above-mentioned evidence highlighted, an altered energy homeostasis with an augmented energy expenditure by the sarcomere could represent a crucial component of HCM pathogenesis, particularly in HCM-Sarc patients [40]. This inefficient energy usage compromises the cardiomyocytes capability to maintain crucial homeostatic functions, such as calcium reuptake [35] and the super relaxed state of myosin filaments [40], leading to impaired diastolic phase of the cardiac cycle. With the MEEi analysis led in this study, we found that the presence of a causal mutation determines a worst mechanical efficacy, and P/V loop was built in order to look closely the cardiac chamber and better understand what precisely happens in an HCM heart during the cardiac cycle. In our opinion, providing the study with a figure (Fig. 2) that allows the reader, with a simple glimpse, to have a quick understanding of P/V relationship in that type of hearts, represents an important enrichment rarely seen in previous literature on that topic. The better MEEi found in noSarc-HCM patients is not linked to a better diastolic phase since both groups have the same filling pressure but only to the stoke volume: for each beat and with the same energy consumption, NoSarc-HCM hearts are capable to pump a bigger amount of blood.

Limitations of the study

The evaluation of myocardial oxygen consumption through echocardiography encompasses a spectrum of assumptions. Nonetheless, this approach stands on a firm foundation, as evidenced by existing research [9]. The functioning of the left ventricle, and its corresponding energy utilization, is notably impacted by variables such as HR, BP, and SV. The non-invasive assessment of LV mechanical efficiency offers valuable insights into cardiac performance and energy usage, primarily by analyzing the ratio of SV to HR. Importantly, this study marks the inaugural application of this methodology in HCM. We believe that disparities observed between patients with and without sarcomeric mutations stem from a precise assumption about the pathophysiology of myocardial oxygen consumption, as quantified through echocardiography. This advances our understanding of HCM and provides further validation for the utility of this method in deciphering the complexities of cardiac intricacies.

Another limitation of our study is the assessment of LV mass. However, although we acknowledge that our method might not have undergone formal validation, it is important to note that it has been acknowledged and regarded positively within the research community. In one study, it was highlighted that 3D echocardiography having cardiac magnetic resonance as gold standard yielded results like those reported in our paper [41].

Conclusion

Within a cohort of individuals diagnosed with HCM, the existence of a sarcomeric mutation exhibited a connection with diminished MEEi, indicating its potential utility as an imaging marker for a positive genetic assessment. Additionally, the presence of a sarcomeric mutation worsened LV performance, as evidenced by increased energy expenditure per cardiac cycle in HCM-Sarc patients. Collectively, the insights gleaned from P/V loop and MEEi analyses propose that individuals with HCM-Sarc are expending more energy while accomplishing a lesser volume of blood circulation.

Clinical relevance

In patients with HCM, sarcomeric mutations determine a reduction of the LV pump performance as estimated by MEEi. Lower MEEi may predict a positive genetic analysis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12265-023-10441-2.

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