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ORIGINAL ARTICLE
Myocardial disease

Myocardial performance during exercise in hypertrophic cardiomyopathy; pressure volume loops and haemodynamic forces analysis

Pietro Amedeo Modesti [1,2,*], Loira Toncelli[1], Edoardo Falconi[1], Gianni Pedrizzetti[3], Mattia Targetti[4], Iacopo Olivotto[2,4,5], and Alessio Pellegrino[1,2]

[1]Sport Medicine Unit, Careggi University Hospital, Via delle Oblate 4, Florence 50134, Italy; [2]Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy; [3]Department of Engineering and Architecture, University of Trieste, Trieste, Italy; [4]Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy; and [5]Pediatric Cardiology, Meyer Children's Hospital IRCCS Meyer Children's Hospital IRCCS

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Abstract

Background Developments in cardiac fluid dynamics imaging have recently increased interest in haemodynamic force (HDF) analysis, which expresses the forces exchanged between blood and surrounding tissues and corresponds to the global value of the intraventricular pressure gradients.

Aims The study was designed to investigate the pattern of HDF during exercise and their relationship with the mechanical characteristics of the left ventricle in patients with hypertrophic cardiomyopathy (HCM), who meet the morphological criteria for HCM despite normal conventional index of systolic and diastolic function.

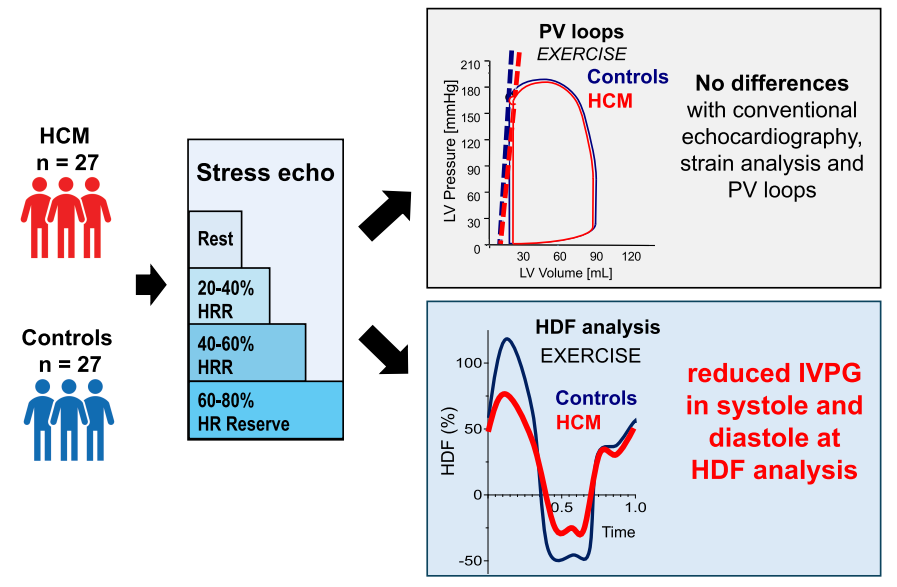
Methods Fifty-four participants (27 with non-obstructive HCM and 27 healthy controls) underwent transthoracic echocardiography at incremental levels of exercise intensity. A novel non-invasive analysis of intraventricular HDF and the study of non-invasive pressure–volume (PV) loops were performed. Differences between groups were investigated using mixed model analysis.

Results HCM patients generate lower longitudinal HDF during exercise compared with controls ($P = .007$ for group × intensity interaction), despite similar values in ejection fraction, strain, and conventional echocardiographic parameters. The findings suggest that only HDF analysis may allow to detect early cardiac dysfunction over the entire cardiac cycle, in systole, and diastole. When selected phases of diastole were studied, an impaired early diastolic relaxation was documented in the absence of any alteration at PV loops analysis.

Conclusions HDF may have the potential to detect early functional impairment in HCM. Prospective studies are needed to define its clinical relevance, to understand future evolution, and whether there are thresholds for risk stratification or how this relates to clinical outcomes.

* Corresponding author. Email: pa.modesti@unifi.it

Graphical Abstract



Haemodynamic forces analysis may have the potential to detect early changes in cardiac function in asymptomatic HCM patients.

Keywords Echocardiography • Hypertrophic cardiomyopathy • Haemodynamic forces • Pressure–volume relationship • Speckle-tracking echocardiography

Introduction

Hypertrophic cardiomyopathy (HCM) is a common autosomal inherited cardiomyopathy, mainly caused by mutations in the sarcomere protein genes,[1] characterized by left ventricular (LV) hypertrophy which abnormal loading conditions cannot fully explain.[2] Current guidelines emphasize the multiple benefits of regular exercise[3] but stipulate an individualized risk assessment and exercise program that can reconcile the balance between exercise and risk.[4,5] The presence of multiple types of anatomic and functional abnormalities and the broad heterogeneity in the clinical manifestations in HCM make risk stratification and accurate clinical treatment decisions challenging.[2] On the other hand, many patients with HCM in the early stages have preserved left ventricular ejection fraction and no obvious symptoms at rest. Previous studies have shown that LV global longitudinal strain (GLS), measured using speckle-tracking echocardiography, is often impaired and constitutes an adverse outcome predictor in HCM patients with preserved ejection fraction.[6] However, GLS remains load-dependent, limiting the assessment of LV function under certain haemodynamic conditions such as abnormal blood pressure or during physical activity. The gold standard measure of load-independent contractility is end-systolic elastance (Ees) assessed with pressure–volume (PV) curves.[7] Advances in echocardiographic imaging have led to important new perspectives, which permit the non-invasive study of PV curves.[8–11] Developments in cardiac fluid dynamics imaging have recently increased interest in HDF (haemodynamic force) analysis, which expresses the forces exchanged between blood and surrounding tissues and corresponds to the global value of the intraventricular pressure gradients (IVPG) responsible for blood flow, integrated into the ventricular volume.[12] The reference standard for HDF exploration is 4-D flow magnetic resonance imaging, a technique burdened by high costs, poor availability, and a complex and time-consuming procedure. Recently, a new approach using a mathematical model based on the first principle of fluid dynamics and mass conservation principles has been proposed.[13] With this new mathematical model, the force associated with a fluid volume can be evaluated from measurements performed at the boundaries of the volume (using the same speckle tracking technique used for strain and strain rate analysis) regardless of flow phenomena developing in the cavity. This approach applied to routinely acquired echocardiographic images offers advantages compared with conventional echocardiographic measures (LV ejection fraction and deformation imaging) because is able to resolve the changes in cardiac mechanics that occur during selected phases of the cardiac cycle. A detailed study of HDF during exercise may therefore have the potential to detect early alterations in cardiac function, their relationship with myocardial contractility and LV chamber stiffness in patients with early HCM.

Therefore, the aim of this study was to investigate HDF during exercise in asymptomatic HCM patients, and their relationship with the mechanical characteristics of the left ventricle.

Methods

Study cohort and ethics

Twenty-seven male patients referred to our unit for HCM were investigated. HCM was defined by unexplained maximum LV wall thickness ≥15 mm on echocardiography.[5,14] All participants underwent clinical and instrumental investigations to exclude undiagnosed cardiomyopathies, coronary heart disease, valvular disease, prior cardiac surgery/interventions, inflammatory diseases, amyloidosis, and other underlying conditions such as hypertension, renal disease, obstructive airway disease, type 1 or type 2 diabetes, obesity, dyslipidaemia, or symptoms (shortness of breath, chest pain, dizziness/syncope). In addition, subjects with implantable cardioverter-defibrillator, unheralded syncope, resting and post-valsalva LV outflow tract gradient >30 mmHg, hypotensive response to exercise (>20 mmHg drop

in systolic blood pressure from peak to post-exercise blood pressure), or history of exercise-induced arrhythmias were also excluded from the study.

Thirty-one sedentary controls who had volunteered to undergo cardiac evaluations between January 2024 and January 2025 were recruited by asking friends, colleagues, and family. Sedentary controls were age- and sex-matched to the HCM patients, had no history of cardiovascular disease at the time of inclusion and exercised less than 150 min of moderate intensity aerobic exercise per week.

The Ethics Board approved the study (Ref. 22843_oss) and written informed consent was received from every participant.

Procedures

All participants were instructed to fast overnight before the day of the enrolment visit and underwent comprehensive clinical evaluation. The initial clinical assessment included a comprehensive family history, ECG, echocardiography, and laboratory parameters. A timetable was then established for the execution of cardiopulmonary exercise testing and exercise echocardiography. Visits and tests were performed between 8 a.m. and 11 a.m.

Anthropometric measurements and blood pressure were measured according to standardized protocols using clinically validated instruments.[15]

HCM risk score for the prediction of Sudden Cardiac Death proposed by the European Society of Cardiology (HCMRisk-SCD) was calculated for all patients.[4]

Participants refrained from moderate/vigorous physical activity, caffeine, and fasted for 2 h before exercise tests.

CardioPulmonary exercise testing

A symptoms-limited maximal CardioPulmonary Exercise test was performed with a personalized ramp protocol (Quark PFT, Cosmed, Rome, Italy) aimed at reaching maximal effort in around 10 min. A breath-by-breath analysis of oxygen, carbon dioxide, and ventilation was performed, and peak values were computed as the highest observed measurements (20 s average).[16] Heart rate and rhythm were monitored continuously throughout exercise using a 12-lead ECG. Blood pressure was measured every 2 min. Heart rate reserve (HRR) was calculated using the maximum heart rate at CardioPulmonary Exercise test.

Exercise echocardiography

All participants underwent a semi-upright bicycle exercise stress echocardiography (Ergoselect 1200, Ergoline, Bitz, Germany) after the resting echocardiogram, using a standard exercise ramp protocol individualized based on the CardioPulmonary Exercise test. Transthoracic echocardiography was performed using an iE33 echocardiography system, equipped with X5-1 transducer (Royal Philips Electronics, Amsterdam, The Netherlands) according to recommendations.[17]

Three submaximal stages were targeted to achieve different exercise intensities based on HRR (Stage 1, by adding 20–40% of HRR to the resting heart rate; stage 2, 40–60 HRR%; stage 3, 60–80 HRR%). At each stage, echocardiographic images were acquired at 4-, 3-, and 2-chamber apical view. Blood pressure and heart rate were monitored as reported above.

Each electrocardiographically gated full-volume data set was digitally stored and exported to QLAB 3DQA software (Philips, Best, The Netherlands) for off-line analysis.

LV end-diastolic and end-systolic volumes were measured using the biplane method of disc summation, and stroke volume and cardiac output were calculated.[18] LV mass was calculated[17] and indexed to body surface area. The ratio of the early mitral inflow velocity over the early diastolic mitral annular velocity (*E*/e′) was determined. GLS and global circumferential strain (GCS) was measured using Speckle-Tracking Echocardiography and a commercial software (2D CPA 1.4.0.158, Medis BV, Leiden NL).

Pressure–volume (PV) curves

PV loops were constructed using dedicated software (QStrain, Medis BV, Leiden, NL). Briefly, the end-systolic pressure volume relationship and the end-diastolic pressure volume relationship were estimated using the single-beat approach according to Chen et al.[9] and to Klotz et al.,[10] respectively, as previously reported.[19] To compare the entire position of the end-diastolic pressure volume relationship, the calculated end diastolic volume at an end diastolic pressure of 20 mmHg ($EDVI_{20}$, ventricular capacitance) was used. The PV loop was then shown for the entire cardiac cycle where each point of the curve was described as Vt, Pt to calculate the Stroke work.

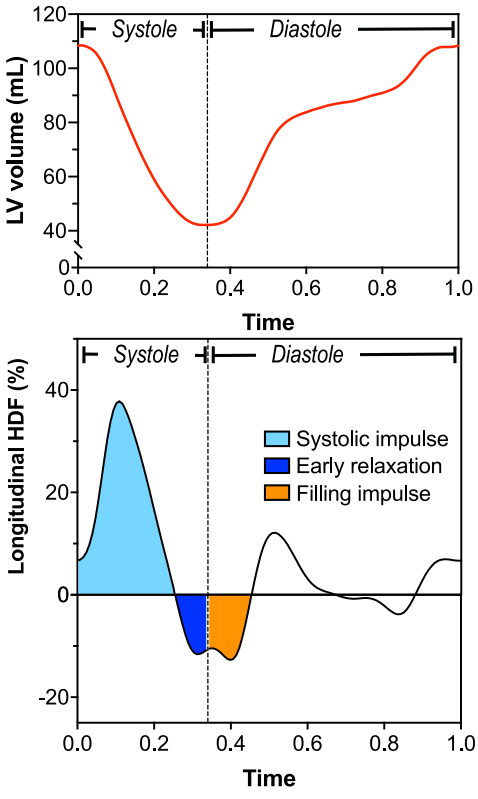


Figure 1 Time profile of left ventricular (LV) volume (upper panel), and longitudinal haemodynamic forces (HDF, lower panel) used to characterize the various phases of the cardiac cycle for HDF analysis. The vertical dashed lines mark the end of systole, corresponding to the closure of aortic valve and coincident with the minimum LV volume. Coloured areas under the curve define systolic impulse, early relaxation, and filling impulse

Haemodynamic forces

HDF correspond to the global value of IVPG integrated over the ventricular volume. HDF are computed from the time course of displacement of the LV endocardial geometry based on the principle of conservation of momentum for the blood flowing inside the chamber. The theoretical background[13] and its application to the clinical context[12,20,21] were previously reported. In a normal left ventricle, HDF occur in the longitudinal (apex-to-base) and in the transversal (lateral-septal) direction, with the longitudinal direction being the most predominant force. Transversal to longitudinal HDF ratio was then calculated.

HDF, expressed in Newton, are divided by the fluid density and gravity acceleration after being initially normalized by the LV volume (HDF%).[12] HDF were calculated using dedicated software (QStrain, Medis BV, Leiden NL), with endocardial tissue movement (tracked at speckle-tracking echocardiography) and areas of the aortic and mitral orifices as inputs.[12] Two temporal landmarks were considered: End-diastole (synchronized to ECG R wave), and end-systole (aortic valve closure coincident with the minimum LV volume). The endocardial border was traced at LV end-diastole and end-systole on the 4-, 3-, and 2-chamber apical views. The tracking algorithm was then applied to propagate the contours across entire cardiac cycles.[19]

The temporal profile of HDF was used to extract parameters describing the various phases of the cardiac cycle[22] (*Figure 1*). The following phases of the cardiac cycle were identified:

Table 1 Characteristics of participants

	Controls ($n = 27$)	HCM ($n = 27$)	P
Age (years)	37.2 ± 14.2	38.6 ± 14.8	.737
Sex (M/F)	22/5	22/5	.351
Height (cm)	176.9 ± 7.8	175.1 ± 8.6	.431
Weight (kg)	72.9 ± 11.5	76.7 ± 8.9	.181
BMI (kg/m^2)	23.0 ± 2.5	25.0 ± 1.9	<.003
BSA (m^2)	1.89 ± 0.18	1.92 ± 0.15	.541
VO_2 max (ml/kg/min)	39.6 ± 9.1	31.7 ± 6.2	<.001
HCM risk-SCD	—	2.3 ± 0.5	–
Max LV thickness (mm)	9.3 ± 1.0	18.2 ± 3.8	<.001
LVMi (g/m^2)	72.9 ± 11.0	113.6 ± 22.9	<.001
Ejection fraction (%)	62.9 ± 5.2	63.5 ± 7.4	.695

Units are mean ± SD; *n*, no. of participants.
BMI, body mass index; BSA, body surface area; VO_2max, maximal oxygen consumption; HCM Risk-SCD, risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy; LVMi, left ventricular mass index.

(1) entire cardiac cycle: overall HDF[23–25];
(2) systolic phase: overall systolic HDF; systolic impulse, the integral over time during the systolic propulsive phase; early relaxation, the final phase of systole when ventricular flow is still exiting but decelerating;
(3) diastolic phase: overall diastolic HDF; filling impulse, the suction gradient responsible for proto-diastolic filling.

Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables. Normal distribution of continuous variables was checked using skewness and kurtosis.

Interobserver and intraobserver variabilities were evaluated in a randomly selected sample of 10 subjects. Two investigators independently conducted measurements of the same examination, and one investigator repeated the analysis after 10 d blinded to prior measurements. The results have already been reported, which showed a low interobserver and intraobserver variability of the method.[19]

Group means were compared using the unpaired *t*-test. The effect of exercise on each repeated measurement was analysed using a linear mixed-effect model with random intercepts (level of exercise intensity and patient category fitted as fixed factors, patient as a random factor) and Bonferroni adjustment. Mixed model analysis was repeated with adjustments for body mass index (BMI) and maximal oxygen consumption (VO_2max).

Statistical significance is a two-sided level of 0.05. Data were analysed using the Statistical Package for the Social Sciences (SPSS Statistics Ver.28, IBM, Armonk, NY).

Results

Characteristics of participants

As expected, HCM patients had greater wall thickness and LV mass than controls (*Table 1*), whereas no differences were detected for ejection fraction, GLS, GCS, and *E*/*e*′ (*Table 2*). HCM patients, compared with controls, had higher BMI and lower VO_2max (*Table 1*).

Myocardial performance

Haemodynamics

The trend of echocardiographic parameters measured at the different intensity levels of physical exercise in controls and HCM patients is reported in *Table 2*. No patient developed significant LVOT obstruction after exercise.

From rest to the last phase of exercise, end-diastolic and end-systolic volume, as well as stroke volume and cardiac output changes did not significantly differ between groups for the interaction between group and intensity at mixed model analysis. No differences between groups were found even considering the conventional echocardiographic indices of global systolic ejection fraction, GLS, GCS, and diastolic function (*E*/*e*′) (*Table 2*).

PV loops

The pattern of exercise-induced changes in Ees, the slope of the end-systolic PV relationship assessed with PV loop investigations, indicates a progressive increase in ventricular contractility during exercise. Ees showed a comparable increase between HCM patients and controls ($P = .186$ for group × intensity interaction) (*Table 2* and *Figure 2*).

On the other hand, the left ventricle of HCM patients had lower capacitance ($EDVI_{20}$) when compared with controls ($P = .044$), with no significant interaction between group and intensity at mixed model analysis ($P = .807$). LV end diastolic pressure did not increase during exercise ($P = .673$ for intensity), showing no differences between groups ($P = .769$ for group × intensity interaction).

Haemodynamic forces

The pattern of HDF differed between the two groups also upon adjustment for BMI and VO_2max (*Table 3*). The increase in longitudinal HDF during exercise was lower in HCM patients than in controls over the entire cardiac cycle and during systole ($P = .006$ and $P = .044$, respectively, for group × intensity interaction), differences being evident also in the final phase of systole when ventricular flow is still exiting but decelerating (early relaxation, $P < .003$) (*Table 3* and *Figure 3*).

The increase in longitudinal HDF was lower in HCM vs controls at the group × intensity interaction also in the entire diastole ($P < .002$). When selected phases of diastole were studied, the exercise-induced increase of the absolute value of filling impulse was lower in patients with HCM than in controls ($P = .004$ for group × intensity interaction) (*Figure 4*), thus revealing an impaired diastolic relaxation.

Transversal component of HDF was reduced both during the entire cardiac cycle and in diastole, with no significant differences in the transversal to longitudinal HDF ratio (*Table 3*).

Discussion

The present study explores for the first time the haemodynamics of exercise in early stage asymptomatic HCM patients, currently candidates for exercise prescription protocols, through non-invasive analysis of PV loops and intraventricular HDF. The main finding is that the left ventricle of this subgroup of patients during exercise generates a lower HDF than sedentary controls, in the absence of alterations in contractility or compliance on conventional echocardiography or PV analysis. Based on the current results, we can therefore distinguish the onset of early functional impairment in patients with early-stage disease. The application of HDF analysis during exercise in HCM addresses an important clinical need: diagnosis of early functional impairment in patients who already meet the morphological criteria for HCM (e.g. LV hypertrophy) despite normal values for conventional echocardiographic indices of systolic and diastolic function.

Table 2 Haemodynamic changes during exercise in controls and HCM patients

Variables	CAT	Rest	Exercise intensity			Mixed model		
			20–40%	40–60%	60–80%	cat *P*	int *P*	cat × int *P*
Clinical parameters								
Heart rate (bpm)	Controls	69.1 ± 11.9	103.8 ± 7.7	129.0 ± 8.7	155.0 ± 8.0			
	HCM	60.1 ± 9.3	98.1 ± 5.0	113.0 ± 15.7	143.0 ± 13.0	<.001	<.001	.135
SBP (mmHg)	Controls	117.4 ± 15.0	140.4 ± 17.3	163.0 ± 20.4	178.3 ± 21.7			
	HCM	115.6 ± 13.5	124.4 ± 19.4	150.6 ± 26.2	164.8 ± 28.1	<.001	<.001	.196
DBP (mmHg)	Controls	72.0 ± 9.8	71.2 ± 10.0	70.6 ± 11.6	66.5 ± 12.5			
	HCM	70.2 ± 10.0	65.6 ± 9.2	67.7 ± 11.0	65.7 ± 13.5	.110	.195	.820
Echocardiographic parameters								
EDV (mL)	Controls	83.0 ± 16.8	86.5 ± 20.7	87.4 ± 19.7	83.6 ± 17.6			
	HCM	78.4 ± 17.3	87.1 ± 23.9	85.7 ± 28.8	75.8 ± 25.9	.321	.302	.854
ESV (mL)	Controls	30.4 ± 7.1	25.4 ± 7.8	24.2 ± 7.0	23.7 ± 6.6			
	HCM	28.6 ± 10.0	30.4 ± 15.1	27.0 ± 11.8	24.2 ± 10.0	.261	.011	.403
SV (mL)	Controls	52.6 ± 12.4	61.1 ± 16.7	63.2 ± 15.9	59.9 ± 12.8			
	HCM	49.8 ± 10.6	56.7 ± 11.9	58.7 ± 18.5	51.5 ± 17.5	.039	.007	.794
CO (l/min)	Controls	3.55 ± 0.65	6.33 ± 1.77	8.08 ± 1.73	9.25 ± 1.87			
	HCM	3.02 ± 0.93	5.55 ± 1.13	6.61 ± 2.29	7.32 ± 2.75	<.001	<.001	.145
E/e′	Controls	10.8 ± 5.5	10.1 ± 4.3	9.8 ± 5.8	10.5 ± 5.2			
	HCM	9.8 ± 7.1	10.7 ± 4.9	12.4 ± 10.9	13.4 ± 9.3	.290	.751	.594
Strain and pressure–volume loops parameters								
GCS (%)	Controls	31.9 ± 4.2	38.0 ± 6.5	39.3 ± 5.9	38.8 ± 4.9			
	HCM	33.6 ± 7.3	35.1 ± 5.3	37.7 ± 6.5	36.3 ± 6.4	.158	<.001	.238
GLS (%)	Controls	23.6 ± 4.1	27.8 ± 4.2	28.5 ± 4.4	29.3 ± 4.0			
	HCM	23.3 ± 5.2	25.0 ± 6.6	28.0 ± 7.6	27.7 ± 4.9	.105	<.001	.682
Beta	Controls	6.23 ± 0.31	6.19 ± 0.27	6.22 ± 0.24	6.29 ± 0.48			
	HCM	6.25 ± 0.34	6.19 ± 0.25	6.39 ± 0.54	6.26 ± 0.53	.484	.531	.636
Ees (mmHg/mL)	Controls	3.78 ± 0.87	5.26 ± 1.58	6.51 ± 1.74	7.08 ± 1.71			
	HCM	4.24 ± 1.79	4.47 ± 1.84	5.76 ± 2.40	6.55 ± 2.22	.044	.021	.807
$EDVI_{20}$ (ml/m^2)	Controls	44.7 ± 7.6	46.8 ± 9.8	47.0 ± 9.2	45.1 ± 7.1			
	HCM	41.4 ± 7.8	45.0 ± 10.9	45.0 ± 13.7	39.6 ± 11.0	.044	.210	.807
ESP (mmHg)	Controls	105.7 ± 13.5	126.3 ± 15.6	146.7 ± 18.4	160.4 ± 19.6			
	HCM	104.0 ± 12.1	112.0 ± 17.5	135.5 ± 23.6	148.3 ± 25.3	<.001	<.001	.196
EDP (mmHg)	Controls	17.8 ± 2.7	17.5 ± 2.4	17.8 ± 2.5	17.9 ± 2.9			
	HCM	17.8 ± 2.8	17.5 ± 2.8	18.6 ± 3.0	17.4 ± 2.9	.859	.673	.769
SW (J)	Controls	0.70 ± 0.21	0.97 ± 0.35	1.13 ± 0.37	1.16 ± 0.32			
	HCM	0.65 ± 0.21	0.74 ± 0.27	0.92 ± 0.34	0.93 ± 0.39	<.001	<.001	.276

Units are mean ± SD.

n, no. of participants; HRR, heart rate reserve; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; CO, cardiac output; *E*/e′, ratio of peak velocity of mitral inflow during early diastole (*E*) over the average of septal and lateral mitral annular early diastolic peak velocities (e′); GCS, global circumferential strain; GLS, global longitudinal strain; Ees, end-systolic ventricular elastance; $EDVI_{20}$, end-diastolic volume index at a pressure of 20 mmHg; ESP, end-systolic pressure; EDP, end-diastolic pressure.

Mixed model analysis with Bonferroni correction: *P* for categories (cat = categories; controls, HCM), zone intensity (int = intensity; 4 stages), and interaction between category and zone intensity (cat × int).

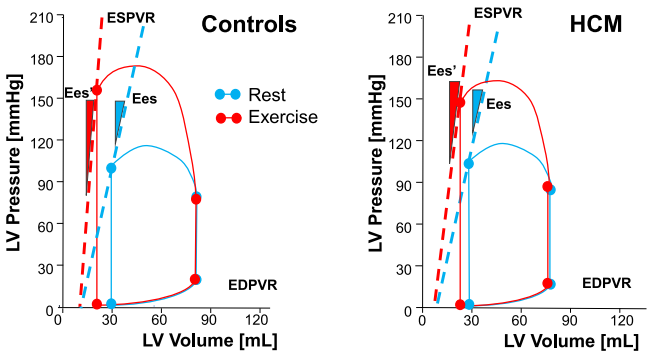


Figure 2 Left ventricular (LV) pressure-volume loop of one control (left panel) and one patient with HCM (right panel) at rest (blue) and during exercise (red) LV pressure is plotted against the LV volume at multiple time points during a single cardiac cycle. The pressure–volume loop area represents stroke work. Slope between the hypothetical volume at zero pressure (V_0), and the point of end-systolic pressure–volume relation (ESPVR), also called end-systolic elastance (Ees and Ees′), defines contractility and are indicated by dashed lines

Echocardiographic examination showed that during exercise HCM patients had ejection fraction and conventional echocardiographic indices of global systolic (GLS, GCS) and diastolic (*E*/*e*′) function not significantly different from controls. The study of PV curves also did not reveal an altered response of the Ees to exercise nor a reduced capacitance of the ventricular chamber ($EDVI_{20}$) compared with controls. It is to be considered that these loops are derived from single-beat estimates based on simplified models and such approximations may not have sufficient sensitivity to allow the detection of initial alterations. In the same line, no EDP increases were observed during exercise. Only the study of the generation of IVPG with HDF analysis highlights the initial functional alteration of the ventricle of these patients with clinically asymptomatic HCM. Indeed, during exercise, HCM patients presented a lower longitudinal HDF than controls during the entire cardiac cycle, in the systolic phase (entire systole, systolic impulse, early relaxation), and during diastole (entire diastole, filling impulse). Reduced longitudinal force gradient generation in systole indicates a reduction in the propulsive force of the blood column towards the outflow tract, an early sign of reduced LV contractility. This is specifically expressed by a reduction in the systolic impulse. The reduction observed in the final phase of systole, early relaxation, appears to reflect a reduction in the left ventricle's capacity for active relaxation prior to the diastolic phase. Finally, the reduced gradient observed in early diastole, seems to disclose a reduced suction capacity of the left ventricle when the mitral valve opens. As mentioned above, these changes are very light, not accompanied by any PV loops changes. When considering transverse forces, a reduction is observed only in diastole. The asymmetric remodelling may potentially disrupt flow symmetry in HCM patients. On the other hand, it can be speculated that initial changes in collagen deposition could mainly influence this phase.

The patient and control groups were similar in age, but differences in weight and, in particular, fitness (VO_2max) were evident. These differences are likely related to the fact that HCM patients may experience physical deconditioning after diagnosis due to fear of engaging in physical activity. It is therefore difficult to dissect whether differences in HDF are due to HCM status or worse conditioning. However, HDF differences were still evident after adjustments for these factors.

Overall, these data indicate that the initial response of the left ventricle to exercise in patients with HCM is characterized by a reduced generation of intraventricular HDF, before conventional indices can be altered.

For the past two decades, experimental and human studies have demonstrated the validity of colour Doppler M-mode echocardiography to estimate non-invasively the instantaneous local pressure differences into LV during ejection and diastolic filling.[26–31] The pressure curves were separately obtained by Doppler-echocardiography in the LV outflow and across the mitral valve for systolic and diastolic gradients, respectively.[26–31] Data were obtained during exercise,[29,32] and in HCM patients.[32] A main novelty introduced by HDF assessment is to assess both systolic and diastolic IVPG giving a global assessment in a single measurement with an automated quantitative analysis tool.[12,21]

The study of the early functional LV alterations in patients with HCM is a point that has attracted great interest in recent years. Previous studies have shown that GLS[33] is often impaired in HCM patients with preserved ejection fraction and constitutes an adverse outcome predictor.[6,34,35] Impaired GLS was also associated with established HCM risk-prediction models.[36] This implies that impaired GLS may aid the identification of individuals with higher-risk HCM phenotypes, which is an important clinical goal.[37] However, the GLS is load-dependent and the search for earlier indicators of altered cardiac function is still necessary. In particular, diastolic dysfunction of some form is thought to be operative in the majority of HCM patients with the non-obstructive form of the disease.[38,39] In a wide variety of cardiac conditions, the mitral early diastolic inflow to early diastolic tissue velocity (*E*/*e*′) ratio has emerged as the most informative parameter that correlates best with LV filling pressure, and is the predominant means of assessing diastolic function.[40] However, conflicting data regarding the reliability of *E*/*e*′ ratio in patients with HCM have been reported.[38,41–43] However, the patient cohorts studied often represent a heterogeneous group (NYHA class II–IV).[38,44] The patients enrolled in the present study were a homogeneous group made up of participants who did not present functional limitations to physical exercise (they were all in NYHA class I), and did not have obstruction of the LV outflow tract. In these patients both GLS and GCS significantly increased during exercise with no differences vs controls. The main strength of this study is to address a weakness in previous studies where investigations were performed at rest. The estimation of PV cycles generated from echocardiographic data using the single-beat method and assessment of HDF, both prospectively evaluated at different levels of exercise intensity, fill this gap. In particular, only the assessment of HDF revealed initial alterations during exercise in these patients.

Table 3 Haemodynamic forces (HDF) (longitudinal, transversal, and transversal to longitudinal ratio) at rest and during exercise in controls and HCM patients

HDF	CAT	Exercise intensity				Mixed model Unadjusted			Mixed model Adjusted for BMI and VO_2max		
		Rest	20–40%	40–60%	60–80%	Cat *P*	Int *P*	Cat × Int *P*	Cat *P*	Int *P*	Cat × Int *P*
Longitudinal HDF (%)											
Entire C.	Con.	14.1 ± 3.9	31.7 ± 12.9	46.5 ± 13.6	65.0 ± 15.9						
	HCM	11.7 ± 5.5	21.4 ± 4.8	32.8 ± 14.4	50.7 ± 18.1	.001	.001	.007	.001	.001	.006
Systole	Con.	21.5 ± 7.0	41.4 ± 18.0	58.9 ± 21.0	77.2 ± 27.8						
	HCM	17.8 ± 7.8	28.4 ± 7.3	41.5 ± 20.7	58.3 ± 25.6	.001	.001	.047	.001	.001	.044
Syst.imp.	Con.	20.5 ± 6.2	39.6 ± 16.9	57.5 ± 23.7	75.7 ± 27.6						
	HCM	17.5 ± 7.9	29.0 ± 7.1	44.6 ± 18.4	55.1 ± 23.5	.001	.001	.049	.001	.001	.056
Early rel.	Con.	−10.9 ± 3.0	−23.1 ± 8.4	−35.4 ± 12.6	−42.9 ± 15.9						
	HCM	−7.6 ± 3.5	−12.9 ± 6.0	−21.7 ± 11.4	−30.1 ± 14.3	.001	.001	.003	.001	.001	.002
Diastole	Con.	6.7 ± 2.0	20.2 ± 9.5	31.5 ± 7.5	50.4 ± 11.8						
	HCM	6.1 ± 3.2	13.1 ± 3.7	22.8 ± 9.3	41.4 ± 16.0	.001	.001	.003	.001	.001	.002
Fill. imp.	Con.	−9.1 ± 3.9	−22.3 ± 7.1	−34.9 ± 14.8	−49.0 ± 21.5						
	HCM	−7.7 ± 5.0	−11.3 ± 6.0	−22.3 ± 11.7	−41.3 ± 21.7	.001	.001	.002	.001	.001	.004
Transversal HDF (%)											
Entire C.	Con.	3.0 ± 1.2	6.6 ± 2.3	9.5 ± 3.9	15.4 ± 5.5						
	HCM	1.9 ± 0.9	3.8 ± 1.4	6.2 ± 2.2	10.7 ± 3.8	.001	.001	.011	.001	.001	.009
Systole	Con.	3.6 ± 1.4	7.3 ± 2.7	9.8 ± 5.1	13.4 ± 6.2						
	HCM	2.3 ± 1.2	4.3 ± 1.2	6.0 ± 2.3	9.8 ± 3.8	.001	.001	.081	.001	.001	.042
Diastole	Con.	2.5 ± 1.4	5.9 ± 2.6	8.8 ± 3.9	16.6 ± 7.2						
	HCM	1.4 ± 0.8	3.1 ± 2.0	6.1 ± 2.7	10.9 ± 5.9	.001	.001	.025	.001	.001	.032
Transversal to longitudinal HDF ratio (%)											
Entire C.	Con.	21.7 ± 8.8	22.0 ± 6.5	21.5 ± 8.4	24.6 ± 9.3						
	HCM	16.5 ± 6.1	19.0 ± 9.5	20.9 ± 9.8	22.3 ± 8.2	.033	.081	.578	.039	.101	.587
Systole	Con.	17.4 ± 5.9	18.7 ± 5.2	17.4 ± 6.9	18.0 ± 7.1						
	HCM	13.7 ± 6.3	15.7 ± 5.4	16.6 ± 7.8	17.8 ± 8.7	.066	.354	.546	.043	.495	.519
Diastole	Con.	36.8 ± 20.6	30.5 ± 12.2	29.2 ± 14.1	34.4 ± 15.3						
	HCM	25.5 ± 11.3	24.5 ± 17.7	29.0 ± 14.5	26.9 ± 12.2	.007	.709	.359	.016	.814	.318

Mixed model analysis with Bonferroni correction: *P* for categories (cat = categories; controls, HCM), zone intensity (int = intensity; 4 stages).
Entire C., entire cardiac cycle; Syst.imp., systolic impulse; Early rel., early relaxation; Fill. imp., filling impulse.

Study limitations

An important limitation of this study is the difficulty in defining the sample that was examined. The study was designed to investigate the cardiac conditions of patients with early stages of HCM, with a low risk of arrhythmic events, and who can be assigned to a physical exercise program. We are aware that patients with HCM have a very variable phenotype, with different degrees of impairment of LV function, and to define categories in such a heterogeneous panorama is very difficult. For this reason, the exclusion criteria were mainly clinical. However, the patients studied had normal conventional indicators of systolic and diastolic cardiac function. Second, the study during exercise was conducted with the objective of reaching 80% of the maximum HRR. The choice of this limit, lower than the maximum load achievable (100%), may have limited the possibility of analysing the mechanical behaviour of the left ventricle at the peak of effort. However, it represents an acceptable compromise which allowed us to study the participants and evaluate the differences in ventricular mechanics under stress, while limiting the influence of movement artefacts. Third, because the reliability of the *E*/e′ ratio in HCM patients is still not clear, the EDP reported and estimated by *E*/e′ may not be accurate. Fourth, the study population is primarily composed of male HCM patients. Given the known sex-related differences in cardiac remodelling and disease expression,[45]

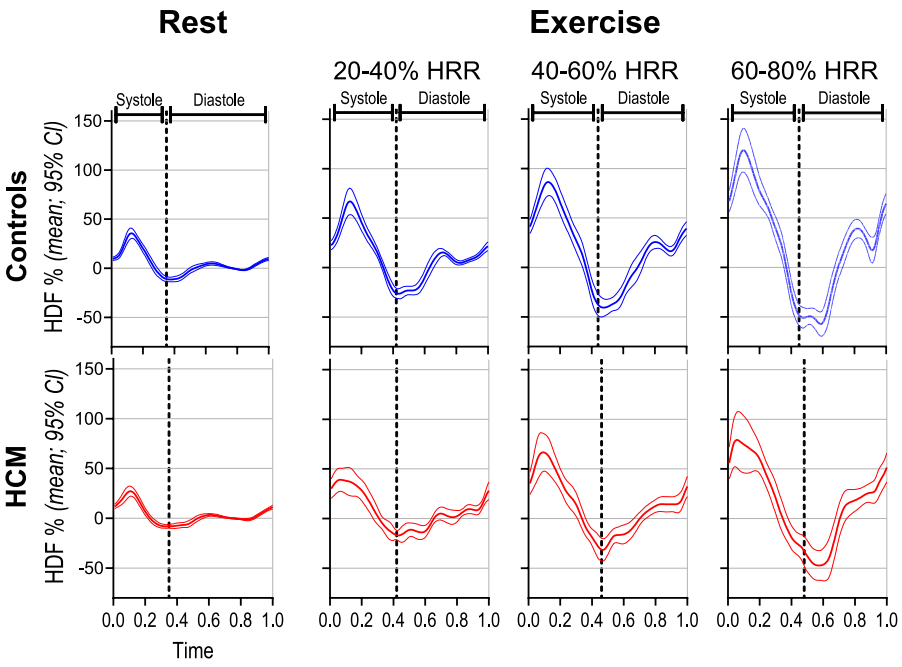


Figure 3 Longitudinal HDF over the entire cardiac cycle in controls (blue lines) and HCM patients (red lines) at rest and at different exercise stages (20–40%, 40–60% and 60–80% of heart rate reserve, HRR) HDF are presented as mean with 95% confidence interval. The end of systole (corresponding to the closure of aortic valve) is marked by a dashed line

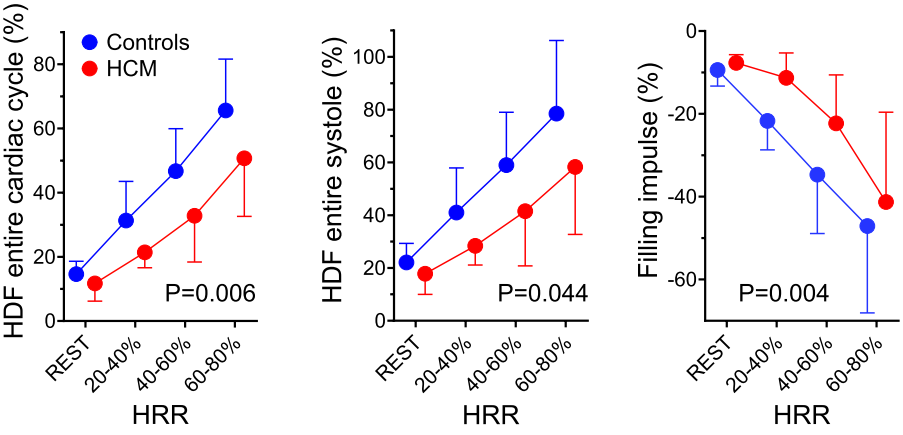


Figure 4 Longitudinal HDF over the entire cardiac cycle (left panel), in systole, and filling impulse (right panel) in controls (blue) and HCM patients (red) at rest (Rest) and at different exercise stages (20–40%, 40–60% and 60–80% of heart rate reserve, HRR) Data are presented as mean ± SD with *P* values for group × intensity interaction at mixed model analysis

this limits the possibility of generalizing the results to all HCM patients. Fifth, the patient and control groups were similar in age, but differences in weight and, in particular, fitness (VO_2max) were evident. These differences are likely related to the fact that HCM patients may experience physical deconditioning after diagnosis due to fear of engaging in physical activity. It is therefore difficult to dissect whether differences in HDF are due to HCM status or worse conditioning. However, HDF differences were still evident after adjustments for these factors. Finally, from a clinical perspective, although the observation that HCM may show differences in HDF before other haemodynamic changes appear is interesting from a mechanistic and hypothesis-generating perspective, these data alone are probably insufficient to support the conclusion that HDF may detect early impairment without exploring the ability to stratify HCM patients (e.g. for exercise intolerance, genotype, fibrosis, risk of outcomes). Prospective studies are needed to understand future evolution, and whether there are thresholds for risk stratification or how this relates to established clinical outcomes.

Conclusions

According to the present results, the response to exercise in patients with asymptomatic HCM is characterized by an early reduced generation of intraventricular gradient, expressed by longitudinal HDF. HDF may have potential for detecting early functional impairment in early-stage HCM.

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Author contributions

Pietro Amedeo Modesti (MD PhD (Conceptualization [lead]; Formal analysis [lead]; Investigation [lead]; Methodology [supporting]; Project administration [lead]; Supervision [lead]; Writing—original draft [lead]; Writing— review & editing [lead])), Loira Toncelli (MD PhD (Investigation [equal]; Methodology [supporting]; Resources [supporting]; Writing—review & editing [supporting])), Pietro Amedeo Modesti (Conceptualization [lead]; Formal analysis [lead]; Writing—original draft [lead]; Writing—review & editing [lead]), Loira Toncelli (Investigation [equal]), Edoardo Falconi (Investigation [equal]), Gianni Pedrizzetti (Conceptualization [equal]; Software [lead]), mattia targetti (Investigation [equal]), Iacopo Olivotto (Conceptualization [equal]; Supervision [equal]; Writing—review & editing [equal]), and Alessio Pellegrino (Formal analysis [equal]; Investigation [equal]; Writing—review & editing [equal]), Edoardo Falconi (MD (Investigation [supporting]; Methodology [supporting]; Resources [supporting]; Writing—review & editing [supporting])), Gianni Pedrizzetti (PhD (Methodology [equal]; Investigation [supporting]; Resources [supporting]; Writing—review & editing [supporting])), Mattia Targetti (MD (Investigation [supporting]; Resources [supporting]; Writing—review & editing [supporting])), Iacopo Olivotto (MD PhD (Conceptualization [supporting]; Investigation [supporting]; Resources [supporting]; Writing—review & editing [equal])), and Alessio Pellegrino (MD PhD (Conceptualization [supporting]; Investigation [supporting]; Methodology [supporting]; Resources [supporting]; Supervision [supporting]; Writing—review & editing [supporting])).

Declarations

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Disclosure of Interest

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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