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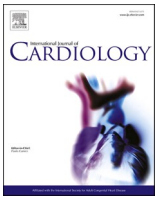

Non-invasive evaluation of left ventricular hemodynamic force abnormalities in hypertrophic cardiomyopathy: Implications for myosin inhibition

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is characterized by abnormal myocardial mechanics, with or without left ventricular outflow tract obstruction (LVOTO). Myosin inhibitors such as mavacamten have shown clinical efficacy in reducing obstruction, but their effects on left ventricular hemodynamic forces (HDF)—a novel marker of myocardial function—are not yet defined. This study aimed to characterize left ventricular HDF patterns in patients with obstructive (oHCM) and non-obstructive (noHCM) HCM compared to healthy controls, and to evaluate the impact of long-term mavacamten therapy on HDF parameters in oHCM.

Methods: We retrospectively analyzed 40 HCM patients (20 oHCM, 20 noHCM) and 20 age- and sex-matched healthy controls. HDF parameters were quantified using echocardiographic strain imaging software (*Qstrain*, *Medis Medical Imaging Systems*). Parameters included systolic and diastolic force amplitudes and time indices. Six oHCM patients receiving mavacamten were assessed at baseline and after three years of therapy.

Results: Compared to controls, HCM patients had significantly reduced systolic time to peak ($p < 0.001$) and diastolic-systolic transition time ($p < 0.001$), indicating premature systolic thrust and impaired relaxation. Diastolic force amplitude was significantly lower in oHCM than noHCM ($p < 0.001$). Mavacamten treatment in oHCM patients significantly prolonged diastolic-systolic transition ($p = 0.030$) and restored longitudinal force dynamics ($p = 0.031$), suggesting improved mechanical coordination and reduced LVOTO.

Conclusions: HDF analysis identifies distinct mechanical impairments in HCM regardless of obstruction status. Mavacamten favorably modulates HDF, delaying systolic thrust initiation and normalizing force distribution, offering new mechanistic insights into its therapeutic action in HCM.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic heart disease whose core pathophysiologic features include asymmetric left ventricular (LV) hypertrophy, myocardial hypercontractility, microvascular ischaemia, myocardial fibrosis and diastolic dysfunction [1]. Dynamic LV outflow tract obstruction (LVOTO), a hallmark of the disease, is associated with increased ventricular systolic work, decreased myocardial perfusion pressure during diastole, and impaired ventricular relaxation. Historically, the mechanisms of dynamic LVOTO have been imputed to a combination of reduced LVOT size, abnormalities of the mitral valve apparatus and LV hypercontractility, resulting in the

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hydrodynamic genesis of systolic anterior motion (SAM) of the mitral valve [2]. Myosin inhibitors have proven to be very effective in reducing obstruction and improving symptoms [3]. However, many questions remain regarding the pathophysiology of obstructive HCM (oHCM) vs non-obstructive HCM (noHCM) and the mechanisms of action of myosin inhibitors in this context.

Hemodynamic forces (HDF) are the global forces exchanged between blood volume and the endocardium, thus describing the complex relationship existing between segmental wall mechanics and the fluid dynamics of LV filling and ejection [4,5]. HDF correspond to the intraventricular pressure gradient integrated over the entire LV cavity, which can be evaluated non-invasively by modern echocardiographic software [6–8]. Current evidence supports HDF application in several clinical settings, offering new echocardiographic biomarkers of disease progression and response to treatment [6–10]. However, this technique has never been employed to investigate HDFs in patients with HCM to date, despite its potential to identify responders to treatment and predict novel hemodynamic targets for myosin inhibitors. Thus, the present study aims to characterize differences in LV HDF patterns among patients with both oHCM and noHCM, compared to healthy controls, and to evaluate the impact of the cardiac myosin inhibitor mavacamten on LV HDF patterns associated with LVOTO.

2. Methods

2.1. Study population

Consecutive patients diagnosed with HCM in accordance with international guidelines [11] and aged >18 years, were retrospectively enrolled at our Center between December 2022 and June 2023. To ensure homogeneity among the study population and avoiding potential confounding factors in the LV intraventricular force analysis, the following exclusion criteria were applied: 1. abnormal infranodal conduction or permanent paced ventricular rhythm, 2. history of atrial fibrillation, 3. primary valve disease, 4. previous septal reduction therapy (myectomy or alcoholic septal ablation), 5. concomitant critical coronary artery disease, 6. suboptimal echocardiographic window, 7. uncontrolled severe systemic hypertension, 8. acute or systemic conditions known to affect cardiac output. HCM patients were divided into two groups based on the presence (oHCM, $n = 20$) or absence (noHCM, $n = 20$) of dynamic LVOTO and results were compared to a group of sex- and age-matched healthy controls ($n = 20$). Dynamic LVOTO was defined, following guideline recommendations [11], as a peak instantaneous LVOT gradient ≥30 mmHg, measured either at rest or during physiological provocation (such as the Valsalva maneuver). This assessment is performed using continuous-wave Doppler echocardiograph from the apical 3- or 5-chamber view, ensuring that the Doppler cursor was aligned with the LVOT jet.

The cohort included a subset of patients ($n = 6$) treated long-term (from March 2019 to February 2023) with mavacamten, originally enrolled in EXPLORER-HCM trial (NCT03470545), and subsequently included in the open-label extension MAVALTE study (A Long-Term Safety Extension Study of Mavacamten in Adults With Hypertrophic Cardiomyopathy; URL: https://www.clinicaltrials.gov; unique identifier: NCT03723655). The demographic, clinical and electrocardiographic characteristics as well as LV deformation imaging features of these six patients have been previously reported [12].

The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethical Committee. Patients enrolled in the MAVA-LTE study provided their informed consent for these post hoc analyses of echocardiographic data.

2.2. Echocardiography and HDF analysis

All patients underwent standard transthoracic echocardiography using a GE Vivid E9 equipment. Conventional echocardiographic parameters such as LV volumes, LV ejection fraction (LVEF), left atrial diameters, wall thickness, LV filling pattern and LVOT gradient, were examined and collected in all HCM patients and controls (Table 1). The six patients included in the open-label extension MAVA-LTE study were assessed at baseline and after three years treatment with mavacamten (Table 2).

For 4-, 3-, and 2-chamber views at a frame rate ≥ 60 images were transferred to a dedicated workstation for post-processing offline analysis. Systolic and diastolic HDFs directed along the “apex-to-base” (also called longitudinal force) of LV axis were determined by two expert operators, blind to clinical history and instrumental data, using a semi-automated mathematical thresholding method incorporated into a dedicated prototype software (QStrain version 1.3.0.79; Medis Medical Imaging System, Leiden, The Netherlands). After applying the software's automatic endocardium contours, the two operators implemented a manual correction as needed. To facilitate comparison between patients with different LV size, the HDFs software arranges the amplitude parameters normalizing for LV volume and then dividing by the fluid density and gravity acceleration. Finally, the parameters are expressed as a percentage of gravity acceleration. The HDF vector is conventionally rendered as a force-over-time curve where positive deflections detail a HDF force directed from the apex to the base of LV, whilst negative deflections report a HDF vector directed from the base to the apex.

The following amplitude parameters were measured (Fig. 1):

- LV impulse (%), calculated as the average magnitude of LV longitudinal force over the ejection phase. This parameter identifies the systolic propulsive phase from the LV chamber to the aorta, calculated from the peak of end diastolic LV volume to the beginning of LV suction phase;
- LV suction, (%), calculated as the average LV longitudinal force during the period following propulsion while the force is negative, or the area under the curve in the interval encompassing the end of systole and the initial part of diastole;
- Deceleration flow force (DFF, %), measured as the mean longitudinal force during diastolic deceleration.
- Longitudinal force depression before systolic thrust (LFD, %), represented by the notch located between the end of diastolic deceleration force and the onset of systolic thrust. It is measured as the difference in absolute value between the peak amplitude of longitudinal force at onset of systole and the amplitude of longitudinal force at nadir of the first deflection.

Similarly, time parameters were measured and indexed to the duration of the entire cardiac cycle:

- Diastolic-systolic transition time index (DSTT), measured as the time interval from LV volume peak to systolic peak;
- Systolic time to peak (STP), calculated as the interval of time from the 0 of the longitudinal HDF curve, corresponding to end-diastolic volume phase of the left atrium and to the systolic peak;
- LV impulse time index (LVIT), calculated as the duration of LV impulse;
- LV suction time index (LVST), calculated as the duration of LV suction.

2.3. Statistical analysis

Continuous variables were reported using median and interquartile range, whereas categorical variables were represented as frequencies and percentages. Differences between the two groups were analyzed by Mann–Whitney test for continuous variables and Chi-Square test for categorical ones. To compare more than two groups, Kruskal-Wallis test was used with pairwise comparisons between all the groups. Non-parametric Wilcoxon paired signed-rank test was used to assess

Table 1
Demographic, clinical, electrocardiographic and echocardiographic characteristics.

Variable	Healthy subjects ($N = 20$)	Obstructive HCM (N = 20)	Non-obstructive HCM (N = 20)	P value
Demographic and clinical characteristics				
Age at visit (years)	50 [35–66]	57 [50–66]	52 [39–61]	0.385
Gender (female)	8 [40.0%]	10 [50.0%]	6 [30.0%]	0.435
BMI (kg/m2)	22.04 [21.85–24.24] $^{\alpha}$	27.25 [23.66–29.62] $^{\mid}$	24.39 [21.85–24.90]	0.008 **
Arterial hypertension	4 [20.0%]	6 [30.0%]	5 [25.0%]	0.766
Diabetes mellitus	0 [0.0%]	2 [10.0%]	1 [5.0%]	0.349
Dyslipidemia	3 [15.0%]	8 [40.0%]	2 [10.0%]	0.029 *
Family history for HCM	0 [0.0%] $^{\alpha}$	7 [35.0%]	0 [0.0%]	0.003 **
Family history for SCD	0 [0.0%]	3 [15.0%]	0 [0.0%]	0.106
Angina	0 [0.0%]	4 [20.0%]	2 [10.0%]	0.108
Syncope	0 [0.0%]	1 [5.0%]	2 [10.0%]	0.349
Palpitations	1 [5.0%]	2 [10.0%]	1 [5.0%]	0.765
Dyspnea	0 [0.0%] $^{\beta}$	8 [40.0%]	3 [15.0%]	0.004 **
Systolic blood pressure (mmHg)	120 [110–134]	144 [124–151]	130 [125–141]	0.128
Diastolic blood pressure (mmHg)	72 [68–84]	81 [75–90]	78 [70–81]	0.245
Electrocardiographic parameters				
Heart rate (bpm)	71 [60–74] $^{\beta,\delta}$	58 [55–62]	59 [53–63]	0.004 **
PR interval (ms)	152 [139–178] $^{\alpha}$	167 [155–201]	164 [144–165]	0.035 *
QRS interval (ms)	91 [89–97]	101 [92–106]	100 [92–107]	0.061
QTc interval (ms)	413 [390–425] $^{\gamma,\varepsilon}$	441 [427–460] †	419 [407–435]	0.003 ***
Echocardiographic parameters				
LVEDDi (mm/m2)	25.28 [23.05–26.69]	23.34 [22.08–24.40]	22.85 [21.47–25.88]	0.101
LA diameter (mm)	31 [28–35] $^{\gamma,\varepsilon}$	44 [41–46] †	38 [33–42]	<0.001 ***
Maximal wall thickness (mm)	9 [8–10] $^{\gamma,\zeta}$	18 [17–22]	17 [15–20]	<0.001 ***
LVEDVi (ml/m2)	56.03 [48.67–59.83]	52.17 [47.84–60.09]	48.54 [44.23–55.51]	0.190
LVEF (%)	59 [56–62] $^{\gamma,\zeta}$	70 [65–72] †	65 [64–68]	<0.001 ***
E/A ratio	1.43 [0.92–1.90]	1.18 [0.94–1.51]	1.36 [1.14–1.40]	0.654
DT (ms)	192 [168–233] $^{\beta}$	238 [219–289] $^{\mid}$	199 [174–223]	0.006 **
E/e' medium	5.20 [4.51–5.75] $^{\gamma,\zeta}$	12.93 [10.39–16.17] $^{\mid}$	9.56 [7.98–12.81]	<0.001 ***
TAPSE (mm)	24 [22–25] $^{\beta}$	22 [21−22] ‡	25 [24–26]	<0.001 ***
SPAP (mmHg)	23 [20–25] $^{\alpha}$	29 [25–30] $^{\mid}$	25 [21–28]	0.022 *
Pharmacological therapy				
Beta-blockers	1 [5.0%] $^{\gamma,\varepsilon}$	16 [80.0%]	11 [55.0%]	<0.001 ***
Ranolazine	0 [0.0%]	1 [5.0%]	0 [0.0%]	0.362
Calcium channel blockers	0 [0.0%]	2 [10.0%]	4 [20.0%]	0.108
ACEi/ARBs	1 [5.0%]	4 [20.0%]	4 [20.0%]	0.308

ACEi/ARBs: angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, BMI: body mass index, DT: deceleration time, LA: left atrial, LVEDDi; left ventricular end-diastolic diameter index, LVEDVi: left ventricular end-diastolic volume index, LVEF: left ventricular ejection fraction, SCD: sudden cardiac death, SPAP: systolic pulmonary arterial pressure, TAPSE: tricuspid annular plane systolic excursion.
Pairwise significance between groups:
- Control vs Obstructive HCM: 'α' ⇒ $p \leq 0.05$, 'β' ⇒ $p \leq 0.01$, 'γ' ⇒ ≤ 0.001.
- Control vs Non-obstructive HCM: 'δ' ⇒ $p \leq 0.05$, 'ε' ⇒ $p \leq 0.01$, 'ζ' ⇒ ≤ 0.001.
- Obstructive HCM vs Non-obstructive HCM: '|' ⇒ $p \leq 0.05$, '†' ⇒ $p \leq 0.01$, '‡' ⇒ ≤ 0.001.

Table 2
Conventional echocardiographic characteristics of 6 patients with obstructive hypertrophic cardiomyopathy before and after mavacamten treatment.

Variable	Baseline	3-year mavacamten	P value
LVOT gradient	90 [75–106]	5 [3–7]	0.031*
LVEDV (mL)	108 [86–116]	128 [125–131]	0.031*
LVEF (%)	68 [66–70]	64 [64–65]	0.036*
E/e' medium	17 [13.5–18.3]	13.1 [10.3–14.7]	0.220

LVOT: left ventricular outflow tract, LVEDVi: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction.

difference between baseline and 3-year mavacamten treatment.

Interobserver variability of HDFs quantification was evaluated by repeated evaluation on the same images by a second operator, blind to the previous results, for all subjects. Intraclass correlation coefficient (ICC) was then derived. An ICC value between 0.5 and 0.75 indicates moderate reliability, a value between 0.75 and 0.9 good reliability and a value greater than 0.90 excellent reliability. All tests were 2-tailed and a p value of ≤ 0.05 was considered statistically significant. Statistical analysis was conducted using R software, version 4.3.1 (R Foundation for Statistical Computing).

3. Results

3.1. Population characteristics

Forty patients with HCM (20 obstructive and 20 non-obstructive) and 20 healthy subjects were analyzed. Table 1 shows the demographic, clinical, electrocardiographic and echocardiographic characteristics of our cohort. Median age of HCM patients was 56 [46–63] years and 50 [35–66] years for controls ($p = 0.385$). There were no differences in terms of male prevalence ($p = 0.435$) and cardiovascular risk factors, except for dyslipidemia and overweight which were more prevalent in HCM patients. In 20 of the 40 HCM patients, a pathogenic or likely pathogenic variant was detected (12 *MYBPC3*, 6 *MYH7 and* 2 in other genes). Among HCM patients, those with oHCM exhibited a larger left atrium, higher LVEF, systolic pulmonary arterial pressure (sPAP) and E/e' ratio compared to noHCM patients.

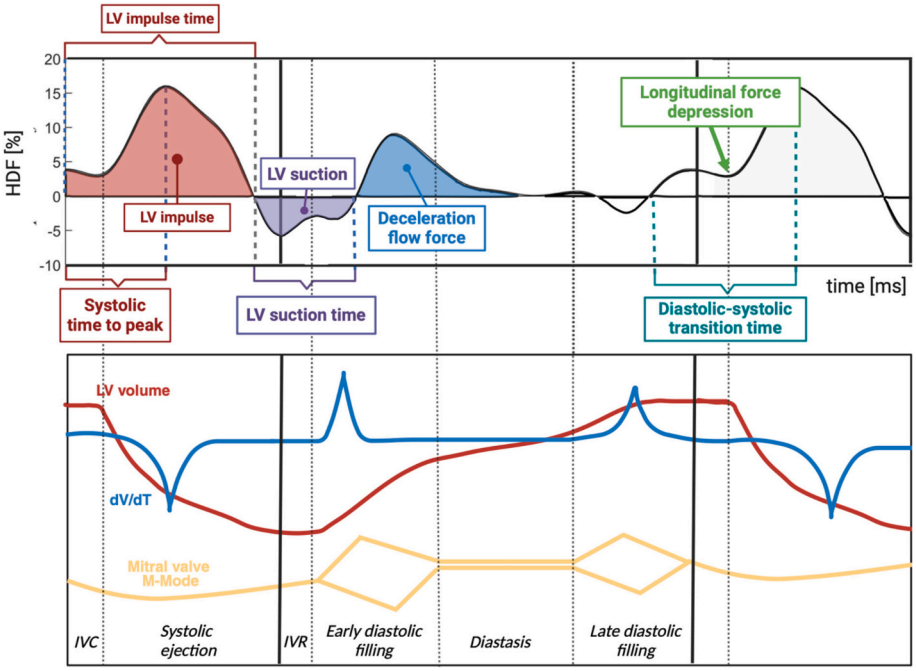

Fig. 1. Graphical representation of hemodynamic forces (HDFs) parameters.
The temporal evolution of left ventricular (LV) hemodynamic forces (HDFs) throughout the cardiac cycle (*top panel*), alongside the different phases of cardiac cycle (*bottom panel*) is represented. In the top panel, the y-axis represents HDF magnitude as a percentage (%) of gravity acceleration, normalized to fluid density. Positive deflections correspond to forces directed from the LV apex to the base, whereas negative deflections indicate forces directed toward the apex. The x-axis represents time (ms). The red-shaded area corresponds to LV impulse, the systolic propulsive force. The blue-shaded area represents diastolic forces, including LV suction and deceleration flow force. The purple-shaded area reflects the transition from systole to diastole, marked by LV suction. In the bottom panel, the LV volume (*red line*), its rate of change (dV/dT, *blue line*), and mitral valve motion (*yellow line*) are plotted across different cardiac phases.
dV/dT, rate of change of LV volume over time; HDF, hemodynamic force; IVC, isovolumic contraction; IVR, isovolumic relaxation; LV, left ventricle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. HDF analysis in HCM patients compared to healthy subjects

All HDF-derived parameters demonstrated excellent interobserver reproducibility (**Supplementary Table 1**).

The HDFs characteristics of oHCM, noHCM patients, and healthy controls are listed in Table 3. HCM and healthy subjects differed in several HDF-derived parameters, during both the systolic and diastolic phases of the cardiac cycle.

HCM patients exhibited a shorter systolic time to peak index (0.23 [0.21–0.24]) compared to controls (0.27 [0.25–0.31], $p < 0.001$). Similarly, LV impulse time was shorter in HCM patients (0.29 [0.26–0.32]) than controls (0.35 [0.31–0.37], $p < 0.001$) but similar in terms of intensity (16.24% [12.26–20.01] vs. (15.32% [13.05–21.95], $p = 0.624$). This shorter time interval was evident also in transition between diastole and systole and numerically expressed by a reduced diastolic-systolic transition time index in the HCM cohort (0.22 [0.21–0.25]) compared to controls (0.26 [0.25–0.29], $p < 0.001$). Conversely, LV suction was longer (0.26 [0.22–0.29] vs. 0.24 [0.22–0.28], $p = 0.029$) but less pronounced in HCM patients compared to healthy subjects (5.95% [4.93–8.81] vs. 8.99% [6.97–12.03], $p < 0.001$). Such impairment was maintained during the early diastolic filling period, where the amplitude of the positive DFF was severely reduced in HCM compared to controls (2.78% [1.86–4,12] vs. 5.21% [4.56–7.35], $p < 0.001$). Finally, LFD was consistently apparent in healthy controls whilst this feature was virtually absent in HCM; in numerical terms the amplitude of LFD was 0% (0.00–1.01) in HCM patients vs 4.05% (2.23–7.90, $p < 0.001$) in controls. All the aforementioned changes in the profile of hemodynamic curves between HCM

Table 3
Hemodynamic forces analysis comparing healthy subjects and patients with hypertrophic cardiomyopathy.

Variable	Healthy subjects ($N = 20$)	Obstructive HCM (N = 20)	Non-obstructive HCM (N = 20)	P value
Depression of longitudinal force before systolic thrust (%)	4.05 [2.23–7.90] $^{\gamma,\varepsilon}$	0.00 [0.00–0.00]	0.00 [0.00–1.42]	<0.001***
LV impulse (%)	15.32 [13.05–21.95]	14.56 [11.93–17.73]	17.92 [13.56–20.34]	0.265
LV suction (%)	8.99 [6.97–12.03] $^{\gamma}$	5.53 [4.62–6.10] $^{|}$	7.76 [5.66–9.00]	<0.001***
Deceleration flow force (%)	5.21 [4.56–7.35] $^{\gamma,\delta}$	2.24 [1.49–2.71] ‡	4.02 [3.00–5.32]	<0.001***
Diastolic-systolic transition time index*	0.26 [0.25–0.29] $^{\gamma,\varepsilon}$	0.22 [0.20–0.24]	0.23 [0.21–0.25]	<0.001***
Systolic time to peak index*	0.27 [0.25–0.31] $^{\gamma,\varepsilon}$	0.22 [0.20–0.24]	0.23 [0.21–0.25]	<0.001***
LV impulse time index*	0.35 [0.31–0.37] $^{\gamma,\varepsilon}$	0.29 [0.24–0.32]	0.29 [0.27–0.32]	<0.001***
LV suction time index*	0.24 [0.22–0.28] $^{\alpha}$	0.28 [0.23–0.31]	0.24 [0.22–0.28]	0.030 *

HCM: hypertrophic cardiomyopathy; LV: left ventricular.
Pairwise significance between groups:
- Control vs Obstructive HCM: ‘α’ ⇒ $p \leq 0.05$, ‘β’ ⇒ $p \leq 0.01$, ‘γ’ ⇒ ≤ 0.001.
- Control vs Non-obstructive HCM: ‘δ’ ⇒ $p \leq 0.05$, ‘ε’ ⇒ $p \leq 0.01$, ‘ζ’ ⇒ ≤ 0.001.
- Obstructive HCM vs Non-obstructive HCM: ‘|’ ⇒ $p \leq 0.05$, ‘†’ ⇒ $p \leq 0.01$, ‘‡’ ⇒ ≤ 0.001.

* Time index parameters are dimensionless, as they are obtained by dividing the time interval (ms) by the total duration of the cardiac cycle (ms).

patients and controls are highlighted in Fig. 2.

3.3. HDF analysis in obstructive compared to non-obstructive HCM patients

Comparative analysis of HDF in oHCM and noHCM patients showed the subsequent results: first, systolic time to peak was shorter in oHCM compared to noHCM patients (0.13 [0.11–0.15] vs 0.16 [0.14–0.17] reflecting an earlier onset of the systolic phase and a fusion of late diastole and systolic thrust. Additionally, oHCM patients showed a less effective LV suction (respectively 5.53% [4.62–6.10] and 7.76% [5.66–9.00], p 0.027) and a less pronounced deceleration flow force (2.24% [1.49–2.71] and 4.02% [3.00–5.32], $p < 0.001$) compared to non-obstructive HCM patients. Finally, LV impulse did not differ between oHCM and noHCM (14.56% [11.93–17.73] and 17.92% [13.56–20.34], p 0.433). Except for time to systolic peak, other time parameters were similar between the two groups (Table 3).

3.4. HDF analysis in oHCM patients treated with mavacamten

Standard echocardiographic parameters of the 6 oHCM patients treated with mavacamten are summarized in Table 2. All patients received betablockers as background therapy. At 3-year follow-up, there was a marked reduction in resting LVOT gradient in all patients (90 [75–106] mmHg at baseline vs 5 [3–7] at 3-year follow-up, $p = 0.031$) and an increase in LV cavity dimensions, with mild reduction in LVEF (68% [66–70] vs 64% [64–65], $p = 0.036$). After three years of mavacamten treatment, several changes were observed compared to baseline in 6 oHCM patients (Table 4, **Graphical Abstract, Supplementary Fig. 1**).

LFD was virtually absent (0.00% [0.00–0.00]) at baseline whilst became consistently measurable and highly prominent on mavacamten treatment (median amplitude 5.05% [2.79–5.19], $p = 0.031$). Both systolic time to peak (0.16 [0.14–0.17] at baseline vs. 0.21 [0.20–0.22]) and diastolic-systolic transition time (0.22 [0.22–0.25] at baseline vs. 0.30 [0.27–0.30]) increased on treatment (p = 0.031 and $p = 0.030$ respectively). LV impulse intensity was significantly decreased by mavacamten (12.94% [12.25–17.11] at baseline vs. 8.84% [8.18–9.70] after 3 years, p = 0.031), whereas its duration was slightly prolonged (0.27 [0.25–0.28] at baseline vs. 0.36 [0.34–0.37] after 3 years; $p = 0.063$). Focusing on the systo-diastolic transition, no differences in LV suction were noted before and after treatment, neither in intensity (4.80% [4.58–7.01] vs. 4.14% [3.38–5.65], $p = 0.999$) nor in duration (0.30 [0.28–0.31] vs. 0.27 [0.27–0.36], p = 0.999). Finally, late-diastolic DFF was not affected by mavacamten treatment (2.78% [2.37–3.40] at baseline vs. 1.84% [1.33–3.39] after 3 years, $p = 0.563$).

Individual trajectories for all six mavacamten-treated patients are shown in **Supplementary Fig. 2.**

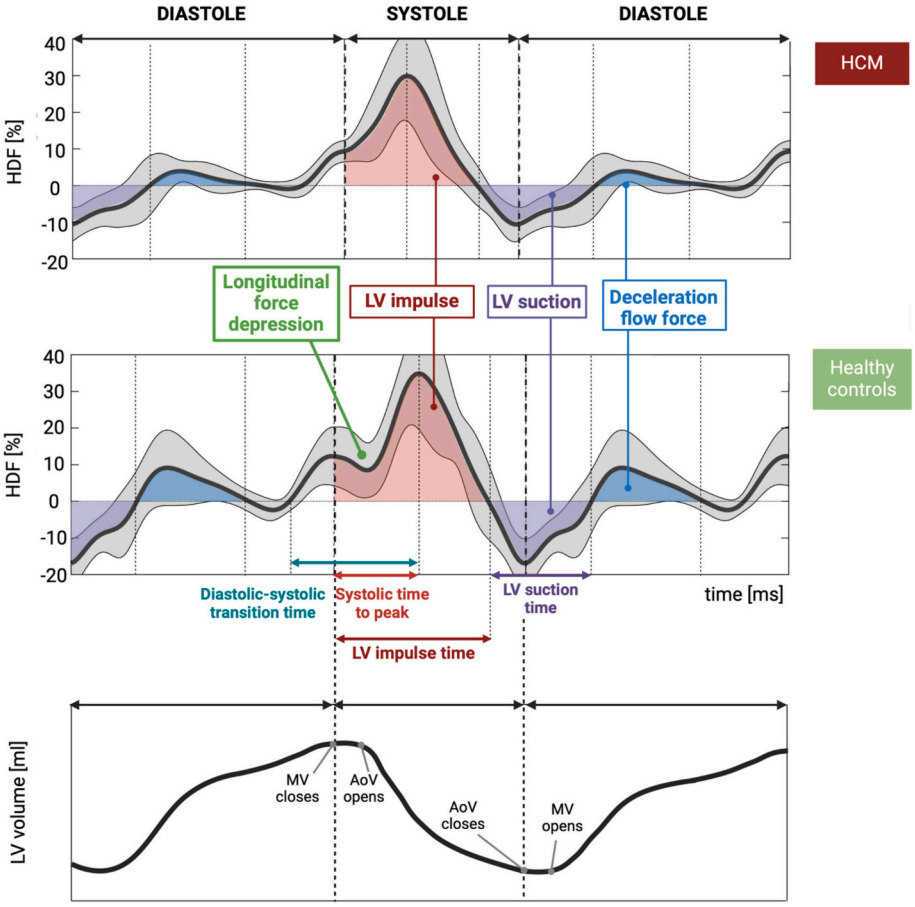

Fig. 2. HDF profiles in hypertrophic cardiomyopathy (HCM) and healthy controls.
HDF curves in healthy controls (*bottom panel*) display a characteristic longitudinal force depression before the onset of systolic thrust, a feature absent in HCM patients (*top panel*). Systolic time to peak and diastolic-systolic transition time are longer in controls, reflecting a more gradual force buildup. In contrast, HCM patients exhibit a premature systolic thrust and a shortened diastolic-systolic transition, indicating an increased clinotropic state. Deceleration flow force is significantly reduced in HCM, suggesting impaired diastolic function. The lower panel illustrates left ventricular (LV) volume changes throughout the cardiac cycle, synchronized with mitral and aortic valve events.
AoV, aortic valve; HCM, hypertrophic cardiomyopathy; HDF, hemodynamic force; LV, left ventricle; MV, mitral valve.

Table 4
Hemodynamic forces analysis of 6 patients with obstructive hypertrophic cardiomyopathy before and after mavacamten treatment.

Variable	Baseline	3-year mavacamten	Median Δ	P value
Depression of longitudinal force before systolic thrust (%)	0.00 [0.00–0.00]	5.05 [2.79–5.19]	+3.53	0.031 *
LV impulse (%)	12.94 [12.25–17.11]	8.84 [8.18–9.70]	−2.70	0.031 *
LV suction (%)	4.80 [4.58–7.01]	4.14 [3.38–5.65]	+0.04	0.999
Deceleration flow force (%)	2.78 [2.37–3.40]	1.84 [1.33–3.39]	−0.90	0.563
Diastolic-systolic transition time index*	0.22 [0.22–0.25]	0.30 [0.27–0.30]	+0.05	0.030 *
Systolic time to peak index*	0.16 [0.14–0.17]	0.21 [0.20–0.22]	+0.05	0.031 *
LV impulse time index*	0.27 [0.25–0.28]	0.36 [0.34–0.37]	+0.08	0.063
LV suction time index*	0.30 [0.28–0.31]	0.27 [0.27–0.36]	−0.01	0.999

LV: left ventricular.
* Time index parameters are dimensionless, as they are obtained by dividing the time interval (ms) by the total duration of the cardiac cycle (ms).

4. Discussion

The main finding of our study is that HCM is characterized by specific hemodynamic features occurring at the diastole-systole transition and early systole, including earlier systolic thrust, increased clinotropism (i.e. velocity of shortening) and loss of the negative deflection evident in healthy subjects. These features are most evident in HCM patients with dynamic obstruction and are considerably mitigated by mavacamten treatment, accounting for the clinical and hemodynamic efficacy of such treatment.

By non-invasive HDF analysis, we identified a number of distinctive hemodynamic features characterizing HCM patients from healthy controls (Fig. 3). Firstly, the hallmark of "normal" HDF shape in our cohort - i.e. the appearance of a notch before the onset of systolic thrust, defined as LFD - was virtually absent in HCM curves. In addition, compared to controls, HCM patients exhibited reduced diastolic-systolic transition time, systolic time to peak and LV impulse time (all $p < 0.001$). These findings consistently reflect an earlier onset of systolic thrust and an increased clinotropism - or higher rate of force generation - in HCM compared to controls, and represent the hemodynamic equivalent of excessive sarcomere activation [13].

HDF systolic profiles were similar between oHCM and noHCM, with the exception of time to systolic peak. Diastolic HDF profiles were also distinctly abnormal in HCM patients, with prolonged time intervals and weaker diastolic forces when compared to controls. These parameters, however, were not significantly affected by mavacamten. Overall, these novel results highlight a peculiar hemodynamic profile of HCM, with relatively minor differences between oHCM and noHCM, constituting a global pathophysiological fingerprint of its molecular underpinnings. These findings advance our understanding of HCM mechanics and support the view of a common treatment strategy for HCM, based on myosin modulation, irrespective of an obstructive milieu [14,15]. Such hypothesis is currently being tested in Phase 3 studies (ACACIA-HCM, NCT06081894; ODISSEY-HCM, NCT05582395).

4.1. Rationale for relief of outflow gradient by Mavacamten

Loss of a clear mechanical separation between the end of diastole and onset of systole, as demonstrated by reduced diastolic length in cardiomyocytes from HCM patients [16], could be interpreted as a relevant mechanism promoting SAM. The premature onset of systolic thrust - reflected by the absence of LFD - at a crucial point of cardiac cycle, when the greater surface area of mitral leaflets is still exposed to the flow drag forces directed from the apex to the aorta while the valve remains closed, is a plausible substrate for LVOTO [17]. HDF analysis performed on HCM patients after 3 years of mavacamten treatment revealed a noticeable normalization of the transition from diastole to systole and consequent reappearance of LFD. In line with this finding, the systolic time to peak returned to a level similar to that of healthy controls. These findings generate the following hypothesis: mitral valve (MV) closure occurs during the final phase of diastole, finalized by the onset of the longitudinal force at early systole. When the end of diastole is fused with the onset of systole, in the presence of an increased clinotropism, the outflow force exerts a suction effect on the surface of the leaflets, inducing SAM. These findings further clarify the late-diastolic and early-systolic mechanisms leading to SAM previously suggested by vector flow mapping studies [18]. Furthermore, these findings are consistent with earlier cellular-level evidence for another drug, disopyramide, which has been shown to reduce early left ventricular ejection flow acceleration (similar to delaying the initiation of systolic thrust) [19]. Conversely, they may be considered contradictory to historical evidence suggesting that right ventricular pacing positively affects LVOTO by reducing native PR interval duration [20]. However, a direct comparison of pre-ejection period between ECG intervals and HDF times is not feasible due to the lack of an established correlation between them. Future research needs to address this issue. Whether conventional HCM therapies such as beta-blockers or calcium channel blockers influence HDF patterns remains unknown; recent findings from MAPLE-HCM showing no reduction in LVOT gradient with metoprolol suggest a limited impact on early systolic forces [21], underscoring the interest of future studies exploring their effects on HDF.

The lack of significant changes in diastolic HDF parameters after mavacamten might be interpreted in light of the distinct mechanisms governing early and late diastole [22]. Mavacamten reduces the number of ON-state myosin heads and accelerates cross-bridge detachment, thereby improving the active phase of relaxation [22], consistent with the recent observed reduction in E/e' without major changes in transmitral filling patterns [23]. In contrast, diastolic HDFs predominantly reflect the passive phase of diastole, which depends on residual cross-bridges, strain-dependent myosin recruitment, myocardial stiffness, and LV geometry. These structural determinants did not substantially change in our cohort, as indicated by stable LV end-diastolic volumes and by the mild baseline diastolic impairment typical of early, less remodeled HCM phenotypes, partly a consequence of the strict exclusion criteria required for reliable HDF analysis. Larger cohorts and longer follow-up will be needed to determine whether prolonged myosin inhibition can modify passive diastolic mechanics reflected by HDF.

On treatment, the coaptation point of MV is located more posteriorly, due to the later onset of contraction, and leaflets become less prone to SAM. Notably, other advanced techniques such as deformation imaging have been explored in mavacamten-treated patients and have demonstrated an overall improvement in myocardial function after treatment [24] but they do not provide sufficient pathophysiological insights on the mechanisms of LVOTO relief. However, it should be noted that, given the small sample size and the observational nature of this analysis, our findings cannot establish a causal relationship between delayed systolic thrust and the prevention of SAM and LVOTO. These mechanistic insights should therefore be interpreted as hypothesis-generating and warrant confirmation in larger prospective studies.

4.2. Pathophysiology of HDF forces in HCM

The earlier onset of systolic thrust, reduced systolic time to peak and reduced LV impulse time all reflect the excess number of actin-myosin cross-bridges recruited in HCM patients compared to normal myocardium [13,16,25]. However, the higher rate of cross-bridges recruitment

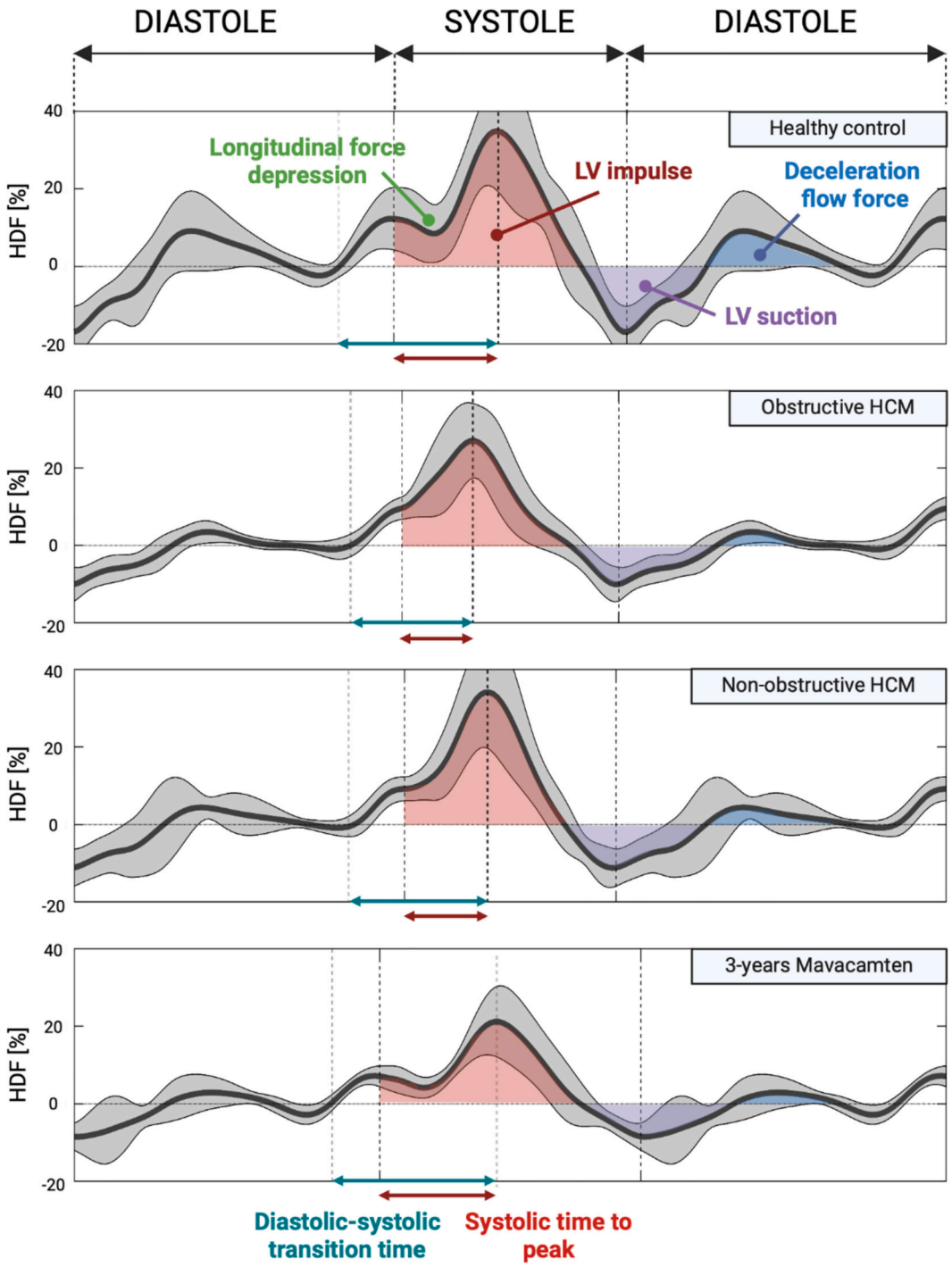

Fig. 3. HDF profiles in healthy, HCM, and mavacamten-treated patients.
This figure compares hemodynamic force (HDF) curves among healthy controls, obstructive hypertrophic cardiomyopathy (oHCM), non-obstructive HCM (noHCM), and patients after three years of mavacamten treatment. Healthy controls exhibit a longitudinal force depression (LFD) before systolic thrust, along with prolonged diastolic-systolic transition time (DSTT) and systolic time to peak (STP). In oHCM, these time intervals are shortened, and LFD is absent, indicating premature systolic thrust initiation. NoHCM shares similar alterations. After mavacamten treatment, the DSTT and STP increase, and LFD reappears, resembling the pattern seen in healthy controls. These findings suggest that mavacamten modulates left ventricular (LV) mechanical function, restoring more physiological HDF patterns.
HCM, hypertrophic cardiomyopathy; HDF, hemodynamic force; LV, left ventricle; noHCM, non-obstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy.

over time does not translate into a more effective systolic thrust as expressed by a similar LV impulse intensity between HCM and controls ($p = 0.395$). Such data suggests that, despite the hypercontractile nature of the HCM myocardium, structural alterations such as myofibrillar disarray or interstitial fibrosis may act to cause a dispersion of the main longitudinal force, affecting systolic thrust. This has been reported in subanalysis of the VALOR trial where HCM patients - despite a hyperdynamic LVEF - showed an abnormally decreased global longitudinal strain at baseline [26]. This proves once more that LVEF alone is insufficient to define the efficiency and functionality of LV in the setting of HCM.

HDF systolic profiles were similar between oHCM and noHCM, with

the exception of time to systolic peak which was shorter in oHCM; these findings support a common pathophysiological alteration in global forces exchanged between blood and endocardium in HCM patients. Conversely, LV outflow obstruction is more dependent on anatomical and geometrical features [27].

Diastolic HDF profiles in HCM patients were also distinctly abnormal, with prolonged time intervals and weaker diastolic forces when compared to controls. Specifically, LV suction, which here encompasses late systole and early diastole, was markedly prolonged but less pronounced in this setting compared to controls, likely reflecting a relaxation impairment from the very beginning of diastole. Such impairment was maintained during the early diastolic filling period, where the amplitude of the positive DFF was severely reduced in HCM compared to healthy subjects. These findings are consistent with the hypothesis that excitation-contraction-relaxation coupling is impaired in HCM.

4.3. Limitations

Limitations of this study include the retrospective and single-centre design that limits its statistical power due to the modest sample size. As a result, the capacity to detect significant differences is reduced and the broader applicability of these exploratory findings must be interpreted with caution. Selection bias represents another potential limitation, as only patients who met the predefined inclusion criteria and possessed echocardiographic images suitable for robust analysis were included. Although inter-observer reproducibility in our study was found to be excellent (see **Supplementary Table 1**), the reliability of HDF analysis continues to depend on both the quality of the images and the proficiency of the operator. The lack of a 3-year follow-up analysis in healthy controls and untreated HCM limits the ability to distinguish treatment-related changes from the natural course of the disease. No corrections for multiple comparisons were applied, which should be considered when interpreting the results, in light of the exploratory nature of the study. However, this pilot study aims to evaluate the role of a new imaging tool and its potential to enhance our understanding of disease mechanisms and treatment efficacy. A 3-year evaluation was not conducted for both the healthy and HCM populations who were not treated with mavacamten, as the scope of the study was to characterize differences in LV HDF patterns among patients with both oHCM and noHCM, compared to healthy controls. Additionally, in the oHCM population, septal reduction therapy was considered during follow-up, since earlier interventions are associated with lower complication rates and better prognosis [28], making it challenging to reanalyse such patients in the same condition after 3 years. Finally, the absence of a morphological assessment by cardiac magnetic resonance for all patients precluded a comparison between HDF parameters and myocardial tissue abnormalities.

5. Conclusion

HDF analysis revealed a previously underappreciated mechanical signature of HCM – earlier systolic thrust initiation, loss of LFD, and impaired diastolic forces - that appear largely independent of obstructive physiology. By complementing conventional imaging, this approach provides a mechanistic perspective on the hemodynamic substrate predisposing to SAM and LVOTO. In the small exploratory cohort treated with mavacamten, HDF parameters consistently shifted toward normalization, with delayed systolic thrust and re-emergence of LFD, offering mechanistic, hypothesis-generating insights into the effects of myosin inhibition. Taken together, these findings highlight the potential of HDF analysis as a clinically relevant adjunct for phenotyping, risk stratification, and therapeutic monitoring in HCM.

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CRediT authorship contribution statement

Chiara Zocchi: Writing – original draft, Data curation, Conceptualization. **Alessandra Milazzo:** Writing – original draft, Data curation, Conceptualization. **Giorgia Panichella:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Manuel Garofalo:** Writing – review & editing, Methodology, Data curation. **Angela I. Fanizzi:** Writing – review & editing, Formal analysis, Data curation. **Maddalena Ragagnin:** Writing – review & editing, Formal analysis, Data curation. **Raffaele Coppini:** Writing – review & editing, Supervision, Methodology. **Raymond H. Chan:** Validation, Supervision, Methodology. **Mattia Zampieri:** Visualization, Validation, Data curation. **Francesco Cappelli:** Visualization, Validation, Supervision. **Maurizio Pieroni:** Visualization, Validation, Supervision. **Gianni Pedrizzetti:** Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Iacopo Olivotto:** Writing – review & editing, Validation, Supervision, Data curation, Conceptualization. **Annamaria Del Franco:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2026.134175.

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