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Effects of Mavacamten on Measures of Cardiopulmonary Exercise Testing Beyond Peak Oxygen Consumption

A Secondary Analysis of the EXPLORER-HCM Randomized Trial

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IMPORTANCE Mavacamten, a cardiac myosin inhibitor, improved peak oxygen uptake (pVO_2) in patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM) in the EXPLORER-HCM study. However, the full extent of mavacamten's effects on exercise performance remains unclear.

OBJECTIVE To investigate the effect of mavacamten on exercise physiology using cardiopulmonary exercise testing (CPET).

DESIGN, SETTING, AND PARTICIPANTS Exploratory analyses of the data from the EXPLORER-HCM study, a randomized, double-blind, placebo-controlled, phase 3 trial that was conducted in 68 cardiovascular centers in 13 countries. In total, 251 patients with symptomatic obstructive HCM were enrolled.

INTERVENTIONS Patients were randomly assigned in a 1:1 ratio to mavacamten or placebo.

MAIN OUTCOMES AND MEASURES The following prespecified exploratory cardiovascular and performance parameters were assessed with a standardized treadmill or bicycle ergometer test protocol at baseline and week 30: carbon dioxide output (VCO_2), minute ventilation (V_E), peak V_E/VCO_2 ratio, ventilatory efficiency (V_E/VCO_2 slope), peak respiratory exchange ratio (RER), peak circulatory power, ventilatory power, ventilatory threshold, peak metabolic equivalents (METs), peak exercise time, partial pressure of end-tidal carbon dioxide ($PETCO_2$), and VO_2/workload slope.

RESULTS Two hundred fifty-one patients were enrolled. The mean (SD) age was 58.5 (11.9) years and 59% of patients were male. There were significant improvements with mavacamten vs placebo in the following peak-exercise CPET parameters: peak V_E/VCO_2 ratio (least squares [LS] mean difference, −2.2; 95% CI, −3.05 to −1.26; $P < .001$), peak METs (LS mean difference, 0.4; 95% CI, 0.17-0.60; $P < .001$), peak circulatory power (LS mean difference, 372.9 mL/kg/min × mm Hg; 95% CI, 153.12-592.61; $P = .001$), and peak $PETCO_2$ (LS mean difference, 2.0 mm Hg; 95% CI, 1.12-2.79; $P < .001$). Mavacamten also improved peak exercise time compared with placebo (LS mean difference, 0.7 minutes; 95% CI, 0.13-1.24; $P = .02$). There was a significant improvement in nonpeak-exercise CPET parameters, such as V_E/VCO_2 slope (LS mean difference, −2.6; 95% CI, −3.58 to −1.52; $P < .001$) and ventilatory power (LS mean difference, 0.6 mm Hg; 95% CI, 0.29-0.90; $P < .001$) favoring mavacamten vs placebo.

CONCLUSIONS AND RELEVANCE Mavacamten improved a range of CPET parameters beyond pVO_2, indicating consistent and broad benefits on maximal exercise capacity. Although improvements in peak-exercise CPET parameters are clinically meaningful, the favorable effects of mavacamten on submaximal exertional tolerance provide further insights into the beneficial impact of mavacamten in patients with obstructive HCM.

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Visual Abstract

Supplemental content

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Hypertrophic cardiomyopathy (HCM) is a complex disease that is caused by excessive cardiac myosin-actin cross-bridging with core pathophysiologic features that include left ventricular hypertrophy, hypercontractility, and multifactorial diastolic dysfunction.[1-5] Consequently, HCM can be a debilitating disease resulting in impaired functionality and quality of life.[6] The most common symptoms of HCM are dyspnea, fatigue, palpitations, chest pain, lightheadedness, and syncope.[7] The burden of disease experienced by patients includes limitations to physical activity and daily activities, negative effects on emotional state, and adverse effects on work productivity.[7]

Cardiopulmonary exercise testing (CPET) is a useful, noninvasive tool to assess functional capacity and understand the underlying mechanisms of exercise intolerance. Given that most patients with HCM do not exercise or exert themselves to peak exercise capacity, the ability of CPET to assess both peak and submaximal exercise responses makes it a unique and powerful indicator of what a patient can physically achieve in their daily activities.[8,9] Furthermore, CPET is a valuable method to estimate prognosis in patients with HCM.[10] Indeed, peak oxygen uptake (pVO_2), and ventilatory efficiency (minute ventilation [V_E]/carbon dioxide output [VCO_2] slope) have been independently associated with overall mortality, death due to heart failure, sudden cardiac death, heart transplant, and functional deterioration.[11-15] Furthermore, circulatory power has been shown to be an independent predictor of death or hospitalization due to heart failure, heart transplant, and progression to New York Heart Association (NYHA) functional class III or IV.[15]

Mavacamten is a first-in-class, small-molecule, selective inhibitor of cardiac myosin that targets the underlying pathophysiology of HCM.[16,17] In the EXPLORER-HCM study (NCT03470545), treatment with mavacamten led to significant and clinically meaningful improvements in symptoms, functional capacity, left ventricular outflow tract (LVOT) gradients, biomarkers, and key aspects of quality of life in patients with symptomatic obstructive HCM.[18] More specifically, mavacamten was associated with a significant improvement in pVO_2 at week 30 compared with placebo.

The objective of this prespecified exploratory analysis of EXPLORER-HCM was to evaluate additional maximal and submaximal parameters from CPET, beyond pVO_2, to examine the effects of mavacamten on exercise physiology in patients with obstructive HCM, and to expand our understanding of this disease.

Key Points

Question What are the effects of mavacamten on peak and submaximal cardiopulmonary exercise testing (CPET) parameters?

Findings This prespecified exploratory analysis of the EXPLORER-HCM study shows that mavacamten improved a range of CPET parameters beyond peak oxygen uptake, including measures at both peak and subpeak exercise.

Meaning The favorable effect of mavacamten on submaximal exertional tolerance provides further insights into the beneficial impact of mavacamten.

Methods

Study Design

The details of the EXPLORER-HCM trial design and primary results have been reported elsewhere.[18,19] The trial protocol and statistical analysis plan are available in Supplement 2 and Supplement 3, respectively. In brief, EXPLORER-HCM was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. Patients were randomized 1:1 to receive mavacamten (starting dose, 5 mg) or placebo for 30 weeks. Study drug (mavacamten or matching placebo, which were identical in appearance) was labeled with a unique identifying number that was assigned to a patient through the interactive response system. The principal investigator, site staff, and participants were masked. Randomization was stratified by current β-blocker use (yes or no), NYHA functional class (II or III), ergometer type (treadmill or bicycle), and consent for cardiovascular magnetic resonance imaging substudy (yes or no). Key inclusion criteria included being 18 years of age or older, having a diagnosis of obstructive HCM (unexplained left ventricular hypertrophy with maximal left ventricular wall thickness of 15 mm or more [or 13 mm or more with a family history of HCM]), having at least 1 peak LVOT gradient of 50 mm Hg or higher at rest or with provocation (Valsalva maneuver or after exercise), having a Valsalva LVOT gradient of at least 30 mm Hg, having a left ventricular ejection fraction of at least 55%, and being able to perform upright CPET with a respiratory exchange ratio (RER) of 1.0 or more or between 0.91 and 1.0 if peak exercise was achieved, as assessed by the core laboratory. Key exclusion criteria included a history of syncope or sustained ventricular tachyarrhythmia with exercise in the 6 months before screening, atrial fibrillation present at screening, and treatment or planned treatment with disopyramide, ranolazine, or a combination of β-blockers and nondihydropyridine calcium channel blockers.

Outcomes and Data Collection

CPET was conducted using a standardized treadmill or bicycle ergometer test protocol at screening and at week 30 prior to dosing with the study drug. The same modality (treadmill or upright bicycle) and the same time of day (as much as possible) were used for all CPET assessments conducted for a given patient. The treadmill protocol was a modified Naughton protocol and the cycle ergometer protocol was an incremental protocol with increases in work rate of 25 watts every 2 minutes. Site technicians were trained and certified for the protocol and followed a detailed CPET manual. Supine testing using a recumbent bicycle was not allowed and symptom-limited exercise tests were performed after a 4-hour fast. In addition to pVO_2, which was a component of the composite primary end point and a prespecified secondary efficacy end point, the following prespecified exploratory cardiovascular and performance parameters were assessed: VCO_2, minute ventilation (V_E), peak V_E/VCO_2 ratio, V_E/VCO_2 slope (determined from rest to peak exercise), peak RER, peak circulatory power

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(pVO_2 × peak systolic blood pressure), ventilatory power (peak systolic blood pressure/V_E/VCO_2 slope), peak metabolic equivalents (METs), partial pressure of end-tidal carbon dioxide ($PETCO_2$), peak exercise time, ventilatory threshold, and VO_2/workload slope. Per protocol, participants receiving β-blockers or calcium channel blockers should have been receiving the same dose at screening and at the end-of-treatment CPET, whenever possible, and these medications were administered prior to CPET. CPET data were analyzed centrally by the core laboratory (Cardiovascular and Metabolic Disease Research Institute, Mountain View, California). Reference values for some key CPET parameters are presented in eTable 1 in Supplement 1.

Statistical Analysis

The end points were summarized by treatment group and visit using descriptive statistics in the intention-to-treat population, defined as all randomized patients, regardless of whether they received the study drug. The estimates of treatment-group differences of the change from baseline to week 30 and the 95% CIs based on normal approximation were calculated. Between-group comparisons were based on analysis of covariance and all statistical tests were conducted at a 2-sided significance α level of .05. Treatment group (mavacamten vs placebo), baseline value of the corresponding end point of interest, and the 3 stratification factors (β-blocker use, NYHA class, and ergometer type) were treated as fixed effects. Least squares (LS) mean differences of the CPET parameters were tested separately and the *P* values generated from exploratory analyses were not adjusted for multiplicity and are considered to be nominal (descriptive). Owing to the low rate of discontinuation, missing data were not imputed. Post hoc correlations (pVO_2 vs N-terminal pro-brain natriuretic peptide [NT-proBNP], V_E/VCO_2 slope vs NT-proBNP, and V_E/VCO_2 slope vs Kansas City Cardiomyopathy Clinical Summary Score [KCCQ-CSS]) were analyzed in the intention-to-treat population using changes in mean values from baseline to week 30 for the relevant outcomes. Nominal *P* values were calculated for the test of correlations. SAS version 9.4 (SAS Institute) was used for statistical analyses.

Results

Patient Population

Patient demographics and baseline characteristics in the EXPLORER-HCM study have been described in detail previously and are presented in **Table 1**.[18,19] In summary, from May 30, 2018, to July 12, 2019, 429 patients were screened and 251 were randomized to receive mavacamten (n = 123) or placebo (n = 128) (**Figure 1**). The mean (SD) age of the patient population was 58.5 (11.9) years and 59% of patients were male. Most patients (183 of 251) had NYHA class II symptoms at baseline (73%) and most were receiving background HCM therapy (β-blockers: 94 of 123 patients for mavacamten [76%] and 95 of 128 patients for placebo [74%]; calcium channel blockers: 25 of 123 patients for mavacamten [20%] and 17 of 128 patients for placebo [13%]; Table 1). In both treatment arms, 45% of patients performed CPET using an exercise bicycle and 55% using a treadmill (Figure 1). Baseline CPET parameter values

Table 1. Demographics and Baseline Characteristics[a]

Demographics and baseline characteristics	No. (%)	
	Mavacamten (n = 123)	Placebo (n = 128)
Age, mean (SD), y	58.5 (12.2)	58.5 (11.8)
Sex		
Male	66 (54)	83 (65)
Female	57 (46)	45 (35)
Background HCM therapy		
β-Blocker	94 (76)	95 (74)
Calcium channel blocker	25 (20)	17 (13)
Neither	4 (3)	16 (13)
Heart rate, mean (SD), bpm	63 (10.1)	62 (10.6)
Blood pressure, mean (SD), mm Hg		
Systolic	128.4 (16.2)	128.4 (14.6)
Diastolic	75.5 (10.8)	76.1 (9.9)
NYHA functional class		
II	88 (72)	95 (74)
III	35 (28)	33 (26)
Peak-exercise CPET parameters, mean (SD)		
Peak VO_2, mL/kg/min	18.9 (4.9)	19.9 (4.9)
Peak V_E/VCO_2 ratio	35.4 (5.2)	34.2 (5.5)
Peak METs	5.4 (1.4)	5.7 (1.4)
Peak circulatory power, mL/kg/min × mm Hg	3087.1 (1165.2)	3284.8 (1173.3)
Peak exercise time, min	10.1 (4.0)	10.5 (4.2)
Peak RER	1.1 (0.1)	1.1 (0.1)
Peak $PETCO_2$, mm Hg	33.7 (4.5)	34.7 (5.1)
Nonpeak-exercise CPET parameters, mean (SD)		
V_E/VCO_2 slope	33.6 (6.2)	32.4 (6.2)
Ventilatory power, mm Hg	4.9 (1.4)	5.2 (1.5)
Ventilatory threshold (ie, anaerobic threshold), mL/kg/min	11.5 (2.3)	11.5 (2.6)
$PETCO_2$ at rest, mm Hg	32.5 (4.2)	33.0 (4.3)
VO_2/workload slope	0.75 (0.25)	0.76 (0.26)
Biomarkers, geometric mean (CV%), ng/L		
NT-proBNP	777 (136)	616 (108)
High-sensitivity cardiac troponin I	12.5 (208)	12.5 (373)
Echocardiographic parameters, mean (SD)		
LVOT gradient, mm Hg		
Rest	52 (29)	51 (32)
Valsalva	72 (32)	74 (32)
Postexercise	86 (34)	84 (36)

Abbreviations: bpm, beats per minute; CPET, cardiopulmonary exercise testing; CV, coefficient of variation; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; MET, metabolic equivalent; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; $PETCO_2$, partial pressure of end-tidal carbon dioxide; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; V_E, minute ventilation; VO_2, oxygen uptake.

[a] β-blocker use and NYHA function classification are based on information captured on electronic case report forms. The heart rate and SBP data presented here are from vital signs as opposed to the data presented in eTable 2 in Supplement 1, which present data measured during the CPET assessment.

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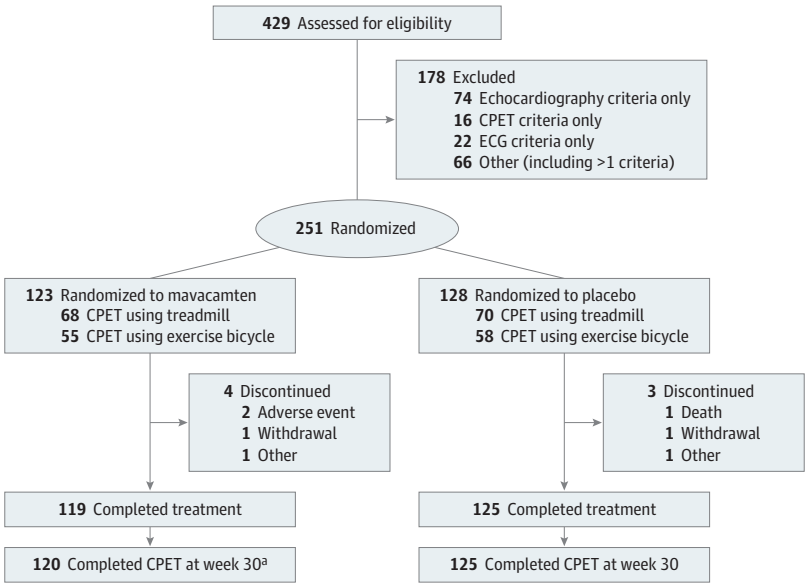
Figure 1. CONSORT Diagram



All randomized patients received at least 1 dose of study drug and were included in the efficacy analyses. Two patients who discontinued for other reasons (mavacamten, n = 1; placebo, n = 1) did not complete the week-30 visits within the window owing to scheduling issues. CPET indicates cardiopulmonary exercise testing; ECG, electrocardiogram.

[a] One patient discontinued treatment, but performed the CPET assessment at week 30.

were similar for both treatment groups (Table 1) and consistent with values reported previously for patients with HCM.[10,20] Heart rate and systolic blood pressure at rest and at peak exercise are summarized in eTable 2 in Supplement 1.

CPET Parameters

Peak-Exercise CPET Parameters

Compared with placebo, mavacamten improved peak V_E/VCO_2 ratio (LS mean difference, −2.2; 95% CI, −3.05 to −1.26; $P < .001$), peak METs (LS mean difference, 0.4; 95% CI, 0.17-0.60; $P < .001$), peak circulatory power (LS mean difference, 372.9 mL/kg/min × mm Hg; 95% CI, 153.12-592.61 mL/kg/min × mm Hg; $P = .001$), peak exercise time (LS mean difference, 0.7 minutes; 95% CI, 0.13-1.24 minutes; $P = .02$), and peak $PETCO_2$ (LS mean difference, 2.0 mm Hg; 95% CI, 1.12-2.79 mm Hg; $P < .001$) (**Figure 2**, **Table 2**). There was no significant difference between treatment groups in peak RER (LS mean difference, 0.02; 95% CI, −0.003 to 0.040; $P = .09$).

Nonpeak-Exercise CPET Parameters

Mavacamten was associated with a significant improvement in V_E/VCO_2 slope compared with placebo (LS mean difference, −2.6; 95% CI, −3.58 to −1.52; $P < .001$). There was a significant increase in ventilatory power (LS mean difference, 0.6 mm Hg; 95% CI, 0.29-0.90 mm Hg; $P < .001$) and in VO_2/workload slope (LS mean difference, 0.04; 95% CI, 0.002 to 0.09; $P = .04$), favoring mavacamten over placebo. Mavacamten also improved $PETCO_2$ at rest (LS mean difference: 0.8 mm Hg; 95% CI, 0.07-1.53 mm Hg; $P = .03$) compared with placebo. However, although there was no significant difference in VO_2 at the ventilatory threshold (LS mean difference, 0.6 mL/kg/min; 95% CI, −0.03 to 1.17 mL/kg/min; $P = .06$) between mavacamten and placebo in exploratory analyses that were not adjusted for multiplicity, a numerical trend toward improvement was observed (**Figure 3**; Table 2).

Correlation Between CPET Parameters and Other Variables

Additionally, the study team sought to determine the association between change in CPET measures and markers of disease severity, including NT-proBNP (a biomarker of cardiac wall stress) and KCCQ-CSS (a patient-reported outcome symptom score).[18,21] It should be noted that reductions in NT-proBNP levels were statistically significantly greater with mavacamten than with placebo.[18] In the mavacamten group, there was a negative correlation between change in pVO_2 and change in $\log_2$ NT-proBNP at week 30 (Pearson correlation coefficient, −0.30; $P = .002$), indicating that improvements in pVO_2 were associated with a decrease in NT-proBNP levels (eTable 3 in Supplement 1). Change in pVO_2 and change in $\log_2$ NT-proBNP levels at week 30 were not correlated in the placebo group (Pearson correlation coefficient, 0.064; $P = .48$). In the mavacamten group, there was a positive correlation between improvements in V_E/VCO_2 slope and reduction in NT-proBNP levels (Pearson correlation coefficient, 0.27; $P = .003$) (eTable 3 in Supplement 1). There were no significant correlations between improvement in V_E/VCO_2 slope and improvement in symptoms, as measured by the KCCQ-CSS, in either treatment group (eTable 3 in Supplement 1).

Discussion

Mavacamten was previously reported to improve pVO_2 in patients with obstructive HCM.[18] The present results indicate that treatment with mavacamten was also able to improve the exercise capacity of patients on a range of CPET parameters, including peak-exercise independent parameters, allowing us to deepen our understanding of the full extent of mavacamten effects on exercise tolerance. The novelty of our findings resides in the fine characterization of the exercise limitation observed in patients with obstructive HCM. Because CPET

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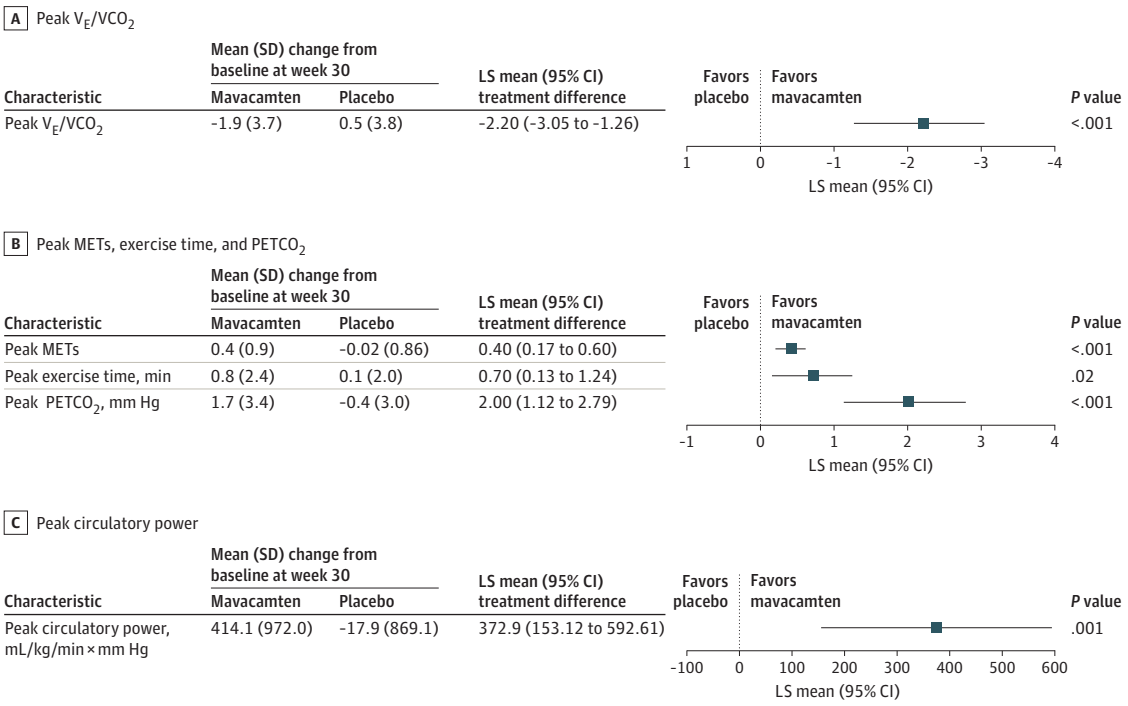
Figure 2. Treatment Difference of the Change From Baseline to Week 30 Between Mavacamten and Placebo in Peak-Exercise Cardiopulmonary Exercise Testing (CPET) Parameters



LS indicates least squares; MET, metabolic equivalent; $PETCO_2$, partial pressure of end-tidal carbon dioxide; VCO_2, carbon dioxide output; V_E, minute ventilation.

Table 2. CPET Parameters at Baseline, at Week 30, and Change From Baseline to Week 30

	Mavacamten			Placebo				
	Mean (SD) [No.]			Mean (SD) [No.]				
	Baseline (n = 123)	Week 30	Absolute difference (SD) [No.][b]	Baseline (n = 128)	Week 30	Absolute difference (SD) [No.][b]	Adjusted difference in difference (95% CI)[a]	*P* value
Peak-exercise CPET parameters								
Peak V_E/VCO_2 ratio	35.4 (5.2)	33.4 (4.8) [120]	−1.9 (3.7) [120]	34.2 (5.5)	34.7 (5.9) [125]	0.5 (3.8) [125]	−2.2 (−3.05 to −1.26)	<.001
Peak METs	5.4 (1.4)	5.8 (1.5) [120]	0.4 (0.9) [120]	5.7 (1.4)	5.7 (1.5) [125]	−0.02 (0.86) [125]	0.4 (0.17-0.60)	<.001
Peak circulatory power, mL/kg/min × mm Hg	3087.1 (1165.2)	3505.9 (1214.4) [119]	414.1 (972.0) [119]	3284.8 (1173.3)	3300.2 (1208.4) [124]	−17.9 (869.1) [121]	372.9 (153.12-592.61)	.001
Peak exercise time, min	10.1 (4.0)	10.9 (4.5) [120]	0.8 (2.4) [120]	10.5 (4.2)	10.6 (4.3) [125]	0.1 (2.0) [125]	0.7 (0.13-1.24)	.02
Peak RER	1.1 (0.1)	1.1 (0.1) [120]	0.0 (0.1) [120]	1.1 (0.1)	1.1 (0.1) [125]	0.0 (0.1) [125]	0.02 (−0.003 to 0.040)	.09
Peak $PETCO_2$, mm Hg	33.7 (4.5)	35.5 (4.8) [110]	1.7 (3.4) [106]	34.7 (5.1)	34.4 (5.2) [113]	−0.4 (3.0) [109]	2.0 (1.12-2.79)	<.001
Nonpeak-exercise CPET parameters								
V_E/VCO_2 slope	33.6 (6.2)	31.1 (5.0) [120]	−2.4 (4.6) [120]	32.4 (6.2)	32.9 (7.0) [125]	0.4 (4.1) [125]	−2.6 (−3.58 to −1.52)	<.001
Ventilatory power, mm Hg	4.9 (1.4)	5.6 (1.3) [119]	0.7 (1.4) [119]	5.2 (1.5)	5.3 (1.7) [124]	−0.03 (1.23) [121]	0.6 (0.29-0.90)	<.001
Ventilatory threshold (ie, anaerobic threshold), mL/kg/min	11.5 (2.3)	12.2 (2.7) [111]	0.7 (2.5) [106]	11.5 (2.6)	11.6 (2.6) [119]	0.1 (2.6) [116]	0.6 (−0.03 to 1.17)	.06
$PETCO_2$ at rest, mm Hg	32.5 (4.2)	33.2 (4.2) [109]	0.6 (3.0) [105]	33.0 (4.3)	32.7 (3.7) [113]	−0.3 (3.2) [108]	0.8 (0.07-1.53)	.03
VO_2/workload slope	0.75 (0.25)	0.79 (0.24) [118]	0.04 (0.17) [116]	0.76 (0.26)	0.76 (0.25) [123]	−0.02 (0.20) [123]	0.04 (0.002-0.086)	.04

Abbreviations: CPET, cardiopulmonary exercise testing; MET, metabolic equivalent; $PETCO_2$, partial pressure of end-tidal carbon dioxide; RER, respiratory exchange ratio; VCO_2, carbon dioxide output; V_E, minute ventilation; VO_2, oxygen uptake.

[a] The adjusted difference in difference corresponds to the LS mean treatment difference.

[b] The absolute difference corresponds to the change from baseline to week 30.

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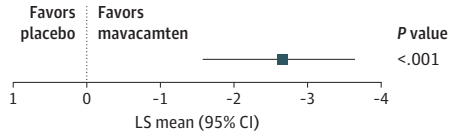
Figure 3. Treatment Difference of the Change From Baseline to Week 30 Between Mavacamten and Placebo in Submaximal Exercise Cardiopulmonary Exercise Testing (CPET) Parameters

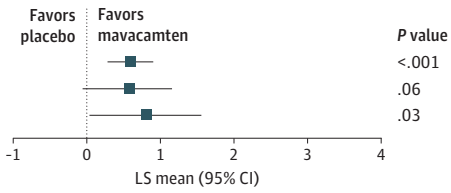
A V_E/VCO_2 slope

Characteristic	Mean (SD) change from baseline at week 30		LS mean (95% CI) treatment difference	P value
	Mavacamten	Placebo		
V_E/VCO_2 slope	-2.4 (4.6)	0.4 (4.1)	-2.60 (-3.58 to -1.52)	<.001



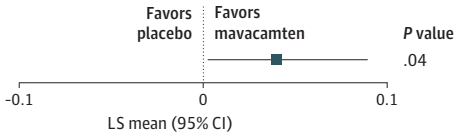
B Ventilatory power, ventilatory threshold, $PETCO_2$ at rest

Characteristic	Mean (SD) change from baseline at week 30		LS mean (95% CI) treatment difference	P value
	Mavacamten	Placebo		
Ventilatory power, mm Hg	0.7 (1.4)	-0.03 (1.23)	0.60 (0.29 to 0.90)	<.001
Ventilatory threshold, mL/kg/min	0.7 (2.5)	0.1 (2.6)	0.60 (-0.03 to 1.17)	.06
$PETCO_2$ at rest, mm Hg	0.6 (3.0)	-0.3 (3.2)	0.80 (0.07 to 1.53)	.03



C VO_2/workload slope

Characteristic	Mean (SD) change from baseline at week 30		LS mean (95% CI) treatment difference	P value
	Mavacamten	Placebo		
VO_2/workload slope	0.04 (0.17)	-0.02 (0.19)	0.04 (0.002 to 0.086)	.04



LS indicates least squares; $PETCO_2$, partial pressure of end-tidal carbon dioxide; VCO_2, carbon dioxide output; V_E, minute ventilation; VO_2, oxygen uptake.

parameters represent reproducible clinical surrogates for functional capacity, our findings suggest that mavacamten may potentially be associated with improvements in the ability of patients to perform physical activities.

Several factors have been identified as potential determinants of the exercise limitation in patients with HCM, including left ventricular diastolic and systolic dysfunction, LVOT obstruction, chronotropic incompetence, ventilation-to-perfusion mismatch, abnormal peripheral oxygen utilization, and the inability to increase stroke volume.[8,22-29] Invasive hemodynamic studies have confirmed left ventricular diastolic dysfunction as a cause of the inability to increase stroke volume, which seems to be exacerbated by LVOT obstruction.[25,28,30-32] The improvements in exercise capacity associated with mavacamten may be mediated by its beneficial effects on measures of diastolic function via an improved ability to increase stroke volume; however, further investigation is needed to confirm this hypothesis.[33-35] Furthermore, the reductions associated with mavacamten in peak V_E/VCO_2 ratio and in V_E/VCO_2 slope are indicative of improved ventilatory efficiency at peak and submaximal exercise, respectively. This may be due to a reduction in exercise-induced diastolic pressures and partial correction of the ventilation-to-perfusion mismatch exacerbated during exercise observed in patients with HCM.[13,36] Moreover, in patients with HCM, impaired ventilatory efficiency has been significantly associated with a composite end point of death, heart transplant, and implantation of a ventricular assist device.[12] Indeed, while V_E/VCO_2 slope of 30 or less might be considered normal, values more than 32 were shown to be powerful predictors of progression to heart failure.[10] Consequently, the reduction in mean V_E/VCO_2 slope from 33.6 to 31.1 associated with mavacamten is clinically meaningful. Additionally, a modest improvement was observed in peak $PETCO_2$ with mavacamten compared with placebo though not to the normal range (eTable 1 in Supplement 1). These associations suggest that mavacamten not only improved symptoms and functional capacity, but also has the potential to improve clinical outcomes.

Given that most patients with HCM do not routinely exercise to peak exercise capacity, submaximal exercise CPET parameters may reflect what patients can typically physically achieve better than peak exercise parameters. In this context, the improvements in V_E/VCO_2 slope, in ventilatory power, in VO_2/workload slope, and in $PETCO_2$ at rest may better reflect the improvement in submaximal cardiopulmonary efficiency that in turn translates to symptomatic benefits that patients are experiencing after treatment with mavacamten. These parameters could be examined by clinicians when performing CPET in patients with HCM.

Although no significant association between V_E/VCO_2 slope and patient-reported symptoms (KCCQ-CSS) was observed in the present study, Nassif et al[37] reported a significant correlation between pVO_2 and KCCQ-CSS in patients enrolled in the EXPLORER-HCM study. Furthermore, mavacamten has been associated with improvements in symptoms and health status in patients with obstructive HCM, as measured by NYHA functional classification and by the KCCQ, respectively.[18,21] These findings, together with the correlation observed between CPET parameters (pVO_2 and V_E/VCO_2 slope) and measures of the neurohormonal effect of disease (NT-proBNP

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levels) are evidence of the beneficial effect of mavacamten on the patients' daily lives.

Our findings suggest that the impaired exercise performance observed in patients with obstructive HCM is reversible with relief of the LVOT pressure gradient, which can be achieved following treatment with mavacamten. Indeed, a number of clinically meaningful CPET parameters consistently improved with mavacamten, and these benefits correlated with improvement in a biomarker of cardiac wall stress. Nevertheless, it seems that symptomatic improvement indicated by the change in KCCQ-CSS is more striking than that seen with CPET, suggesting that the pathophysiology of symptoms is not wholly captured by this testing. Thus, the benefits of mavacamten seem to extend beyond improvement in CPET parameters and fully understanding this represents an unmet need, and may help unravel further the pathophysiology of this complex disease. These considerations would be critical for the design of future trials in patients with obstructive or nonobstructive HCM.

Limitations

The results presented here should be interpreted in the context of several limitations. These analyses are exploratory in nature and should be viewed as hypothesis generating. However, it should be noted that most CPET parameters consistently improved with treatment and that no specific parameter was weighed over another, although some are likely correlated, the clinical interpretation of each parameter is conducted separately. Furthermore, the analytical strategy used here was aligned with the EXPLORER-HCM trial. The single-time point CPET measurement after treatment is also a limitation, as is the variability of symptom status in HCM. Another limitation is the lack of direct measures of daily living or energy expenditure. While multiple mechanisms of exercise impairment were assessed, the extent to which they overlap cannot be entirely accounted for. Additionally, the type of ergometer used can affect the measures of the CPET parameters; however, this potential issue was overcome because randomization was stratified by type of ergometer.

Conclusions

In conclusion, mavacamten therapy improved a range of CPET parameters beyond pVO_2, indicating consistent and broad benefits on maximal exercise capacity. The favorable effects of mavacamten on submaximal exertional tolerance provide further insights into the beneficial effect of mavacamten in patients with obstructive HCM.

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