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The impact of surgical myectomy on exercise capacity among patients with obstructive hypertrophic cardiomyopathy: Insights from Echo-CPET analysis

Short title: Exercise capacity after surgical myectomy in HCM: An EchoCPET evaluation

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by left ventricular wall (LV) thickening unexplained by other causes. Almost 2/3 of HCM patients manifest left ventricular outflow tract obstruction (LVOTO), leading to obstructive HCM (oHCM), that can cause dyspnea, exercise intolerance, and syncope.

When LVOTO is symptomatic, European Society of Cardiology guidelines [1] suggest starting the treatment with β -blockers (BBs) or non-dihydropyridine calcium channel blockers if BBs are not effective, tolerated, or are contraindicated. If the patient remains symptomatic, disopyramide or mavacamten can be used. The latter belongs to a recently introduced class of molecules, cardiac myosin inhibitors that might revolutionize disease management [2].

When pharmacological therapy is not successful in relieving symptoms deriving from LVOTO, septal reduction therapies are recommended [1], with surgical myectomy being the most frequently used.

Obstructive HCM patients have impaired exercise capacity [3]. BBs and calcium channel blockers have failed to demonstrate improvements in peak oxygen consumption (pVO_2) measured by cardiopulmonary exercise test (CPET) and there is very little evidence about the role of Disopyramide in this regard [4]. So far, cardiac myosin inhibitors are the only class of drugs to have proven an effect on increasing pVO_2 although only in registrative trials [5, 6].

Surgical myectomy has proven to be very effective in improving symptoms and quality of life by reducing LVOTO gradient [7], although inconsistent in restoring pVO_2 and exercise performance, with pVO_2 decreasing in some patients (“non-responders”).

To best characterize oHCM patients, both the functional status and the structural and hemodynamic characteristics of LVOTO and mitral regurgitation are key factors to evaluate. Such alterations can directly impair exercise performance. The gold standard methods for this evaluation are CPET and exercise echocardiography. Performing both techniques simultaneously (Echo-CPET) is crucial for quickly correlating exercise impairment with cardiac disease and guiding therapeutic decisions.

Nevertheless, there is a lack of evidence about the concurrent evaluation of these variables utilizing the integrated methods of Echo-CPET in oHCM. In light of this gap in literature, we simultaneously employed both diagnostic approaches to assess the impact of myectomy on exercise capacity and dynamic left ventricular gradient.

METHODS

Data collection was performed retrospectively between April and May 2024. The initial cohort consisted of 412 patients with hypertrophic cardiomyopathy (203 non-obstructive, 209 obstructive) evaluated between 2002 and 2023. From the obstructive group, we included patients who remained obstructive despite maximal medical therapy, underwent septal myectomy, and had combined maximal cardiopulmonary exercise testing with stress echocardiography both before and after surgery. Patients who were not fulfilling these inclusion criteria were excluded from the analysis.

In total, 19 patients with obstructive HCM fulfilled these criteria and were evaluated with Echo-CPET before and after surgical myectomy at the Cardiomyopathy Unit of San Camillo Forlanini Hospital (Rome, Italy). All patients enrolled in the study underwent genetic testing. We exclusively included patients with sarcomeric mutations in the analysis.

Symptom burden was assessed *via* the New York Heart Association (NYHA) class, and reporting limiting symptoms at peak exercise.

Resting echocardiography was performed according to the European Association of Cardiovascular Imaging recommendations [8, 9] by an experienced cardiologist. Subsequently, symptom-limited Echo-CPET was performed on an upright bicycle ergometer using individualized ramp treadmill protocols [10].

A respiratory exchange ratio greater than 1.05 was chosen as a criterion for denoting a maximal effort.

Before each test, the machine was calibrated with reference gases. A standard 12-lead electrocardiography was recorded at rest and continuously monitored throughout exercise and recovery; blood pressure was manually measured every two minutes by a dedicated nurse.

Exhaled gases were sampled using a mouthpiece-mounted sensor and analyzed to continuously measure oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation; pVO_2 , the minute ventilation VCO_2 slope, and oxygen pulse were then calculated.

Transthoracic echocardiography was performed by an experienced cardiologist, during the CPET, using a GE Vivid E90 echocardiogram. The following parameters were acquired at rest, at maximal effort, and after 1 min of recovery.

- Two-dimensional (2D) images: 2D apical 4-, 2-, and 3-chamber views, to evaluate LV global and regional contractile function;
- Doppler evaluation of LV blood velocity flows, including peak LVOT velocity to calculate LVOT gradient, and tricuspid regurgitation peak velocity flow evaluation to estimate systolic pulmonary artery pressure (sPAP);
- M-mode evaluation: tricuspid annular plane systolic excursion/sPAP ratio, to evaluate right ventricular–pulmonary arterial coupling.

All data were digitally stored, and measurements were taken upon the completion of each study. HCM was considered obstructive if a peak gradient >30 mm Hg was recorded at rest or during exercise.

The study was approved by the Ethics Committee Lazio Area 4 and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0. Continuous variables are expressed as mean (standard deviation) when considered normally distributed, and as median (interquartile range) when considered non-normally distributed. Comparisons between pre- and post-operative

values were performed using the paired Student's t-test for parametric variables or the Wilcoxon signed-rank test for non-parametric variables. Categorical variables are presented as counts and percentages, and were compared using Fisher's exact test, while paired categorical data (e.g., NYHA class) were analyzed using the McNemar test. All tests were two-tailed, and a P -value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 47 (15); 15 patients (63%) were males. Eleven patients (60%) had a mutation in the β -myosin heavy chain (*MYH7*) gene and 8 patients (40%) in the myosin binding protein C (*MYBCP3*) gene. The median follow-up time was 23 months (interquartile range 18–29).

Prior to surgery, 15 patients received BBs, 8 were administered dysopiramide, and 6 were treated with a combination of BBs and dysopiramide. No patient received treatment with cardiac myosin inhibitors. Two patients could not tolerate any pharmacological treatment. After surgery, BBs were continued in 14 patients, predominantly for rate control in those with atrial fibrillation (AF), while disopyramide was discontinued in all cases due to resolution of LVOTO following myectomy.

Before surgery, 11 patients (52%) were classified as NYHA class II, while 8 patients (48%) were classified as NYHA class III. After surgery, 11 patients (52%) were classified as NYHA class I, 7 patients as NYHA class II and 1 patient as NYHA class III ($P = 0.002$).

After surgery, functional capacity improved significantly: 16 (4) ml/kg/min vs. 18.7 (4) ml/kg/min ($P = 0.02$); with a trend toward improvement in VE/VCO₂ ($P = 0.10$), whereas oxygen pulse did not differ significantly ($P = 0.20$).

Five patients (26%) failed to improve pVO₂ during follow-up ("non-responder group"). The mean pVO₂ of non-responders was 11 ml/kg/min prior to surgery and 11.4 ml/min/kg following surgery.

No significant changes were found in the resting and exercise echocardiogram parameters before and after surgery, including ejection fraction ($P = 0.75$), diastolic function ($P = 0.6$), sPAP at rest ($P = 0.8$) and peak exercise ($P = 0.98$), or right ventricular systolic function ($P = 0.18$) (Table 1).

After myectomy, the resting LVOT gradient significantly decreased from 52 (36–78) to 11 (5–12) mm Hg ($P = 0.0001$), and peak exercise gradient decreased from 60 (42–85) to 17 (10–23) mm Hg ($P = 0.001$) (Table 1). Before surgery, 10 patients (53%) exhibited systolic anterior motion of the anterior mitral leaflet along with mitral regurgitation (no patient had severe mitral insufficiency), whereas none of the patients exhibited either post-surgery. The left atrial size showed a significant reduction following surgery 70 (12) mm pre-surgery vs. 57 (24) mm post-surgery ($P =$

0.01). During follow-up, 11 patients experienced AF, which required reintroduction or up-titration of BB therapy.

Finally, we noted a significant improvement in NYHA class ($P = 0.002$).

DISCUSSION

This study shows that surgical intervention to relieve the high LVOT gradient in patients with drug-refractory symptomatic obstructive hypertrophic cardiomyopathy improves exercise capacity and mitigates symptoms.

Consistent with prior studies [3, 7], we also demonstrated that a limited proportion of patients did not show enhancements in exercise ability (“non-responder group”). Since the latter is associated to an increased risk of all-cause mortality [7], it is crucial to identify the factors that affect exercise capacity after septal myectomy. In a large cohort of patients undergoing septal myectomy, Smith et al. [7] demonstrated that demographic factors (i.e., female sex), absence of cardiac rehabilitation enrollment, and cardiovascular risk factors (i.e., history of dyslipidemia) were predictors of lack of VO₂ peak improvement following septal myectomy surgery.

In our cohort, the non-responder group consisted entirely of male patients, two of whom had dyslipidemia, and none participated in post-surgical cardiac rehabilitation. In contrast to Smith’s research, where the non-responder group had almost normal pVO₂ (86% of predicted) before surgery, all of our non-responders had a significantly reduced exercise capacity prior to myectomy. The only difference between non-responders and responders was a higher prevalence of AF: 60% (3 out of 5) of non-responders had AF prior to surgery, while 0% had AF in the responder group. This suggests that reduced response to myectomy could reflect a more advanced disease and underscores the importance of appropriate timing for surgical intervention.

Prior research [11] has failed to demonstrate a significant correlation between resting and peak LVOT pressure gradient and peak VO₂; this finding is not unexpected given the known lability of LVOT obstruction in patients with HCM.

In our study, Echo-CPET demonstrated that surgical myectomy is effective in relieving LVOTO and correcting mitral regurgitation, without impairing LV systolic function both at rest and during exertion. However, no significant improvements were observed in diastolic function.

This finding suggests that persistent diastolic dysfunction may represent a critical determinant of exercise limitation in HCM [12]. In this context, cardiac myosin inhibitors — unlike other drug classes — have been shown to improve pVO₂ by directly enhancing diastolic relaxation through the release of myosin heads from actin filaments [5, 6].

Beyond exercise capacity the primary goal of septal myectomy is to alleviate the symptoms and improve the quality of life in obstructive hypertrophic cardiomyopathy patients when medication is no longer effective [1], we confirmed that after surgery there was a significant improvement in NYHA class.

This in line with the results from the Quality of Life and Functional Capacity Following Septal Myectomy in Obstructive Patients with Hypertrophic Cardiomyopathy (SPIRIT-HCM) trial [13] in which the authors observed an increase of more than 20 points in Kansas City Cardiomyopathy Questionnaire summary score in 80% of patients.

Limitations

This study has several limitations. The small sample size ($n = 19$) reduces statistical power and reflects the stringent inclusion criteria. The lack of randomization and of a control group limits causal inference. However, randomization would not have been ethically feasible in this clinical setting. Biomarker data (e.g., N-terminal pro-B-type natriuretic peptide, troponin) were not consistently available and could not be analysed. Finally, the single-center design may limit generalizability.

Despite these limitations, the study retains scientific validity due to its intra-subject design and the use of combined stress echocardiography and CPET, which provide a comprehensive and objective assessment of functional outcomes.

CONCLUSIONS

Surgical myectomy effectively reduces LVOT obstruction and improves pVO_2 and NYHA class of oHCM patients. In some patients, pVO_2 fails to improve after surgery.

Article information

Conflict of interest: None.

Data availability: Anonymous and limited data can be made available on request. The data underlying this article will be shared upon reasonable request to the corresponding author.

Declaration of artificial intelligence use: During the preparation of this work the authors declare to use Pubmed. The authors take(s) full responsibility for the content after using this tool.

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Table 1. Demographics and Echo-CPET results at baseline and after myectomy

	Baseline	After myectomy	P-value
Age, years (SD)	47 (15)		
Male, n (%)	12 (63)		
BMI, kg/m ² , mean (SD)	26 (5)	26 (5)	1.00
Hypertension, n (%)	4 (21)	4 (21)	1.00
Diabetes	0	0	
Dyslipidemia, n (%)	5 (26)	5 (26)	1.00
CAD, n (%)	2 (10)	2 (10)	1.00
Pacemaker/ICD, n (%)	10 (53)	10 (53)	1.00
NYHA class, n (%)			0.002
I	0	11 (58)	
II	11 (58)	7 (37)	
III	8 (42)	1 (5)	
IV	0	0	
pVO ₂ , ml/kg/min (SD)	16 (4)	18.7 (4)	0.02
pVO ₂ , % (SD)	57 (19)	65 (18)	0.09

Power, Watt (SD)	89 (24)	90 (35)	0.44
HR rest, bpm (SD)	71 (12)	68 (9)	0.82
HR peak, bpm (SD)	123 (25)	110 (31)	0.85
HR% (SD)	75 (11)	69 (21)	0.64
SBP rest, mm Hg (SD)	110 (17)	112 (11)	0.74
DBP rest, mm Hg (SD)	70 (10)	76 (7)	0.41
PETCO ₂ rest (SD)	37 (5)	33 (2)	0.37
PETCO ₂ peak (SD)	43 (7)	38 (4)	0.75
VE/VCO ₂ (median, IQR)	30 (26–36)	28 (26–30)	0.14
HR/VO ₂ (median, IQR)	10 (6–11)	11 (9–14)	0.2
LVEF, % (SD)	69 (8)	65 (7)	0.75
Rest gradient (median, IQR)	52 (36–78)	11 (5–12)	<0.001
S _{peak} Gradient (median, IQR)	60 (42–85)	17 (10–23)	0.001
E/e ¹ rest (SD)	11 (7)	12 (3)	0.6
E/e ¹ peak (SD)	13 (4)	13 (3)	0.6
TAPSE rest, mm (SD)	22 (4)	17 (4)	0.18
TAPSE peak, mm (SD)	26 (5)	21 (4)	0.18
sPAP rest, mm Hg (SD)	29 (10)	29 (16)	0.8
sPAP peak, mm Hg (SD)	38 (13)	31 (24)	0.98

Abbreviations: BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; DBP, diastolic blood pressure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PETCO₂, partial pressure of end tidal CO₂; pVO₂, maximum oxygen consumption at peak exertion (ml/kg/min); SBP, systolic blood pressure; SD, standard deviation; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; VE/VCO₂, ventilation (l/min) over carbon dioxide production (l/min)