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ORIGINAL RESEARCH

Cardiopulmonary Fitness and Personalized Exercise Prescription in Patients With Hypertrophic Cardiomyopathy

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BACKGROUND: Patients with hypertrophic cardiomyopathy (HCM) are generally restricted regarding participation in competitive sports based on the potential risk of sudden cardiac death and malignant arrhythmias. As a result, they are often inactive and experience the negative consequences of a sedentary lifestyle. Hence, the need arises to strike the right balance between these 2 extremes through personalized exercise prescription. The aims of this study were (1) to assess the characteristics of patients with HCM practicing regular aerobic physical activity compared with sedentary patients; (2) to perform a personalized moderate-intensity exercise prescription and evaluate its effects.

METHODS AND RESULTS: Patients with HCM were evaluated through clinical assessment, ECG, ambulatory ECG monitoring, echocardiography, and cardiopulmonary testing. A personalized moderate-intensity exercise prescription was performed, and the same investigations were repeated. Physically active patients with HCM demonstrated better cardiopulmonary functional capacity than sedentary patients (oxygen consumption$_{peak}$/kg 32.9±7.4 versus 25.2±7.4 mL/min per kg P≤0.0001, ventilation/carbon dioxide production slope 26.7±4.3 versus 29.9±5.2 P=0.004), with similar prevalence of ventricular arrhythmias (P=0.43). Sedentary subjects showed a borderline higher prevalence of obesity (P=0.07) than physically active subjects. Moderate-intensity exercise prescription led to improved cardiopulmonary fitness without occurrence of adverse events.

CONCLUSIONS: Patients with HCM practicing regular aerobic exercise have a better functional capacity in the absence of relevant events than sedentary patients. Conversely, a sedentary lifestyle led to a deterioration of cardiopulmonary functional capacity and fitness. The tailored moderate-intensity personalized exercise prescription appears to be a feasible approach in carefully selected patients with HCM to counterbalance the negative effects of sedentary behavior without significant major events.

Key Words: cardiopulmonary functional capacity ■ cardiopulmonary testing ■ hypertrophic cardiomyopathy ■ personalized exercise prescription ■ sedentary lifestyle

Hypertrophic cardiomyopathy (HCM) has been considered one of the leading causes of cardiovascular death in athletes due to early and limited evidence suggesting that exercise might increase arrhythmic risk.[1,2] However, more recently, further studies indicate that the risk of sudden cardiac death (SCD) during exercise may be considerably lower than initially considered.[3–6] To date, most athletes with HCM are restricted from competitive sports and enter a gray zone where they have limited or no information about

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CLINICAL PERSPECTIVE

What Is New?

- In patients with hypertrophic cardiomyopathy, a sedentary lifestyle led to a deterioration of cardiopulmonary functional capacity and fitness, whereas regular moderate-intensity exercise led to better cardiopulmonary functional capacity, performance, and ventilatory efficiency without adverse events.

What Are the Clinical Implications?

- A tailored moderate-intensity personalized exercise prescription appears to be a feasible approach in carefully selected patients with hypertrophic cardiomyopathy to counterbalance the negative effects of sedentary behavior without major adverse cardiac events during follow-up.
- The persistence of a sedentary lifestyle was associated with worsening exercise capacity over a relatively short term.

Nonstandard Abbreviations and Acronyms

CPET	cardiopulmonary exercise test
HCM	hypertrophic cardiomyopathy
SCD	sudden cardiac death
SVT	sustained ventricular tachycardia
Vco_2	carbon dioxide production
Vo_2	oxygen consumption
VT1	first ventilatory thresholds
VT2	second ventilatory thresholds

what activities they can or cannot practice to maintain an active lifestyle.[7] On the other hand, physicians are often hesitant to offer guidance due to the scarcity of data and their limited confidence in prescribing exercise for patients with cardiovascular diseases.[7,8] As a result, patients with HCM are often inactive and at high risk of developing cardiovascular risk factors and atherosclerotic disease due to sedentary behavior.[9–11] In this context, the need for exercise prescription has arisen to strike a proper balance between the extremes of excessively high-intensity competitive sports and sedentary behavior.[7] However, few studies address personalized exercise training for patients with HCM in clinical practice.[12,13] The present study aimed to assess the characteristics of patients with HCM practicing regular aerobic physical activity compared with sedentary patients with HCM and to evaluate the effects of a personalized moderate-intensity exercise prescription and its safety, expressed as survival free of SCD, aborted SCD, appropriate implantable cardioverter-defibrillator shocks, or sustained ventricular tachycardia (SVT).

METHODS

Patient Selection

The authors will make the data, methods used in the analysis, and materials used to conduct the research available to researchers for purposes of reproducing the results or replicating the procedure upon reasonable request. We enrolled patients with a definitive diagnosis of HCM aged between 18 and 55 years, consecutively referred to our center for a tailored exercise prescription between September 2019 and August 2023 and enrolled in the referral centers of Florence and Siena. HCM was diagnosed as defined by increased left ventricular (LV) wall thickness that was not solely explained by abnormal loading conditions.[14,15] The population included sedentary individuals with HCM and patients who maintained an active lifestyle (ie, regularly engaged in physical activity by personal initiative, following exclusion from competitive sports according to the national Italian protocols on sports eligibility and disqualification).

The exclusion criteria of the study were New York Heart Associatikon functional class III or IV; impossibility of performing functional tests; noncardiac causes of functional limitation; septal reduction therapy or cardioverter-defibrillator implantation in the previous 3 months; acute heart failure (HF) or hospitalization in the previous 3 months; severe ventricular dysfunction, changes in the therapy in the previous 3 months; and pregnancy.

Clinical Assessments

- Personal history and clinical profile: clinical evaluation, including personal and family history, physical examination, comorbidities, drug therapy, and cardiac symptoms at rest or during effort (ie, palpitations, dyspnea, syncope, chest pain) were assessed. We collected information on the beta-blocker therapy taken by patients, and we calculated equivalent doses considering metoprolol 200 mg as 100%; for example, daily doses of 10 mg bisoprolol were considered as 100% dose equivalent, and nadolol 80 mg was defined as 50% dose equivalent.[16] Genetic counseling and testing were offered systematically to all patients when the diagnosis was established. We assessed the results of the cardiac magnetic resonance, paying particular attention to the presence and percentage of late gadolinium enhancement.
- Information about the lifetime history of exercise, the type of exercise, and the intensity and volume

of training per week was systematically collected via an interview during the clinical evaluation. Physical active patients were defined as individuals who performed more than 3 hours of organized exercise per week. We assigned a metabolic equivalent of task for all activities[17] and calculated the physical activity volume by multiplying the metabolic equivalent of task score by the reported physical activity volume (session duration x frequency/week).[18]

- ECG: Resting heart rate, sinus rhythm, the presence of T-wave inversion, and bundle-branch blocks were evaluated; left atrium enlargement was defined as a P-wave duration >120 milliseconds or a negative portion of the P-wave of ≥0.1 mV in-depth and ≥40 milliseconds in duration in the lead V_1.[19] LV hypertrophy was defined based on Sokolow–Lyon criteria voltage.[15,20] Q waves ≥40 milliseconds in duration or ≥25% of the R wave in depth or ≥3 mm in depth in at least 2 contiguous leads except aVR were considered pathological.[15,20]
- Twelve-lead 48-hour ambulatory ECG monitoring: the presence of rhythm abnormalities, supraventricular arrhythmias, ventricular arrhythmias, and other abnormal findings were investigated annually or more often if clinically indicated.[15]
- Echocardiogram: LV and right ventricular dimensions and function, aortic root diameters, and atrial dimensions were obtained as recommended.[21,22] LV volume measurements were calculated from the apical 4- and 2-chamber views using the modified Simpson's rule, and ejection fraction was calculated.[21] Doppler LV outflow tract pressure gradient at rest or during physiological provocation such as Valsalva maneuver and exercise was calculated to evaluate the presence of LV outflow tract obstruction.[14,15] Doppler interrogation of the tricuspid regurgitant jet was used to estimate pulmonary artery systolic pressure. The early (E) and late (A) pulsed-wave Doppler diastolic peak-flow velocities and tissue Doppler imaging assessment of early (e′) and late (a′) diastolic peak velocities and their ratio were measured to assess diastolic function.[21] Two-dimensional speckle-tracking echocardiography analysis was performed and analyzed offline using dedicated automated software (EchoPAC PC, Version 112; GE Health Care, Milwaukee, WI, USA). LV global longitudinal strain was measured as the average of the LV longitudinal strain peaks obtained from 2-, 3-, and 4-chamber views.[23] Right ventricular global longitudinal strain included the interventricular septum and right ventricular free wall peak systolic longitudinal strain, measured as the average of the lateral wall's 3 segments (basal, midcavity, and apical).[24] Peak atrial longitudinal strain and peak atrial contraction strain, measures of the atrial reservoir and active function, respectively, were obtained by calculating the average values obtained from the 4-chamber and 2-chamber view (left atrial global peak atrial longitudinal strain and global peak atrial contraction strain).[24]

  Echocardiograms were also performed during exercise to evaluate the LV outflow tract gradient, which is the most important aspect of exercise echocardiography in patients with HCM.[25]

- Cardiopulmonary exercise test (CPET) was performed using a cycle ergometer (Quark CPET, CosMed USA Inc., Concord, CA, USA) equipped with software OMNIA (CosMed USA Inc., Concord, CA, USA, 1.6.5). The test (ramp protocol) included a 1-minute preexercise resting period sitting upright on the bike, a 2-minute unloaded warmup cycling phase, followed by an incremental exercise cycling period with an increasing workload of 5 to 40 W per minute, dependent on the patient's clinical status and aiming to complete the CPET within 8 to 12 minutes, as recommended.[26–28] Oxygen consumption (Vo_2), carbon dioxide production (Vco_2), and ventilation during exercise were analyzed breath by breath. Peak VO_2, first (VT_1) and second (VT_2) ventilatory thresholds, ventilatory efficiency through ventilatory equivalent for carbon dioxide ventilation/Vco_2 slope, the respiratory exchange ratio (defined as the ratio between Vco_2 and Vo_2), exercise breathing reserve, the partial end-tidal pressures of O_2 and CO_2, the Vo_2/work rate ratio, and peak exercise oxygen pulse (calculated as Vo_2/heart rate, providing an estimate of LV stroke-volume changes during exercise) were evaluated.[27] The determination of noninvasive VTs was based on the analysis and integration of data derived from some of the 9 CPET panels.[29] The methods for VT_1 determination were the following: V-slope method (change in the slope of Vco_2 versus Vo_2 ratio from an increase with a slope ≤1 to a slope >1); the nadir of the first increase in ventilation/Vo_2, without a simultaneous increase in ventilation/Vco_2; and the nadir of partial end-tidal pressures of O_2, while partial end-tidal pressures of CO_2 remains constant or is increasing.[26,29] The VT_2 was determined by analyzing the inflection of ventilation versus work rate, the nadir of ventilation/Vco_2 increase, and the zenith and deflection point of partial end-tidal pressures of CO_2.[26,29] Chronotropic competence, resting/peak blood pressure, oxygen saturation, supraventricular/ventricular arrhythmias, and symptoms during exercise were also analyzed. The CPET was preceded by spirometry, which evaluated respiratory parameters and classified them as normal or pathological according to standardized criteria.[30]

- Personalized exercise prescription

First, we assessed the presence of contraindications to physical activity (eg, history of syncope/hypotension during effort, clinically relevant arrhythmias particularly during effort, presence of severe provocable obstruction at rest or during effort, presence of extensive late gadolinium enhancement (>15%) on cardiac magnetic resonance).[7] In case of a clinical risk deemed excessively high and the impossibility of temporarily practicing exercise, we suggested a revaluation for an exercise program after implementing optimal medical or interventional therapy (eg, after reducing a significant LV outflow tract obstruction).[8,31] Exercise prescription was tailored according to the patient's characteristics, the drugs administered, the personal history, the response to exercise, the previous training experience, the aims to reach, and the different health profiles to improve,[7,32] based on the so-called FITT-VP model (frequency, intensity, time, and type)[3,29]:

- *Frequency* is the number of sessions/weeks; it was suggested that patients start with 2 sessions/week until reaching a target of 3 to 5 times/week.[29]
- *Intensity* is the amount of energy expenditure/time unit during training sessions. The CPET gives the unique opportunity to delineate the ventilatory thresholds (VT_1 and VT_2), representing the most reliable method to identify the correct intensity of aerobic exercise.[26,29,33] The intensity of aerobic exercise can be classified as light, moderate, high, and very high. Moderate intensity of aerobic exercise is slightly above or around VT_1; therefore, the heart rate value corresponding to the VT_1 was derived and used as an objective indicator for prescribing moderate aerobic exercise.[29,32]
- *Time* represents the duration of a training program in weeks or months, training days/week, training session times/day, and duration of training sessions in hours. We suggested reaching 150 to 300 min/week of aerobic exercise with intensity corresponding to VT_1.[29]
- *Type of exercise* included aerobic continuous training (eg, running, cycling, swimming, walking, etc.).[29] In nonobstructive patients, strength activities were prescribed with an intensity corresponding to 40% to 70% of 1 repetition maximum, adapted individually.[7,29]
- *Volume* indicates the total amount of weekly exercise.[8,29]
- *Progression* is how the program advances. Specific instructions were provided regarding the program's progression to increase the exercise dose gradually, considering the patient's adaptation to exercise, age, and clinical characteristics.[29,32]

The exercise programs and the patients were reassessed with the same investigations (ie, personal history and clinical profile, ECG, echocardiography, ambulatory ECG monitoring, and CPET) within 6 to 12 months after the first evaluation and followed up for a maximum of 3 years. During the revaluation, information about the exercise volume per week and adherence to the training program were obtained, including information about rate of perceived exertion. Furthermore, patients with a low exercise volume were encouraged to practice more hours of training during the week.

After the rationale and protocol of the study were explained, the participants gave their written informed consent. The local Ethical Committee of the University of Siena approved the study.

Statistical Analysis

Continuous variables were reported as mean±SD, and the qualitative variables were reported as absolute numbers or percentages. The unpaired *t* test or the Mann–Whitney *U* test was used to assess the statistical significance difference between the 2 groups. The qualitative variables were studied using the chi-square test. A *P* value <0.05 was considered statistically significant for all the analyses. Univariate regression analysis was performed to explore the association between the functional capacity (expressed as $VO_{2\ peak}$ index) and main demographic and clinical variables. Variables included were age, sex, type of sports, metabolic equivalent of task scores of training per week, use of beta-blocker therapy, and main dimensional echocardiographic parameters. The analysis was conducted using the SPSS version 21.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA).

Equity, Diversity, and Inclusion Statement

The study was designed to include both males and females. Study participants were enrolled regardless of sexual identity, gender identity, socioeconomic background, or ethnicity.

RESULTS

Baseline Features and Level of Activity

The study population comprised 71 patients with HCM, 33 physically active (97% male; mean age: 39±14 years) and 38 sedentary (84% men; mean age: 38±14 years). None had severe comorbidities (Table 1).

Mutations in the genes encoding beta-MYH7 (myosin heavy chain 7) and MYBPC3 (myosin-binding protein C) accounted for the majority of genotype-positive individuals, accounting for 12% and 15%, respectively, in the group of physically active patients, 16% and 10%

Table 1. Demographic, Clinical, and Electrocardiographic Features of Sedentary Versus Physically Active Patients With Hypertrophic Cardiomyopathy

Variables	Sedentary with HCM	Physically active with HCM	*P* value
Male sex, n (%)	32 (84)	32 (97)	0.07
Female sex, n (%)	6 (16)	1 (3)	0.08
Age, y	38±14	39±14	0.76
Body surface area, m^2	2.0±0.2	1.9±0.2	0.63
Body mass index, kg/m^2	26.1±3.6	24.7±2.7	0.09
Normal weight, n (%)	18 (47)	20 (61)	0.27
Preobesity (25–30 kg/m^2), n (%)	14 (37)	12 (36)	0.97
Obesity (>30 kg/m^2), n (%)	6 (16)	1 (3)	0.07
Family history of SCD/HCM, n (%)	17 (45)	11 (33)	0.33
NYHA			0.21
NYHA I, n (%)	32 (84)	33 (100)	
NYHA II, n (%)	6 (16)	0 (0)	
Presyncope, n (%)	4 (10)	2 (6)	0.52
Presyncope during effort, n (%)	3 (8)	2 (6)	
Syncope, n (%)	4 (10)	2 (6)	0.47
Syncope during effort n (%)	2 (5)	0 (0)	
Angina n (%)	1 (3)	2 (6)	0.48
Palpitations n (%)	7 (18)	1 (3)	0.042
Metabolic equivalent of task-h-wk^{-1}	NA	31±16	NA
Ambulatory ECG monitoring			
Atrial fibrillation	5 (13)	0 (0)	0.03
Nonsustained ventricular tachycardia	6 (16)	8 (24)	0.43
Malignant arrhythmias, n (%)	1 (3)	1 (3)	0.95
Implantable cardioverter-defibrillator, n (%)	6 (16)	1 (3)	0.07
SCD risk score	2.9±2.1	2.4±1.4	0.64
Beta-blocker therapy, n (%)	24 (63)	15 (45)	0.14
Type of beta-blocker			0.14
Nadolol, n (%)	17 (71)	5 (33)	
Bisoprolol, n (%)	6 (25)	9 (60)	
Metoprolol, n (%)	1 (4)	1 (7)	
Beta-blocker dose equivalent, %	34±17	34±18	0.95
Other therapies			
Amiodarone, n (%)	2 (5)	0 (0)	
Ranolazine, n (%)	3 (8)	1 (3)	
Disopiramide, n(%)	0 (0)	1 (3)	
Late gadolinium enhancement on cardiac magnetic resonance, n (%)	22 (58)	24 (73)	
Resting heart rate, bpm	64±15	67±16	0.39
Resting ECG			0.44
TWI, n (%)	14 (37)	11 (29)	
Q waves, n (%)	3 (8)	5 (15)	
LAE, n (%)	1 (3)	0 (0)	
Left BBB, n (%)	1 (3)	2 (6)	
LVH, n (%)	2 (5)	1 (3)	
TWI and Q waves, n (%)	6 (16)	2 (6)	
TWI and LVH, n (%)	2 (5)	4 (12)	
Q waves and LAE, n (%)	1 (3)	1 (3)	
TWI, LAE, and LVH, n (%)	1 (3)	0 (0)	
TWI, Q waves, right BBB, n (%)	1 (3)	0 (0)	

BBB indicates bundle-branch block; HCM, hypertrophic cardiomyopathy; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; SCD, sudden cardiac death; andTWI, T-wave inversion.

in the sedentary group. Less commonly affected genes included cardiac troponin I (6% in the active group, 3% in the sedentary). Genetic analysis yielded negative results in 13% of the sedentary group and 18% of active patients. The remaining patients either had a mutation of uncertain significance, were awaiting the results, or had not undergone the test.

The body surface area and the body mass index were slightly greater in sedentary patients, resulting in more frequent obesity than in active patients (*P*=0.07).

All physically active subjects were in New York Heart Association functional class I, compared with 84% of sedentary patients, due to 6 (16%) in class II in the latter group. No significant differences were found regarding symptoms at rest or during effort (ie, presyncope, syncope, angina). However, sedentary patients reported more frequent palpitations than the physically active group (*P*=0.04). Most physically active patients practiced aerobic training (eg, walking, running, cycling, swimming), and only 2 engaged in strength-training activities. The average time of exercise was 4.5±1.3 hours per week. Three patients engaged in very high-intensity cycling against medical advice.

Sixty-three percent of patients with HCM in the sedentary group and 45% in the active group received beta-blocker therapy (*P*=0.14). A higher incidence of atrial fibrillation (AF) in the sedentary group was observed (*P*=0.03; Table 1). The incidence of complex ventricular arrhythmias did not differ between the groups; however, 16% of sedentary patients underwent cardioverter-defibrillator implantation versus 3% in the physically active group (*P*=0.07), in most cases in primary prevention. Notably, the HCM risk–SCD score was higher in the sedentary group, but this difference was not statistically significant (*P*=0.64).

The typical anomalies of HCM were found on 12-lead resting ECG, with no significant differences in the 2 groups regarding the presence of LV hypertrophy, left atrium enlargement, pathological Q waves, T-wave inversion, and bundle-branch blocks.

The echocardiographic characteristics were substantially comparable between the 2 groups (Table 2).

Table 2. Standard and Advanced Echocardiographic Features of Sedentary vs Physically Active Patients With Hypertrophic Cardiomyopathy

Variables	Sedentary with HCM	Physically active with HCM	*P* value
Aortic root, mm	32.7±4.1	34.1±2.8	0.07
IVST, mm	15.8±5.1	14.5±4.3	0.22
Posterior wall thickness, mm	10.8±2.1	11.1±1.8	0.32
IVST max, mm	17.5±4.8	16.7±5.3	0.27
LA anteroposterior diameter, mm	35.9±8.0	37.3±7.7	0.50
LA volume, mL	69.8±23.6	69.7±20.2	0.77
LA volume index, mL/m^2	34.7±11.2	35.3±9.3	0.56
LV ejection fraction, %	62.7±7.6	63.2±5.8	0.75
LV EDD, mm	46.1±5.9	46.9±5.1	0.52
LV end-systolic diameter, mm	27.4±6.8	26.3±6.2	0.48
LV end-diastolic volume, mL	109.8±32.3	108.8±25.1	0.91
LV end-systolic volume, mL	45.4±23.5	42.7±14.8	0.90
Resting LVOT gradient, mm Hg	6.0±2.7	8.1±10.2	0.58
LVOT gradient after Valsalva maneuver, mm Hg	7.3±5.4	12.3±15.6	0.69
LVOT gradient during exercise, mm Hg	12.6±17.8	25.9±27.5	0.05
Pathological LVOT gradient during exercise, n (%)	1 (3)	7 (21)	0.01
E wave, cm/s	69.4±15.9	75.2±22.7	0.34
A wave, cm/s	50±13.5	56.4±16.4	0.11
E/A ratio	1.4±0.5	1.4±0.5	0.44
s', cm/s	8.6±2.1	8.3±2.5	0.73
e′, cm/s	9.3±2.7	9.6±0.59	0.43
a′, cm/s	7.5±2.9	7.6±2.8	0.55
E/e′ ratio	7.8±2.4	8.1±2.6	0.81
RV midcavity EDD, mm	29.8±5.4	31.1±4.7	0.34
RV s', cm/s	13.6±2.48	13.5±2.19	0.84
RV e′, cm/s	11.6±1.9	11.5±2.7	0.88
RV a′, cm/s	13.7±3.8	12.1±2.9	0.16
RV fractional area change, %	43±4.8	41.9±7.8	0.50
Tricuspid annular plane systolic excursion, mm	23.9±3.4	23.8±3.3	0.70
Pulmonary hypertension, n (%)	0	0	NA
Inferior vena cava, mm	17.5±2.6	18.1±3.4	0.49
LV mean strain, %	−15.9±6.5	−17.6±3.6	0.45
LA mean peak atrial longitudinal strain, %	23.7±10.6	26.6±7.5	0.23
LA mean peak atrial contraction strain, %	9.1±5.4	11.2±5.8	0.17
RV strain (free wall), %	−23.7±8.5	−20.8±5.2	0.53
RV strain (6 segments), %	−20.0±6.5	−18.1±3.9	0.29

EDD indicates end-diastolic diameter; IVST, interventricular septum thickness; LA, left atrial; LV, left ventricular; LVOT, left ventricle outflow tract; NA, not appliable; and RV, right ventricular..

None of the patients had LVOT gradients >50 mm Hg at rest, and mean values at rest were similar between the 2 cohorts. However, more patients developed a hemodynamically significant gradient during exercise among the active (21%) compared with sedentary patients (3%, *P*=0.01). Two-dimensional speckle-tracking echocardiography analysis did not reveal statistically significant differences in the LV, right ventricular, and left atrial mean strain parameters.

CPET Analysis

CPET parameters are described in Table 3. Physically active patients with HCM achieved higher workloads compared with sedentary patients with HCM, both at peak effort (*P*<0.0001) and at VT_1 (*P*=0.01) and VT_2 (*P*=0.001).

The Vo_{2peak} was greater in active than in sedentary patients (*P*≤0.0001), with higher values at VT_1 (*P*=0.004) and VT_2 (*P*=0.001). Moreover, physically active patients with HCM demonstrated greater ventilatory efficiency (ventilation/Vco_2 slope, *P*=0.004) and higher peak exercise oxygen pulse (*P*=0.03) and Vo_2/work rate (*P*=0.002). No pulmonary limitation to exercise was identified. No significant arrhythmias occurred during the test, and none of the patients exhibited chronotropic incompetence or symptoms. A hypertensive response was observed in a few patients, mainly in the sedentary group (8% versus 6% in physically active patients with HCM), without significant differences between the 2 groups (*P*=0.5).

The univariate regression analysis demonstrated that $V_{O2peak\ index}$ was significantly correlated with being active (β=0.47, *P*<0.001), weekly metabolic equivalent of task scores of training (β=0.46, *P*=0.007), normal weight (β=0.42, *P*<0.001), and inversely with beta-blocker therapy (β=−0.36, *P*=0.002), and age (β=−0.28, *P*<0.02). The main findings of the CPET analysis are shown in Figure 1.

Follow-Up

Thirteen patients were evaluated after an average of 24±12 months from the initial evaluation. We divided these patients into 4 groups: group 1 was composed of physically active patients with HCM who continued to practice exercise according to our prescription—in this group, one patient practiced cycling with higher intensity than the one prescribed; group 2 included physically active patients who performed high-intensity activity until our first evaluation, and afterwards, they started to practice physical activity according to the prescription, with a moderate intensity; group 3 was composed of sedentary subjects with HCM who started the training program according to our prescription; and group 4 included sedentary patients with HCM who remained sedentary despite our exercise prescription.

The groups' trajectories of the percentage of predicted Vo_{2peak}, observed during the follow-up, are

Table 3. Cardiopulmonary Exercise Testing Parameters Collected in Sedentary and Physically Active Patients With Hypertrophic Cardiomyopathy

Variables	Sedentary with HCM	Physically active with HCM	*P* value
Peak cycling power output, Watt	178.7±44.8	223.2±45.9	≤0.0001
Metabolic equivalent of $Task_{peak}$	7.2±2.1	9.4±2.1	≤0.0001
Respiratory exchange $ratio_{peak}$	1.1±0.1	1.1±0.1	0.06
Vo_{2peak}, mL/min	2053.5±587.1	2569.7±516.2	0.01
Vo_{2peak}/kg, mL/min per kg	25.2±7.4	32.9±7.4	≤0.0001
Vo_{2peak}, %	73.6±16.5	92.0±22.0	0.01
HR_{peak}, bpm	138.8±24.1	151.2±20.9	0.02
HR_{peak}, %	75.9±11.5	83.2±9.8	0.008
VT_1 Vo_2, mL/min	1081.1±357.9	1255.9±375.1	0.04
VT_1 Vo_2/Kg, mL/min per kg	13.4±4.9	16.1±5.2	0.004
VT_1, Vo_{2peak}, %	52.4±9.5	48.8±9.4	0.05
VT_1, predicted Vo_2, %	38.8±9.9	45.5±17.1	0.15
VT_1, HR, bpm	93.9±20.7	99.1±16.1	0.11
VT_1, HR_{peak}, %	68.1±9.7	64.7±8.7	0.12
VT_1 power, W	80.9±29.3	98.6±32.6	0.01
VT_2 Vo_2, mL/min	1788.5±475.8	2170.1±503.8	0.002
VT_2 Vo_2/Kg, mL/min per kg	21.7±6.9	27.8±7.5	0.001
VT_2 Vo_{2peak}, %	82.2±15.6	84.2±8.5	0.79
VT_2 HR, bpm	125.5±24.4	135.7±18.3	0.03
VT_2 HR_{peak}, %	86.7±16.0	89.5±5.6	0.7
VT_2 power, W	150.4±37.9	186.2±44.2	0.001
Delta HR thresholds	30±13	35.8±11.9	0.08
Ventilation/Vco_2 slope	29.9±5.2	26.7±4.3	0.004
VT_1 ventilation/Vco_2 slope	31.1±4.8	28.5±3.3	0.02
$Ventilation_{peak}$, l/min	76.5±20.1	81.7±16.7	0.39
Breathing reserve%	53.5±10.5	50.2±11.8	0.34
$Vo_2/HR_{,peak}$ mL/beat	14.9±3.6	17±3.7	0.03
$Vo_2/HR_{,peak}$, %	97.6±19.6	112±23.5	0.01
Vo_2/work $rate_{,peak}$ mL/min per W	9.5±1.7	10.5±0.7	0.002
HR reserve, bpm	79.1±22.4	83.9±18.4	0.14
Vo_2 reserve, mL/min	20.0±7.6	27.6±7.7	≤0.0001
Exercise hypertensive response, n (%)	3 (8)	2 (6)	0.5

HR indicates heart rate; Vo_2, oxygen uptake; Vco_2, exhaled carbon dioxide; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold; and W, Watt.

shown in Figure 2. In group 1 (n=5), we observed stable values; in group 2 (n=3), a slight reduction and in group 3 (n=2) an increase was observed. Conversely, in group 4 (n=3), a deterioration occurred. Figure S1 describes the individual trajectories. There were no major adverse events in any of the groups, including death, aborted SCD, appropriate implantable cardioverter-defibrillator shocks, or SVT. However, non-SVT occurred at rest in a patient who exercised beyond the prescribed thresholds and in a sedentary patient.

DISCUSSION

In this study, we analyzed the clinical, electrocardiographic, echocardiographic, and cardiopulmonary characteristics of patients with HCM based on their baseline level of activity and response to training. The main findings of the study are the following: (1) physically active patients demonstrated better cardiopulmonary functional capacity, performance, and ventilatory efficiency than sedentary patients; (2) no significant differences at baseline were observed between the groups regarding ventricular arrhythmias; and (3) regular individualized training was safe and led to measurable functional improvement, whereas the persistence of sedentary lifestyle was associated with worsening of exercise capacity over a relatively short term.

In our study, Vo_{2peak} was greater in patients practicing physical activity than in sedentary individuals with HCM, with higher values also at VT_1 and VT_2. Although the sedentary patients with HCM in this study had a slightly higher Vo_{2peak} than those generally reported in the general population of patients with HCM,[12,34] active individuals showed an additional gain in Vo_{2peak}.

Maintaining a high Vo_{2peak} has inherent prognostic implications in HCM. Indeed, the risk of death or transplant in with HCM patients is reduced by 21% for each 1 mL/kg/min increase in Vo_{2peak} and 29% for each 1 mL/kg per min increase in VT_1.[35] Moreover, among patients with obstructive HCM and mild or no symptoms, a low metabolic exercise capacity is associated with an increased risk of death and subsequent development of severe symptoms.[36] It has also been demonstrated that, in patients with HCM with a percentage of predicted Vo_{2peak}<60%, the 4-year survival rate free of death and severe symptoms was only 59%.[36] In chronic HF, CPET is widely accepted as an objective means of defining functional status, and low Vo_{2peak} values are known to identify patients at higher mortality risk with a Vo_{2peak} of 14 mL/kg per min selected as a criterion for acceptance for cardiac transplant.[37,38]

Moreover, in our study, physically active patients with HCM demonstrated greater ventilatory efficiency, that is, better ventilation/Vco_2 slope, than sedentary subjects. This is another pivotal point because the ventilation/Vco_2 slope is a well-known prognostic parameter for patients with cardiac conditions, and, specifically for HCM, the risk of death or transplant increases by 18% for each 1 U increase in ventilation/Vco_2.[35] Indeed, in patients with HCM, impaired ventilatory efficiency has been significantly associated with a composite

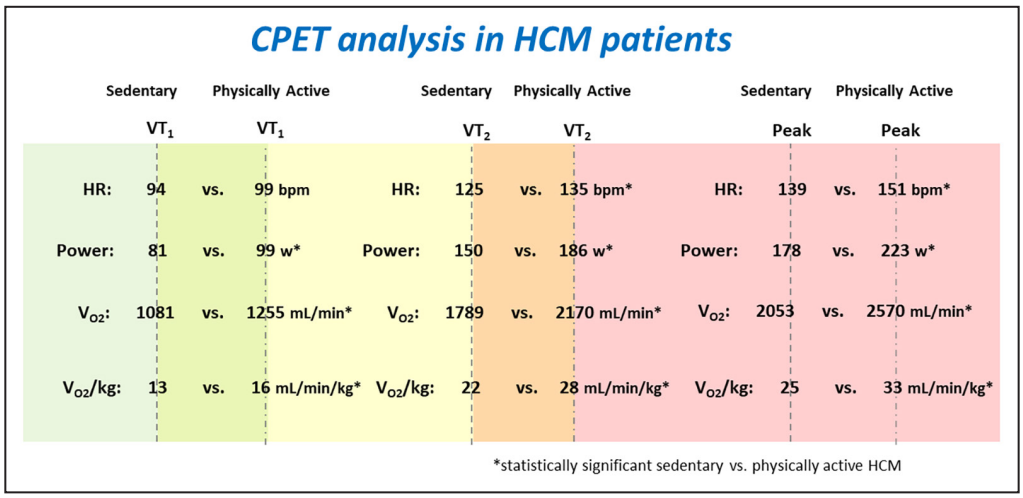

Figure 1. Main findings of the cardiopulmonary exercise testing analysis in sedentary vs physically active patients with hypertrophic cardiomyopathy.
HCM indicates hypertrophic cardiomyopathy; HR, heart rate; Vo_2, oxygen consumption; VT_1, first ventilatory threshold; VT_2, second ventilatory threshold.

end point of death, heart transplant, and implantation of a ventricular assist device.[39] In general, the ventilation/Vco_2 slope is a prognostic indicator of cardiac events in a heterogeneous group of patients with heart disease, that is, ischemic heart disease, dilated cardiomyopathy, valvular disease, and hypertensive heart disease.[40] In chronic HF, the ventilation/Vco_2 slope has a prognostic role in predicting cardiovascular events, such as death, ventricular assist device implantation, or heart transplant.[41] In patients with diastolic HF, the ventilation/Vco_2, rather than Vo_{2peak}, holds clinical and prognostic impact and is a powerful prognostic marker in this increasing subset of patients.[42]

In our study, no significant differences regarding ventricular arrhythmias were observed between physically active and sedentary patients with HCM at rest, and no one in any group exhibited complex arrhythmias during the CPET. Our study demonstrates the safety of a regular, moderate-intensity exercise practice, with the absence of an increased arrhythmic risk induced

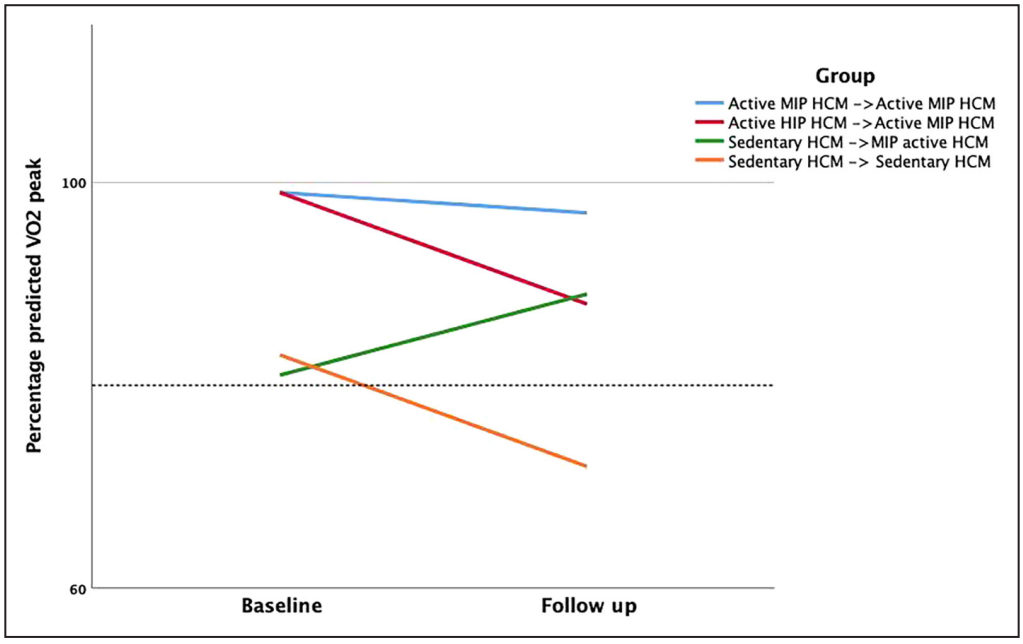

Figure 2. The groups' trajectories of the percentage of predicted Vo_{2peak}, observed during the follow-up in patients with hypertrophic cardiomyopathy.
HCM indicates hypertrophic cardiomyopathy; HIP, high-intensity physical activity; MIP, moderate-intensity physical activity; and Vo_2, oxygen consumption.

by physical activity, and these findings agree with the recent emerging literature. Dejgaard et al did not find differences related to ventricular arrhythmias between subjects with HCM with and without a lifetime history of vigorous exercise, and there were no differences in lifetime vigorous exercise between subjects with and without ventricular arrhythmias.[43] Conversely, a higher prevalence of a history of non-SVT in the most active phenotypic was found in a study exploring the relationship between lifelong physical activity and HCM phenotype expression.[18] In our study, during the follow-up, no complex arrhythmias were found in patients who practiced exercise according to our prescription, whereas non-SVT occurred at rest in patients who practiced exercise beyond the prescribed thresholds and in sedentary patients. Notably, in our cohort, a higher incidence of AF was observed in the sedentary than in the active group. In patients with HCM, AF is associated with significant morbidity, impaired quality of life, and high risk of all-cause death, SCD, and HF-related death[44]; moreover, AF is associated with a substantial stroke risk as the risk of systemic embolization is high in HCM patients with AF.[44,45] Furthermore, sedentary patients are often overweight, and preobesity and obesity are independently associated with AF.[10] Therefore, being active seems not only to induce ventricular arrhythmias but to protect from AF, with a well-known positive impact on the clinical outcome of HCM.

A small group of patients with HCM in our cohort were followed up for 24±12 months from the first evaluation for exercise prescription. Sedentary patients, who were referred to our center for exercise prescription and followed the moderate-intensity exercise program, increased their Vo_{2peak}. In contrast, active patients who performed high-intensity exercise until our first evaluation and afterwards started to practice moderate-intensity physical activity according to the prescription experienced a slight reduction in Vo_{2peak}, which, however, remained within normal levels, allowing them to engage in a safe exercise program. Already active patients who continued to practice physical activity according to the prescription demonstrated a stable, functional capacity despite their underlying illness. In line with our results, in the RESET-HCM (Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy), a randomized clinical trial of individualized moderate-intensity aerobic exercise training versus usual activity in patients with HCM, an improvement in Vo_{2peak} after 16 weeks of exercise was observed, with an absolute increase of 1.27 mL/kg/min in the exercise group compared with the usual-activity group, representing an absolute increase of 6%.[12] Klempfner et al also demonstrated a significant improvement in functional capacity and New York Heart Association functional class in patients with HCM enrolled on a supervised cardiac rehabilitation exercise program (moderate-to-high intensity).[13] Notably, sedentary patients with HCM who did not follow the training program further exacerbated the adverse effects of their sedentary lifestyle, not benefiting from the exercise-induced increase in functional capacity. Given that physical inactivity is a well-recognized leading risk factor for obesity, diabetes, ischemic heart disease, cancer, chronic conditions, and ultimately all-cause mortality and major cardiovascular events,[8,9] the advice to practice exercise and its prescription represents a relevant opportunity for patients with HCM to counteract the comorbidities and the negative relation between sedentary lifestyle and adverse events. On the contrary, long-term lack of physical activity and excess weight are expected to significantly contribute to cardiovascular morbidity and mortality, further increasing the burden of the natural progression of HCM.[7,10] However, alternative options exist between maximal, competitive engagement and complete inactivity[7] and personalized exercise prescription should be offered to patients with HCM, given that a tailored moderate-intensity exercise prescription is feasible for these patients, leading to an increase in Vo_{2peak} in sedentary patients and maintaining stability in active patients without adverse events.

Limitations

The main limitation of the study is the small sample size. However, the study population was selected according to strict criteria, and patients were enrolled based on their potential willingness to practise exercise.

Unfortunately, in this study, women are underrepresented, whereas White patients represent the vast majority of the participants (96% versus 4% of non-White patients), with no investigation into the impact of ethnicity. Therefore, even if the demographic characteristics of the present study are in agreement with the national registries of patients with HCM, these findings cannot be generalized to women. Furthermore, the high prevalence of male patients seems to be influenced by the greater inclination of male patients to practice physical activity after the diagnosis as compared with women. Therefore, it becomes essential to promote physical activity in all patients with HCM, particularly in women, to prove whether it is safe and effective also in female patients with HCM.

Another limitation is that a small number of patients were analyzed in the follow-up after the initial exercise prescription. This is due to various reasons: first, the COVID-19 pandemic markedly influenced patients' participation: indeed, on the one hand, the pandemic initially halted and then slowed down our clinical activities in this regard; on the other hand, patients were not allowed to practice physical activity due to imposed lockdown and limitations. This is in line with

several studies highlighting a significant reduction in the amount of physical activity performed during the COVID-19 pandemic compared with the period preceding the lockdown; unfortunately, this trend was evident not only in the general population but particularly in individuals with chronic conditions.[46] Second, exercise prescriptions could not be provided to some patients due to clinical risk deemed to be excessively high and the impossibility of temporarily practicing exercise (ie, after implementation of the medical therapy or reducing a significant LV outflow tract obstruction). Additionally, despite the patients referred to our center for specific indications related to exercise prescription, some did not start exercising and remained sedentary against our advice.

Furthermore, the training program was not supervised. This is mainly because most patients came to our center from distant regions of Italy to receive guidance on personalized exercise prescriptions, dramatically limiting the opportunity to follow the program for at least some weeks in a dedicated gym. However, patients consistently attended regular visits at our center or their reference centers, including prolonged ambulatory ECG monitoring. Moreover, most of the patients preferred to practice outdoor exercise, such as running. Furthermore, available evidence suggests that home-based rehabilitation may provide an alternative option for rehabilitation services for stable patients with cardiovascular diseases,[47] enhancing patient participation by providing increased flexibility and options for activities, in agreement with the current European guidelines on cardiovascular disease prevention.[48]

In this study we did not monitor the adherence to exercise programs via apps or specific devices. During the revaluation, detailed information on the training volume and intensity per week were collected and patients practiced a lower volume per week were encouraged to practice more hours of personalized training. However, the lack of detailed data on the adherence to training programs represents a limitation of this study. Further researchers are needed to understand the best strategy to monitor in patients with HCM the effects of exercise programs, particularly in studies with a midterm follow-up, where a regular monitoring may be particularly difficult.

CONCLUSIONS

Physically active patients with HCM demonstrate better cardiopulmonary functional capacity, performance, and ventilatory efficiency than sedentary patients in the absence of significant differences in the prevalence of complex arrhythmias compared with the sedentary group. On the contrary, a sedentary lifestyle led to a deterioration of cardiopulmonary functional capacity and fitness, negatively affecting well-known prognostic parameters. A tailored moderate-intensity personalized exercise prescription appears to be a feasible approach in carefully selected patients with HCM to counterbalance the negative effects of sedentary behavior without complex exercise-induced arrhythmias and significant major events. Further research is needed to confirm the present findings in studies with large sample sizes and in women and identify strategies to increase patients' compliance with cardiomyopathies to tailored exercise programs.

ARTICLE INFORMATION

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None.

Supplemental Material

Figure S1

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