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EPICH- Exercise Prescription In Cardiomyopathies and Heart Transplant

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Summary

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) has always been considered one of the leading causes of cardiovascular death in athletes due to the evidence that exercise increases the risk of sudden cardiac death (SCD) and malignant arrhythmias in HCM patients(1, 2). However, more recently, further studies indicate that the risk of SCD during exercise may be considerably lower than initially considered(3-6). To date, most HCM athletes are restricted from competitive sports and enter a grey zone where they have limited or no information about what activities they can or cannot practice to maintain an active lifestyle(7). On the other hand, physicians may be 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, HCM patients are often inactive and at high risk of developing cardiovascular risk factors, including atherosclerotic disease, increasing their cardiovascular and non-cardiovascular mortality due to sedentary behaviour(9-11). In this context, the need for exercise prescription has arisen to strike a proper balance between this dichotomy, high-intensity competitive sports on one side and sedentary behaviour on the other(7). Unfortunately, there are few studies on personalized exercise training for HCM patients to guide clinical practice(12, 13). Therefore, the aims of this study were: 1) firstly, to assess the characteristics of HCM patients who practised regular aerobic physical activity compared to sedentary HCM patients; 2) secondly, to perform a personalized moderate-intensity exercise prescription when feasible and evaluate its effects in terms of functional capacity and the occurrence of major adverse events, including death, aborted SCD, appropriate implantable cardioverter defibrillator (ICD) shocks, or sustained ventricular tachycardia (SVT).

1. HYPERTROPHIC CARDIOMYOPATHY

A cardiomyopathy is defined as “a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease (CAD), hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality”(14). Hypertrophic cardiomyopathy (HCM) is defined by “the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions”(15). Several methodologically diverse studies report a disease prevalence of 0.02–0.23% in adults among different ethnic groups(16, 17).

1.1 Genetic basis

In up to 60% of adolescents and adults with HCM, the disease is an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes(15). Mutations in the genes encoding beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) account for the majority of cases; less commonly affected genes include cardiac troponin I and T (TNNI3, TNNT2), tropomyosin alpha-1 chain (TPM1) and myosin light chain 3 (MYL3)(15, 18, 19). Generally, individuals harboring a mutation in sarcomere proteins, particularly those with multiple mutations in sarcomeric proteins, tend to exhibit earlier onset, more pronounced hypertrophy, microvascular dysfunction, and myocardial fibrosis and report a higher prevalence of family history of HCM and SCD than those without a mutation(18-20). Figure 1.1

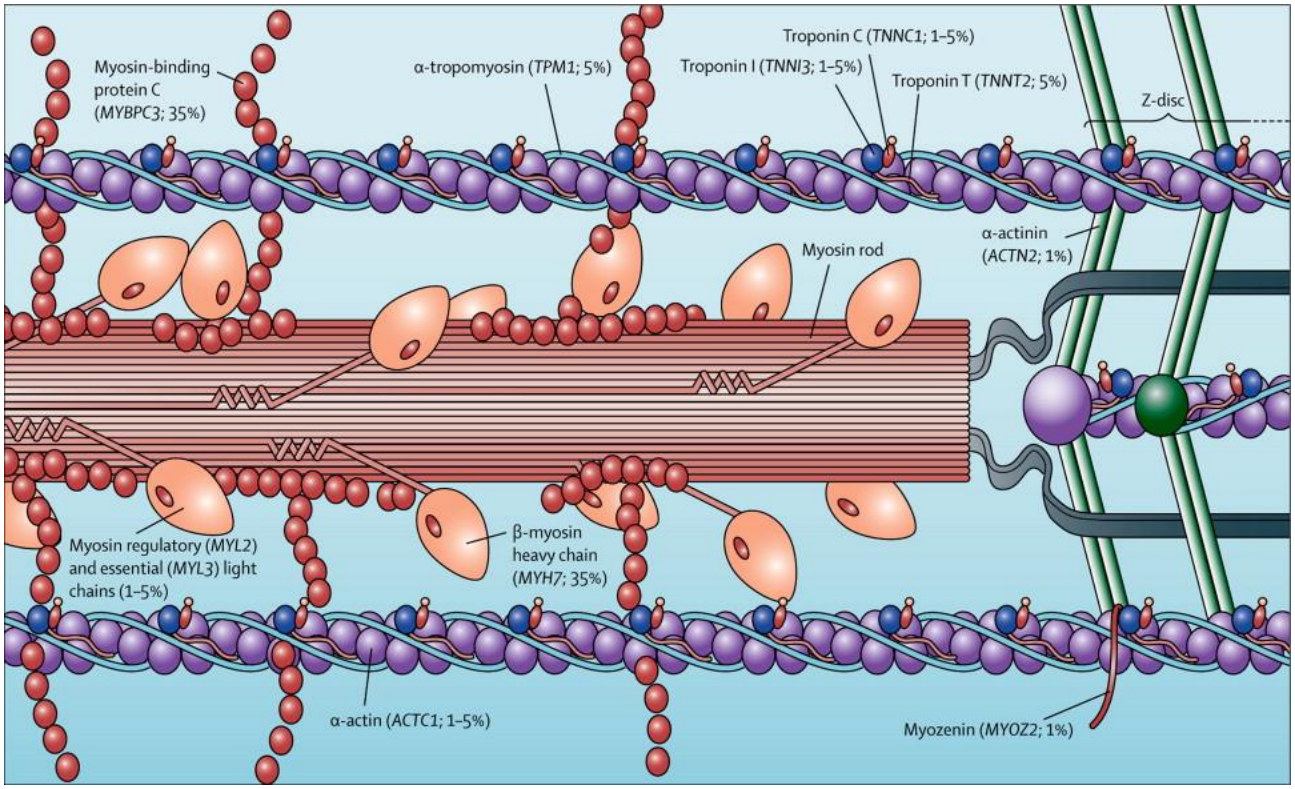
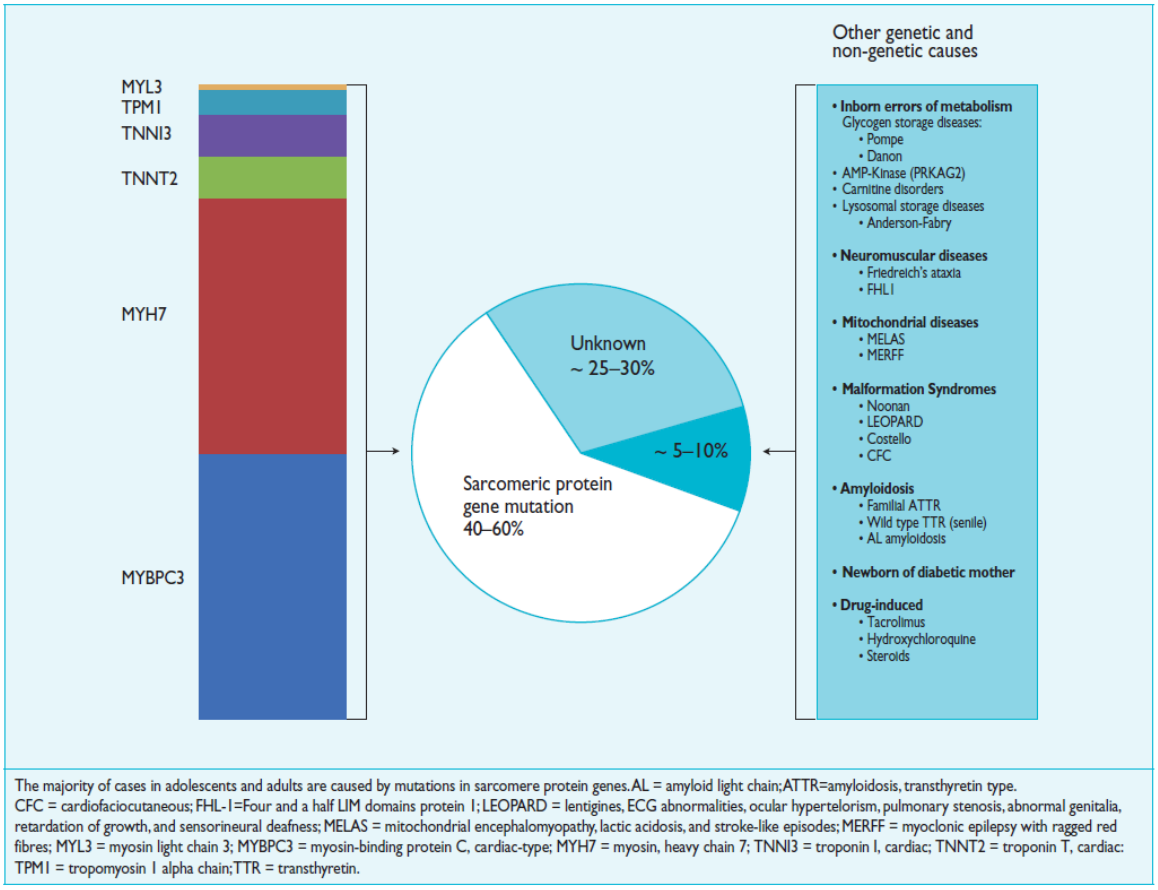


Figure 1.1 Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy(21).

In addition to these "sarcomeric" forms, five to ten percent of cases are caused by other genetic disorders, including inherited, metabolic (e.g., Danon disease caused by lysosome-associated membrane protein 2 LAMP-2 mutations, Anderson-Fabry disease, caused by a α-galactosidase deficiency) and neuromuscular diseases (e.g., Friedreich's ataxia), mitochondrial (caused by mutations in nuclear or mitochondrial DNA), chromosome abnormalities and genetic syndromes (the most common are those caused by mutations in genes that code for proteins of the Ras/mitogen activated protein kinase (MAPK) pathway, including Noonan, LEOPARD and Costello syndromes)(15, 22). Figure 1.2



The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR=amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1=Four and a half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNNI3 = troponin I, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

Figure 1.2 Diverse aetiology of hypertrophic cardiomyopathy(15).

1.2 Histopathology

Regarding the histopathology of HCM, hypertrophied cardiac muscle cells (myocytes) exhibit bizarre shapes and are arranged in chaotic and disorganized architectural patterns(23). At autopsy, most HCM patients exhibit areas of cell disarray and intramural coronary arterioles characterized by significant thickening of the vessel walls due to smooth muscle hyperplasia in the media, causing deformation and narrowing of the lumen. This microvascular disease affecting small blood vessels is responsible for recurrent episodes of asymptomatic myocardial ischemia leading to myocyte death, with a repair process that leads to myocardial fibrosis(23). Figure 1.3.

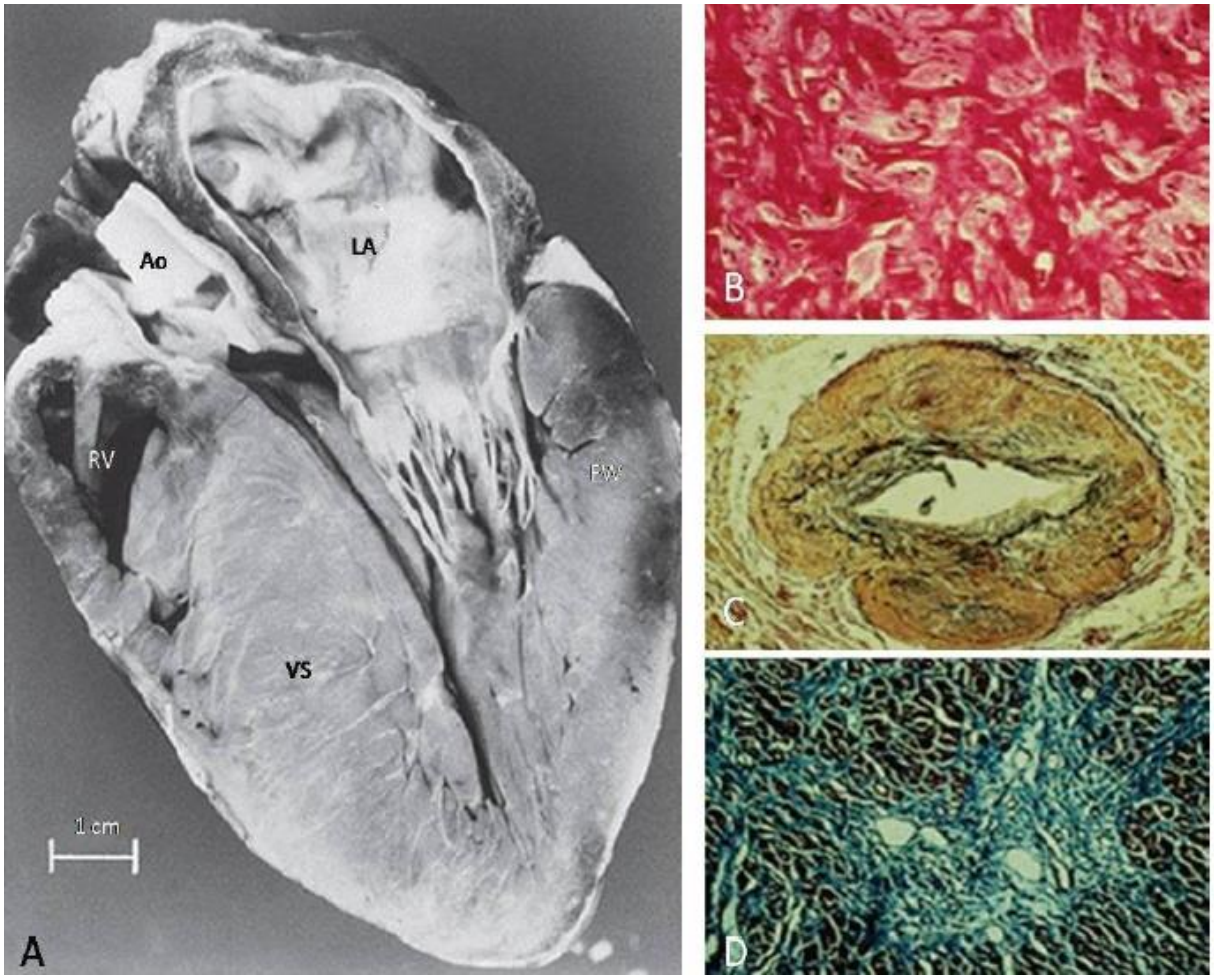


Figure 1.3. "Gross heart specimen shown in a cross-sectional plane similar to that of the echocardiographic (parasternal) long axis; pattern of LV hypertrophy is asymmetric, disproportionately involving the ventricular septum (VS), which typically bulges into the left ventricular outflow tract. Ao = aorta; FW = free wall of the left ventricle; LA = left atrium; RV = right ventricle. B, Histopathology characteristic of the left ventricle in HCM with septal myocardium showing markedly disordered architecture with adjacent hypertrophied cardiac muscle cells arranged at perpendicular and oblique angles. C, Intramural coronary artery with narrowed lumen and thickened wall, due primarily to medial (M) hypertrophy. D, Scar in ventricular septum, representing repair process after clinically silent ischemia and myocyte death"(23).

1.3 Pathophysiology

From a macroscopic point of view, hypertrophy is the most relevant and characteristic anatomical aspect of HCM. LV hypertrophy (LVH) in HCM is asymmetric, frequently extensive, involving ventricular septum and LV free wall, with one or more regions of LV chamber thicker than other areas, often with sharp transition in thickness between adjacent areas or noncontiguous patterns of segmental hypertrophy(21, 24). However, in the apical HCM, wall

thickening is limited to segmental areas, including the most distal portion of the LV chamber. LVH can undergo a dynamic evolution, sometimes remaining incomplete until adolescence. During this period, accelerated growth and maturation of the individual can be associated with a spontaneous increase in LV wall thickness and a more extensive distribution of hypertrophy(21, 24).

In patients with HCM, in addition to asymmetric hypertrophy, numerous other macroscopic alterations may be present in variable combinations, such as thickening and elongation of the mitral leaflets, the presence of anomalous papillary muscles (e.g., insertion of the papillary muscles directly into the anterior leaflet mitral valve without interposition of the chordae tendineae)(15, 21).

All these mechanisms can lead to the development of LV outflow tract obstruction (LVOTO). In most patients, the systolic anterior motion (SAM) of the mitral valve in which elongated leaflets bend sharply at 90 degrees and contact the septum during mid systole, contributes to produce the obstruction(25, 26). Approximately one-third of patients exhibit resting SAM, resulting in LVOTO, while another third experience latent obstruction only during specific situations, such as changes in loading conditions or LV contractility, including exercise. It's important to note that LVOTO in HCM is dynamic and can be reduced or eliminated through interventions that decrease myocardial contractility, such as the use of beta-adrenergic blocking drugs, or by increasing ventricular volume or arterial pressure through actions like squatting, isometric handgrip(25, 26). On the other hand, gradients can also be amplified in situations where arterial pressure or ventricular volume decreases, such as during the Valsalva manoeuvre, administration of substances like nitroglycerin or amyl nitrite, blood loss, or dehydration. An increase in LV contractility can also contribute to the LVOTO increase(25, 26).

By convention, LVOTO is defined as “an instantaneous peak Doppler LV outflow tract pressure gradient ≥30 mm Hg at rest or during physiological provocation such as Valsalva maneuver, standing and exercise”(15). A gradient of ≥50 mm Hg is usually considered the threshold at which LVOTO becomes hemodynamically important(15). Occasionally, intraventricular obstruction can arise at the mid-cavity level due to systolic contact between the septum and a papillary muscle that is abnormally positioned. Figure 1.4

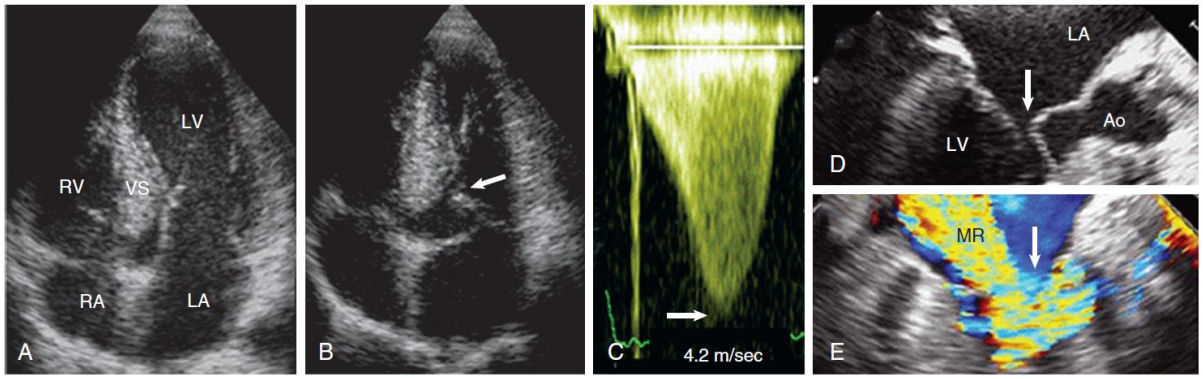


Figure 1.4. Dynamic LV outflow obstruction due to systolic anterior motion of the mitral valve(25, 26).

Hypertrophy, interstitial fibrosis, and disorganised cellular architecture collectively contribute to impaired LV relaxation and filling. As a result, diastolic dysfunction ensues, causing symptoms in individuals with non-obstructive disease. This diastolic dysfunction becomes the underlying mechanism for progressive heart failure (HF) to develop despite preserved LV systolic function(21).

1.4 Diagnosis

Physical examination findings in HCM can vary, and they are often associated with the patient's hemodynamic status. In individuals with LVOTO, a characteristic ejection systolic murmur can be auscultated at the left sternal border and apex. This murmur tends to vary in

intensity and can be accentuated by manoeuvres that decrease ventricular preload or afterload, such as standing up from the squatting position and forceful attempted exhalation against a closed airway (Valsalva manoeuvre)(15).

Many individuals with HCM complain of few, if any, symptoms. In such cases, the diagnosis can be incidental or the result of screening(15). The most frequent symptom is dyspnea, especially during exertion(15). Patients could complain of chest pain (without CAD) resulting from structural microvasculature abnormalities(21). Patients also may experience syncope or pre-syncope, potentially explained by arrhythmias or LVOTO. Palpitations are common and may be related to ventricular or supraventricular tachyarrhythmias(15).

The standard 12-lead ECG can be normal at presentation but generally shows a variable combination of LVH, ST- and T-wave abnormalities, and pathological Q-waves(15).

Echocardiography is the central method for diagnosis and follow-up, as it can define the location, extent, and severity of hypertrophy, the anatomy of the valves and papillary muscles and the presence of obstruction(15). In most patients, LVH preferentially involves the interventricular septum and basal segments of the LV but often extends into the lateral wall and the LV apex (15). The most relevant parameter is the maximum wall thickness, measured in end-diastole, preferably in the short axis, and it is crucial to conduct a thorough examination of all LV segments, recording the wall thickness at multiple levels, specifically at the mitral, mid-LV and apical level(15). The cut-off defined by the current guidelines is 15 mm, with values of 13-15 mm falling within the grey zone of the differential diagnosis with other conditions causing mild hypertrophy (e.g., arterial hypertension, athlete's heart)(15). Identification of LVOTO is important in managing symptoms and assessing SCD risk(14). Two-dimensional and Doppler echocardiography during a Valsalva manoeuvre is recommended in all patients(14).

Exercise echocardiography is recommended in symptomatic patients if bedside manoeuvres fail to induce LVOTO ≥50 mmHg(14).

Echocardiography is also useful for evaluating the systolic function, LV filling pressures, diastolic dysfunction, and left atrial (LA) dimensions and for observing any anomalies affecting the mitral valve(15).

Moreover, echocardiography is helpful in the differential diagnosis of HCM with the numerous conditions associated with secondary LVH, in particular hypertensive heart disease, aortic stenosis and "athlete's heart" (the latter suggested in particular by a positive training history of intense sports, associated with a normal systo-diastolic function, mild parietal hypertrophy with increased ventricular chambers), especially in the presence of mild hypertrophy with wall thicknesses in the range between 13 and 15 mm(15).

Additionally, certain echocardiographic characteristics can provide valuable clues for a specific diagnosis. For instance, concentric hypertrophy is more frequently observed in metabolic and infiltrative disorders. Conversely, a sparkling or granular myocardial texture, a small pericardial effusion, and thickening of the interatrial septum may suggest the possibility of myocardial storage disease or infiltration as an underlying cause(14, 15).

By applying the speckle tracking echocardiography (STE), which analyzes the global and regional function of the myocardium through various myocardial deformation parameters(27), Huang et al. observed that in HCM patients, the LV global longitudinal strain (GLS) was lower than in healthy subjects, not only in the myocardium affected by hypertrophy but also in the non-hypertrophic portions of the myocardium(28). Moreover, Alfonso et al. demonstrated that right ventricular (RV) GLS was impaired in patients with HCM(29).

D'Andrea et al. demonstrated that RV myocardial systolic deformation is negatively associated with increased septal thickness in HCM, while it is positively influenced by preload increase in

athletes(30). Therefore, STE may represent a useful tool in the differential diagnosis between athlete's heart and HCM, underlining the different involvement of RV myocardial function in either physiological or pathological LV hypertrophy(30).

In the differential diagnosis between HCM and "athlete's heart", not only the STE method can be useful, but the presence of the following factors must be taken into account, the positivity of which points towards the diagnosis of cardiomyopathy: family history of SCD/HCM, major ECG abnormalities (ST segment/T wave inversion, wide, and deep Q waves), normal or reduced LV cavity size (<54 mm), asymmetric hypertrophy, abnormal LV cavity geometry and/or segmental LVH, LVOTO, abnormal LV diastolic relaxation/filling, LA remodelling disproportionate to LV remodelling, unchanged LV wall thickness after detraining, positive Late gadolinium enhancement (LGE) on Cardiovascular magnetic resonance (CMR)(31).

CMR imaging offers detailed information on cardiac morphology, ventricular function, and myocardial tissue properties, and it surpasses echocardiography in the LVH evaluation and in the detection of LV apical and anterolateral hypertrophy, aneurysms, and thrombi(15). CMR is a valuable tool for identifying myocardial interstitial expansion attributed to fibrosis. LGE can be observed in approximately 65% of patients, and it typically exhibits a patchy mid-wall pattern in areas of hypertrophy and at the anterior and posterior RV insertion points(14, 15, 32). Moreover, LGE extent quantification is crucial to obtain a more complete and accurate risk assessment of HCM patients because the extent of LGE≥10% can recognize additional patients at increased risk for malignant arrhythmic episodes in a population with a low-intermediate SCD risk score(33). **Figure 1.5**

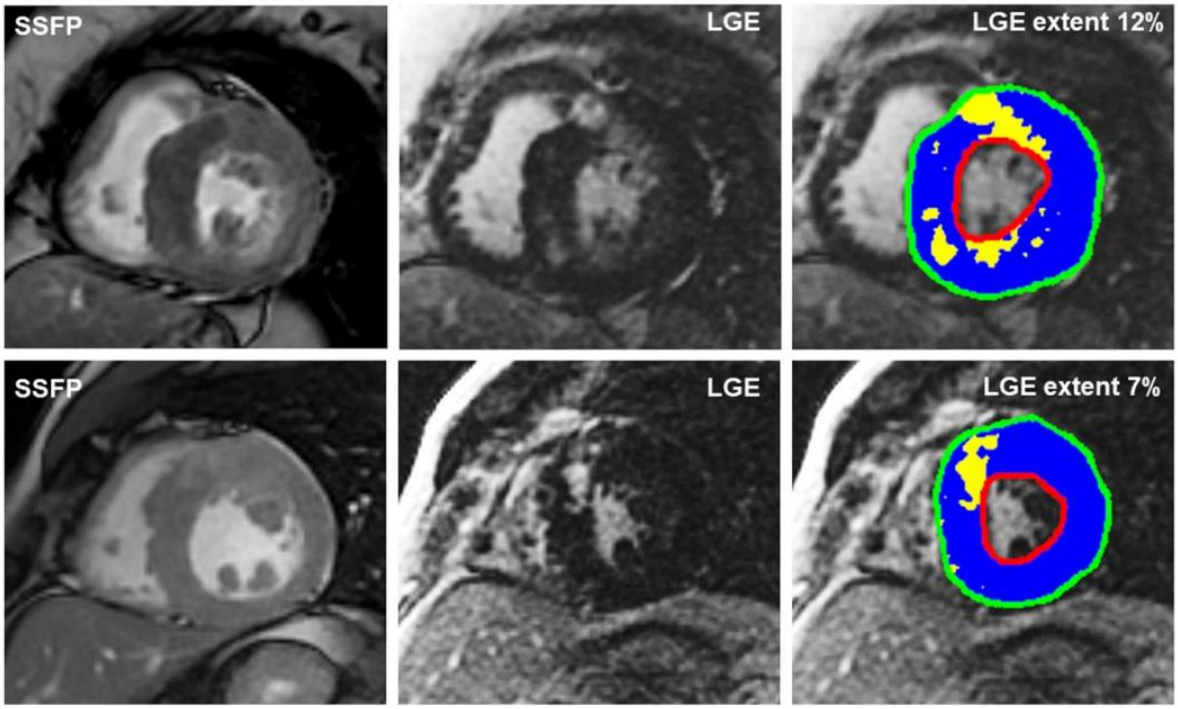


Figure 1.5 CMR images of two HCM patients with LGE extent ≥10% and <10% (respectively in upper and lower panels)(33).

1.5 Therapy

Pharmacological therapy is mostly administered on an empirical basis to improve functional capacity and reduce symptoms(14). The treatment approach for symptomatic patients with LVOTO aims to alleviate their symptoms through drugs, surgical intervention, or alcohol septal ablation. The treatment approach for symptomatic patients who do not exhibit significant LVOTO primarily centres on managing arrhythmias, lowering LV filling pressures, and managing angina and HF symptoms(15). In cases where patients with progressive LV systolic or diastolic dysfunction do not respond to medical therapy, they may be considered potential candidates for cardiac transplantation(14). In obstructive HCM, arterial and venous dilators, including nitrates, can exacerbate LVOTO and should be avoided(14). Patients with symptomatic LVOTO have been treated initially with non-vasodilating beta-blockers, gradually increasing the dose to the maximum level tolerated(14, 15). If beta-blockers alone prove ineffective, disopyramide may be considered an additional option, with the dose titrated up

to the maximum tolerated level(15). Verapamil can be used when beta-blockers are contraindicated or ineffective(14). Mavacamten is a first-in-class cardiac myosin adenosine triphosphatase (ATPase) inhibitor that acts by reducing actin–myosin cross-bridge formation, reducing contractility and the LVOTO and improving exercise capacity(14). Patients with an LVOTO gradient ≥50 mmHg, severe symptoms, and/or exertional or unexplained recurrent syncope despite maximally tolerated drug therapy should consider invasive treatment to reduce LVOTO(14, 34). Figure 1.6

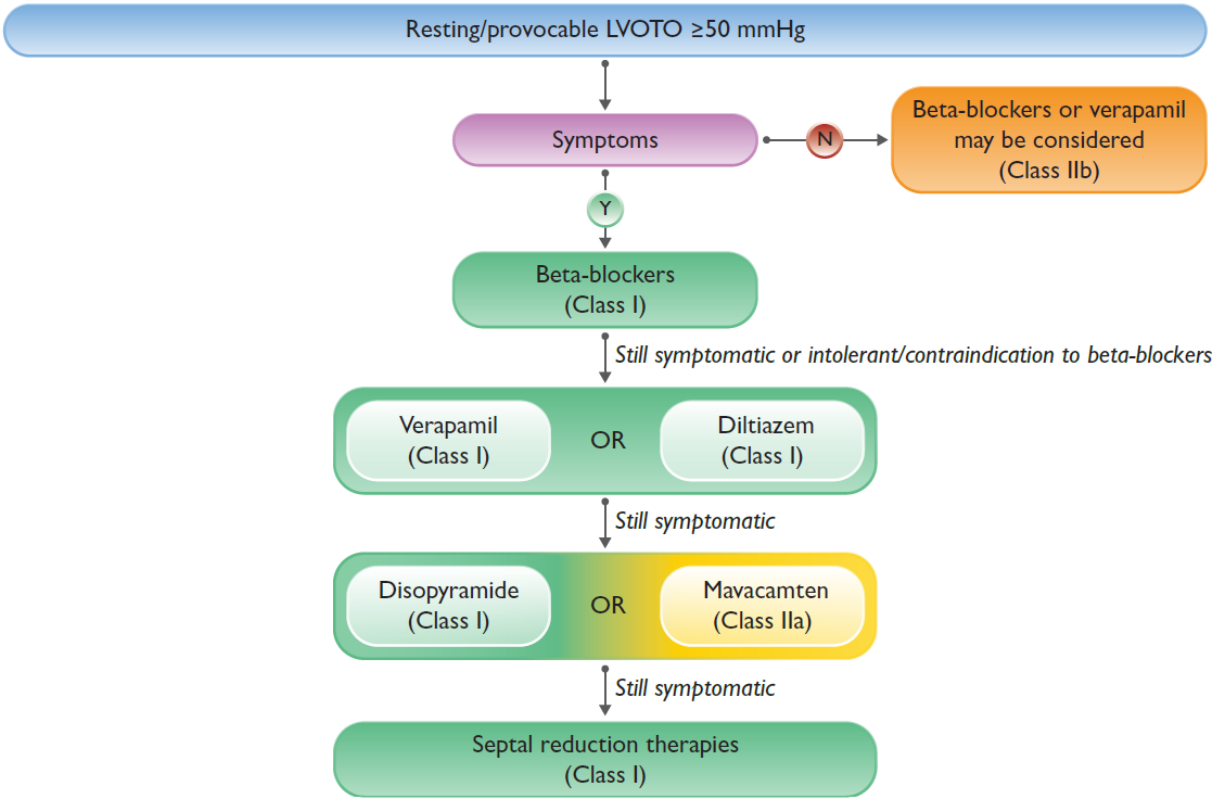


Figure 1.6 Flow chart on the management of left ventricular outflow tract obstruction. LVOTO, left ventricular outflow tract obstruction(14).

Most recent studies involving adult patients with HCM indicate an annual cardiovascular death rate of approximately 1–2% due to SCD, HF, and thromboembolism (14, 35). The most frequently documented fatal arrhythmic event among these patients is spontaneous

ventricular fibrillation, but asystole, atrioventricular block, and pulseless electrical activity have also been described as contributing to the mortality associated with HCM(14, 36). Estimation of SCD risk is an integral part of clinical management. ESC guidelines recommend the risk estimation using the validated HCM Risk-SCD score that provides an estimation of individual 5-year risk based on parameters such as maximum wall thickness, LA diameter, LV outflow gradient, family history of SCD, presence of non-sustained ventricular tachycardia (NSVT), unexplained syncope, and age at the time of evaluation(14, 37). Using this score, the patient is categorized into an SCD low/intermediate/high-risk group, which is useful for clinicians to implant an ICD for primary prevention(37).

2. HYPERTROPHIC CARDIOMYOPATHY AND PHYSICAL ACTIVITY

2.1 COMPETITIVE SPORT ACTIVITY

Current international guidelines and expert consensus documents agree that most HCM patients should be excluded from high-intensity competitive sports(3), as sports activity has a triggering effect on arrhythmias, presumably related to the increased sympathetic tone and release of catecholamines(38). Furthermore, intense physical exercise may act as a precipitating factor for initiating severe arrhythmias in certain cardiomyopathies and simultaneously precipitate their clinical evolution(2). In patients with HCM, pathological changes in cardiac structure and vasculature can result in myocardial ischemia, which is not solely attributable to an imbalance between the oxygen demand and supply to the hypertrophic muscle but is also influenced by perfusion abnormalities secondary to compressive deformation of intramyocardial blood vessels during systole and subsequent remodelling of these vessels(39). Reduced exercise tolerance is a frequently observed characteristic among HCM patients thatarises from the heart's inability to sustain an adequate cardiac output during physical exertion. This is primarily attributed to the reduced compliance of the fibrotic myocardium, leading to compromised diastolic filling, which in turn contributes to the onset of symptoms and a decline in exercise capacity(40). In fact, diastolic dysfunction is present in 80% of subjects with HCM, and the E/e' ratio (an index of ventricular filling pressures) correlates with New York Heart Association (NYHA) functional class and exercise capacity(40). Ciampi et al. observed that HCM patients could show an abnormal blood pressure response induced by physical exercise, an inability to increase systolic pressure by >20 mmHg during exertion, resulting in a lower cardiac output increase and associated with a high risk of SCD(41).

Finally, approximately half of the HCM patients show a phenomenon known as chronotropic incompetence, defined as the heart's inability to increase its rate in proportion to increased activity or demand. Chronotropic incompetence plays a pivotal role in determining exercise capacity and is recognized as an independent predictive factor for cardiovascular events and mortality(42).

The current recommendations regarding restricting competitive sport in patients with HCM stem from early evidence that vigorous exercise can trigger malignant arrhythmias and SCD. In fact, previous evidence has shown that HCM was a common cause of SCD in athletes(1). In particular, Maron et al., after compiling a comprehensive registry of SCD in competitive American athletes over a 27-year period, observed that HCM was the most frequent cardiovascular cause of SCD, accounting for one-third of these deaths(1). Figure 2.1

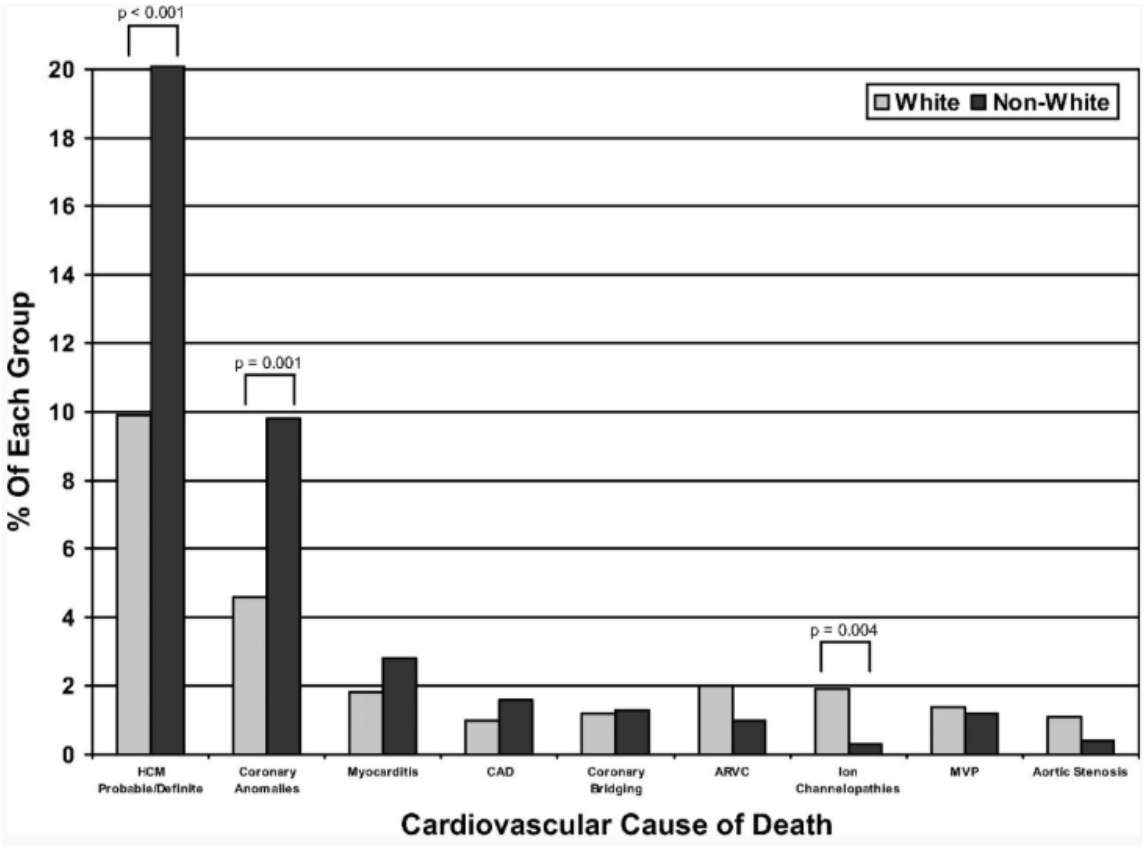


Figure 2.1 Cardiovascular deaths according to race, with respect to the number of white and nonwhite athletes with each disease(1). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy; CAD, coronary artery disease, and MVP, mitral valve prolapse.

Subsequently, another study by Maron et al., aimed at accurately defining the incidence and causes of SCD in U.S. college student-athletes, reiterated that HCM was the most frequent cardiovascular cause of SCD, accounting for 44% of deaths due to cardiac causes(2).

A lower prevalence of HCM-associated SCD (i.e., 8%) was then demonstrated by Harmon et al. in a database of National Collegiate Athletic Association deaths (2003–2013), with another 8% due to 'idiopathic left ventricular hypertrophy/possible cardiomyopathy'(43). In the UK, Finocchiaro et al. confirmed that 6% of SCDs were due to HCM, with the highest percentage (8%) observed in the range of age between 18–35 years(6). Figure 2.2

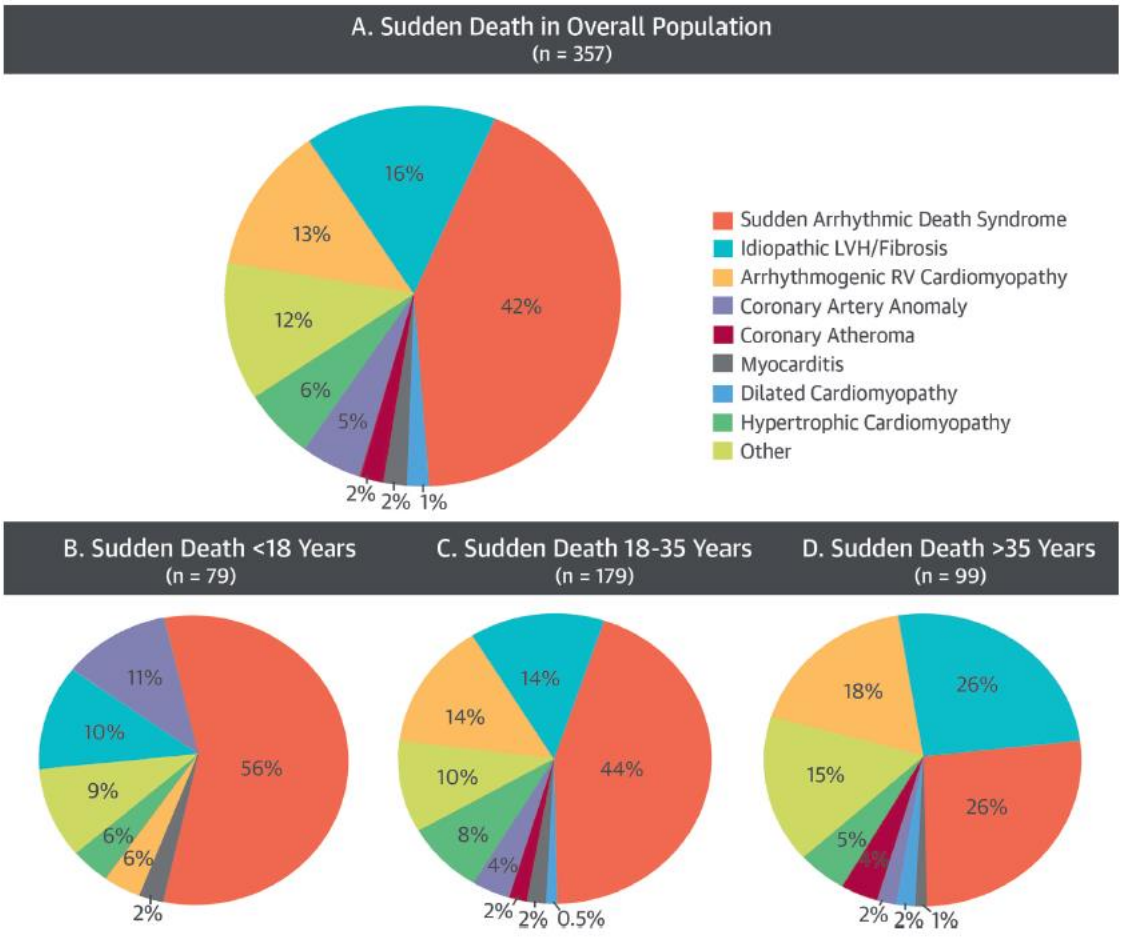


Figure 2.2 Sudden death is shown in the overall population (A), in subjects <18 years of age (B), subjects 18 to 35 years of age (C), and subjects >35 years of age (D)(6).

Nevertheless, when evaluating this matter, it is important to recognize that focusing exclusively on individuals who have experienced SCD during athletic activities can lead to a skewed perspective(7). A more comprehensive analysis, considering the circumstances and triggers of all instances of SCD within HCM cohorts, suggests that the association between arrhythmic events and exercise is not as strongly pronounced. In the study by Finocchiaro et al., 13 HCM individuals died while exercising, while seven events occurred at rest(6). If idiopathic LV hypertrophy is also considered, 34 cases occurred during exertion, and 25 cases died at rest(6).

In addition, other studies have emphasized that a significant number of ventricular arrhythmias interrupted by ICDs occurred irrespective of physical exercise involvement(44). Pelliccia et al. conducted a study to determine whether sports participation had a detrimental impact on the clinical progression of individuals with HCM by comparing athletes who continued their competitive sports activities with athletes who adopted a more sedentary lifestyle(4). The results from a 9-year follow-up revealed no significant differences between the two groups regarding symptom-free survival and cardiac events, suggesting that the occurrence of such complications was largely independent of whether or not individuals continued their training programs(4).

Therefore, while intensive exercise and competitive sports participation may trigger SCD due to accompanying alterations in hydration, electrolyte and acid-base status and surges in catecholamine levels, other mechanisms also seem to be involved in HCM, and the notion that less intense forms of exercise pose a significant risk remains uncertain(4, 45). Although some degree of uncertainty remains regarding the long-term safety of engaging in exercise at varying levels of intensity for individuals with HCM, a growing body of evidence suggests that

the associated risks are considerably lower than the initial estimations made more than a decade ago(46).

Indeed, the latest recommendations have taken a more liberal approach regarding exercise in individuals with low-risk HCM, effectively challenging the traditional notion that exercise and HCM are fundamentally incompatible(3).

Furthermore, in submaximal, tailored activity, the estimated risk is expected to be even lower and possibly not different from that associated with HCM in resting conditions or during routine daily activities(7).

2.2 BENEFITS OF PHYSICAL ACTIVITY

It has been known that physical activity brings cardiovascular benefits as it can modify risk factors such as hypertension, dyslipidemia, and diabetes, improve the quality of life, and reduce all-cause mortality and the risk of cancer, fractures, functional limitation, cognitive decline, and depression(9, 47). Conversely, the body quickly adapts to physical inactivity, which, if prolonged, can substantially reduce both quantitative and qualitative years of life(48). Physical inactivity is a risk factor for overweight, obesity, diabetes, ischemic heart disease, cancer, chronic conditions, all-cause mortality, and major cariovascular events(9). As a result, regular physical activity is strongly recommended by international guidelines and should be regarded as a therapeutic strategy deserving prescription, akin to any other medication, in a personalized approach based on patients' characteristics, personal and medical history, and individual response(3, 7). Despite a considerable body of evidence supporting physical activity, it is still underprescribed by healthcare professionals, and personalized prescription remains more of an exception than the norm(7). Consequently,

individuals with HCM are less active and spend significantly less time engaged in recreational physical activity than the general population(49). This observation applies not only to the small subset of individuals who are constrained to inactivity due to functional limitations resulting from disease progression or worsening dynamic obstruction but extends to the majority of young individuals who exhibit minimal or no symptoms and who were previously engaged in competitive sports(49, 50). Some data indicate that most HCM patients do not meet the minimum recommended level of physical activity and are overweight or even obese(10, 50). Obesity, in turn, is associated with adverse cardiac remodelling in HCM patients, leading to increased LV mass and a higher likelihood of dynamic obstruction and congestive symptoms(10, 11). Furthermore, in the long term, physical inactivity and weight gain can significantly impact cardiovascular morbidity and mortality, exacerbating the natural progression of HCM(11). Therefore, while physical exercise may not cure HCM, its benefits can help patients improve their well-being and life expectancy.

Although some uncertainty still exists regarding the long-term safety of exercise at various intensity levels, the current evidence suggests that the risk is lower than previously estimated(46). Moreover, in the submaximal, personalized activity, the expected risk is lower and potentially not different from that associated with HCM at rest and during daily activities(46).

3. CARDIOPULMONARY EXERCISE TEST AND EXERCISE PRESCRIPTION

The Cardiopulmonary Exercise Test (CPET) combines the integrated analysis of ventilation (VE), oxygen saturation, oxygen consumption (Vo2), and carbon dioxide production (Vco2) with parameters typically assessed during incremental exercise ECG testing. These parameters include power output (watt), heart rate (HR), blood pressure (BP), ECG changes, and subjective symptoms. This comprehensive approach offers a holistic view of the mechanisms involved in the transport and utilization of oxygen during physical exercise(51, 52).

The importance of increasing the number of measurable responses allows for diagnostic conclusions that would not otherwise be possible with the evaluation of data from the traditional stress test alone(51). Therefore, this method significantly increases the quantity of valuable information in assessing the origin of dyspnea (cardiac or pulmonary), the patient's functional capacity, prognostic stratification, prescription of physical exercise, as well as the assessment of treatment effectiveness and the evaluation of perioperative and postoperative surgical risk and of valvular heart disease(52, 53).

In terms of methodology, CPET incorporates an ECG recording system and a system for measuring VE, exhaled gases (Oxygen consumption Vo_2 and carbon dioxide production Vco_2), which can be performed on a breath-by-breath basis, a method most frequently employed in clinical settings(52). It is advisable to prioritize "ramp" protocols, which involve a gradual increase in load over a short period, over "stepped" protocols(52). Various ramp gradients are commonly utilized for patients, with 10 W/min and 15 W/min being the most favoured options(51).

To date, the most used analysis scheme shows nine different graphs (Figure 3.1)(54). This format was initially introduced by Wasserman in 1986 and has been refined in subsequent versions(52, 55).

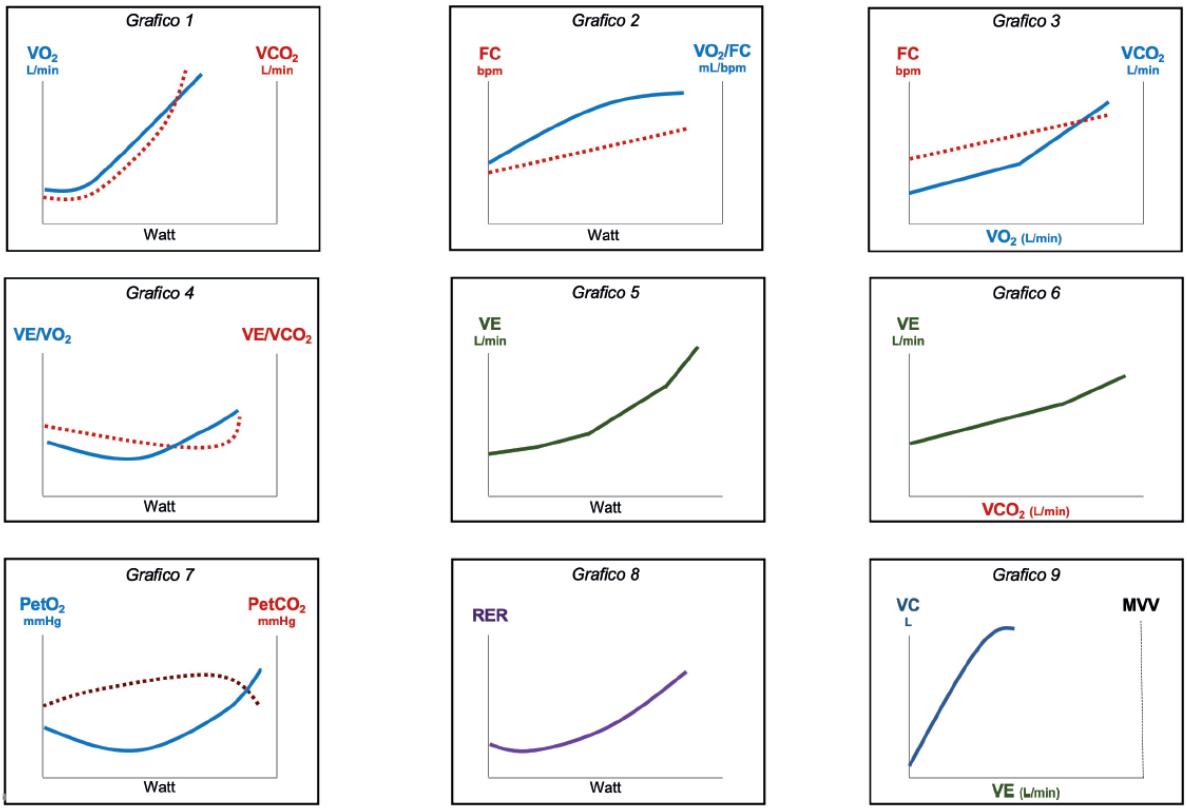


Figure 3.1 Cardiopulmonary exercise testing and 9-panel representation of the data. CV, vital capacity; CI, inspiratory capacity; MVV, maximal voluntary ventilation; HR; heart rate; Pet, partial pressure of end-tidal; RER, respiratory exchange ratio; VC, current volume; Vco2, carbon dioxide production; Vo2, oxygen consumption; VE, minute ventilation(52, 55).

- Panel 1: This graph illustrates the analysis of gas kinetics (Vo_2, Vco_2) over time. As the work rate (WR) increases, there is a continuous linear rise in V_2o When correctly formatted (with a Vo_2 to WR ratio of 10 mL/min to 1 watt), Vo_2 and WR should exhibit a parallel increase until peak exercise (or shortly before). Vco_2 demonstrates a linear increase until the first ventilatory threshold (VT_1) is reached, after which it increases disproportionately(52).

- Panel 2: this graph displays HR and oxygen pulse (Vo_2/HR) over time, serving as an indicator of cardiac performance and systolic output. According to the Fick principle, the oxygen pulse is the product of stroke volume and the difference in arteriovenous oxygen content. A pattern of flattening or decline in the oxygen pulse typically suggests altered stroke volume, possibly due to LV or RV dysfunction (e.g., exercise-induced ischemia)(52).
- Panel 3: This panel displays HR and Vco_2 plotted over Vo2. The slope of Vco_2 over Vo_2 remains equal to or less than 1 until VT_1 is attained. Beyond VT_1, Vco_2 increases at a higher rate than Vo_2, leading to a change in the slope (greater than 1), and the steepness of this change depends on the efficiency of the lactic acidosis buffering systems(52).
- Panel 4: This graph illustrates the ventilatory equivalent for Vo_2 and Vco2 plotted over time (VE/Vo_2, VE/Vco_2). Under normal physiological conditions, ventilatory equivalents decrease until they reach their lowest point at VT_1 for VE/Vo_2 and at the second ventilatory threshold (VT_2) for VE/Vco_2, which is traditionally associated with respiratory compensation and is sometimes referred to as the 'respiratory compensation point'(52).
- Panel 5: This panel illustrates the trend in ventilation during a progressive increase in workload, with a change in the slope occurring above VT_1. This change results from an elevation in respiratory drive following increased circulatory co_2. Additionally, this panel displays another change in slope at VT_2, driven by the saturation of buffering systems, resulting in acidosis (accumulation of lactate) and further stimulation of hyperventilation(52).

- Panel 6: This graph represents the relationship between VE and V_{CO_2}, serving as a measure of ventilatory co_2 elimination efficiency(52).
- Panel 7: This panel displays the analysis of partial end-tidal pressures of o_2 ($Peto_2$) and Vco_2 ($Petco_2$), offering insights into ventilation/perfusion mismatch(52).
- Panel 8: This graph illustrates the respiratory exchange ratio (RER) over time. RER is the ratio of Vco_2 to Vo_2, and it provides valuable information regarding energy expenditure and the relative contribution of different substrates, such as carbohydrates and fatty acids(52).
- Panel 9: This panel displays tidal volume (TV) as a function of VE, providing insights into the relationship between breathing patterns and ventilation(52).

The non-invasive determination of ventilatory thresholds (VTs) relies on analysing and integrating data derived from some of the nine panels (Figure 3.2).

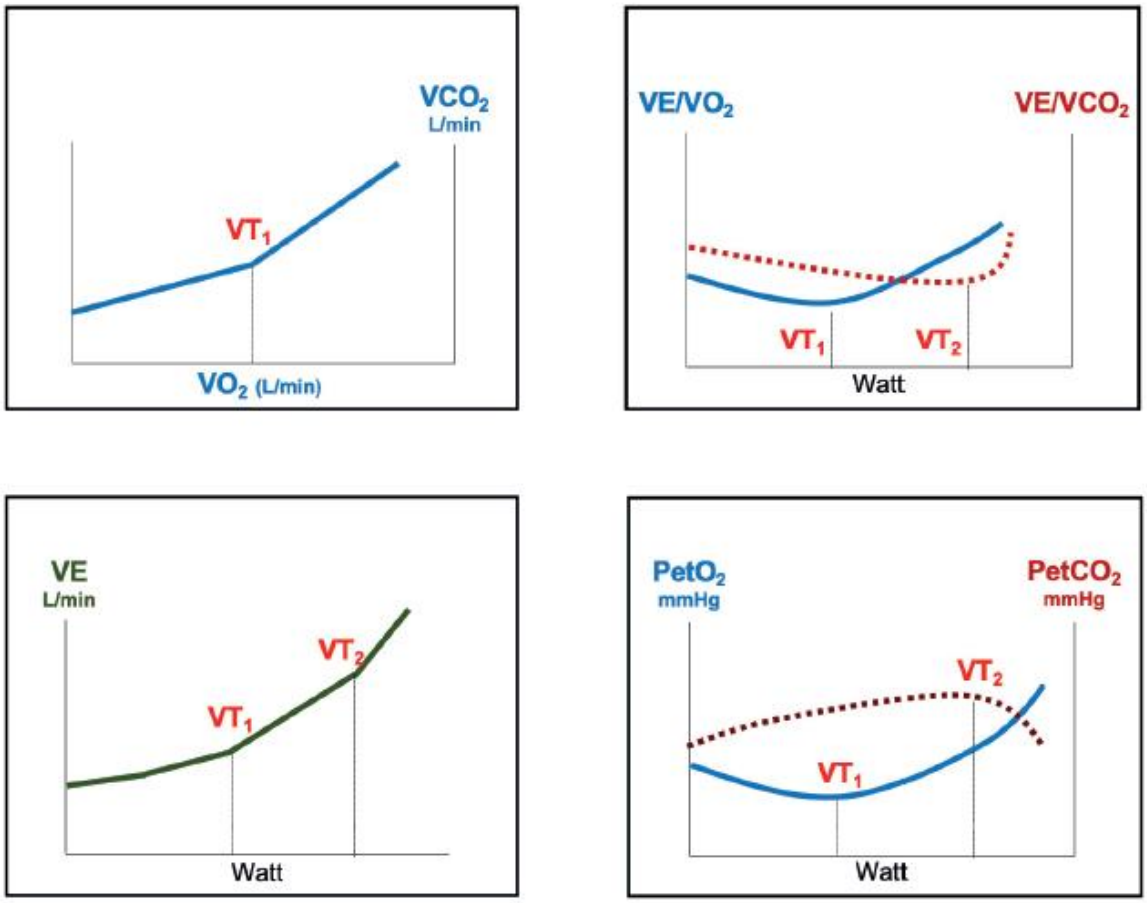


Figure 3.2 Methods to determine the first and second ventilatory thresholds by a cardiopulmonary exercise test. Pet, partial pressure of end-tidal; Vco2, carbon dioxide production; VE, minute ventilation; Vo2, oxygen consumption; VT1, first ventilatory threshold; VT2, second ventilatory threshold(52, 55).

The methods for VT_1 determination are the following: V-slope method (A change in the slope of Vco_2 versus Vo_2 ratio from an increase with a slope less than or equal to 1 to a slope greater than 1); The nadir of the first increase in VE/Vo_2, without a simultaneous increase in VE/Vco_2; The nadir of Peto2, while Petco2 remains constant or is increasing(52). The VT_2 is determined by analyzing the inflexion of VE vs. WR, the nadir of $VE/V_{\dot{c}}$ increase, and the Zenit and deflection point of $Petco_2$(52). VT_1 represents the limit that defines the transition from mild to moderate exercise intensity, while VT_2 represents the transition from heavy to very heavy exercise intensity(52). Indeed, VT_1 and VT_2 divide physical exercise into three phases. During the first phase of exercise, there is an increase in tissue oxygen extraction, along with increased

co_2 production and expiration, without a concurrent increase in blood lactate concentration(52, 55). As exercise intensity rises beyond VT_1, the second phase begins, during which lactic acid production surpasses its removal by muscle cells, resulting in its accumulation in the systemic circulation. The simultaneous increase in H+ ions is buffered by bicarbonate, leading to an elevated production of co_2 (Vco_2) and a continuous increase in the fraction of co_2 in the exhaled air ($Petco_2$). This central stimulation translates into an increase in minute ventilation while the increase in Vo_2 remains linear. With increased exercise intensity beyond VT_2, muscle lactate production exceeds the systemic elimination rate, resulting in an exponential rise in blood lactate levels.Bicarbonate buffering is insufficient to break down the H+ accumulation, leading to an increased ventilatory drive(52, 55).

CPET plays a role in prognostic stratification In HCM patients. A multicenter Italian study investigated the ability of CPET to improve current strategies for stratifying the risk of SCD in a total of 623 HCM patients from five third-level Italian centres(56). The study demonstrated that the VE/Vco_2 slope ratio derived from CPET was independently associated with SCD and appropriate ICD discharges. Specifically, a VE/Vco_2 slope cut-off of 31 showed the best accuracy in predicting the SCD endpoint in the entire study cohort, significantly enhancing the risk stratification of SCD, particularly in low-intermediate risk patient groups(56). Similarly, a study examined 182 patients with obstructive HCM and minimal or absent cardiovascular symptoms who underwent maximal exercise testing(57). Multivariate analysis revealed that the severity of outflow obstruction and Vo_{2peak} relative to predicted values were independent prognostic factors for SCD and the development of severe symptoms. Particularly, in patients with Vo_{2peak} < 60% of predicted, the 4-year survival free from SCD and severe symptoms was only 69%, underscoring how low exercise capacity, even without symptoms, was associated with an increased risk of adverse events(57). Lastly, a study

involving a cohort of approximately 1900 patients with a 12-year follow-up analyzed all CPET-derived parameters significantly associated with death or heart transplantation, highlighting that Vo_{2peak}, the VE/Vco_2 ratio, and VT_1 could predict an unfavourable outcome(58). The authors also quantified the magnitude of risk relative to the variables examined, revealing that the risk of death or transplantation decreased by 21% for every mL/kg/min increase in Vo_{2peak} and by 29% for every mL/kg/min increase in VT_1. Additionally, the mentioned risk increased by 18% for every 1 U increase in the VE/Vco_2 ratio(58).

Furthermore, in addition to its clear prognostic utility, CPET also plays a central role in the emerging field of personalized exercise prescription, which is gaining ground as a compromise between disqualification from competitive sports and complete physical inactivity. The most recent example is RESET-HCM, a randomized controlled study in which 67 HCM patients were assigned to a 16-week moderate-intensity training program while the control group, consisting of 69 patients, continued their usual activities(12). It's worth noting that in the intervention group, the training program was individually prescribed based on heart rate reserve (HRR) obtained through CPET. Specifically, they started with an intensity of 60% HRR for a minimum of three sessions per week, each lasting at least 20 minutes, progressively increasing to 70% HRR until the end of the training protocol. The results showed a significant increase in Vo_{2peak} in the intervention group, in contrast to the control group, where it remained stable. Furthermore, there were no adverse events in both groups, such as sustained ventricular arrhythmias, SCD, or ICD discharges(12).

In a prospective non-randomized study by Klempfner et al., 20 HCM patients experiencing significant limitations in physical activities in NYHA class II or III despite adequate therapy were enrolled in a supervised cardiac rehabilitation training program(13). The training program began with a minimum of two one-hour sessions per week, starting at an intensity of 50-60%

of HRR (calculated from the stress test) and gradually reaching 65-85%(13). The patients were continuously monitored using wireless telemetry systems and under medical supervision, completing an average of about 40 hours of aerobic training without adverse symptoms or sustained arrhythmias(13). Furthermore, the results demonstrated a 46% increase in functional capacity expressed in terms of metabolic equivalents (METs) obtained from the stress test. NYHA class also improved compared to baseline in half of the patients, with most reporting a subjective improvement in their clinical condition(13). Despite the limited number of patients and the absence of a control group, this study highlights how HCM symptomatic patients can benefit from a personalized exercise prescription.

In line with the emerging available evidence, personalized exercise prescription should primarily take into consideration individual characteristics, medical history, the individual's response to physical activity, prior training experience, the stage of each patient's disease, and all clinical characteristics that may serve as contraindications to physical activity (e.g., history of syncope or hypotension during exertion, recent HF, the presence of malignant ventricular arrhythmias, particularly during exertion, etc.)(7).

The exercise prescription bases its principles on the so-called 'FITT-VP' model(3, 52, 59):

- ✓ *Frequency*, that is, the number of sessions per week (3–5 days per week)(52).
- ✓ *Intensity* is the amount of energy expenditure/time unit during training sessions(3, 52). Various methods are available to determine the exercise intensity, categorized as subjective and objective approaches. Subjective methods include the Borg scale (perceived exertion scale) and the talk test (assessing the ability to speak during exercise). Objective methods involve calculating the percentage of maximal HR, HRR, or VO2 max(7, 52, 59). However, CPET provides a unique opportunity to establish ventilatory thresholds, representing the most reliable method for determining the

appropriate aerobic exercise intensity(52, 55, 60). Indeed, prescribing exercise intensity based on derived percentages rather than individually determined VTs may lead to inaccurate estimations of exercise intensities(60). This, in turn, could cause patients to train at an exercise intensity level that differs from what has been demonstrated to offer distinct clinical benefits(60). This is crucial because it has been demonstrated that plasma catecholamine levels remain consistently low at exercise intensities below VT_2 but increase rapidly at higher exercise intensities, serving as a trigger for malignant arrhythmias in predisposed individuals(38). Aerobic exercise intensity can be classified as light, moderate, high, and very high(3). Moderate aerobic exercise falls slightly above or around VT_1, allowing the HR value corresponding to VT_1 to serve as an objective reference for prescribing moderate aerobic exercise(3).

- ✓ *Time*, the duration of training sessions and the entire program (150–300 min/week of aerobic exercise intensity corresponding to VT_1)(52, 61).
- ✓ *Type of exercise*, for example, aerobic exercise, resistance training, balance and flexibility, stretching(52).
- ✓ *Volume* indicates the total amount of weekly exercise (8, 52).
- ✓ *Progression* is how the program advances. The exercise dose should be progressively and regularly increased rather than rapidly and intermittently, considering factors related to the patient(7, 52).

Once the program is prescribed, it is essential to emphasize to the patient the need for strict compliance with the instructions to prevent inadequate training from nullifying the benefits of personalized exercise activity(7).

4. AIM OF THE STUDY

The aims of this study were: 1) firstly, to assess the characteristics of HCM patients who practised regular aerobic physical activity compared to sedentary HCM patients; 2) secondly, to perform a personalized moderate-intensity exercise prescription when feasible and evaluate its effects in terms of functional capacity and the occurrence of major adverse events, including death, aborted SCD, appropriate ICD shocks, or SVT.

5. METHODS

5.1 Study group

We consecutively enrolled patients with a definitive diagnosis of HCM aged between 18 and 55 years, referred to our Center for a tailored exercise prescription between September 2019 and August 2023. HCM was diagnosed as recommended and defined by increased LV wall thickness that was not solely explained by abnormal loading conditions(14, 15). The population included sedentary individuals with HCM and patients with HCM who maintained an active lifestyle. The latter consisted of individuals who were engaged in physical activity on their own to stay active, as most of them had been excluded from competitive sports based on national protocols.

The exclusion criteria of the study were: NYHA functional class III-IV; impossibility to perform functional test; non-cardiac causes of functional limitation; septal reduction therapy and/or ICD implantation in the previous 3 months; acute HF or hospitalization in the previous 3 months; severe ventricular dysfunction, changes in the therapy in the previous 3 months; pregnancy.

5.2 Investigations

The patients were subjected to the following investigations:

- **Personal history and clinical profile:** clinical evaluation, including personal and family history, physical examination, genotype evaluation, comorbidities, drug therapy, and cardiac symptoms at rest or during effort (i.e., palpitations, dyspnoea, syncope, chest pain) were assessed. Information about the lifetime history of exercise, the type of exercise, and the intensity and volume of training per week were 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.
- **Electrocardiogram (ECG):** Resting HR, sinus rhythm, the presence of T-wave inversion (TWI), and bundle branch blocks were evaluated; LA enlargement (LAE) was defined as a P-wave duration > 120 ms or a negative portion of the P-wave of ≥0.1 mV in-depth and ≥40 ms in duration in the lead V_1(62). LVH was defined based on Sokolow-Lyon criteria voltage(15, 63). Q waves ≥40 ms in duration and/or ≥25% of the R wave in-depth and/or ≥3 mm in depth in at least two contiguous leads except aVR were considered pathological(15, 63).
- **Twelve-lead 48-hour ambulatory ECG monitoring:** the presence of rhythm abnormalities, supraventricular arrhythmias, ventricular arrhythmias, and other abnormal findings were investigated(15).
- **Echocardiogram**: LV and RV dimensions and function, aortic root diameters, and atrial dimensions were obtained as recommended(64, 65). LV volume measurements were calculated from the apical four- and two-chamber views using the modified Simpson's rule, and ejection fraction (EF) was calculated(64). Doppler LV outflow tract pressure gradient at rest or during physiological provocation such as Valsalva manoeuvre and exercise was calculated to evaluate the presence of LVOTO(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 (TDI) assessment of early (e') and late (a') diastolic peak velocities and their ratio were measured to assess diastolic function(64). 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 GLS was measured as the average of the LV longitudinal strain peaks obtained from two-, three-, and four-chamber views(66). RV GLS included the interventricular septum and RV free wall peak systolic longitudinal strain, measured as the average of the lateral wall's three segments (basal, mid-cavity, and apical)(67). Peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS), 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 (LA global PALS and global PACS)(67).

Echocardiograms were also performed during exercise to evaluate the LVOT gradient, the most important aspect of exercise echocardiography in HCM patients(68).

- **Cardiopulmonary Exercise Test:** The CPET data were realized on 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 exercise test (ramp protocol) included a 1-minute pre-exercise resting period sitting upright on the bike, a 2-minute unloaded warm-up cycling phase, followed by an incremental exercise cycling period with an increasing workload of 5–40W per minute, dependent on the patient's clinical status and aiming to complete the CPET within 8–12 minutes, as recommended(60, 69, 70). Oxygen consumption (Vo_2), carbon dioxide production (Vco_2), and ventilation (VE)

during exercise were analyzed breath by breath. Vo_{2peak}, first (VT_1) and at second (VT_2) ventilatory thresholds, ventilatory efficiency through ventilatory equivalent for carbon dioxide VE/Vco_2 slope, the respiratory exchange ratio (RER, defined as the ratio between Vco_2 and Vo_2), exercise breathing reserve, the partial end-tidal pressures of O_2 ($Peto_2$) and CO_2 ($Petco_2$), the Vo_2/WR ratio, peak exercise oxygen pulse (calculated as Vo_2/HR and provides an estimate of LV stroke-volume changes during exercise) were evaluated(69). The non-invasive VTs determination was based on the analysis and integration of data derived from some of the nine CPET panels(52). The methods for VT_1 determination were the following: V-slope method (a change in the slope of Vco_2 versus Vo_2 ratio from an increase with a slope less than or equal to 1 to a slope greater than 1); The nadir of the first increase in VE/Vo_2 without a simultaneous increase in VE/Vco_2; The nadir of $Peto_2$, while $Petco_2$ remains constant or is increasing(52, 60). The VT_2 was determined by analyzing the inflexion of VE vs. WR, the nadir of VE/Vco_2 increase, and the Zenit and deflection point of $Petco_2$(52, 60). Chronotropy competence, resting/peak blood pressure, oxygen saturation, supraventricular/ventricular arrhythmias and/or symptoms during exercise were also analyzed. The CPET was preceded by spirometry with the evaluation of respiratory parameters and classified as normal or pathological according to standardized criteria(71).

- **Personalized exercise prescription**

First of all, we assessed the presence of contraindications to physical activity (e.g., history of syncope/hypotension during effort, clinically relevant arrhythmias particularly during effort, presence of severe provocable obstruction at rest or during effort…)(7). In case of a clinical risk deemed to be excessively high and the impossibility

to temporarily practice exercise, we suggested a revaluation for an exercise program after the implementation of the medical therapy (e.g., after reducing a significant LVOTO)(8, 34). 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, 59).

The exercise prescription was based on the so-called 'FITT-VP' model (frequency, intensity, time, and type)(3, 52):

- *Frequency* is the number of sessions/weeks; patients were suggested to start with two sessions/week until reaching a target of 3–5 times/week(52).
- *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(52, 55, 60). 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 HR value corresponding to the VT_1 was derived and used as an objective indicator for prescribing moderate aerobic exercise(52, 59).
- *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 to reach 150–300 min/week of aerobic exercise with intensity corresponding to VT_1(52).
- *Type of exercise* included aerobic continuous training (e.g., running, cycling, swimming, walking, etc.)(52). In non-obstructive patients, strength activities

were prescribed with an intensity corresponding to 40%–70% of 1 repetition maximum, adapted individually(7, 52).

- *Volume* indicates the total amount of exercise per week(8, 52).
- *Progression* is how the program advances. Specific instructions were provided regarding the Progression of the program to increase the exercise dose gradually, considering the patient's adaptation to exercise, age, and clinical characteristics(52, 59).

The exercise programs and the patients were reassessed with the same investigations (Personal history and clinical profile, ECG, echocardiography, ambulatory ECG monitoring, and CPET).

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 project.

6. STATISTICAL ANALYSIS

Continuous variables were reported as mean±standard deviation (SD), and the qualitative variables were reported as absolute numbers or percentages. The normal distribution was evaluated with the Shapiro-Wilk test. As appropriate for data distribution, the unpaired t test or the Mann-Whitney test was used to assess the statistical significance difference between the two groups. The qualitative variables were studied using the Chi-squared test. A p-value <0.05 was considered statistically significant for all the analyses. The analysis was conducted using the SPSS version 21.0 (Statistical Package for the Social Sciences Inc. Chicago, Illinois).

7. RESULTS

The study population comprised 71 HCM patients: 33 physically active patients (97% males; mean age: 39±14 years) and 38 sedentary patients (84% males; mean age: 38±14 years). The demographic, clinical, and electrocardiographic characteristics of the study cohort are reported in Table 1.

Mutations in the genes encoding beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) accounted for the majority of cases (12% and 15%, respectively, in the group of physically active patients, 17% and 5% in the sedentary group); less commonly affected genes included cardiac troponin I (TNNI3) (6% in the first group, 3% in the sedentary). Genetic analysis yielded negative results in the 12% of active patients and in the 18% of the other group; the remaining patients had not undergone the genetic test.

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

All physically active subjects were in NYHA functional class I, compared to 84% of sedentary patients, where the remaining 6 (16%) were in class II. No significative differences were found between the groups regarding symptoms at rest or during effort (i.e., presyncope, syncope, angina). However, sedentary patients reported more frequent palpitations than the other group (p=0.04). Physically active HCM patients more frequently practised aerobic training (e.g., walking, running, cycling, swimming), while two patients did strengthen activities. The average time of exercise was 4.5 ±1.3 hours per week. Three of them engaged in very high-intensity cycling despite medical advice.

More than half of HCM patients in the sedentary group and less than half in the active group were under beta-blocker therapy, with no significant differences between the two groups

(p=0.14). In the sedentary group, a higher incidence of atrial fibrillation (AF) was observed (p=0.03). The incidence of complex ventricular arrhythmias did not differ between the groups; however, 16% of sedentary patients underwent ICD implantation versus 3% in the active group (p value= 0.07), in most cases in primary prevention. The HCM risk-SCD score was higher in the sedentary group without significant differences between the two groups (p=0.26).

The typical anomalies of HCM were found on 12-lead resting ECG, with no significant differences in the two groups regarding the presence of LVH, LAE, pathological q waves, TWI, and bundle branch blocks.

Table 1. Demographic, clinical, electrocardiographic features of sedentary versus physically active patients with hypertrophic cardiomyopathy.

VARIABLES	Sedentary HCM	Physically active HCM	P value
Males, n (%)	32 (84.2)	32 (96.9)	0.07
Age, years	38±14	39±14	0.69
BSA, m^2	2.0±0.2	1.9±0.2	0.63
BMI, kg/m^2	26.1±3.6	24.7±2.7	0.09
Preobese (25-30 kg/m^2)	12 (32)	12 (36)	0.97
Obese (>30 kg/m^2)	6 (16)	1 (3)	0.07
Family history for 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)	
Pre-syncope n (%)	4 (10)	2 (6)	0.52
Pre-syncope 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**
Ambulatory ECG monitoring			
Atrial fibrillation	5 (13)	0 (0)	0.03
NSVT	6 (16)	8 (24)	0.43
Malignant arrhythmias n (%)	1 (3)	1(3)	0.95
ICD, n (%)	6 (16)	1 (3)	0.07
SCD risk score	2.9±2.1	2.4±1.4	0.26
Betablocker therapy n (%)	24 (63)	15 (45)	0.87
Type of beta-blocker			0.14
Nadolol n (%)	17 (71)	5 (33)	
Bisoprolol n (%)	6 (25)	9 (60)	

Metoprolol n (%)	1 (4)	1 (7)	
Other Therapies			
Amiodarone n (%)	2 (5)	0 (0)	
Ranolazina n (%)	3 (8)	1 (3)	
Disopiramide n(%)	0 (0)	1 (3)	
Resting ECG			0.435
TWI n (%)	14 (37)	11 (29)	
Q waves n (%)	3 (8)	5 (15)	
LAE n (%)	1 (3)	0 (0)	
LBBB 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, RBBB n (%)	1(3)	0(0)	

HCM: hypertrophic cardiomyopathy; BSA: Body Surface Area; BMI: Body Mass Index; SCD: Sudden Cardiac Death; NYHA: New York Heart Association; NSVT: non sustained ventricular tachycardia; ICD: Implantable cardioverter defibrillator; TWI: T-wave inversion; LAE: left atrial enlargement; LBBB: left bundle branch block; LVH: left ventricular hypertrophy; RBBB: right bundle branch block.

The echocardiographic characteristics were substantially comparable between the two groups (Table 2). The interventricular septum thickness (IVST) was increased in both groups as an expression of cardiomyopathy. The biventricular diameters, volumes and function, LA dimension and diastolic parameters were comparable between the two groups. A hemodynamically significant LVOT gradient (>50 mmHg) was not found at rest, with mean values at rest similar between the two cohorts. However, some patients developed a hemodynamically significant gradient during exercise (21% versus 3% in the active vs. sedentary group, p =0.01). In these cases, we have carried out a therapeutic implementation.

The 2D STE analysis did not reveal statistically significant differences related to the LV, RV, and LA mean strain parameters.

Table 2. Standard and advanced echocardiographic features of sedentary vs. physically active patients with hypertrophic cardiomyopathy

VARIABLES	Sedentary HCM	Physically active 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
PWT, mm	10.8±2.1	11.1±1.8	0.31
IVST max, mm	17.5±4.8	16.7±5.3	0.27
LA diameter, mm	35.9±8.0	37.3±7.7	0.51
LA volume, mL	69.8±23.6	69.7±20.2	0.76
LA volume/BSA, mL/m^2	34.7±11.2	35.3±9.3	0.56
LV EF, %	62.7±7.6	63.2±5.8	0.75
LV EDD, mm	46.1±5.9	46.9±5.1	0.52
LV ESD, mm	27.4±6.8	26.3±6.2	0.47
LV EDV, ml	109.8±32.3	108.8±25.1	0.90
LV ESV, ml	45.4±23.5	42.7±14.8	0.90
Resting LVOT gradient, mmHg	6.0±2.7	8.1±10.2	0.58
LVOT gradient after Valsalva manoeuvre, mmHg	7.3±5.4	12.3±15.6	0.68
LVOT gradient during exercise, mmHg	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	0.22
A wave, cm/s	50±13.5	56.4±16.4	0.08
E/A ratio	1.4±0.5	1.4±0.5	0.55
s', cm/s	8.6±2.1	8.3±2.5	0.72
e', cm/s	9.3±2.7	9.6±0.59	0.42
a', cm/s	7.5±2.9	7.6±2.8	0.55
E/e' ratio	7.8±2.4	8.1±2.6	0.80
RV mid-cavity EDD, mm	29.8±5.4	31.1±4.7	0.29
RV s', cm/s	13.6±2.4	13.5±2.2	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 FAC %	43±4.8	41.9±7.8	0.50
TAPSE, mm	23.9±3.4	23.8±3.3	0.70
Pulmonary Hypertension n (%)	0	0	
IVC, mm	17.5±2.6	18.1±3.4	0.49
LV mean strain %	-15.9±6.5	-17.6±3.6	0.21
LA mean PALS %	23.7±10.6	26.6±7.5	0.23
LA mean PACS %	9.1±5.4	11.2±5.8	0.17
RV strain free wall %	-23.7±8.5	-20.8±5.2	0.14
RV strain 6 segments %	-20.0±6.5	-18.1±3.9	0.20

IVST, interventricular septum thickness; PWT, posterior wall thickness; LA, left atrial; LV, left ventricular; EF, ejection fraction; EDD, end-diastolic diameter; ESD, end-systolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; LVOT, left ventricle outflow tract; RV, right ventricular; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; IVC, inferior vena cava; PALS, Peak atrial longitudinal strain; PACS, peak atrial contraction strain

CPET parameters are described in Table 3. Physically active patients achieved higher workloads compared to sedentary 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 HCM patients ($p\leq0.0001$), with higher values also at VT_1 ($p=0.004$) and VT_2 ($p=0.001$). Moreover, physically active HCM patients demonstrated greater ventilatory efficiency (VE/Vco_2 slope, $p=0.004$) and higher peak exercise oxygen pulse ($p=0.03$) and Vo_2/WR ($p=0.002$) than sedentary HCM patients. No pulmonary limitation to exercise was identified. No significant arrhythmias occurred during the test, and no one exhibited chronotropic incompetence or symptoms. A hypertensive response was observed in a few patients, mainly in the sedentary group, without significant differences between the two groups ($p=0.5$).

Table 3. Cardiopulmonary exercise testing parameters collected in sedentary and physically active patients with hypertrophic cardiomyopathy.

VARIABLES	Sedentary HCM	Physically active HCM	P value
Peak Cycling Power Output, Watt	178.7±44.8	223.2±45.9	**≤0.0001**
$METS_{peak}$	7.2±2.1	9.4±2.1	**≤0.0001**
RER_{peak}	1.1±0.1	1.1±0.1	0.05
Vo_{2peak}, mL/min	2053.5±587.1	2569.7±516.2	**0.01**
Vo_{2peak} /kg, mL/min/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/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	0.1
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/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±12	0.08
VE/Vco_2 slope	29.9±5.2	26.7±4.3	**0.004**
VT_1 VE/Vco_2 slope	31.1±4.8	28.5±3.3	**0.02**

VE_{peak}, l/min	76.5±20.1	81.7±16.7	0.38
BR%	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/WR, $_{peak}$ mL/min/W	9.5±1.7	10.5±0.7	**0.002**
HRR, 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

METS: Metabolic Equivalent of Task; RER: Respiratory Exchange Ratio; Vo_2: oxygen uptake; HR: heart rate; VT_1: first ventilatory threshold; VT_2: second ventilatory threshold; Vco_2: exhaled carbon dioxide; VE: ventilation; BR: breathing reserve; WR: Work Rate; HRR: heart rate reserve.

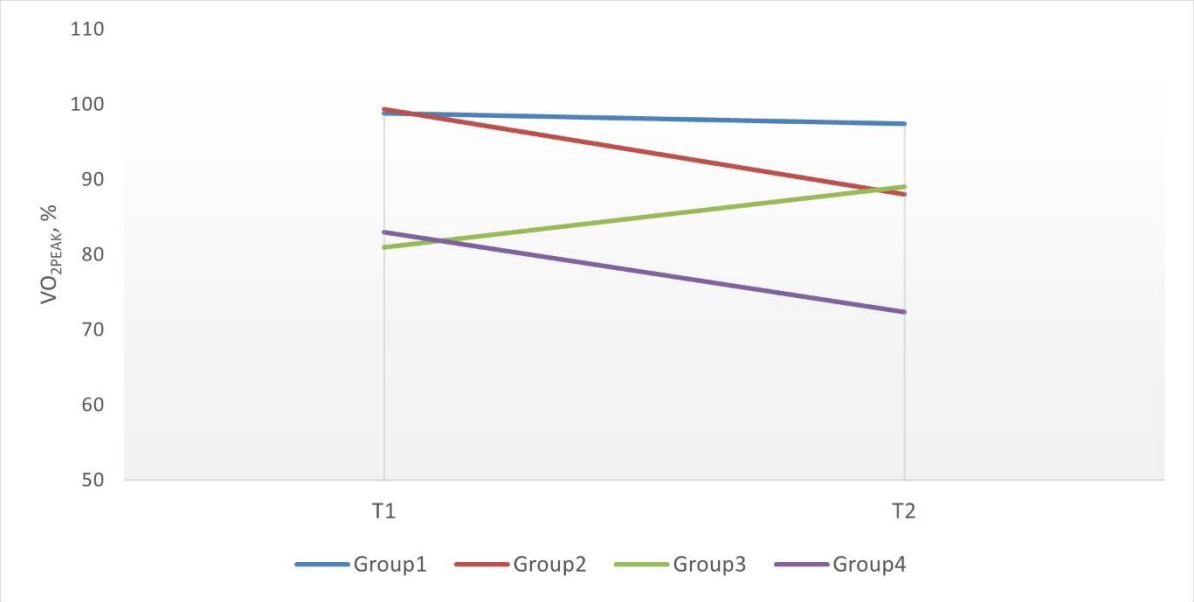
FOLLOW UP

Thirteen patients were evaluated after an average of 24±12 months from the first evaluation. The low number of patients in the follow-up is due to various reasons: firstly, unfortunately, the main limitation is related to the COVID-19 pandemic, which, on the one hand, initially halted and then slowed down our clinical activities in this regard, and on the other hand, did not allow patients to engage in physical activity due to imposed closure. Secondly, exercise prescriptions could not be provided to some patients due clinical risk deemed to be excessively high and the impossibility to temporarily practice exercise (i.e., after implementation of the medical therapy or reducing a significant LVOTO). Additionally, despite the patients referred to our center for specific indications related to exercise prescription, some of them did not start exercising and remained sedentary.

We divided these patients into four groups: group 1 was composed of HCM active patients who continued to practice exercise according to our prescription; one patient of this group

practised cycling with higher intensity than what was prescribed; group 2 included active patients who performed high-intensity activity until our first evaluation, and afterwards, they started to practice physical activity according to the prescription; group 3 was composed of HCM sedentary subjects who started the training program according to our prescription; group 4 included sedentary HCM patients who remained sedentary despite our exercise prescription.

In terms of percentage of predicted Vo $_{2peak,}$ in group 1, we observed a stability, in group 2, a slight reduction; in group 3, a significant increase; in group 4, a deterioration occurred (Central Figure). There were no major adverse events in any of the groups, including death, aborted SCD, appropriate ICD shocks, or SVT. However, NSVT occurred at rest in the patient who exercised beyond the prescribed thresholds and in a sedentary patient.



Central Figure: Percentage of predicted Vo_{2peak} trends between the first and second evaluation in the 4 patient groups (see text).

8. DISCUSSION

In this study, we analysed the clinical, electrocardiographic, echocardiographic, and cardiopulmonary characteristics of HCM patients, comparing physically active versus sedentary patients and we reassessed them in the follow-up after the prescription of the personalised exercise program. The main findings of the study are: i) Physically active HCM patients demonstrated better cardiopulmonary functional capacity, performance and ventilatory efficiency than sedentary patients; ii) no significant differences at baseline were observed between the groups regarding ventricular arrhythmias; iii) Moderate intensity exercise prescription led to improvement in cardiopulmonary fitness without the occurrence of malignant arrhythmias; iv) The sedentary lifestyle led to a deterioration of cardiopulmonary functional capacity and to a higher prevalence of obesity.

In our study, the Vo_{2peak} was greater in patients practising physical activity than in sedentary HCM individuals, with higher values also at VT_1 and VT_2. Although the sedentary HCM patients in this study have a slightly higher Vo_{2peak} than the values generally reported in the general population of HCM patients(12, 72), the 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 HCM patients is reduced by 21% for each 1 mL/kg/min increase in Vo_{2peak} and 29% for each 1 mL/kg/min increase in VT_1(58). 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 the subsequent development of severe symptoms(57). It has also been demonstrated that for HCM patients with a percentage of predicted Vo_{2peak}

<60%, the 4-year survival rate free of death and severe symptoms was only 59%(57). 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/min selected as a criterion for acceptance for cardiac transplant(73, 74). Moreover, in our study, physically active HCM patients demonstrated greater ventilatory efficiency, i.e., lower VE/Vco_2 slope than sedentary subjects. This is another pivotal point because the VE/Vco_2 slope is a well-known prognostic parameter for cardiac patients, and, specifically for HCM, the risk of death or transplant increases by 18% for each 1 U increase in VE/Vco_2(58). Indeed, 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(75). In general, VE/Vco_2 slope is a prognostic indicator of cardiac events in a heterogeneous group of patients with heart disease, i.e., ischemic heart disease, dilated cardiomyopathy, valvular disease, hypertensive heart disease(76). In chronic HF, VE/Vco_2 slope has a prognostic role in predicting cardiovascular events, such as death, ventricular assist device implantation, or heart transplant(77). In patients with diastolic HF the VE/Vco_2, rather than Vo_{2peak}, holds clinical and prognostic impact and is a powerful prognostic marker in this increasing subset of patients(78).

In our study, the active patients reported a higher, non-significant incidence of NSVT at rest. However, more sedentary patients underwent defibrillator implantation than the other group, in most cases in primary prevention, but without statistically significant differences with the active group, in the absence of significant differences in terms of morphological remodelling between the two groups. Dejgaard et al. did not find differences related to ventricular arrhythmias between HCM subjects 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(79). Conversely, a higher prevalence of a history of NSVT in the most active phenotypic group was found in a study exploring the relationship between lifelong physical activity and HCM phenotype expression(80).

In our cohort, a higher significant incidence of AF was observed in the sedentary group. Indeed, sedentary patients are often overweight, with negative implications for the outcome, as pre-obesity and obesity are independently associated with AF(10). In patients with HCM, AF is associated with significant morbidity, impaired quality of life, and high risk of all-cause death, SCD, HF-related death(81); furthermore, AF is associated with a substantial stroke risk as the risk of systemic embolization is high in HCM patients with AF(81, 82).

In this study, sedentary patients, who followed the moderate-intensity exercise program that we prescribed, increased their Vo_{2peak}. In contrast, 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, a randomized clinical trial of individualized moderate-intensity aerobic exercise training vs 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 training group compared with the usual-activity group, representing an absolute increase of 6%(12). Klempfner et al. demonstrated a significant functional capacity and NYHA functional class improvement in HCM patients enrolled on a supervised cardiac rehabilitation exercise program (moderate to high intensity)(13).

In our study, no significative arrhythmias were found in patients who practised exercise according to our prescription, while NSVT occurred at rest in a patient who practised exercise beyond the prescribed thresholds and in a sedentary patient. In the RESET-HCM, there were no major adverse events, including death, aborted SCD, appropriate ICD shocks, or SVT in

either group; however, a higher incidence of NSVT was reported in the group randomized to exercise(12). In the supervised exercise program of Klempfner et al., there were no adverse events, SVT or ICD discharges(13).

In our study, sedentary individuals had worse Vo_{2peak} than active patients, and continuing their sedentary lifestyle further exacerbated it, not benefiting from the exercise-induced increase in functional capacity. Moreover, 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). Furthermore, sedentary HCM patients showed a higher prevalence of obesity than active subjects of our study: obesity is highly prevalent among patients with HCM and is associated with an increase in LV mass, increased likelihood of obstructive physiology and adverse outcomes, particularly owing to HF and AF, and may dictate the progression of HF symptoms(10, 11). 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). The exercise restriction in HCM patients derives from early evidence that HCM was a frequent cause of SCD in competitive athletes(1, 2). However, endless alternative options exist between maximal, competitive engagement and complete inactivity(7). Therefore, it is pivotal to find the right balance in this dichotomy, and personalized exercise prescription plays a crucial role in this context for the prevention of disease-related complications. We observed that the tailored moderate-intensity exercise prescription is feasible for these patients, leading to a significant increase in Vo_2 values in sedentary patients and maintaining its stability in active patients, in the absence of adverse events.

LIMITATIONS

The main limitation of the study is that it analyzed a small number of patients in the follow-up, primarily due to the restrictions imposed by the COVID-19 pandemic. Indeed, the COVID-19 pandemic has imposed a general lockdown in most countries and consequently, the clinical activity had to slow down, and many patients were unable to engage in the recommended physical activity. Indeed, most studies highlighted a significant reduction in the amount of performed physical activity compared to before lockdown; this trend was evident not only in the general population but also among individuals with chronic conditions(83). Another limitation is that physical exercise was not supervised, also related to the fact that most of patients came from distant regions of Italy to our center to receive guidance on personalized exercise prescription; however, patients consistently attended regular visits, including prolonged ambulatory ECG monitoring, at their reference centers. Moreover, available evidence suggests that home-based rehabilitation may provide an alternative option for rehabilitation services for stable patients with cardiovascular diseases(84). The European guidelines on cardiovascular disease prevention state that home-based rehabilitation programs have the potential to enhance patient participation by providing increased flexibility and options for activities(85). A systematic review, comparing home-based and center-based rehabilitation, revealed no disparities in outcomes, adherence, or costs in both the short term and up to a 24-month period(85, 86).

9. CONCLUSIONS

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 HCM patients to counterbalance the negative effects of sedentary behaviour without significant major events.

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