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Review Article

Physical cardiac rehabilitation effects on cardio-metabolic outcomes in the patients with hypertrophic cardiomyopathy: a systematic review

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Abstract: Objectives: This systematic review aimed to review existing evidence to evaluate the effects of physical cardiac rehabilitation on cardio-pulmonary outcomes in the patients with hypertrophic cardiomyopathy (HCM). Methods: We conducted a systematic search of the databases PubMed, Web of Science, Embase, Scopus, and Google Scholar. The initial search led to 1222 citations after removing duplicate results. We included only English-written studies published since 2013 (2013-2023). Ultimately, we retrieved five studies, involving 235 participants. We used the Cochrane Risk of Bias Tool for randomized trials (RoB2) and risk of bias in non-randomized studies of intervention (ROBINS-I) for evaluating the risk of bias in randomized and non-randomized studies, respectively. Results: Results showed that four training programs improved participants' functional capacity by up to 46%. Improvements in weight, BMI, echocardiography, and remodeling parameters (left atrium volume index, premature ventricular contraction burden, pulmonary artery systolic pressure), exercise test results (minute ventilation/carbon dioxide production, peak workload, heart rate reserve, exercise duration, peak heart rate, peak systolic pressure, and blood pressure response to exercise normalization), and a decrease in N- Terminal Pro-Brain Natriuretic Peptide (NT-pro BNP) were reported in these studies. No major adverse events, including sustained tachyarrhythmia, implantable cardioverter-defibrillator discharge, and sudden cardiac death were reported. Conclusion: Supervised exercise training is safe and helpful for patients diagnosed with HCM. It can improve exercise capacity and is considered an adjunctive therapeutic option.

Keywords: Hypertrophic cardiomyopathy, HCM, heart failure, cardiac rehabilitation, exercise

Introduction

Hypertrophic cardiomyopathy is the most common type of hereditary cardiomyopathy that arises from autosomal dominant mutations in sarcomere protein genes that impacts heart muscle form and function [1, 2]. Clinical presentation of hypertrophic cardiomyopathy (HCM) exhibits considerable variability, encompassing asymptomatic individuals to those experiencing characteristic symptoms including, exertional dyspnea, tiredness, chest discomfort, and instances of pre-syncope or syncope. The diversity of phenotypes may be attributed to differing thicknesses of the left ventricular septum. However, some individuals carry the genetic mutation without left ventricular hypertrophy [3, 4]. Symptomatic hypertrophic cardiomyopathy profoundly affects patients' lifestyle and daily activities, leading to impairment and diminished functionality. Individuals with no prior physical restriction ultimately experience a decline in their physical activity capacity following the gradual development of symptoms, necessitating a reduction in their activities after diagnosis [5]. A sedentary lifestyle and lack of exercise inevitably result in decreased cardiovascular and res-

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piratory fitness, reduced functional capacity, decreased bone density, and a restricted range of motion in joints [6, 7].

Historically, hypertrophic cardiomyopathy was considered the primary reason for sudden cardiac death (SCD) in athletes [8-10]. International recommendations led to the exclusion of athletes with this condition from most competitive sports [11, 12]. However, recent studies suggest that the risk of SCD following exercise in individuals with HCM may not be as significant as previously thought. New post-mortem research has been shown that HCM contributes less to SCD in athletes [13, 14]. Studies on cardiac rehabilitation programs in older patients with HCM have demonstrated the safety and benefits of supervised exercise within appropriate limitations and moderation [15, 16]. Even murine models and clinical studies in athletes with HCM indicate that exercise may lead to favorable cardiac remodeling [6, 17]. Over the last ten years, researchers have examined the safety, benefits, and effects of cardiac rehabilitation on lifestyle, exercise capacity, and other factors in patients with HCM [15, 16, 18]. Also, the most recent guideline on HCM affirms the beneficial effects of exercise on the patients [19].

Cardiac rehabilitation (CR) is a physician-supervised schedule that consists of physician prescribed exercise, psychosocial counseling, nutritional recommendations, weight management, cardiovascular risk factor management, including tobacco cessation, blood pressure, and lipid management, which lead to patients' prognosis improvement. Strong evidence has shown the beneficial effects of cardiac rehabilitation programs on the patients living with various cardiovascular diseases [20-22]. One of the core components of CR programs is exercise training (ET), which has demonstrated the ability to increase exercise tolerance, lower cholesterol levels, alleviate patients' symptoms, and reduce mortality rates [23]. The most recent guidelines on HCM management emphasize the role of healthy supervised exercise programs as a beneficial treatment option. However, the participation rate of HCM patients in physical CR remains low due to the risk of ventricular arrhythmias and SCD during exercise [19].

Recently, studies have shown that supervised exercise can be considered a safe treatment option for HCM patients. According to the most recent guidelines, light exercise (<3 metabolic equivalent tasks (METs)), moderate (3-6 METs), and severe intensity grades of exercise (>6 METs) were not associated with an increased risk of arrhythmias in HCM patients. Furthermore, recent studies have shown that the risk of SCD following exercise in individuals with HCM may not be as significant as previously considered. New post-mortem research has also shown that HCM contributes less to SCD in athletes [13, 14].

Recent studies generally recommend regular physical activity plans for all HCM patients under expert team supervision. However, patients participating in moderate to severe competitive sports require an initial risk assessment to establish an individual training plan that aligns with their capacity [24]. In this review study, our objective is to examine studies that include exercise training components in cardiac rehabilitation programs for patients with HCM, and to explore the impact of physical training on patient outcomes.

Materials and methodology

The present study is a systematic review of various databases, conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [25]. Additionally, we have prospectively registered the study protocol on the International Prospective Registry of Systematic Reviews (PROSPERO), under the registration number CRD42023464385.

Search strategy

This systematic review contains a comprehensive search of electronic literature across multiple databases, namely PubMed/Medline, Scopus, Web of Science, Google Scholar, and Embase. We utilized all pertinent keywords for "hypertrophic cardiomyopathy", including "HOCM", "HCM", and the exact phrase, in addition to synonyms for "cardiac rehabilitation", such as "cardiac rehab*", "cardiovascular rehabilitation", "exercise", and "training". The specific search strategy for each database is available in Supplementary Table 1. Additionally, we

limited our search to studies published since 2013 (10 years backward).

Eligibility criteria and study selection

In this systematic review, we focused on (1) original studies including, clinical trials, cohort, and case-control studies. (2) Only English-written studies were included. (3) Only studies involving patients with a diagnosis of hypertrophic cardiomyopathy older than 18 years old, (4) and participants underwent supervised cardiac rehabilitation programs with physical training components for a specified period, were included. We included (5) comparative studies that either compared the intervention group with a control group or measure the effectiveness of rehabilitation training by comparing results before and after the intervention. (6) The included studies must report cardio-metabolic outcomes, which were defined as a) cardiac adverse events including arrhythmias, implantable cardioverter-defibrillator discharge, and sudden cardiac death; b) cardiovascular risk factors including, diabetes mellitus, blood pressure, lipid levels, obesity, and BMI; c) cardiovascular system function indices, including echocardiography parameters, BNP level, functional capacity, peak heart rate during exercise, exercise duration, and peak workload.

Exclusion criteria

Systematic reviews, meta-analyses, narrative reviews, case series, and case reports were excluded. Studies written in languages other than English, abstracts, posters, and experimental and animal studies were also excluded. Additionally, we excluded studies published before 2013.

Data extraction

The screening of titles and abstracts was carried out independently by four co-investigators, using the inclusion and exclusion criteria as well as considering the relevance of the topic. All studies were screened by at least two independent co-investigators, and disagreements were addressed by the consultation with a third reviewer. The final decision on which studies to include was made after all full texts were reviewed through discussion and agreement among all team members. We assessed the studies for their methodological quality once we included them.

Evaluation of bias

We evaluated the methodological quality of the included randomized controlled trials (RCTs) using the revised Cochrane Risk-of-Bias tool (RoB 2) [26]. This tool assesses bias in five domains, including selection bias (random sequence generation and allocation concealment), performance bias (blinding of patients and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting). We also used the risk of bias in non-randomized studies of intervention (ROBINS-I) tool for quality assessment of the non-randomized studies, which consists of pre-intervention (cofounding, selection of participants, classification of interventions) and post-intervention domains (deviations from the intended interventions, missing data, measurement of the outcomes, selection of the reported results) of bias [27].

Results

Literature search results

The initial search resulted in 1609 documents, including 257 from PubMed/Medline, 581 from Scopus, 621 from Web of Science, 105 from Embase, and 45 from Google Scholar. After removing 387 duplicated results, 1222 citations underwent title and abstract review, and after excluding irrelevant citations, 21 studies were considered for full-text review. Finally, we included 5 studies in this systematic review, as shown in the PRISMA flowchart (**Figure 1**).

Included and excluded studies

Table 1 shows that only 5 studies met the inclusion criteria, and 235 participants were included. The authors excluded 16 studies because they were published in languages other than English, contained only congress abstracts or posters, lacked enough information, or were of poor quality.

Risk of bias assessment

We used the Cochrane Risk of Bias Tool (Rob 2) for the evaluation of the risk of bias in a ran-

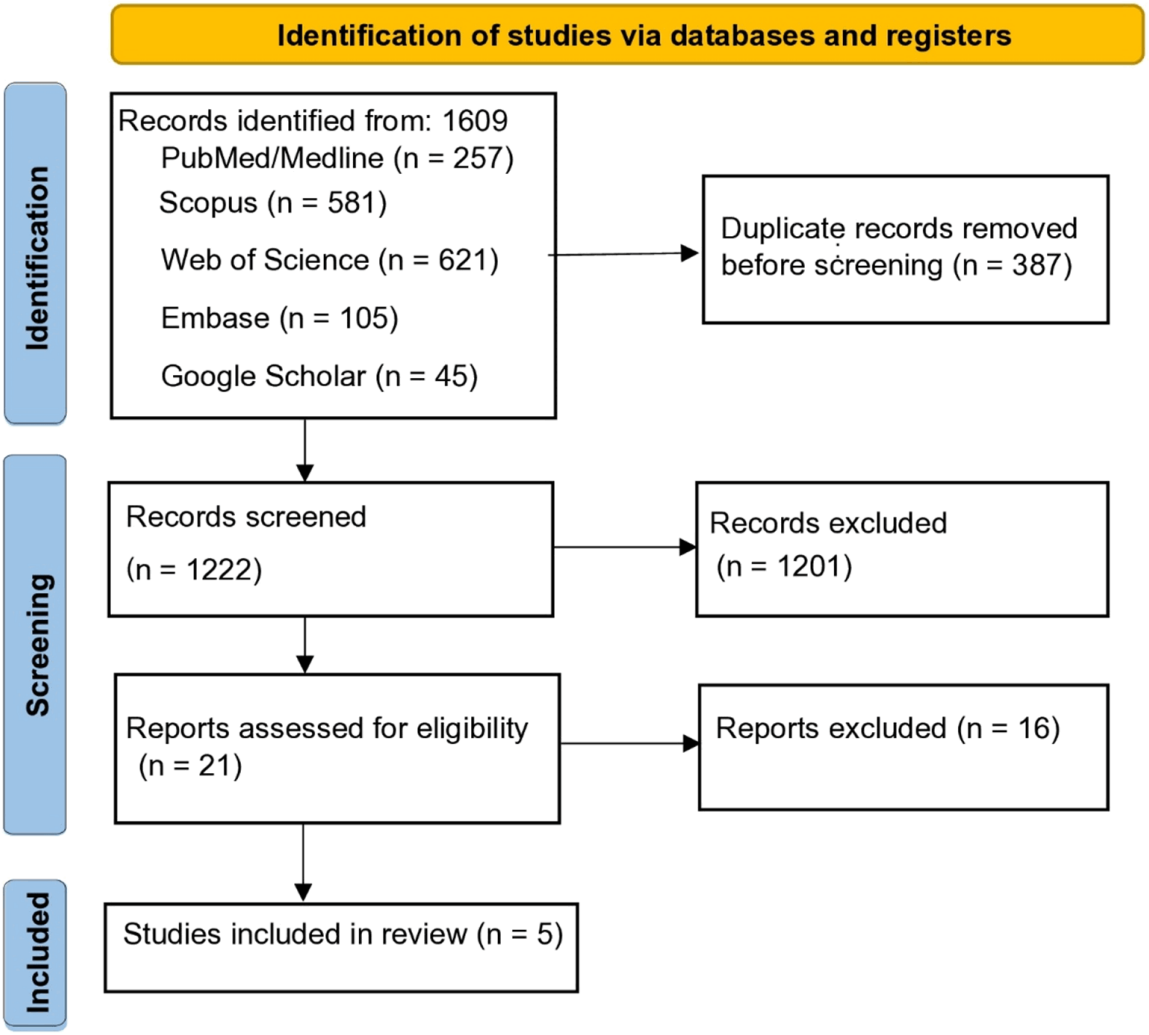

Figure 1. PRISMA Flow chart for systematic reviews with search results of various databases and registers.

domized controlled trial, as shown in **Table 2** [26, 27]. According to this scale, the study by Sara Saberi et al. can be considered low-risk of bias [16]. We also used the ROBINS-I tool for the methodological evaluation of non-randomized studies [27]. Regarding the domain of 'cofounding bias', we categorized all studies as having a "moderate risk of bias" due to using regression tools to attenuate the effects of the well-known cofounders. Regarding the 'selection of participants' domain, we considered all studies as having "low risk of bias" because there was no clear correlation between the selection criteria and the outcomes. In the domain of 'classification of intervention' all studies were categorized as "low risk of bias"; the process of classification of intervention was not prospective in the studies. Similarly, all studies were considered "low risk of bias" in the domain of 'deviations from the intended interventions'; there was no evidence of deviation from assignments with an impact on the results among participants.

Regarding the 'missing data' domain, all studies demonstrated a low risk of bias. The risk of bias in the domain of 'measurement of the outcomes' was "low" in all studies; the methods of measurement in groups were similar and the outcome measures seemed unlikely to be influenced by the participants' knowledge. We categorized the studies by Idan Hecht et al. [28] and Giuseppe Limongelli et al. [29] as having "low risk of bias" in 'selecting the reported results' because they referenced a previous study protocol. Others did not have a prior plan

Table 1. Studies summary of the effects of physical cardiac rehabilitation programs on patients with hypertrophic cardiomyopathy

Author, Year	Study Design	Country	Participants (size, gender, age)	Rehabilitation programs details	Intervention duration/frequency	Reported Results
Robert Klempfner et al. [2015]	Single-arm prospective non-randomized clinical trial	Israel	20 patients, 70% male, 62 ± 13 years	Each session commenced with a 10-minute warm-up phase at 40-50% of the heart rate reserve (HRR), followed by aerobic exercise (treadmill, arm ergometer and upright cycle exercise), concluding with a prolonged 15 minutes of cool-down (total duration: 60 minutes). The beginning exercise intensity aimed for 50-60% of the HRR, progressively escalated to 65-85% of HRR. On average, they were engaged in 41 ± 8 hours of aerobic exercise.	24 weeks, Twice a week	An enhancement in functional capacity (METs) from 4.7 ± 2.2 to 7.2 ± 2.8 (P<0.01), representing a 46% increase was noted, alongside an improvement of ≥1 in NYHA functional class in 50% of participants, with no deterioration reported in any patient. Heart rate reserve and exercise duration rose from 38 ± 19 to 45 ± 20 bpm, representing a 19% enhancement, and from 6.24 ± 2.48 to 8.13 ± 2. 29 minutes respectively (all P<0.05). No significant adverse effects were reported.
Sara Saberi et al. [2017]	Randomized clinical trial	USA	136 patients, 58% male, 50.4 ± 13.3 years	In the exercise group, sessions commenced at 60% of each individual's heart rate reserve and progressively escalated to a perceived effort range of 11-14 on the Borg scale (moderate intensity). Exercise modalities included cycling, walk-jog programs, and elliptical training. Each session endured 20-60 minutes. The control group maintained their regular daily activity.	16 weeks, 4-7 sessions a week	The peak oxygen consumption (VO2 peak) exhibited a 6% absolute increase in the exercise group vs to the regular activity group (between-group difference: +1.29 mL/kg/min; P=.02). Also, the SF-36v2 physical functioning scale shown substantial increase in the exercise group (difference, +8.2 points [95% CI, 2.6 to 13.7 points]). Additionally the exercise group exhibited a significant reduction in PVC burden (difference: -0.91 [95% CI, -1.76 to -0.05] PVC/h). No major adverse events were reported. One patient exhibited exercise-induced non-sustained ventricular tachycardia (NSVT).
Idan Hecht et al. [2017]	Observational study	Israel	107 patients (14 participants with HCM Without exact information)	The cardiac rehabilitation program included cardiac-related advice, dietary counseling, lifestyle modification, and a personalized exercise plan. The details of the exercise plans were not provided.	16-28 weeks, Twice a week	93% of patients with HCM (13 out of 14) had a normalized blood pressure response to exercise following the rehabilitation program; a rate significantly beyond that of participants without HCM (93% vs 62%, P: 0.03). No major adverse events were reported in the HCM cohort.
Yishay Wasserstrum et al. [2019]	Observational study	Israel	45 patients, 58 ± 13 years, 69% male	Each training session comprised a 15-minute warm-up period, followed by 45 minutes of exercise on a treadmill, a stair machine, and a bicycle, aimed at 60-70% of the heart rate reserve, often between 90 and 95 bpm, or a perceived exertion level of 13 Borg scale.	18 weeks, Twice a week	An enhancement in exercise capacity (METS, 5.3 ± 2.5 to 6.7 ± 2.5; P=0.01), peak heart rate (110 ± 23 to 120 ± 23 beats/min; P=0.05), and peak systolic blood pressure (144 ± 24.4 to 152 ± 30.0 mmHg; P=0.05) was observed. Additionally, 44% indicated enhancement in everyday functioning, subjective well-being, or physical activity levels. Only one patient experienced non-sustained ventricular tachycardia during exercise, with no other major adverse events.
Giuseppe Limongelli et al. [2021]	Observational study	Italy	20 patients, 45.3 ± 12.1 years, 65% male	During the first 6 months, engage in a minimum of 30 minutes of light physical activity on most days (4 to 5) of the week including walking briskly (<3 METS). Over the subsequent 18 months, each session included 20 minutes of cycling (60-80% of VO2 max), succeeded by resistance training, and concluded with body movements (3<METs<6). -All patients adhered to a Mediterranean diet.	96 weeks, 3 sessions a week	An increase in VO2 max (16.9 ± 4.6 vs 17.7 ± 4.4 mL/kg/min), peak workload (101.9 ± 30.2 vs 111.5 ± 26.0 watts), and a decrease in weight, BMI, left atrium volume index (44.9 ± 10.1 vs 42.7 ± 10.1 mL/m^2), and PASP (34.8 ± 9.4 vs 32.0 ± 7.7 mmHg), VE/VCO2 slope (30.5 ± 3.6 vs 30.5 ± 3.6), NT-proBNP (468.8 ± 269.5 vs 418.1 ± 290.9), LVEF (57.7 ± 9.6 vs 50.6 ± 8.3), and maximal wall thickness (21.0 ± 6.1 vs 20.5 ± 6.2) were observed; (all P<0.05). Four individuals developed incidental atrial fibrillation, whereas five patients experienced non-sustained ventricular tachycardia.

PASP: pulmonary artery systolic pressure, VE/VCO2: minute ventilation/carbon dioxide production, VO2max: maximal oxygen uptake, AF: atrial fibrillation, NSVT: non-sustained ventricular tachycardia, PVC: premature ventricular contraction, METs: metabolic equivalence tasks, NT-pro-BNP: N- Terminal Pro-Brain Natriuretic Peptide, NYHA: New York Heart Association, LVEF: left ventricle ejection fraction.

Table 2. Evaluating the risk of bias of the included studies according to cochrane risk of bias tools for randomized (RoB 2) and non-randomized (ROBINS-I) studies

Study	Cofounding	Selection of participants	Classification of interventions	Deviations from the intended interventions	Missing data	Measurement of the outcomes	Selection of the reported results	Overall (ROBINS-I)
Robert Klempfner et al. [2015]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Idan Hecht et al. [2017]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Yishay Wasserstrum et al. [2019]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Giuseppe Limongelli et al. [2021]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Study	Randomization process		Deviations from the intended interventions	Missing data		Measurement of the outcomes	Selection of the reported results	Overall (RoB 2)
Sara Saberi et al. [2017]	Low risk		Low risk	Low risk		Low risk	Low risk	Low risk

and showed some concerns in this regard. Generally, all studies had a moderate risk of bias.

Inter-examiner reliability had a high level of agreement (k=0.850).

Physical cardiac rehabilitation effects on cardio-pulmonary indicators in HCM

Generally, the studies that were looked at mostly didn't report any harmful effects that could have been fatal, including sustained ventricular arrhythmia, sudden cardiac arrest, appropriate defibrillator shock, and death during rehabilitation sessions. This suggests that supervised physical cardiac rehabilitation is almost safe in the patients with HCM. Methodological heterogeneity between studies and the limited number of studies with the same outcomes prevented us from conducting a meta-analysis.

Functional capacity (peak oxygen uptake (VO2 peak) or METs) was evaluated in 4 studies; all of them showed statistically significant improvement in exercise capacity indicators (up to 46%) after rehabilitation programs [16, 29-31]. Additionally, an increase in New York Heart Association (NYHA) classification, without deterioration in any subject [30], SF-36v2 physical functioning scale [16], and exercise duration [30] were observed in the studies.

Three of the included studies also evaluated the hemodynamic test results, which included peak workload, peak heart rate, blood pressure response to exercise, peak systolic blood pressure, and heart rate reserve. All the mentioned parameters increased after completing rehabilitation programs [28, 29, 31].

One study examined echocardiography parameters. Left atrium volume index (LAVI), pulmonary artery systolic pressure (PASP), minute ventilation/carbon dioxide production (VE/VCO2) slope, left ventricle ejection fraction (LVEF), maximal wall thickness, and premature ventricular contraction (PVC) burden showed a decrease after physical rehabilitation. It is noteworthy that changes in some of these parameters, such as LVEF, were not statistically significant after conducting multivariate regression, which indicates the effect of CR on cardiac remodeling in HCM patients [29].

Discussion

We performed a systematic review of 235 participants assessed in five studies to investigate the effectiveness and safety of physical-based cardiac rehabilitation programs in patients with HCM. The present review reveals three principal findings: (1) cardiac rehabilitation can significantly improve patients' functional capacity, including METs and peak VO2; (2) it also effectively improves weight, BMI, NYHA class, left heart remodeling, hemodynamic test results, and blood pressure normalization; (3) no significant adverse events including, sudden cardiac death, sustained tachyarrhythmia, and implantable cardiac defibrillator discharge, were reported, making it a safe therapeutic option for HCM patients.

Functional capacity improvement

There were four studies that evaluated physical CR efficacy on the exercise capacity of HCM subjects and all of them reported improvement. Saberi et al. conducted a randomized clinical trial of 136 individuals to evaluate the effect of moderate-intensity aerobic exercises on functional capacity in HCM patients [16]. The study assessed patients with HCM in two groups: exercise training and regular daily activity. After 16 weeks, the mean change in peak oxygen consumption in ET and regular activity groups was estimated at +1.35 (95% CI, 0.50 to 2.21) ml/kg/min and +0.08 (95% CI: -0.62 to 0.79) ml/kg/min, respectively, and the between-group difference was measured at 1.27 (95% CI, 0.17 to 2.37; p: 0.02) ml/kg/min. The results showed that walking 4-7 days per week for at least 30 minutes can improve functional capacity in HCM patients. This study also showed at least 1 score improvement in patients' NYHA class in half of the ET group, which is a major indicator of patients' clinical manifestations and quality of life and indicates the therapeutic potential of ET in the subjects [16]. In another study by Limongelli et al. [29], they evaluated 20 HCM patients in 12 and 24 months and proved that aerobic exercise training can cause significant functional capacity improvement. This study indicated significant changes in Vo2max (16.9 ± 4.6 ml/kg/min at baseline and 17.7 ± 4.4 ml/kg/min after 24 months; p: 0.029), peak workload (101.9 ± 30.2 at baseline and 107.9 ± 26.0 after 12 months; p:

0.005), and VE/VCO2 (30.5 ± 3.6 at baseline and 29.3 ± 2.8 after 12 months; p: 0.005) [29]. Yishay Wasserstrum also examined the effects of cardiac rehabilitation on 45 patients with HCM and reported a significant increment in functional capacity after 3 months. The mean increase in METs was +1.4 from the baseline (from mean 5.3 to 6.7; p: 0.01), and the cut-off of 6.8 METs was also defined as a threshold for maximum benefit from exercise interventions (p: 0.008) [31]. Similarly, the study by Robert Klempfner et al. produced positive results. This study was conducted on 20 symptomatic HCM patients and the exercise intensity gradually increased from 50% to 85% of the baseline heart rate reserve and indicated an improvement in METs after an average of 42 hours of aerobic ET (increased from 4.7 ± 2.2 to 7.2 ± 2.8 METs; p: 0.01) [30].

Previous studies showed that peak VO2 reduction is associated with increased mortality in HCM patients, as 1 ml/kg/min lower VO2 max is associated with a 16% increase in all-cause mortality. Researchers have not found any medical treatment that can improve this index in these patients [32-34]. Physical activity's effects on the cardiovascular system, which include remarkable adaptation in skeletal muscles, could potentially explain the reported improvement in functional capacity indices. Previous research also showed that physical activity can induce arteriovenous oxygen difference, widening peripheral blood flow, and endothelial tissue activity. Additionally, peripheral perfusion can increase the production of prostaglandins and nitric oxide (NO), which plays a big part in improving flow-mediated vasodilation. All of these processes will result in more oxygen reaching tissues [35-38]. Considering the beneficial effects of exercise training, setting an individual exercise plan for HCM patients would improve functional capacity by providing them with better oxygen delivery. Additionally, the enhanced functional capacity would enable them to engage in more activities and abandon a sedentary lifestyle and its negative consequences.

Heart rate, blood pressure, and reverse remodeling modulation

Previous investigations elucidated the effect of rehabilitation on changes in peak heart rate and blood pressure. In one study, 32 participants completed three months of the rehabilitation program. It showed noticeable changes in the peak heart rate (110 ± 23 to 120 ± 23 beats/min; p: 0.05) and peak systolic blood pressure (144 ± 24.4 to 152 ± 30.0; p: 0.05) [31]. In another study, 20 patients with symptomatic HCM completed an average of 41 ± 8 hours of the instructed ET program (twice a week, 60 minutes in each session). This study showed a significant increase in the heart rate reserve (38 ± 19 bpm to 45 ± 20 bpm; p: 0.048) after exercise [30]. Low heart rate reserve was reported as an independent factor of mortality in HCM [39].

Physiologically, exercise increases the demand on the heart, leading to a withdrawal of vagal tone, which provokes an increase in a heart rate. In addition, catecholamine release occurs at the nerve endings, which affects the secretion of epinephrine and norepinephrine into the systemic circulation, resulting in heart rate and contractility increase. Given the impaired chronotropic response in HCM patients, stemming from various factors like medications or myocardial damage, their increased heart rate and blood pressure could potentially reflect their enhanced functional capacity [40, 41]. Moreover, exercise training can improve endothelial function and facilitate heart rate increment [42-44]. Considering the beneficial effects of exercise and physical activity on heart and vessels, together with the improved patients' cardiovascular indices (i.e., blood pressure), ET programs should be considered safe and helpful in HCM patients.

Limongelli et al., who were investigating the simultaneous effectiveness of aerobic exercises and the Mediterranean diet on the weight loss of heart failure patients, concluded that supervised aerobic exercises are well-tolerated in patients with HCM and concomitantly can cause significant improvement in obesity status, which was reported to be a protective factor against dyspnea and AF incidence [29]. This study significantly revealed that physical activity can cause reverse left atrial (LA) and left ventricle (LV) remodeling and vascular function improvement in patients with heart failure, including patients with HCM. Owing to the scarcity of studies on this topic, future clinical investigations are necessary to confirm the reported

reverse remodeling potential of exercise in HCM [45, 46].

Another study indicated that patients suffering from heart failure due to HCM showed a higher rate of normalization of blood pressure in response to the graded exercise testing after at least 3 months of CR for one hour per session, twice a week, compared to patients with other causes of heart failure (93% vs 62%, respectively; p: 0.03). This study proved that ET can significantly refine this abnormal blood pressure response to exercise (ABPRE) [28]. ABPRE is considered to be linked to LV systolic dysfunction, oxygen consumption impairment, and a poor prognostic sign in HCM, which increases the risk of death. All the above-mentioned adverse effects can be attenuated by CR in HCM patients [47, 48]. Exercise stimuli may cause a decline in baroreflex sensitivity, which controls blood pressure, resulting in a drop in arterial pressure and LV systolic function. It is also worthy to point out the role of exercise in endothelial function improvement, heart rate adjustments, and venous return [42-44, 49, 50]. Therefore, providing HCM patients with ET plans would improve their vascular function, blood pressure response to exercise, and prognosis.

All included studies did not observe any cases of sudden cardiac death or lethal adverse events such as sustained tachyarrhythmia or implanted cardioverter-defibrillator discharge. Only four patients of incidental AF and six cases of non-sustained VT were reported in Limongelli and Wasserstrum's studies [29, 31], which indicates that supervised physical rehabilitation can be considered a safe therapeutic option for the patients with HCM.

Conclusion

Generally, patients affected by HCM can benefit from supervised exercise training programs with no major adverse effects. Supervised exercise training programs led by an expert team should be considered a safe and effective treatment option in HCM. According to the mentioned studies, the patients showed improvement in exercise capacity, blood pressure, pulmonary pressure, clinical manifestation, and PVC burden after several sessions of training. Considering the sedentary lifestyle and its consequences, a supervised ET program designed in accordance with the patients' capacity can noticeably improve their cardiovascular health, quality of life, and prognosis and could be considered as a safe adjunctive therapeutic option. However, we need to conduct additional studies on HCM patients to compare the effectiveness and safety of various exercise programs, such as high intensity versus moderate intensity continuous training, with various programs' duration, and to tailor specific exercise programs for each patient in the future.

Limitations

There are some limitations to our systematic review study. First, the number of the included studies is low, and we cannot reach a definite conclusion or do a meta-analysis on the results. Second, four of the included studies were observational studies with their inherent bias, including a lack of randomization and matching, with potential selection and cofounding bias that affects the results.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Search strategy

Search engine	Search strategy	Search date	Results
Pubmed	((("Cardiac Rehabilitation"[Mesh]) OR (cardiac rehabilitation[Title/Abstract]) OR (cardiac rehab[Title/Abstract]) OR (cardiovascular rehab[Title/Abstract]) OR (cardiovascular rehabilitation[Title/Abstract]) OR (exercise rehab[Title/Abstract]) OR (exercise rehabilitation[Title/Abstract]) OR (training[Title/Abstract]) OR (exercise training[Title/Abstract])) AND (("Cardiomyopathy, Hypertrophic"[Mesh]) OR (hypertrophic cardiomyopathy[Title/Abstract]) OR (hypertrophic cardiomyopathies[Title/Abstract])OR (hypertrophy cardiomyopathy[Title/Abstract]) OR (hypertrophy cardiomyopathies[Title/Abstract]) OR(HOCM[Title/Abstract]) OR (HCM[Title/Abstract]))	9/9/2023	257
Embase	#1 'heart rehab*':ti,ab,kw,exp OR 'cardiac rehab*':ti,ab,kw,exp OR 'coronary rehab*':ti,ab,kw,exp OR 'myocard* infarct8 rehab*':ti,ab,kw,exp OR 'infarct* rehab*':ti,ab,kw,exp OR 'cardiovascular rehab*':ti,ab,kw,exp OR 'heart rehab*' #2 'hypertroph* cardiomyopath*':ti,ab,kw,exp OR 'hypertroph* cmp':ti,ab,kw,exp OR 'asymmetrical septal hypertroph*':exp,ti,ab,kw OR 'asymmetric septal hypertroph*':ti,ab,kw,exp OR 'hypertroph* cardiomyopath*' OR 'hocm':ti,ab,kw,exp OR 'hcm':ti,ab,kw,exp #1 AND #2	9/9/2023	105
Web of Science	((TI=(cardiac-rehabilitation) OR AB=(cardiac-rehabilitation) OR AK=(cardiac-rehabilitation) OR TS=(cardiac-rehabilitation) OR TI=(cardiac-rehab*) OR AB=(cardiac-rehab*) OR AK=(cardiac-rehab*) OR TS=(cardiac-rehab*) OR TI=(cardiovascular-rehabilitation) OR AB=(cardiovascular-rehabilitation) OR AK=(cardiovascular-rehabilitation) OR TS=(cardiovascular-rehabilitation) OR TI=(cardiovascular-rehab*) OR AB=(cardiovascular-rehab*) OR AK=(cardiovascular-rehab*) OR TS=(cardiovascular-rehab*) OR TI=(training) OR AB=(training) OR AK=(training) OR TS=(training) OR TI=(exercise-training) OR AB=(exercise-training) OR AK=(exercise-training) OR TS=(exercise-training)) AND (TI=(hypertrophic cardiomyopathy) OR AB=(hypertrophic cardiomyopathy) OR AK=(hypertrophic cardiomyopathy) OR TS=(hypertrophic cardiomyopathy) OR TI=(hypertrophic cardiomyopathies) OR AB=(hypertrophic cardiomyopathies) OR AK=(hypertrophic cardiomyopathies) OR TS=(hypertrophic cardiomyopathies) OR TI=(hypertrophy cardiomyopathy) OR AB=(hypertrophy cardiomyopathy) OR AK=(hypertrophy cardiomyopathy) OR TS=(hypertrophy cardiomyopathy) OR TI=(hypertrophy cardiomyopathies) OR AB=(hypertrophy cardiomyopathies) OR AK=(hypertrophy cardiomyopathies) OR TS=(hypertrophy cardiomyopathies) OR TI=(HCM) OR AB=(HCM) OR AK=(HCM) OR TS=(HCM) OR TI=(HOCM) OR AB=(HOCM) OR AK=(HOCM) OR TS=(HOCM)))	9/9/2023	621
Scopus	TITLE-ABS-KEY (exercise-rehabilitation OR exercise-rehab OR training OR cardiovascular-rehabilitation OR cardiac-rehabilitation OR cardiac-rehab OR cardiovascular-rehab OR exercise-training) AND TITLE-ABS-KEY (hypertrophic-cardiomyopathy OR hocm OR hcm OR hypertrophy-cardiomyopathy OR hypertrophic-cardiomyopathies OR hypertrophy-cardiomyopathies)	9/9/2023	581
Google Scholar	("training exercise" OR "cardiac rehabilitation" OR "cardiovascular rehabilitation") AND ("hypertrophic cardiomyopathy" OR "HOCM" OR "HCM") AND ("training")	9/9/2023	45