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Review Article

Advantages of Exercise Training in Hypertrophic Cardiomyopathy: Considering Risks and Benefits

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Abstract

Hypertrophic cardiomyopathy (HCM) is one of the most common cardiac genetic disorders. The prevalence of this disease is 1 in 500 live births. It is stated to be the most frequent cause of sudden death in young adults. Therefore, some guidelines recommend to restrict physical activity and exercise. On the contrary, latest data show that active lifestyle and exercise in HCM patient provide significant benefits in cardiovascular function with no significant adverse reactions. Following to that, some experts might be reveal that its benefits might be outweigh risks.

There is a paucity of studies that examine the effectiveness of exercise for HCM. American Heart Association (AHA) and (European Society of Cardiology) ESC established exercise recommendations for HCM individuals based on discussion and consensus of experts. We found three studies that investigate the efficacy of exercise in HCM individuals. Outcomes of our interest were differences in cardiovascular function, quality of life and safety issues. All studies found positive significant differences in main outcomes measure in which the HCM subjects on exercise had better or improved outcomes. None reported adverse reaction such as fatal arrhythmia or sudden death related to exercise.

Old belief regarding exercise restrictions on HCM need to be reconsidered, given that at present exercise have been shown to provide significant benefits for reducing cardiovascular risk factors. Nevertheless, exercise in patients with HCM must be specifically considered regarding the risk and benefit. Practicing active lifestyle and exercise on HCM individual is an exciting possibility that need further study.

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Keywords: hypertrophic cardiomyopathy, exercise training, risks and benefit, physical activity

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Introduction

Physical activity restriction induces hypertrophic cardiomyopathy (HCM) patient to be inactive and sedentary.[1-2] Problems such as obesity, coronary heart disease, type 2 diabetes mellitus arise as an implication of undergoing sedentary lifestyle that increases the risk of cardiac events.[2] However, the relationship between exercise and sudden death

remains unclear, because there is insufficient scientific evidence.[3-6]

In this article, we discuss a narrative review about HCM and its pathophysiology related to exercise, provide summary of international guideline recommendations and review both positive potential benefits and negative risks of exercise training in HCM based on currently clinical and experimental data in some latest studies.

Hypertrophic Cardiomyopathy

HCM is characterized by a thickened but non-dilated left ventricle in the absence of other cardiac or systemic conditions (e.g., aortic valve stenosis, systemic hypertension, and some expressions of physiologic athlete's heart) capable of producing the magnitude of left ventricular (LV) hypertrophy evident.[4] HCM prevalence ranges from 0.2% - 0.5% of the total population worldwide (1: 500-1: 700).[1,3-10] In the United States, there is 600.000-700.000 individuals diagnosed with HCM.[4,7] Meanwhile in Indonesia, there is no data regarding the prevalence of HCM.

HCM is an autosomal dominant genetic disorder caused by a variety of mutations in genes encoding sarcomeric proteins and characterized by a broad and expanding clinical spectrum.[4] There are approximately 1400 mutations from 11 gene types associated with HCM events.[3] Almost 60% of HCM in adults are caused by mutations in the sarcomeres of the heart muscle protein. The most common mutations involving the beta-myosin heavy chain and myosin binding protein C account for more than 70% mutations identified in patient who are with genotype positive.[3,4,10,11]

Pathophysiology HCM is a complex mechanism. Initially, there is presence of myocytes hypertrophy which causes several abnormalities, such as obstruction of Left Ventricular Outflow Tract (LVOT), diastolic dysfunction, mitral regurgitation, myocardial ischemia and arrhythmia. Those four abnormalities mentioned earlier cause symptoms of dyspnea, syncope or sudden death.[4,7,12]

HCM can be asymptomatic or with severe clinical conditions. Typically, clinical symptoms of HCM appear before the age of 30-40 years.[4,7] Symptoms of heart failure (with preserved LV function) may develop unpredictably at any age, with functional limitation due to exertional dyspnea or fatigue, and in advanced stages by orthopnea or paroxysmal nocturnal dyspnea.[4] HCM end stage provides clinical features similar to heart failure and atrial fibrillation patient. [4,7]

Echocardiography is a gold standard modality in establishing diagnosis of HCM. It is usually recognized by maximal LV wall thickness ≥15 mm, with wall thickness of 13 to 14 mm considered borderline, particularly in the presence of other compelling information, like family history of HCM. Other supporting examinations are cardiac magnetic imaging resonance and computed tomography.[4,7,13]

Sudden Cardiac Death in Hypertrophy Cardiomyopathy

The risk of sudden death in HCM is recorded at only 0.1% per year, and is dominated by athletes. HCM is recognized as one of the most frequent causes of sudden death for ages <35 years,[1,3-10] as shown in figure 1.14 However, the actual number remains unclear.[3-6] Saberi (2017) stated that the incidence of sudden death in HCM is 1-3 in 100,000 cases.[5] This data is similar to sudden death incidence in the general population.[5,9,14]

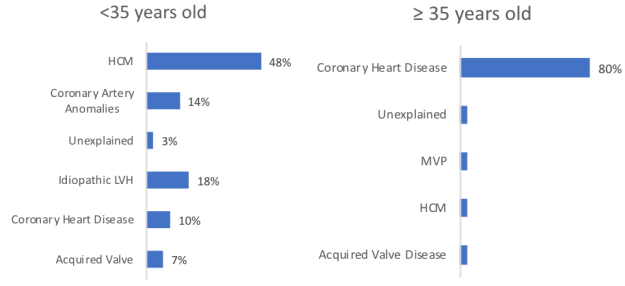

Figure 1. Cause of sudden death
Source : Lavie CJ, Milani RV, Mark P, Gruiter M. Exercise and the heart : risks, benefits, and recommendation for providing exercise prescriptions. The Ochsner Journ. 2001; 207-212

Sudden death mechanism in HCM related to exercise is unexplained. During exercise, there are several physiological changes that might induce sudden death, such as myocardial ischemia, vagal sympathetic imbalance, dehydration, electrolyte disturbances, metabolic acidosis and hemodynamic changes. However, to date, there has been no validated research to prove the exact cause of sudden death.[4,5,7] In fact, in some recent studies, sudden death commonly occur at rest condition, only about 11% occur during exercise.[5] In a

large-scale study conducted in England involving 1380 HCM patients given exercise testing, only 24 patients developed non-sustained ventricular tachycardia and 3 patients experienced ventricular fibrillation.[3]

Exercise and Hypertrophic Cardiomyopathy

Factors that increase the LVOT dynamic obstruction, fatal arrhythmias and disease progression need to be considered when prescribing an exercise program. Most of HCM patients can live a normal life, only a small proportion experienced premature death and complications. From previous data, mortality of HCM patients is mostly due to non-cardiovascular causes. Therefore, active lifestyle is reasonable in reducing the risk of disease progression.[5,6,10]

Intensive and rigorous exercise are hypothesized to cause changes in cardiac structure. It increases heart muscle mass and size of the left ventricle. Following to that, it can also be accompanied by acute right ventricular dysfunction. In HCM patient, there may be an increase in left ventricular hypertrophy, myocardial ischemia, myocardial fibrosis and decreased systolic and diastolic function.[4,7] At present, there are no cohort studies in humans that monitor the long-term effects of exercise on HCM progression.[3] Interestingly, in studies using HCM rat subjects with negative phenotypes, exercise prevented fibrosis and myocytes disarray hence there were no increase in hypertrophy. In subjects with positive phenotype, exercise alleviate myocytes disarray and markers of hypertrophy, but has no effect on fibrosis. Overall, there is a lack evidence study stating that exercise causes acceleration of HCM progression.[3,6,15]

Guideline Recommendations For Exercise in Hypertrophic Cardiomyopathy

Exercise guidelines for HCM was first announced in 1985 at Bethesda Conference. Individuals with left ventricular hypertrophy, LVOT obstruction, history of syncope and arrhythmias or a family history of sudden death, are prohibited from practicing competitive sports except for low intensity aerobic exercise such as bowling and golf (class IIa, level of evidence C).6,16 HCM patient are allowed to do recreational sports (class IIa, level of evidence C) as shown in Table 1.[16] Type of sports is given a score ranging from 0-5, scored 4-5 are the most recommended, scored 2-3 require special evaluation, and 0-1 are strongly recommended to be avoid.[3,6,17]

Guidelines by the American Heart Association /

Table l. Type of sports recommended by AHA/ACC for HCM[3,6]

High Intensity		Moderate intensity		Low intensity	
Sports	Score	Sports	Score	Sports	Score
Basketball	0	Baseball	2	Bowling	5
Body building	1	Biking	4	Walking	5
Gymnastic	2	Hiking	3	Golf	5
Ice hockey	0	Motorcycling	3	Horse racing	3
Squash	0	Jogging	3	Scuba diving	0
Climbing	1	Sailing	3	Skating	5
Sprint	0	Surfing	2	Snorkeling	5
Skiing (downhill)	2	Swimming	5		
Skiing (cross country)	2	Tennis (double)	4		
Soccer	0	Treadmill/stationary bicycle	5		
Tennis (single)	0	Weightlifting (free weight)	1		
Windsurfing	1				

Note :
AHA = American Heart Association, ACC= American College of Cardiology, HCM = hypertrophic cardiomyopathy

American College of Cardiology (AHA / ACC, 2011) and the European Society of Cardiology (ESC, 2014) provide recommendations for exercise programs in HCM individuals. Low intensity aerobic exercise is the most recommended (class IIa, level of evidence C). Individuals are not allowed to do sports or exercise that are competitive, but are allowed for recreational exercise (class IA sports) (Figure 2). Recreational exercise is equivalent to low intensity (< 4 METs) to medium intensity (4 – 6 METs) of aerobic exercise. [3,6,17]

Patients are advised to always be vigilant with the intensity of the exercise, if during exercise the patient feels one of the cardiovascular symptoms, exercise must be immediately terminated.[3,6,17] Experts also provide more specific recommendations on how HCM patients exercise and do recreational sports, such as to avoid "burst exertion" (exercise with sudden acceleration and deceleration phases for short distance) like sprint running, basketball, soccer, to avoid exercise at extreme ambient temperatures and in state of dehydration, to avoid heavy isometric exercise such as lifting weight, and use specifically designed exercise program to achieve optimal levels of conditioning.[3,6,16]

In 2015, AHA issued a new consensus that competitive training restrictions were applied only to HCM positive genotypes with positive phenotypes (HCM LVH +). In HCM positive genotypes with negative phenotypes (HCM LVH-), there is no restriction to competitive training, as long as there are no family history of sudden death (class IIa, level of evidence C). Individuals with HCM LVH + but with no clinical symptoms, are still not allowed to do competitive training, except for low intensity exercise (class III, level of evidence C). HCM patient without obstruction and no clinical symptoms, with no history of tachycardia during training or ambulatory monitoring using holter, and no history of syncope, can be considered to participate in competitive exercise (class IIb, level of evidence C).[3,18]

In 2014 the ESC also issued recommendations for exercise training on HCM. The recommendations issued are similar to those from AHA. HCM patients are recommended to do low intensity aerobic exercise (Figure 2.) and prohibited to participate in competitive exercise. ESC established more stringent restrictions that all HCM individuals are not allowed to participate in

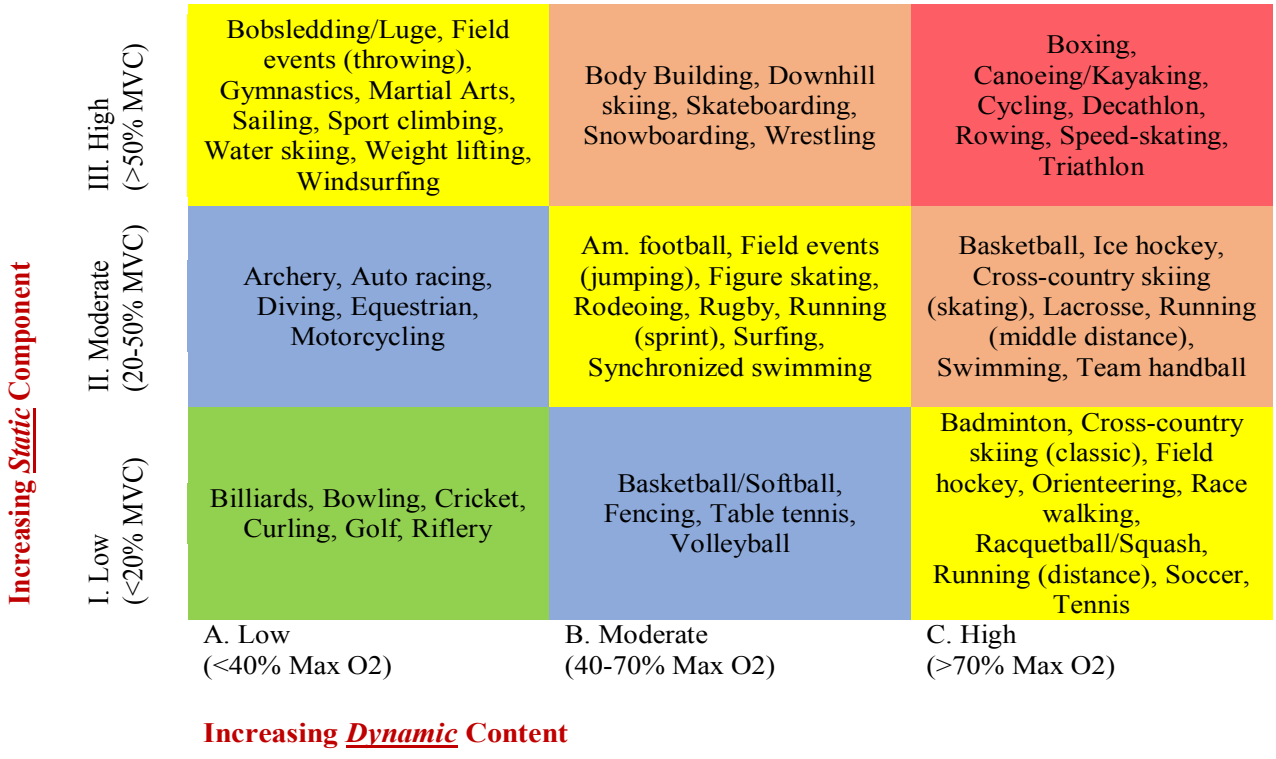

Figure 2. Sports classification based on static component and dynamic and peak O2
Source : Owens DS. Lifestyle modification: diet, exercise, sports, and other issues. In : Naidu SS (editor). Hypertrophic cardiomyopathy. London:Springer Verlog,2015.

Table 2. Comparison between AHA/ACC and ESC Recommendation.[6,17,19]

	AHA	ESC
HCM LVH +		
Competitive sports	Class IA	Class IA sports with low risk. If not, all competitive sports are prohibited
Recreational sports	Some restrictions	Some restrictions
HCM LVH-		
Competitive sports	No restriction	Prohibited
Recreational sports	No restriction	No restriction

Note :
AHA = American Heart Association, ESC= European Society of Cardiology, HCM = hypertrophic cardiomyopathy, LVH = left ventricular hypertrophy

competitive sports, irrespective of their phenotypes.[17,19]

Weighing Risks and Benefits of Exercise in Hypertrophic Cardiomyopathy

HCM patient who are physically inactive, are still at risk of having other cardiovascular and metabolic diseases such as coronary heart disease, diabetes mellitus, stroke, myocardial infarction, heart failure and premature death. Physical inactivity is the number four cause of death in all cases.[1] For general health, low to moderate intensity exercise (40-75% of maximum capacity) is a safe regimen and can decrease the risk of sudden death.[20]

In general population, it is well acknowledged that exercise can reduce the risk of death. The beneficial effect of exercise on the structure of the heart is possibly caused by inhibition of apoptosis process at the molecular level.[3,21] In a systematic review about heart failure patients, data shows that regular exercise can increase VO¬2 peak by 4-18%, this is highly correlated with a reduced risk of death, re-hospitalization rate and improvement in quality of life.[22] This might be also apply to HCM patient, however there is a paucity of research on this subject.

To date, there are still no evidence-based guidelines to prescribe exercise in HCM. Theoretically, rigorous and intense exercise might cause exacerbations of pathological factors that can impact to cardiovascular disorders. In one study concluded that HCM individuals are at risk of exercise-induced systolic dysfunction.[3] Conversely, a research conducted by Dejgaard (2017) stated that HCM individuals who has an active lifestyle have better cardiovascular function compared to inactive.[23] In line with Dejgaard, in an animal study conducted by Kim et al, mice induced with troponin I mutations without HCM phenotype, showed that exercise could reduce heart rate and increase contraction function.[15] In human studies, some researcher suggested that exercise was found to improve cardiac pathological structures in HCM patient by reducing myocytes disarray, decreasing clinical markers of ventricular hypertrophy and signal apoptosis.[3,6,15] In addition, it was also found that exercise did not cause worsening of pathological structures or induce sudden death in experimental mice.[6,15] These findings support latest studies conducted by Saberi et al which stated that exercise with low to moderate intensity can reduce the risk of cardiovascular events.[24]

It is reasonable to apply those results to HCM patient due to the beneficial effects of exercise in cardiovascular outcomes, such as improvement in blood flow, autonomic function, skeletal muscle metabolism, and endothelial repair. However, some precaution need to be considered, due to the risk of alteration of cardiovascular function associated with exercise.[6,20]

Practical Guide to Individual Hypertrophic Cardiomyopathy Exercise

Initial assessment is an important stage in determining exercise prescription and recommendations for HCM patients. It includes history, physical examination and supportive findings. The main components of initial assessment are risk stratification and patient's cardiorespiratory capacity.

Individual with HCM can be stratified into high, intermediate or low risk category. High-risk category includes those who are in a sustained ventricular tachycardia or multiple repetitive non-sustained ventricular tachycardia, unexplained syncope, abnormal exercise blood pressure response, and massive left ventricle hypertrophy.3,6 History of familial sudden death and cardiac arrest are also in this high risk category.[3] Some potential arbitrators, such as end stage phase, left ventricle apical aneurysm, marked LVOT at rest, extensive delayed enhancement, alcohol septal ablation, and coronary heart disease are included as intermediate and low risk category.[3,6]

Patient's cardiorespiratory capacity can be

determined by performing exercise testing. In a recent study, this exercise testing was a safe procedure and did not associate with an increase in cardiovascular risk factors. This test is the most accurate test in determining functional capacity, the physiological hemodynamic response to stress, the presence or absence of ischemia, or obstruction of the outflow tract, also helps determining whether clinical symptoms are really related to cardiology or respiration problems. The main parameters obtained from this procedure are peak oxygen uptake. The peak oxygen uptake rate is the most influential determinant for functional capacity. By conducting an exercise testing, it is possible to get results or data regarding the presence or absence of obstruction in HCM patients provoked by exercise. In addition, the patient's tolerance for exercise and functional limitation can also be determined. Following to that, recommendation of proper daily activities can be encouraged and tailored based on patient's functional capacity.[25]

The type of exercise and physical activity is also determined based on patient's preference. Patients select the type of recreational exercise with low intensity in accordance with the guidelines. Exercise must be carried out at reasonable ambient temperatures and the patient needs to avoid dehydration.[20]

In symptomatic patients, Finocchiaro (2016) recommended general approach exercise prescription for symptomatic HCM patient. Aerobic exercise and static exercise are the main core. Initially, a measurement of heart rate at the anaerobic threshold using cycle ergometer with incremental ramp protocol of 10 W per minute is conducting, then patient is instructed to perform aerobic exercise for 20 minutes, 3-5 times a week at the heart rate coinciding with the anaerobic threshold (with cardiopulmonary exercise testing).[20] On the occasion that anaerobic threshold heart rate cannot be determined, intensity can be set using 70-80% of the predicted heart rate (220-age). In patients with beta blockers, exercise is recommended to reach 60-70% of the maximum predictive heart rate. For static exercise, muscle strengthening can also provide benefits, but only at low intensity (< 20% body weight on upper limb, < 50% body weight on lower limbs). Isotonic strengthening exercise using a load of 0.5-1 kg, 20-30 repetitions are safe to be carried out 2-3 times a week. On occasion patients cannot attain this level, walking daily or using static cycle to a point that patients can "talk but cannot sing."[20] This type recommendation was designed for home programmed exercise.

Another recommendation in prescribing exercise for HCM patients conducted by Saberi et al, a structured and unsupervised exercise program individually prescribed based on exercise testing, is safe to be performed in HCM patient who are not at high risk. Exercise prescription should be designed to increase duration of exercise by 5 to 10 minutes, up to 60 minutes per session at the level of moderate intensity. The intensity can be set at 60% heart rate reserve (HRR), and then incrementally increase training intensity to a goal of 70% HRR. Mode of exercise include cycling, walking and elliptical training.[24]

Exercise training for HCM has its own uniqueness associated with the possibility of exercised-induced arrhythmia, so the security aspect is very important. In addition to the exercise regimen, some lifestyle modifications need to be adapted by HCM patients. HCM individuals must always pay attention to their diet and fluid needs. The recommended diet is a small but frequent portion, it should not be eaten to excess, because it is related to when the postprandial splanchnicus blood flow increases, resulting in a decrease in preload and increased LVOT obstruction. HCM individuals must also avoid dehydration because they can also increase LVOT obstruction. In addition, there are some foods that should also be avoided such as coffee and alcohol.[2]

There is a lack literature that states about how cardiac rehabilitation (CR) in HCM patients should be performed. Someribba et al conducted an example of CR in cardiomyopathy patients. It is generally divided into 2 phases, intensive phase and maintenance phase. The intensive phase consists of 12 weeks of practice with 2 visits per week, carried out in the hospital. The type of exercise given is low-moderate aerobic exercise, on average 1 hour, including heating and cooling. Other types of exercises such as resistance training (low intensity) and flexibility training can be considered. The maintenance phase lasts 6 months with 2 hospital visits in 1 month. Exercise can be done at home. Patients must always be educated by modifying a healthy lifestyle.[13]

Evidence-Based Research For Exercise in Hypertrophic Cardiomyopathy

Table 4. Summary of studies result

Outcomes	Saberi et al			Klempner et al			Dejgaard et al		
	E	UA	P	Pre	Post	P	A	LA	P
METs	1.35	0.08	0.024 (6%)	4.7	7.2	0.001 (46%)			
LV-end diastolic volume (cm3/m2) Stroke volume							47	39	0.001
EF (%) for each NYHA class			II=35 III=65	I=25 II=45 III=30	0.001 (50%)		58	47	0.001
NYHA class							1.6	2	0.03
Quality of life (SF-36)	5.7	-2.5	0.004						
Arrhythmia event, death, appropriate ICD shock	No significant difference		Log rank 0.36		None		11	17	0.82
LVOT obstruction	No significant difference				-		No significant difference		

Note :
E = exercise, UA = usual activity, A = active individuals, LA = less active individuals, p= p value, NYHA= New York Heart Association, EF= ejection fraction, ICD=implantable cardioverter-defribrillator, LVOT=left ventricle obstruction outflow

There is a paucity of studies that examine the effectiveness of exercise for HCM. AHA and ESC established exercise recommendations for HCM individuals based on discussion and consensus of experts.[17,19] We found three studies that investigate the efficacy of exercise in HCM individuals. Outcomes of our interest were differences in cardiovascular function, quality of life and safety issues. All studies found positive significant differences in main outcomes measure in which the HCM subjects on exercise had better or improved outcomes. None reported adverse reaction such as fatal arrhythmia or sudden death related to exercise.[2,15,23,24]

Saberi et al (2017) used 113 HCM samples which were randomized into two groups; training group and control group (usual activities). This research is referred to The Randomized Exploratory Study of Exercise in Hypertrophic Cardiomyopathy (RESET-HCM). Subjects were given individualized aerobic exercise with moderate intensity. Each training session has a duration of 20 minutes initially, three sessions per week, with a limit of 60% HRR (resting heart rate + 0.6 (maximal heart rate - resting heart rate)) or using a Borg scale (11-14). Exercise is increased by 5-10 minutes each week until it reaches a maximum limit of 60 minutes. Increased exercise performance limits to a maximum of 70% of HRR and exercise is continued until the 16th week. The types of exercise selected in this study were: cycling, walking, and elliptical training.[24] The results showed that improvement in peak VO2 in training group increased +1.35 ml / kg / min compared to only 0.08 ml / kg / min in non-exercise group. In exercise group there was no worsening of the anatomical and functional structures of the heart and no increase in LVOT obstruction. In exercise group, there is increase of 5.7 points in the physical function domain of the Short Form Health Survey (SF-36). There is no report regarding adverse reaction.[24] This study is the first large-scale randomized clinical trial conducted to determine the effect of exercise on HCM patients. [24]

In 2015, Klempfner et al. analyzed the effectiveness of exercise in HCM patients following a heart supervision program. Patients with NYHA II and III, with average ejection fraction at 53%. Exercise was prescribed based on HRR from a symptom limited graded exercise test. The intensity of exercise started from 50% and were increased gradually to 85% HRR. From this study, the results of functional capacity improved from 4.7 METs to 7.2 METs (increased by 46%), 50% of patients experienced improvement in NYHA ≥ 1 level, and none experienced a decline in functional levels, with no adverse reactions such as arrhythmias and sudden death occured.[15]

Dejgaard et al conducted a study to determine whether HCM individuals who lived an active lifestyle have better cardiovascular function outcomes than less active individuals. In this study, 187 samples were

divided into group with active lifestyle (>6 METs) and group with less active lifestyles (<6 METs). Interviews were carried out on physical activities and daily training in the past 6 years. All subjects underwent echocardiographic examination to determine cardiac function parameters and genetic testing was conducted to determine the genotype of the subject.[23] The results of the study stated that in the group with active lifestyle of at least 4 hours per week with HCM LVH + had better NYHA functional levels than HCM LVH + with groups with less active lifestyle. In HCM LVH + and HCM LVH - , the active lifestyle has a better end-systolic volume and ventricular diastolic end. The incidence of arrhythmia in group active lifestyle is 11 samples and in group of less active lifestyle is 17 samples; which are not correlated with exercise.[23]

Table 3. Summary of training protocol[15,23,24]

Training protocol	Saberi et al	Klempner et al	Dejgaard et al
Frequency	3x/weeks	2x/weeks (CR) Community walking 2x weeks (RPE 11-12)	Daily
Total duration	16 weeks	Mean 41± 8 h	4 hours/ weeks / throughout the year
Exercise	Ergocycle, brisk walking, elliptical training	Treadmill, arm ergocycle, static cycle	Self-selected (cycling)
Intensity	Initial : 60% HRR Up to 70% HRR	Initial : 50-60% HRR Up to 85% HRR	Activities >6 METs

Note :
CR = Cardiac Rehabilitation, RPE= Rate Perceived Exertion, HRR = heart rate reserve, METs = Metabolic Equivalents

Conclusion

Old belief regarding exercise restrictions on HCM need to be reconsidered, given that at present exercise have been shown to provide significant benefits for reducing cardiovascular risk factors. Nevertheless, exercise in patients with HCM must be specifically considered regarding the risk and benefit. Practicing active lifestyle and exercise on HCM individual is an exciting possibility that need further study.

Publication approval

Author has approved the publication of this article and fully understand the content of the manuscript that is submitted to the journal.

Conflict of interest

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List of Abbreviations

HCM: hypertrophic cardiomyopathy
LV: left ventricular
LVOT: Left Ventricular Outflow Tract
LVH: left ventricular hypertrophy
HRR: heart rate reserve
CR : cardiac rehabilitation

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