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Original article

Efficacy and safety of exercise rehabilitation in patients with hypertrophic cardiomyopathy

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ABSTRACT

Background: While physical rehabilitation has been shown to be beneficial and safe for patients suffering from heart failure, data on rehabilitation for hypertrophic cardiomyopathy (HCM) patients are limited.
Methods: Forty-five HCM patients participated in an exercise rehabilitation program. Exercise capacity was measured in metabolic equivalent of task (METs) units and functional status was defined according to the New York Heart Association (NYHA). Self-reported measurements addressed the quality of life and daily life function.
Results: Of the 45 participants, 32 completed at least 3 months of rehabilitation and had data from two sequential exercise tests. A significant increase in exercise capacity (from mean 5.3 to 6.7 METs, $p = 0.01$), was achieved at higher peak heart rates. Eighteen patients (56%) who showed improvement in exercise capacity did not differ in their NYHA class, clinical, electrocardiographic, or echo-Doppler parameters compared to those who did not improve. The benefit from training was associated with a lower exercise capacity at baseline and was most pronounced in those capable of less than 6.8 METs ($p = 0.008$). No significant arrhythmias or adverse events were recorded in HCM patients during participation. In ~40% of participants, training improved the subjective perception of functional capacity and quality of life; only 4 patients (9%) discontinued their participation due to discomfort during or following training. The improvement in exercise capacity was comparable between HCM and a reference group of dilated cardiomyopathy patients.
Conclusions: Exercise rehabilitation appears to be applicable and safe in HCM. It mainly benefits patients suffering from significant functional limitation. Larger prospective studies are needed to validate these findings and better characterize patients expected to benefit from these programs.

Introduction

Hypertrophic cardiomyopathy (HCM) is a structural heart disease defined by an increase in left ventricular (LV) wall thickness in the absence of other causes of hypertrophy [1]. It is considered a familial disease, with an autosomal dominant transmission pattern and prevalence of ~1:500 [2,3] in the general population independent of ethnicity [4–6]. HCM is associated with structural heart changes in the LV that include a small cavity, hyperdynamic contraction, and LV outflow tract obstruction [1,7]. The clinical phenotype is also characterized by LV diastolic dysfunction and coronary insufficiency.

HCM often has a profound clinical impact on patients, causing disability and interference in daily activities. Its clinical course may include progressive heart failure, arrhythmias, and eventually death. Patients that have been asymptomatic for many years, with no physical disability, will eventually develop symptoms that reduce their capacity for physical activity, or be advised to diminish

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their daily routine by their physician [8]. Because of the well acknowledged association between sudden arrhythmic death and strenuous physical activity, patients often adopt a sedentary lifestyle losing physical fitness. Improving the quality of life without jeopardizing the long-term outcomes for these patients is therefore a significant clinical challenge. Sedentary lifestyle and avoidance of exercise leads to further reduction in cardiorespiratory fitness, functional capacity, sarcopenia, skeletal bone density reduction, and restriction in articular range of motion [9,10].

Previous studies have shown that controlled physical exercise improves functional capacity and may reduce risk of hospitalization of heart failure patients [11]. Most studies were carried out on patients with reduced LV function, regardless of etiology. Nevertheless, there is ample evidence indicating that physical exercise could also benefit patients with predominantly diastolic dysfunction [12]. These studies did not include HCM patients. Our preliminary report on HCM patients indicated that physical exercise in a rehabilitation program could be beneficial without significant risk [13]. These results were recently confirmed in a randomized controlled study which showed a modest increase (1.3 ml/kg/min, 4% of baseline) in peak VO_2 after 16 weeks of training [14].

Because of the diversity in clinical manifestations of HCM and potential variability in individual responses to exercise intervention, the main aim of the current study was to define the patients expected to benefit from rehabilitation/training.

Materials and methods

This was an observational study of patients participating in the cardiac rehabilitation program at the Leviev Heart Center, Chaim Sheba Medical Center, Tel-Ha'Shomer, Israel. We reviewed the files of patients who were referred to the Cardiac Rehabilitation Center between January 1st 2011 and December 31st 2016.

Electronic medical records of the participants were accessed for extraction of personal data, medical background, and history of their cardiac disease including: electrocardiography data, echocardiography, and ergometry data. The effort capacity was quantified using metabolic equivalent of task (METs) units, derived from ergometry tests executed according to the Bruce protocol, the modified Bruce, and the Belke protocol. The training protocol originally developed for a heart failure cohort was previously described [15]. Finally, each patient was contacted by telephone and requested to respond to questionnaires relating to their health status and functional capacity and post-rehabilitation. Reasons for their decision to discontinue the rehabilitation program and/or other physical activity, were recorded.

Study population

HCM study participants were singled out from the patient population treated in the Leviev Heart Center. Most are evaluated and followed in the Cardiomyopathy Clinic of The Heart Failure Institute. We also used data from a group of patients suffering from dilated cardiomyopathy (DCM) who underwent a similar rehabilitation program.

Inclusion criteria

A. HCM diagnosis: minimal thickness of the left ventricular wall was 15 mm, without evidence of pathophysiology that might cause secondary myocardial hypertrophy. Inclusion criteria for the reference group of DCM was reduced LV ejection fraction (lower than 45%), with normal or dilated LV of any etiology in the absence of wall hypertrophy or coronary artery disease.
B. Age over 18 years.
C. Any clinical indication for referral to cardiac rehabilitation.
D. Participation in the cardiac rehabilitation program for at least 3 consecutive months.
E. Availability of exercise test data prior to starting training.

Safety and ethics

This study was approved by the institutional ethics committee in the Chaim Sheba Medical Center. All HCM patients were continuously monitored during their rehabilitation exercises.

Outcomes

The primary outcome was improvement in functional capacity as reflected by units of METs in the exercise test. We focused on comparing patients who benefited from rehabilitation and those who did not. Associated parameters recorded included heart rate and blood pressure during rest, exercise, and recovery. In addition, we retrospectively collected subjective assessment of the improvement in functional capacity, fitness, and the general wellbeing during the period spent at the rehabilitation center. Echo-Doppler data were obtained within 3 months prior to the first ergometry at onset of training and within 3 months after the second ergometry. Safety parameters were recorded, including syncope and arrhythmia events during exercise, as well as hospitalizations and total mortality during the first year of study participation.

Statistical analysis

We focused on HCM patients with available exercise test data at baseline and at least 3 months after beginning the exercise program. All data were stratified according to an improvement in functional capacity achieved, that was defined as increased METs in the second ergometry.

Categorical variables were described in numbers and percentage and continuous variables as mean (±SD). Between-group variability was assessed using the χ^2 test by either Pearson or Fisher test for independence according to estimated group sizes. A sign test was used in cases where the same variable was tested at different times. Continuous variable distributions were assessed by Shapiro–Wilk test and visually by histograms. Since many of our study variables had an abnormal distribution, inter-group variability between the same patients at different times was assessed by the Mann–Whitney and Wilcoxon tests, accordingly.

Statistical analysis was done in the R language, version 3.4.1 (The R foundation, Vienna, Austria), using the R-studio software, version 1.0.143 (R studio Inc.). Two tailed $p < 0.05$ was accepted as significant.

Results

We reviewed the records of 162 HCM patients who were referred for evaluation in the cardiac rehabilitation center during the years 2011–2017. Forty-five met the inclusion criteria. The main reasons for exclusion from this analysis were inconsistent diagnosis or inability to afford participation in the rehabilitation program due to lack of insurance coverage. Baseline characteristics of the study group are summarized in Table 1: mean age was 58 years, 31% were females, mean septal thickness was 17 mm. Fifty-one percent had LV outflow obstruction and 44% had history of paroxysmal or were in chronic atrial fibrillation. Most (76%) were in New York Heart Association (NYHA) II-III. Patients underwent a total of 874 rehabilitation months (average 19 months per patient).

Table 1
Baseline characteristics of patients suffering from hypertrophic cardiomyopathy.

Demographics	Age at diagnosis	49 (±18)
	Age at admission	58 (±13)
	Male gender	31 (69%)
Medical history and cardiovascular risk factors	Body mass index	29.6 (±5.1)
	Hypertension	24 (53%)
	Diabetes mellitus	6 (13%)
	Coronary artery disease	11 (24%)
	s/p Myocardial infarction	9 (20%)
	s/p Percutaneous coronary intervention	9 (20%)
	s/p Coronary bypass graft	2 (4%)
	CVA/TIA	5 (11%)
	Chronic respiratory disease	7 (16%)
	Estimated GFR	95.3 (±39.9)
Clinical features	Angina pectoris	8 (18%)
	Atrial fibrillation	20 (44%)
	History of non-sustained VT	8 (18%)
	Personal history VT/VF	7 (16%)
	Family history hypertrophic cardiomyopathy	3 (8%)
	Family history sudden cardiac death	10 (26%)
Cardiomyopathy features	NYHA functional class	
	I	11 (24%)
	II	21 (47%)
	III	13 (29%)
Electrocardiography	LV hypertrophy criteria	23 (64%)
	Rhythm	
	Sinus	31 (74%)
	Atrial fibrillation	9 (21%)
	Ventricular pacing	2 (5%)
	Ventricular conduction abnormalities	
	RBBB	3 (7%)
	LBBB	5 (12%)
	IVCD	2 (5%)
Echocardiography	LV diastolic dimension (mm)	46 (±6)
	Interventricular septum (mm)	17 (±4)
	Posterior wall (mm)	13 (±7)
	LV ejection fraction (%)	59 (±12)
	Left atrial diameter (mm)	29 (±9)
	Obstructive HCM	23 (51%)
	Mitral regurgitation > mild	4 (13%)
	Systolic pulmonary atrial pressure (mmHg)	38.2 (±11.8)

Total HCM population, $n = 45$; categorical parameters are presented as n(%), continuous parameters are presented as mean(±SD) CVA\TIA, cerebrovascular accident\transient ischemic attack; GFR, glomerular filtration rate; LV, left ventricular; NYHA, New York Heart Association; VT, ventricular tachycardia; VF, ventricular fibrillation; R\LBBB, right\left bundle branch block; IVCD, intraventricular conduction delay; HCM, hypertrophic cardiomyopathy.

Thirty-two participants had two consecutive ergometry tests for comparison. Improvement in exercise capacity was recorded (5.3 ± 2.5 to 6.7 ± 2.5 METS; $p = 0.01$). Concomitantly there was a significant increase 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 mmHg; $p = 0.05$). The prevalence of abnormal blood pressure response to exercise (defined as an increase of less than 20 mmHg) was slightly lower following training but did not reach statistical significance. The echocardiographic parameters did not differ between pre- and post-rehabilitation period.

Comparison of patients who benefited from training

Among those 32 patients who had 2 available ergometry datasets, 18 (56%) demonstrated an increase in functional capacity, while 14 patients did not improve or deteriorated after participation in the program (Table 2).

There were no differences in baseline demographic and clinical characteristics, besides a higher rate of previous cerebrovascular events being recorded in patients who derived no benefit (Suppl. Table 1). Cardiomyopathy characteristics, comorbidities, New York Heart Association class or therapies received did not differ between patients who did or did not benefit from rehabilitation. (Suppl. Tables 1 and 2). Patients who benefited had a significantly lower baseline exercise capacity, but no other differences in stress test parameters or echocardiography when compared to the patients who did not benefit from the rehabilitation program. To better define those who benefited from training we performed a *classification and regression tree analysis* of the baseline exercise capacity. The best separation between improvers and non-improvers was found at baseline exercise capacity of 6.8 METS ($p = 0.008$). Among 20 HCM patients accomplishing less than 6.8 METS at baseline, 16 (80%) improved and only 4 (20%) failed to improve their performance (Fig. 1A). There was a strong negative correlation in a linear regression model between baseline exercise capacity and the change in exercise capacity after rehabilitation ($R^2 = 0.31$, Fig. 1B).

While this study was not designed to determine the effect of exercise training on left ventricular outflow gradient, the mere presence of outflow obstruction did not influence the ability to derive a functional benefit from training (Table 2). Given the notion that hearts of apical HCM better adapt to athletic activity [16], we analyzed the hypertrophy patterns in our subgroups [17]. We found no difference in benefit from exercise training according to LV hypertrophy pattern. Only 2 patients had an apical HCM pattern. Noteworthy, is that both benefited quite well from rehabilitation, with gains in METs of 4.8 and 5.5, respectively.

There were 4 patients in this study who had the highest baseline exercise capacity (METS >10), and who did not improve with exercise training. All patients had a well documented compliance to participation in the rehabilitation program. Analysis of their individual records provides some insight to their clinical course. One had a hypokinetic HCM while 2 started rehabilitation after surgical myectomy. Interestingly, one of these patients, having the worst decrease in METS (10.2–4.6), suffered from a gradual increase in LV outflow tract gradient following an apparently failed surgery. The fourth patient had no change in METS.

Patient reported outcome measures

Patient reported outcomes for all 45 HCM patients are shown in supplementary Table 2. The response rates were ~70%. The majority of responders reported positive improvements in daily function, an awareness of general well-being, functional capacity, and participation in recreational physical activity. Only few patients reported negative outcomes or adverse experience in these measures.

The reasons for terminating their participation in the rehabilitation program were as follows: 19 (42%) left for financial reasons, mainly end of insurance coverage; 6 (13%) started to exercise on their own; 4 (9%) reported feeling unwell during exercise; and another 4 (9%) reported no benefit from training.

Safety measures

Throughout the entire duration of participation in the rehabilitation program, only 1 patient suffered from a non-lethal event of non-sustained ventricular tachycardia during exercise. No instances of syncope, or hospitalization for heart failure occurred during the period of training. No death occurred during participation and the first year of follow-up.

Comparison to DCM patients

We analyzed the exercise data of 46 DCM patients who were trained for at least 3 months in our institution according to the

Table 2
Comparison of cardiac characteristics among hypertrophic cardiomyopathy patients who derived benefit from exercise training and those who did not.

			No benefit ($n = 14$)			Benefit ($n = 18$)			p
Age			58 (±11)			60 (±15)			NS
Male gender			11 (79%)			12 (67%)			NS
Months between pre- and post-rehabilitation exercise tests			38 (±26)			36 (±30)			NS
Cardiomyopathy features	Obstructive HCM		7 (50%)			9 (50%)			NS
	NYHA functional class								
	I		4 (29%)			2 (11%)			
	II		6 (43%)			11 (61%)			
	III		4 (29%)			5 (28%)			NS
Electrocardiography	LV hypertrophy criteria		6 (55%)			9 (56%)			NS
	Rhythm								
	Sinus		8 (62%)			13 (72%)			
	Atrial fibrillation		3 (23%)			3 (17%)			
	Ventricular pacing		1 (8%)			1 (6%)			NS
	Ventricular conduction abnormalities								
	RBBB		1 (8%)			2 (11%)			
	LBBB		2 (17%)			2 (11%)			NS
	IVCD		0 (0%)			1 (6%)			
		Before rehabilitation	After rehabilitation	p^a	Before rehabilitation	After rehabilitation	p^a	p^b	
Echocardiography	LV diastolic dimension (mm)	46 (±6)	48 (±9)	NS	47 (±7)	41 (±17)	NS	NS	
	Interventricular septum (mm)	15 (±3)	17 (±4)	NS	17 (±5)	16 (±4)	NS	NS	
	Posterior wall (mm)	12 (±2)	11 (±3)	NS	14 (±11)	11 (±2)	NS	NS	
	Maximal LV wall thickness	16 (±3)	17 (±4)	NS	19 (±10)	16 (±3)	NS	NS	
	LV ejection fraction (%)	57 (±13)	57 (±10)	NS	63 (±13)	60 (±16)	NS	NS	
	Left atrial area (mm)	28 (±9)	30 (±9)	NS	31 (±10)	34 (±10)	NS	NS	
	Mitral regurgitation > mild	0 (0%)	1 (11%)	NS	1 (8%)	2 (15%)	NS	NS	
	Systolic pulmonary atrial pressure (mmHg)	41 (±16)	42 (±10)	NS	37 (±9)	40 (±12)	NS	NS	
Exercise test	Exercise capacity (METS)	6.7 (±2.8)	5.5 (±2.4)		4.3 (±1.6)	7.7 (±2.2)		0.01	
	Rest heart rate	68 (±11)	69 (±9)	NS	68 (±17)	67 (±12)	NS	NS	
	Resting systolic blood pressure	122 (±14)	122 (±16)	NS	120 (±22)	126 (±23)	NS	NS	
	Peak heart rate	118 (±24)	113 (±23)	NS	104 (±21)	126 (±22)	0.003	NS	
	Peak systolic blood pressure	146 (±18)	149 (±27)	NS	142 (±29)	154 (±33)	NS	NS	
	Abnormal stress blood pressure response	5 (36%)	3 (21%)	NS	6 (33%)	5 (29%)	NS	NS	
	Heart rate after 1-min recovery	100 (±21)	87 (±16)	0.03	86 (±19)	92 (±25)	NS	NS	

Categorical parameters are presented as n(%), continuous parameters are described as mean (SD) for comfort, and statistically significant differences were assessed using the Mann–Whitney or paired Wilcox tests due to the variables' distribution (see 'Methods'). HCM, hypertrophic cardiomyopathy; LV, left ventricle; R\LBBB, right\left bundle branch block; IVCD, intraventricular conduction delay; METs, metabolic equivalent of task units; NS, not significant; NYHA, New York Heart Association.
[a] Comparing values before and after rehabilitation.
[b] Comparing baseline characteristics between groups.

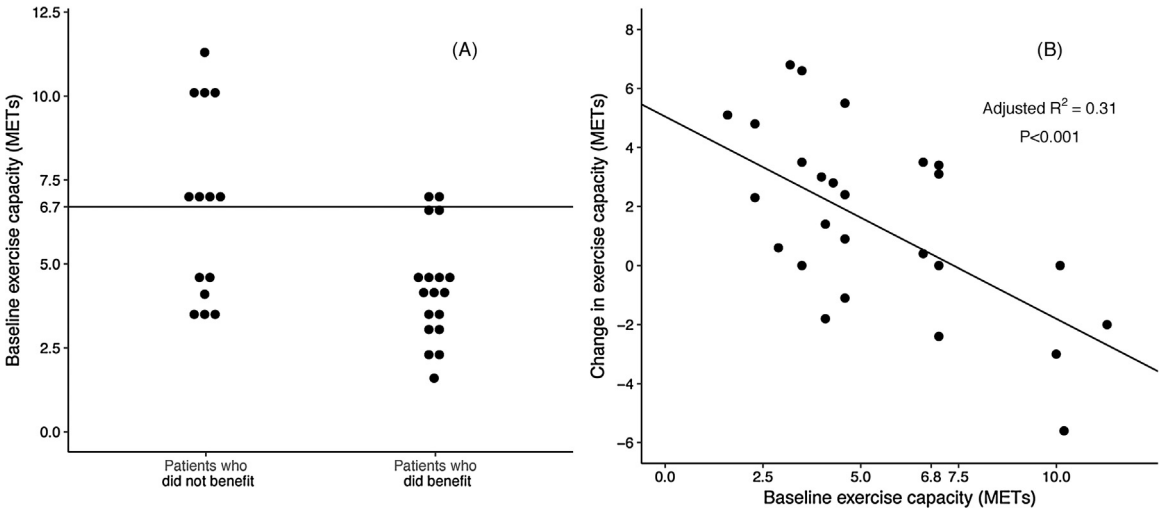

Fig. 1. Benefit from exercise rehabilitation according to baseline exercise capacity in hypertrophic cardiomyopathy patients: (A) Baseline exercise capacity (METS) according to benefit or no benefit in exercise capacity from rehabilitation program. (B) Change in exercise capacity after rehabilitation according to baseline exercise capacity (METS). METs, metabolic equivalent of task units.

same protocol, where ergometry and echocardiography data were also available. Patients suffering from DCM as a whole benefited from exercise training in terms of functional capacity as expressed in METS (7.4 ± 3.5 to 8.2 ± 3.5, $p = 0.006$). These patients' data are presented in Table 3. A comparison between HCM and DCM patients revealed that: (1) HCM patients started the rehabilitation program at a lower exercise capacity, relative to DCM patients, as expressed in METs (5.3 ± 2.5 vs. 7.4 ± 3.5; $p = 0.009$). Following the

Table 3
Comparison of cardiac characteristics among dilated cardiomyopathy patients who derived benefit from exercise training and those who did not.

		No benefit (n = 15)			Benefit (n = 31)			p
Age		48 (±11)			58 (±15)			0.02
Male gender		10 (67%)			20 (65%)			NS
		Before rehabilitation	After rehabilitation	p[a]	Before rehabilitation	After rehabilitation	p[a]	p[b]
Echocardiography	LV diastolic dimension (mm)	58 (±10)	57 (±11)	NS	59 (±9)	57 (±9)	0.04	NS
	Interventricular septum (mm)	10 (±2)	10 (±2)	NS	10 (±2)	10 (±2)	NS	NS
	Posterior wall (mm)	10 (±2)	10 (±2)	NS	10 (±2)	10 (±2)	NS	NS
	Maximal LV wall thickness	10 (±2)	11 (±2)	NS	10 (±2)	11 (±2)	NS	NS
	LV ejection fraction (%)	33 (±12)	38 (±13)	0.06	29 (±11)	35 (±14)	0.009	NS
	Left atrial area (mm)	21 (±5)	22 (±6)	NS	25 (±9)	21 (±6)	0.03	NS
	Mitral regurgitation > mild	2 (17%)	1 (10%)	NS	2 (8%)	5 (26%)	NS	NS
	Systolic pulmonary atrial pressure (mmHg)	34 (±9)	28 (±5)	0.07	36 (±12)	32 (±7)	NS	NS
Exercise test	Exercise capacity (METS)	9.2 (±4.0)	7.5 (±3.5)		6.6 (±2.9)	8.6 (±3.5)		0.04
	Rest heart rate	75 (±14)	75 (±12)	NS	71 (±15)	69 (±11)	NS	NS
	Resting systolic blood pressure	131 (±10)	123 (±25)	NS	113 (±16)	118 (±19)	NS	NS
	Peak heart rate	141 (±24)	131 (±19)	NS	120 (±24)	124 (±25)	NS	0.007
	Peak systolic blood pressure	153 (±28)	155 (±22)	NS	142 (±22)	152 (±24)	0.02	NS
	Heart rate after 1-min recovery	114 (±19)	103 (±15)	NS	101 (±20)	98 (±19)	NS	NS

Categorical parameters are presented as n(%), continuous parameters are described as mean (SD) for comfort, and statistically significant differences were assessed using the Mann–Whitney or paired Wilcox tests due to the variables' distribution (see 'Methods'). LV, left ventricle; METs, metabolic equivalent of task units; NS, not significant.
[a] Comparing values before and after rehabilitation.
[b] Comparing baseline characteristics between groups.

rehabilitation period, the exercise capacity of HCM patients, while improved, was still decreased compared to DCM (6.7 ± 2.5 vs. 8.2 ± 3.5 METS; p = NS). (2) The benefit of training was of a similar magnitude. (3) At baseline, HCM patients had a lower mean heart rate at peak exercise, compared to DCM patients (110 ± 23 vs. 127 ± 26 beats/min; p = 0.008). The peak heart rate differences disappeared at the end of the rehabilitation period (120 ± 23 and 126 ± 23 for the HCM and DCM patients respectively, Tables 2 and 3).

We then compared the DCM patients who benefited in terms of increase in their exercise capacity to those who did not improve their performance. The responders were older, and had a lower exercise capacity and lower peak-exercise heart rate at baseline (Table 3). There was a weak negative correlation between the METS at baseline and the change in exercise capacity (R^2 = 0.1, p = 0.02, Fig. S1). This relationship was markedly stronger in HCM patients (Fig. 1).

Discussion

Physical rehabilitation is an effective tool to improve and maintain functional capacity of heart failure patients, which may be crucial for achieving better quality of life for these patients. Previous studies have shown the efficacy and safety of physical rehabilitation in patients with a wide variety of etiologies of heart failure, both with preserved and reduced LV ejection fraction (HFpEF and HFrEF, respectively) [11,12]. It is reasonable to assume that rehabilitation would benefit HFpEF patients, but the extent to which it could help HCM patients is largely unclear [9,10]. It should also be noted that in contrast to most heart failure patients, HCM patients have been historically singled out and advised to avoid exercise in order to prevent lethal ventricular tachyarrhythmia.

A pivotal signal for rehabilitation efficacy and safety of moderate intensity exercise among HCM patients was described in our original work [13] and later confirmed in a larger randomized trial [14]. While higher intensity exercise may be even more beneficial in terms of functional capacity, LV adaptation, and improving diastolic function, a concern still exists regarding disease progression and arrhythmia [10]. Thus, it might be suggested that those HCM patients who did not improve their performance in our study, might benefit from a different, more intense training protocol [10,18]. While no such signal was ever reported in HCM, strenuous athletic activity was shown to accelerate disease progression in arrhythmogenic and Lamin A/C cardiomyopathies [19–21].

Many HCM patients are limited in terms of daily life activities, despite receiving optimal medical therapy. Some suffer from difficulty to initiate activity but do better than expected on a graded exercise test with "warm up". Occasionally, physical limitation cannot be attributed to objective findings, but originate from deconditioning, or anxiety causing them to avoid physical activity.

In the current study we studied patients with HCM who suffered from functional disability and were considered eligible and capable to participate in a supervised rehabilitation program, specifically tailored for heart failure patients. In contrast to recent publications discussing the global impact of exercise and training protocols in HCM [18], we examined the utility of cardiac rehabilitation in this disease. Our results indicate that physical rehabilitation could be beneficial for HCM patients. The improvement is primarily seen in terms of increased exercise capacity, without a significant change in physiological or echocardiographic parameters. These changes in exercise performance were comparable to a reference DCM group, constituting the most validated "gold standard" for such intervention (Tables 2 and 3). Importantly, the mean increase seen by us in terms of METS (+1.4 METS, 26% over baseline) was much higher than the increase obtained by Saberi et al. [14] in peak VO_2 (+1.3 ml/kg/min, 4% over baseline). We assume that some of the improvement in performance does not reflect an increased oxygen capacity but occurs due to a non-specific effect of physical conditioning on the cardiovascular system. This includes an improved skeletal muscle activity, improved endothelial function, better peripheral vascular blood flow, and higher oxygen extraction in peripheral tissues [22–24].

Patient selection is particularly important in HCM which has a huge phenotypic variability and a theoretical risk of exercise-induced arrhythmia, ischemia and disease progression [10]. We therefore opted to define the group expected to benefit most from the intervention. Importantly, those HCM patients who had a lower baseline functional capacity show more improvement (Fig. 1 and Table 2). Since there were no differences in NYHA class (which is a subjective measure of functional disability) we suggest that cardiac

and non-cardiac issues such as deconditioning or hesitation to perform physical activity significantly contributed to disability in those with lower exercise capacity [8]. We assume that could explain why those with a lower exercise capacity, benefited most from exercise rehabilitation and may be the best candidates for a supervised exercise program.

There has previously been a discussion about the role of baseline exercise capacity on the response to exercise training programs, and the higher benefit in clinical outcomes associated with improvement in physical activity in the least active heart failure patients [25,26]. The HF-ACTION trial, in patients with heart failure due to systolic dysfunction, did not identify a consistent relationship between baseline functional capacity (measured by peak VO_2 or 6-min walk) and the effect of exercise training [27]. A smaller study by Bakker et al. [28] demonstrated a negative correlation between baseline peak VO_2 and response to exercise capacity. This study included a wide range of patients, with both ischemic and non-ischemic etiologies, and LV function ranging from preserved to severely impaired. It has also been suggested that non-responders may benefit from exercise training programs in other ways other than functional or exercise capacity [29].

That been said, none of these studies discuss either HCM or HFpEF exclusively. DCM and HCM significantly differ in their clinical course, medication selection, exercise physiology, prognosis, etc. In the current study we found a comparable benefit from exercise training in HCM and DCM groups (which may be defined as HFpEF and HFrEF, respectively). However, the inverse relationship between baseline performance and the improvement with training was clearly more prominent with HCM. It remains to be elucidated if this is a specific characteristic of HCM patients or may be generalized to other types of HFpEF, as well as if exercise leads to better tolerance to exercise-induced LV outflow tract gradient and if it benefits patients post myectomy.

Regarding safety and tolerability, there were two major issues in this patient population, we found the rehabilitation both safe and well tolerated. During the whole exercise period of our HCM patients there were no cases of mortality, related morbidity, or significant arrhythmias. Exercise training was well tolerated and the main cause for quitting was lack of insurance coverage. The contribution of rehabilitation to individual feeling and perception of quality of life should not be underestimated (Supplementary Table 2).

We believe that establishing an inverse relationship between the basal performance and the functional benefit from training is the main contribution of this study (Fig. 1). Since not all HCM patients improve, and because there is still concern regarding long-term safety, as well as coverage issues, defining a threshold for intervention would be helpful. In our cohort we defined a cut-off of 6.8 METs as a threshold ensuring maximal benefit from exercise intervention (80% of participants with baseline ergometry below 6.8 METS improved, Fig. 1).

Limitations

This study included a relatively small group of patients who did not all qualify for final analysis. The high rate of patient drop-out might indicate the potential for a selection bias and therefore, generalization for the entire HCM population is hampered. With a short period of training, no effect on cardiac function or morphology should be expected. Therefore, our echo-Doppler data are more applicable for comparing baseline characteristics and to ensure safety. The exact mechanisms of improving vs. failure to improve with exercise training would require a meticulous analysis of stress echocardiography and cardiorespiratory test results which were not available for most of our study group.

Conclusion

Moderate intensity exercise training is safe in HCM. It benefits most patients with decreased baseline performance independent on age, gender, comorbidities, NYHA class, therapy, HCM morphology, and outflow obstruction. The improvement in functional capacity was similar for HCM and DCM patients despite major physiological differences between these two patient groups. Future studies are needed to assess the role of various mechanisms determining the functional capacity of cardiomyopathy patients, including deconditioning and patient anxiety, on the response to supervised exercise training.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.04.013.

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