American Heart Journal Plus: Cardiology Research and Practice 22 (2022) 100202

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research Paper

Moderate continuous or high intensity interval exercise in heart failure with reduced ejection fraction: Differences between ischemic and non-ischemic etiology☆

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ARTICLE INFO

Keywords:
Exercise intensity
Training
HIIT
Heart failure
Etiology

ABSTRACT

Background: Exercise for heart failure (HF) with reduced ejection fraction (HFrEF) is recommended by guidelines, but exercise mode and intensities are not differentiated between HF etiologies. We, therefore, investigated the effect of moderate or high intensity exercise on left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and maximal exercise capacity (peak VO_2) in patients with ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM).

Methods: The Study of Myocardial Recovery after Exercise Training in Heart Failure (SMARTEX-HF) consecutively enrolled 231 patients with HFrEF (LVEF ≤ 35 %, NYHA II-III) in a 12-weeks supervised exercise program. Patients were stratified for HFrEF etiology (ICM versus NICM) and randomly assigned (1:1:1) to supervised exercise thrice weekly: a) moderate continuous training (MCT) at 60–70 % of peak heart rate (HR), b) high intensity interval training (HIIIT) at 90–95 % peak HR, or c) recommendation of regular exercise (RRE) according to guidelines. LVEDD, LVEF and peak VO_2 were assessed at baseline, after 12 and 52 weeks.

Results: 215 patients completed the intervention. ICM (59 %; n = 126) compared to NICM patients (41 %; n = 89) had significantly lower peak VO_2 values at baseline and after 12 weeks (difference in peak VO_2 2.2 mL/(kg*min); $p < 0.0005$) without differences between time points ($p = 0.11$) or training groups ($p = 0.15$). Etiology did not influence changes of LVEDD or LVEF ($p = 0.30$; $p = 0.12$), even when adjusting for sex, age and smoking status ($p = 0.54$; $p = 0.12$). Similar findings were observed after 52 weeks.

☆ This manuscript, or part of it, has neither been presented/published nor is currently under consideration for publication by any other journal.

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https://doi.org/10.1016/j.ahjo.2022.100202
Received 23 March 2022; Received in revised form 31 August 2022; Accepted 2 September 2022
Available online 5 September 2022

Conclusions: Etiology of HFrEF did not influence the effects of moderate or high intensity exercise on cardiac dimensions, systolic function or exercise capacity.
Clinical Trial Registration–URL: http://www.clinicaltrials.gov. Unique identifier: NCT00917046.

1. Introduction

Etiology of heart failure (HF) with reduced ejection fraction (HFrEF) is classified as ischemic cardiomyopathy (ICM) or non-ischemic cardiomyopathy (NICM). ICM represents ~70 % of HFrEF and the underlying causes are coronary artery disease (CAD) and myocardial infarction. NICM represents ~30 % of HFrEF and the underlying causes include long-term untreated arterial hypertension, valvular heart disease, toxic agents, myocarditis, immune-mediated and inflammatory disease, endocrine disorders, infiltrative disease, prolonged tachycardia and genetic cardiomyopathies [1]. While medical HF therapy is similar between entities, indications for implantable cardioverter defibrillator (ICD) [2,3] as well as prognosis differ significantly [4].

Exercise training is recommended by guidelines alongside pharmacological therapy in HF and moderate continuous training (MCT) has the highest level of evidence, whereas high intensity interval training (HIIT) may be considered in low-risk patients [1,5]. A meta-analysis has revealed that HIIT significantly increases cardiorespiratory exercise capacity by almost double that of MCT in patients with coronary artery disease, HF, hypertension, metabolic syndrome and obesity [6], although recent data in HF with preserved ejection fraction could not confirm different effects between MCT and HIIT [7]. The positive data in HFrEF are based on a pilot study by Wisloff and colleagues [8], safety data from a Norwegian registry [9], and a large randomized controlled trial investigating different exercise intensities in HFrEF, the Study of MyocArdial Recovery afTer EXercise training in HF (SMARTEX-HF) [10]. This latter study found significant reductions after 12 weeks of supervised exercise of left ventricular dimensions during HIIT and comparable improvements of oxygen uptake (peak VO_2) for HIIT and MCT compared to the control group receiving advice to exercise at home according to current recommendations and attending a session of moderate intensity training every 3 weeks [10].

Etiology of HFrEF is not considered for exercise recommendations in current HF guidelines [1]. Patients with ICM may be at increased risk for ischemia during exercise, especially when exercising at high intensities. Moreover, ICM and NICM differ significantly regarding myocardial scarring [11], inflammatory and immune response, microvascular dysfunction, mitochondrial dysfunction and interstitial collagen content [11–13], factors which may also influence exercise-induced arrhythmias [2,3,14].

As a predefined subgroup analysis within the SMARTEX-HF trial [15], we analyzed the effects of 12 weeks of HIIT, MCT and a recommendation of regular exercise (RRE) on cardiac dimensions, cardiac function and exercise capacity in patients with NICM or ICM etiologies of HFrEF. The hypothesis of this sub-analysis is that response to exercise training differs between HF etiologies (ICM vs. NICM) regarding left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and peakVO_2 and this is dependent on exercise training group allocation (HIIT, MCT or RRE).

2. Materials and methods

2.1. Study design

Details of rationale, design, methods, sample size calculations, randomization, organization, primary endpoints [15] and primary results of the SMARTEX-HF study have been previously published [10]. As outlined in the original study protocol, a subgroup analysis regarding the effects of etiology of HF had been predefined [15], and accordingly patients were stratified by HF etiology e.g., ICM versus NICM, at randomization [10]. National ethics committees for medical research approved the study in all countries. All patients gave written informed consent. The study was registered in the clinical trial database before the start (NCT00917046) and conducted in conformity with the policy statement for the use of human subjects of the Declaration of Helsinki.

2.2. Patients and intervention

HFrEF patients with LVEF <35 %, stable but symptomatic (NYHA II-III), on optimal medical therapy, with no signs of myocardial ischemia at exercise testing were randomized 1:1:1 to a 12-week supervised exercise program. The randomization groups were a) MCT, b) HIIT, or c) RRE according to current guidelines as previously described [8,10,15]. Briefly, HIIT and MCT included three supervised sessions per week on treadmill or cycle ergometer. HIIT sessions were to be performed as four 4-minute intervals at 90–95 % of peak heart rate (HR) interspersed with 3-minute active recovery periods at 60–70 % of peak HR. HIIT sessions lasted 38 min including warm-up and cool-down at moderate intensity. MCT sessions were to be performed at 60–70 % of peak HR and lasted 47 min as described in the original study [8]. Patients randomized to RRE were advised to perform unsupervised exercise according to individual preference based on current recommendations [5]. No structured exercise recommendations were given; however, patients were offered to attend a maximum of one session of moderate intensity training at 50–70 % of peak HR every third week to motivate them for post-intervention testing and to reduce the impact of learning on the post-intervention test results. After 12 weeks of supervised training all patients were encouraged to continue the prescribed exercise unsupervised for 40 weeks.

2.3. Clinical assessments

Screening procedures and outcome assessments at baseline, after 12 weeks and 52 weeks were performed at local study centers as previously described [10,15]. Briefly, medical history, anthropometrics, physical examination including fasting blood sampling, quality of life questionnaires, cardiopulmonary exercise testing (CPET) and echocardiography were performed locally. Echocardiographic recordings (EchoPAC SW; version BT 11–13; GE Ultrasound, Horten, Norway) and cardiopulmonary exercise test results were analyzed by core labs (Echo in Trondheim, CPET in Antwerp), where all investigators were blinded to group assignment but not always to time point of assessment.

2.4. Endpoints

This predefined sub-analysis was performed as part of the SMARTEX-HF study in which the following endpoints were stratified by NICM and ICM: The primary endpoint was the comparison of training groups (HIIT vs. MCT) in terms of change in LVEDD from baseline to 12 weeks and 52 weeks assessed by echocardiography. Key secondary endpoints were changes in LVEF and peak VO_2 after 12 and 52 weeks. An independent blinded endpoint committee classified all adverse events [15], but the trial was not powered to analyze safety.

2.5. Statistical analysis

Post-hoc analysis of this pre-defined hypothesis of the influence of HFrEF etiology on primary and secondary endpoints had been outlined previously [10,15]. The analysis was pre-specified as mixed models with robust standard errors, including the baseline, 12 week, and 52 weeks

outcome values as the dependent variable, timepoint, intervention group (HIIT, MCT or RRE), and etiology (ischemic or non-ischemic) as explanatory variables, and adjustments for clinical site. The coefficients for timepoint and the two other explanatory variables were tested for significance. Mixed models were used because they can handle correlations of repeated measurements within patients by inclusion of patient as a random factor, and missing data due to drop-outs during follow-up. An alternative model also included adjustments for sex, age, and present vs. former/never smoking. If the main effect of etiology was significant, indicating an overall difference between the ICM and NICM groups, an interaction term between etiology and intervention group (HIIT, MCT or RRE) was tested. A significant interaction term implies that the effect of the exercise intervention on the endpoint was different between the ICM and NICM groups.

Power calculations for the SMARTEX-HF study were based on the main outcome, i.e., comparison between the experimental groups with respect to change in LVEDD from baseline to 12 weeks. Etiology of HFrEF was not included in the primary power calculations [15].

Unless otherwise specified, data are presented as medians with 95 % CI, or as frequencies with percentages. Model fit was checked by residual plots and estimated contrasts are presented as means with 95 % confidence intervals. Statistical analyses were performed with Stata (v14.1, StataCorp, College Station, Texas, USA).

3. Results

A total of 247 patients were allocated to the trial, of which 231 started the exercise intervention program. 215 patients completed the 12-week intervention program and were evaluated for this sub-analysis after 12 weeks, and 202 were evaluated at 52 weeks (details of drop-outs are presented in the main paper) [10]. Drop-out rates for HIIT, MCT, and RRE were 5, 8, and 3 (p = 0.95) at 12 weeks and 12, 11, and 6 at 52 weeks (p = 0.92), respectively. Drop-out rates for NICM and ICM were 9 and 7 at 12 weeks (p = 0.83) and 13 and 16 at 52 weeks (p = 0.94), respectively. Patient characteristics are outlined in Table 1. Besides statin use for secondary prevention of CAD, and higher percentage of ICD in ICM, the use of HF medication was not different between etiology groups (Table 1) and revealed optimal medical management according to HF guidelines [1].

Exercise intensity target achievement was similar in the NICM and ICM groups. In the MCT group, 92 % of NICM patients and 72 % of ICM patients trained at a higher intensity than the protocol target (p = 0.10). In the HIIT group, 61 % of the NICM patients and 43 % of the ICM patients trained at a lower intensity than the protocol target (p = 0.16), which is in accordance with the reported training intensity results from the main study [10]. Table 2 describes observed (unadjusted) values for LVEDD, LVEF, peak VO_2, and NT-proBNP at baseline, 12, and 52 weeks. NT-proBNP measurements were within the expected ranges for HF patients.

3.1. Cardiac structure and function

Baseline LVEDD and LVEF did not differ between NICM and ICM. There was no difference in the change of LVEDD from baseline to 12 weeks between the ICM and NICM groups (1 (−1–3) mm, p = 0.30). This finding remained after including sex, age and smoking status into the model (p = 0.54). Likewise, the influence of etiology on LVEF in the model was not statistically significant (change in LVEF -1 (−3–0) %, p = 0.12), even after including sex, age, and smoking status (p = 0.12). The results were similar after 52 weeks. As previously reported, the main study observed a small but statistically significant within-group reduction in the primary endpoint of LVEDD at 12 weeks in the HIIT group, but not in the MCT group [10].

Table 1
Patient characteristics for non-ischemic (NICM) and ischemic cardiomyopathy (ICM).

Characteristics	Non-ischemic etiology (NICM) N = 89	Ischemic etiology (ICM) N = 126	p-Value
Age, years	57 (55–61)	64 (60–66)	0.008
Women	23(26 %)	17(13 %)	0.022
HF < 12 months	18(20 %)	17(13 %)	0.18
NYHA class			0.24
II	66(74 %)	84(67 %)	
III	23(26 %)	42(33 %)	
LVEF	30(28–32)	29(27–31)	0.56
Previous MI	3(3 %)[a]	109(87 %)	<0.001
Previous CABG	0	51(40 %)	<0.001
Previous PCI	2(2 %)	86(68 %)	<0.001
Device therapy			0.26
Pacemaker	2(2 %)	2(2 %)	
ICD	32(36 %)	64(51 %)	
Resynchronization therapy	2(2 %)	3(2 %)	
Atrial fibrillation			0.90
Chronic	13(15 %)	16(13 %)	
Paroxysmal	12(13 %)	16(13 %)	
History of hypertension	37(42 %)	45(36 %)	0.41
History of diabetes mellitus	17(19 %)	34(27 %)	0.18
History of COPD	3(3 %)	13(10 %)	0.06
Current smoking	17(19 %)	21(17 %)	0.65
Alcohol drinks/week	1(1–2)	2(1–3)	0.07
Medications			
ACE-I/ARB	85(96 %)	116(92 %)	0.31
Beta-blocker	86(97 %)	119(94 %)	0.45
Aldosterone-receptor antagonist	54(61 %)	68(54 %)	0.33
Diuretic	64(72 %)	95(75 %)	0.66
Digoxin	15(17 %)	16(13(%)	0.39
Statin	26(29 %)	116(92 %)	<0.001
BMI, kg/m^2	28.0(26.7–29.0)	27.0(26.2–28.0)	0.36
Systolic BP, mmHg	120 (113–120)	118(115–120)	0.75
Diastolic BP, mmHg	78(70–80)	73(70–75)	0.40
NT-proBNP, ng/L	964(616–1133)	1038(802–1162)	0.35
Intervention groups sample size			0.87
RRE	32(36 %)	41(33 %)	
MCT	26(29 %)	39(31 %)	
HIIT	31(35 %)	46(37 %)	

HF, Heart failure; NYHA, New York Heart Association; LVEF, Left ventricular ejection fraction; MI, Myocardial Infarction; CABG, Coronary artery bypass graft; PCI, Percutaneous coronary intervention; ICD, Implantable cardioverter-defibrillator; COPD, Chronic obstructive pulmonary disease; ACE-I/ARB, Angiotensin Converting Enzyme-Inhibitors/ Angiotensin II Receptor Antagonists; BMI, Body Mass Index; BP, Blood Pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; RRE, Recommendation of regular exercise according to guidelines; MCT, Moderate continuous training; HIIT, High intensity interval training.

[a] Patients were classified by centers according to ICM and NICM. Data are medians with 95 % confidence interval of the medians, or frequency with percentages.

3.2. Peak oxygen consumption (peak VO_2)

At baseline and 12 weeks NICM patients had a statistically significant higher peak VO_2 than ICM patients (p < 0.001) (Fig. 1). The mean increase in peak VO_2 from baseline to 12 weeks was similar for both etiologies (0.7 (0.3–1.1) mL/(kg*min), p = 0.11). There was no significant effect of etiology on peak VO_2 between the exercise groups (HIIT, MCT or RRE, p = 0.15 for interaction with etiology), nor did the effect of etiology differ at the three timepoints (p-value = 0.11 for interaction of etiology with time). The difference in peak VO_2 between ICM and NICM was similar across sex (p = 0.67), age (p = 0.11) and smoking status (p = 0.57). In the best model for peak VO_2, the coefficients were as follows (adjusted for center and intervention group): Ischemic etiology as compared to non-ischemic etiology −2.2 mL/(kg*min) (−3.4, −1.0; p < 0.001, female sex −2.1 (−3.6, −0.6; p = 0.005), present smoker −1.7

Table 2
Observed data for Left Ventricular End-diastolic Diameter (LVEDD), Left Ventricular Ejection Fraction (LVEF), Peak Oxygen Uptake (peak VO_2), and NT-pro Brain Natriuretic Peptide (NT-proBNP).

	Etiology	Intervention	Baseline	12 weeks	52 weeks
LVEDD (mm)	NICM	RRE	68 (64–69)	68 (63–72)	65 (59–68)
		MCT	69 (65–74)	68 (61–70)	62 (56–66)
		HIIT	69 (62–73)	65 (61–69)	62 (59–66)
	ICM	RRE	68 (66–70)	69 (67–72)	67 (63–69)
		MCT	69 (67–73)	67 (65–72)	65 (63–67)
		HIIT	67 (64–70)	63 (61–70)	64 (62–68)
LVEF (%)	NICM	RRE	32 (29–34)	29 (25–31)	30 (26–39)
		MCT	28 (23–32)	30 (25–38)	33 (22–42)
		HIIT	29 (25–32)	32 (30–36)	32 (26–39)
	ICM	RRE	29 (25–31)	28 (25–31)	28 (26–31)
		MCT	29 (26–33)	27 (23–32)	33 (25–37)
		HIIT	30 (26–31)	30 (27–33)	27 (24–30)
peak VO_2 (mL/kg/min)	NICM	RRE	20.0 (17.9–20.7)	20.5 (17.4–23.0)	21.1 (16.9–21.7)
		MCT	17.4 (14.6–19.7)	18.0 (15.6–22.1)	18.2 (14.9–23.6)
		HIIT	17.9 (15.9–20.3)	20.2 (16.0–22.8)	18.9 (15.1–22.4)
	ICM	RRE	17.2 (14.9–18.6)	15.4 (14.6–17.5)	16.4 (15.3–18.6)
		MCT	15.9 (14.9–18.7)	16.9 (15.2–18.5)	15.8 (14.6–17.9)
		HIIT	16.0 (14.3–16.8)	17.3 (15.2–19.5)	16.8 (15.5–18.3)
NT-proBNP (ng/L)	NICM	RRE	520 (387–1098)	430 (345–915)	275 (156–587)
		MCT	1008 (550–1678)	774 (379–1513)	595 (132–1070)
		HIIT	1052 (607–1943)	893 (601–1694)	826 (509–1705)
	ICM	RRE	1053 (707–1275)	1142 (799–1654)	1001(592–1769)
		MCT	825 (664–1417)	823 (576–1141)	780 (612–1316)
		HIIT	1051 (791–1561)	924 (627–1626)	677 (566–1864)

Data are given as medians with 95 % confidence interval of the medians due to non-normal distributions.
LVEDD, Left Ventricular End-diastolic Diameter; LVEF, Left ventricular ejection fraction; peak VO_2, Peak oxygen uptake; NT-proBNP, N-terminal pro b-type natriuretic peptide; NICM, Non-ischemic etiology; ICM, Ischemic etiology; RRE, Recommendation of regular exercise according to guidelines; MCT, Moderate continuous training; HIIT, High intensity interval training.

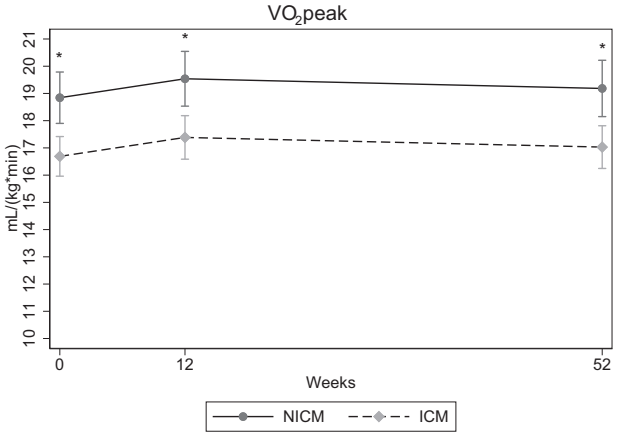

Fig. 1. Maximal exercise capacity.
Maximal exercise capacity (peak VO_2 in mL/(kg*min)) during exercise intervention (combined for all participants) at baseline, after 12 and 52 weeks for non-ischemic cardiomyopathy (NICM) and ischemic cardiomyopathy (ICM).
*p < 0.001, analyzed using mixed model.

(−3.1, −0.2; p = 0.026), age (per year −0.2 (−0.2, −0.1; p < 0.001).

3.3. Adherence

During the 36 supervised exercise session from baseline to 12 weeks in the HIIT and MCT groups, adherence was similar (median 35 (34–35) sessions, p = 0.94) in both groups. This was similar for NICM and ICM.

3.4. Safety

The study was underpowered for safety analysis, so findings can only be hypothesis-generating. Over 52 weeks, five fatal events occurred in ICM and two in NICM. In the ICM patients, 3 out of 5 fatal events (1 in MCT, 2 in HIIT) had a cardiovascular origin, while in the NICM or RRE groups, fatal events were non-cardiovascular. All fatal events occurred outside of the training environment.

4. Discussion

In this predefined subgroup analysis, HF etiology (ischemic versus non-ischemic) was not a determinant of changes in LV dimensions, LV ejection fraction or peak exercise capacity in patients with HFrEF. Specifically, there were no differences between those who performed HIIT or MCT when comparing patients with ICM or NICM etiology, both over 12 weeks of supervised exercise and subsequent 40 weeks of non-supervised training (Table 2).

The results of this SMARTEX subgroup analysis are in accordance with previous trials applying exercise training as a therapy for HF. The largest trial in HFrEF, the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, revealed a modest but statistically significant benefit of exercise training on the primary combined outcome of all-cause mortality or all-cause hospitalization after adjusting for relevant predictors [16]. In that study etiology of HF did not have any effect on the primary outcome (hazard ratio between ischemic and non-ischemic etiology (HR [95 % CI], ICM: 0.94 [0.82–1.08]; NICM: 0.91 [0.78–1.05], p = 0.73 for interaction). A previous meta-analysis on exercise training studies investigating the effect of etiology on mortality in HFrEF patients (ExTraMATCH) reported similar findings (Hazard Ratio [HR; 95 % CI] ICM 0.54 (0.35 to 0.83) vs. NICM 0.93 (0.52 to 1.68), p = 0.10 for interaction), but stated a non-significant trend towards a higher efficacy of exercise in ICM than NICM acknowledging that the studies were largely underpowered for this analysis [17]. However, these studies have only investigated the effects of exercise at moderate intensity. Therefore, our SMARTEX-HF data also including high intensity exercise add important clinical information that etiology of HFrEF is not an important criterion for prescribing moderate or high intensity exercise training.

Nonetheless, differences between ICM and NICM were observed. In our cohort a lower peak VO_2 at baseline was evident for the ICM

compared to the NICM group. This might be explained by the fact that participants in the ICM group were significantly older, received statins more frequently (Table 1) and might, because of the origin of disease, experience ischemia during exercise, which may have overall limited their exercise efforts or peripheral adaptations. Moreover, age is inversely associated with peak VO_2 in patients with HFrEF and affects trainability [18]. Furthermore, statin use has been addressed to have an impact on muscular function, exercise capacity, and trainability, although these data are still equivocal [19,20]. Also exercise-induced ischemia cannot be excluded, but ICM and NICM patients were not different regarding potential confounders of exercise capacity such as NYHA class or NTproBNP levels (Table 2).

Although the SMARTEX-HF trial is one of the largest randomized controlled exercise intervention studies in HFrEF and currently overall the largest study including moderate as well as HIIT, it is still too small for adequate assessment of mortality particularly between ICM and NICM. Results revealed a numerical difference in mortality between etiology groups with three fatal cardiovascular events in the ICM exercise groups and none in the NICM exercise groups nor in the exercise recommendation group. This finding should be recognized but interpreted cautiously. Safety issues have previously not been observed in large intervention or HF cohort studies [9,16,21] or the SAINTEX study including high intensity interval training in ischemic heart disease patients [21]. Nonetheless, as all three cardiovascular deaths were observed in the exercise ICM group, particularly ICM patients should be well evaluated before starting exercise and more closely followed during exercise interventions. Clearly, safety assessment of exercise particularly in ICM should be addressed in larger trials in the future.

A strength of the SMARTEX-HF trial is the randomized design including both two supervised training groups and the RRE group, which permits consideration of the substantial individual variation in the endpoints with standard care when evaluating the effects of the supervised interventions. The use of mixed models for statistical analysis in the present study adequately handles this design as well as repeated measures, multiple comparisons among groups, loss to follow-up, and carries no assumptions about identical variable trajectories in all patients within each group, which would not be possible using inadequate methods such as evaluating overlapping 95 % CI, performing *t*-tests, analysis of variance, or analysis in the three groups separately.

There are important limitations. By dividing the primary group regarding entity, study sample size for each group is reduced, which limits generalizability. Moreover, the number is too low to determine clinical side effects, which is particular important when applying HIIT in HFrEF. Nevertheless, the SMARTEX-HF study is so far the largest study investigating this entity in a randomized controlled trial.

5. Conclusions

Patients with HFrEF with ischemic etiology had significantly lower baseline exercise capacity than those of non-ischemic etiology. HF etiology (ICM vs. NICM) did not affect exercise-induced myocardial remodeling or peak oxygen capacity in optimally treated patients with HFrEF. These data were similar for moderate and high intensity training.

Funding

This work was supported by St. Olavs Hospital; Faculty of Medicine, Norwegian University of Science and Technology; Norwegian Health Association; Danish Research Council; Central Norwegian Health Authority/Norwegian University of Science and Technology; and Société Luxembourgeoise pour la recherche sur les maladies cardiovasculaires. MH received financial institutional funding from the DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany, outside the present study.

CRediT authorship contribution statement

Conception and design: *Halle, Prescott, Craenenbroeck, Beckers, Videm, Karlsen, Linke, Ellingsen, Delagardelle.*

Analysis and interpretation of data: *All authors.*

Drafting of the manuscript: *Halle.*

Revising the manuscript critically for important intellectual content: *All authors.*

Final approval of the manuscript submitted: *All authors.*

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolve: *All authors.*

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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