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Original article

Moderate-intensity continuous exercise is superior to high-intensity interval training in the proportion of VO_{2peak} responders after ACS

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A B S T R A C T

Introduction and objectives: We compared the effects of 12 weeks of low-volume high-intensity interval training (LV-HIIT) vs moderate-intensity continuous exercise training (MICET) on cardiopulmonary exercise test parameters and the proportion of non/low responders (NLR) to exercise training in post-acute coronary syndrome (ACS) patients.
Methods: Patients with a recent ACS were randomized to LV-HIIT, MICET, or a usual care group. LV-HIIT consisted of 2 to 3 sets of 6 to 10 minutes with repeated bouts of 15 to 30 seconds at 100% of peak workload alternating with 15 to 30 seconds of passive recovery. Cardiopulmonary exercise test parameters were assessed, and key exercise variables were calculated. Training response was assessed according to the median VO_{2peak} change post vs pretraining in the whole cohort (stratification NLR vs high response).
Results: Fifty patients were included in the analysis (LV-HIIT, n = 23; MICET, n = 18; usual care, n = 9) and 74% were male. The proportion of NLR was higher in the LV-HIIT group than in the MICET group (LV-HIIT 61%, MICET 21%, and usual care 80%; $P = .0040$). VO_{2peak}-dependent variables (VO_{2peak}, percent-predicted VO_{2peak}) improved in both training groups ($P = .002$ and $P < .0001$ for time with LV-HIIT and MICET, respectively), but the improvement was more pronounced with MICET ($P = .004$ and $P = .001$ for interaction, respectively). The $\Delta VO_2/\Delta$workload slope improved only with MICET ($P = .021$).
Conclusions: In patients with a recent ACS, several prognostic VO_{2peak}-dependent variables were improved after LV-HIIT, but the improvement was more pronounced or only found after MICET. Low-volume HIIT resulted in a higher proportion of NLR than isocaloric MICET.
Clinical trialsregistered at ClinicalTrials.gov (Identifiers: NCT03414996 and NCT02048696)

El ejercicio continuo de moderada intensidad es superior al ejercicio interválico de alta intensidad en mejorar el VO_2 pico en pacientes tras SCA

Palabras clave:
Síndrome coronario agudo
Ejercicio de alta intensidad
Ejercicio continuo
VO_2 pico
Respuesta al ejercicio

R E S U M E N

Introducción y objetivos: Se comparó los efectos de 12 semanas de ejercicio interválico de alta intensidad y de bajo volumen (EIAI-BV) frente a un ejercicio continuo de intensidad moderada (ECIM), sobre los parámetros de la prueba de esfuerzo cardiopulmonar y la proporción de no respondedores o con baja respuesta (NBR) al ejercicio físico en pacientes que sufrieron un síndrome coronario agudo (SCA).
Métodos: Se aleatorizó a pacientes con un SCA reciente a EIAI-BV, ECIM y a cuidados habituales. EIAI-BV constó de 2 a 3 sesiones de 6-10 minutos con periodos de repetición de 15 a 30 s al 100% de la carga de trabajo alternados con 15-30 segundos de recuperación pasiva. Los parámetros de la prueba de ejercicio cardiopulmonar se evaluaron y se calcularon las variables claves. La respuesta al ejercicio se evaluó con la mediana de VO_2 pico de cambio (post- frente a preejercicio) en toda la cohorte estratificada en NBR al ejercicio frente a alta respuesta.
Resultados: Se incluyó a 50 pacientes en el análisis (EIAI-BV, n = 23; ECIM, n = 18; cuidados habituales, n = 9), el 74% eran varones. La proporción de NBR fue mayor en el EIAI-BV en comparación con el grupo ECIM y el grupo de cuidados habituales (el 61 frente al 21 y el 80%, respectivamente; p = 0,0040). Las variables dependientes del VO_2 (VO_2 pico y porcentaje VO_2 pico predicho) mejoraron en ambos grupos

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de entrenamiento (p = 0,002 y p < 0,0001 para EIAI-BV y ECIM, respectivamente), pero la mejora fue más pronunciada con ECIM (p = 0,004 y p = 0,001 para la interacción, respectivamente). El $\Delta VO_2 / \Delta$ pendiente de la carga de trabajo ha mejorado únicamente con ECIM (p = 0,021).

Conclusiones: En pacientes con un SCA reciente, varias variables pronósticas dependientes del VO_2 pico mejoraron después de EIAI-BV, pero la mejora fue más pronunciada o bien mejoró únicamente después de ECIM. El EIAI-BV resultó en una mayor proporción de NBR en comparación con el ECIM isocalórico.

Ensayos registrados en ClinicalTrials.gov (Identificadores: NCT03414996 and NCT02048696)

Abbreviations

ACS: acute coronary syndrome
CHD: coronary heart disease
CPET: cardiopulmonary exercise test
LV-HIIT: low-volume high-intensity interval training
MICET: moderate-intensity continuous exercise training
NLR: non/low responders

INTRODUCTION

Exercise-based secondary prevention programs reduce cardiovascular mortality and morbidity in patients with coronary heart disease (CHD), including patients after acute coronary syndrome (ACS).[1,2] Maximal cardiorespiratory fitness (ie, VO_{2peak}) is a powerful predictor for all-cause mortality in CHD patients,[3,4] and a VO_{2peak} improvement is associated with a reduction in mortality, morbidity, and health care costs.[4–7] However, there is a considerable individual heterogeneity in VO_{2peak} improvement to standardized exercise training programs in patients with CHD.[8–11] In this population, 14% to 22% can be classified as non/low responders (VO_{2peak} improvement),[8,10,11] which has recently been associated with a higher mortality risk.[8]

Moderate continuous exercise training (MICET) is a guidelines-based aerobic endurance training modality for CHD patients.[12–14] High-intensity interval training (HIIT) has been proposed as a modality that is complementary to MICET.[14,15] In CHD patients, HIIT protocols have been previously classified as having short (≤ 60 seconds), medium (1-3 minutes) or long intervals (> 3 minutes).[16] A recent meta-analysis comparing VO_{2peak} improvements with either HIIT or MICET in stable CHD patients found more pronounced effects with HIIT.[17] Of note, most of the studies included (70%) used long interval HIIT protocols, and the superiority of HIIT over MICET disappeared when isocaloric protocols were used. Moreover, the intensity of the HIIT protocol (4 minutes at 90%-95% of peak heart rate) in the SAINTEX-CAD study was hard to maintain for most of the CHD patients.[18] Similarly, we showed that longer interval HIIT protocols (60 to 90 seconds) were less well tolerated and were associated with lower total exercise time in CHD.[19]

Accordingly, we developed an optimized HIIT protocol with short intervals (15-30 seconds) that is safe, very well tolerated by CHD patients, and produces physiological responses very similar to those of MICET.[20,21] However, this optimized LV-HIIT protocol has not been compared with isocaloric MICET with regards to the proportion of non/low responders (based on changes in VO_{2peak}) and key cardiopulmonary exercise test (CPET) variables in post-ACS patients. We hypothesized that optimized LV-HIIT would result in a similar proportion of training non/low responders (NLR) and similar VO_{2peak} changes compared with MICET.

The main aims of our study were: *a)* To assess the proportion of NLR and high responders (based on VO_{2peak}) in post-ACS patients after structured aerobic exercise training (LV-HIIT, MICET) or usual care; *b)* to compare peak and submaximal CPET parameters between the 2 training modalities; *c)* to assess the independent predictors of VO_{2peak} NLR in post-ACS patients.

METHODS

Participants

All patients were referred for a multi-disciplinary secondary prevention program at the Cardiovascular Prevention and Rehabilitation Center (EPIC Center) of the Montreal Heart Institute and included in a randomized training intervention study. Details on the inclusion and exclusion criteria have been previously described elsewhere.[22,23] Essentially, all CHD patients were under optimal medical therapy following coronary revascularization for ACS. Patients had to be stable with regard to symptoms and medication doses during the 4 weeks prior to enrolment. For this analysis, data from 2 prospective randomized exercise-intervention studies were pooled. The first study comprised post-ACS patients who were randomized (1:1) to either LV-HIIT or MICET. The primary endpoint was VO_{2peak}. In the second pilot study, post-ACS patients were randomized (1:1) to either LV-HIIT or usual care, with lymphocyte GRK2 mRNA levels as the primary endpoint. This explains the disproportionate number of patients randomized in each group (LV-HIIT, MICET, usual care). The study protocols were approved by the Research Ethics and New Technology Development Committee of the Montreal Heart Institute. Both studies were registered on ClinicalTrials.gov (ClinicalTrials.gov identifier numbers: NCT03414996 and NCT02048696). Written informed consent was obtained by each patient.

Study design and measurement

Baseline clinical data, and CPET were assessed at baseline and after completion of the program. Baseline clinical data assessment included data on personal medical history, event details, and cardiovascular risk factor profile.

Maximal cardiopulmonary exercise testing

Maximal CPET was performed on a cycle ergometer (Ergoline 800S, Bitz, Germany) according to the recommendations of the American Heart Association, and as previously published.[19,21,24,25] Following a 3-minute warm-up phase at an initial workload of 20 W, an incremental exercise test was performed with 15 Watt increments per minute until exhaustion at a pedaling speed > 60 rpm. The recovery phase consisted of 2 minutes of active recovery at 20 W at pedaling speed between 50 rpm and 60 rpm, followed by 3 minutes of passive recovery. Gas exchange parameters were continuously measured at rest, during exercise, and during recovery using a metabolic system (Oxycon Pro, CareFusion, Jaeger, Germany) as recently published.[19,21,25] There was continuous ECG monitoring (Marquette, case 12, St. Louis, Missouri, USA). Blood pressure and rate of perceived exertion were measured every 3 minutes throughout the test. The highest VO_2 value reached during the exercise phase was considered as the VO_{2peak} and peak workload was defined as the workload reached at the last fully completed stage. Oxygen uptake efficiency slope, ventilatory efficiency (VE/VCO_2) slope, and $\Delta VO_2/\Delta$workload slope were calculated according to recent recommendations.[26]

Exercise training intervention

All patients performed 2 to 3 exercise training sessions a week on a bicycle ergometer. The aerobic exercise training consisted of 2 different training modalities: low-volume high-intensity interval training (LV-HIIT) or moderate-intensity continuous exercise training (MICET), which were isocaloric according to previously published methods.[21] Additional resistance training was performed following each aerobic exercise session. All training was center-based and performed under the supervision of a certified kinesiologist.

Low-volume high-intensity interval training

The HIIT protocol was evaluated in a prospective randomized trial and optimized in that specific population (ie, CHD patients) as recently published.[19,21] Following a 5-minute warm-up at 30% of peak workload obtained at the CPET, patients performed 2 to 3 sets of 6 to 10 minutes with repeated bouts of 15 to 30 seconds at 100% of peak workload alternating with 15 to 30 seconds of passive recovery. The target rating of perceived exertion (rate of perceived exertion 6-20) was set at 15 during the HIIT bouts. The sets were separated by a 5-minute active recovery phase at 30% of peak workload. The training session was terminated by a 5-minute cool-down phase at 30% of peak workload (figure 1).[27] The term low-volume refers to the fact that the weekly training volume with the protocols used was < 150 minutes (MICET) or < 75 minutes (LV-HIIT) for high/vigorous intensity, which are the minimal thresholds recommended by most international guidelines.[28,29]

Moderate-intensity continuous exercise training

Following a 5-minute warm-up at 30% of peak workload, patients performed continuous exercise at 60% of peak workload for 24 minutes. At the end of the session, the patients performed 5 minutes of recovery at 30% of peak workload (figure 1). The total time was 34 minutes and the training was isocaloric with the LV-HIIT session.[21] A recent meta-analysis in CHD patients underlined the importance of matching energy expenditure during the training when comparing exercise modalities (HIIT vs MICET).[17] Indeed, the superiority of HIIT vs MICET on VO_{2peak} improvement disappears when both protocols are isocaloric.[17] Our isocaloric calculation method was strongly based on a direct measure of metabolic energy expenditure with gas exchange (VO_2 uptake) during similar acute HIIT and MICET protocols in CHD patients.[21]

Resistance training program

Resistance training consisted of 20 minutes of circuit weight training performed with elastic bands and free weights adapted to each patient's capacity. For each muscle group, patients performed 1 set of 15 to 20 repetitions, followed by a 30-second rest at a target rate of perceived exertion of 15.[27]

Usual care group

The control group received recommendations on physical activity for a period of 12 weeks by their discharging cardiologist. If there were no recommendations at discharge, physical activity recommendations consistent with recent guidelines were given. Patients were encouraged to take 30 to 60 minutes of moderate-intensity exercise at least 5 days per week (target rate of perceived exertion of 12-14).[30]

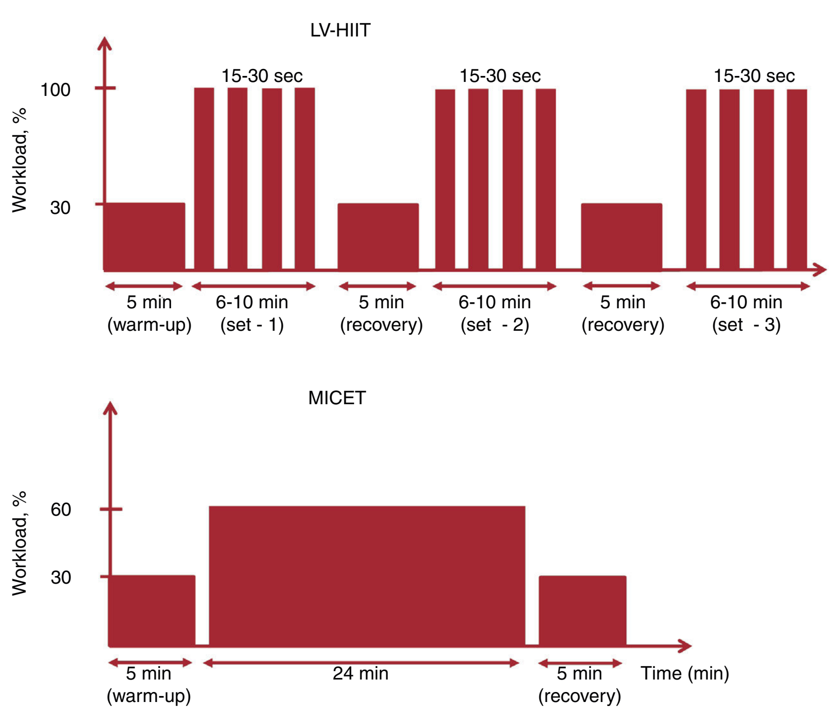

Figure 1. LV-HIIT and MICET protocol. LV-HIIT, low-volume high-intensity interval training; MICET, moderate-intensity continuous exercise training.

Statistical analyses

Data are presented as mean ± standard deviation or median ± interquartile range as appropriate for continuous variables, while frequencies and percentages are presented for categorical variables. Baseline characteristics were compared between the 3 groups using 1-way ANOVA and categorical variables were compared using the chi-square or Fisher exact tests. Repeated measures ANOVA models were used to study the CPET parameters across time and between groups. Models with time, group and group × time interaction as independent variables were used. The main focus of the analysis was the group × time interaction as it tested the difference in the change (post-pre) between the 3 groups. In addition, under the repeated measures ANOVA model, the change (post-pre) within each group was formally tested against zero. For the analysis of training response, VO_{2peak} high response vs NLR was defined as the median value for change in peak oxygen uptake (ΔVO_{2peak} in mL/min/kg) post- and pretraining in the whole cohort.[8] Training response with a $\Delta VO_{2peak} < 2.1$ mL/min/kg was defined as NLR, while a $\Delta VO_{2peak} > 2.1$ mL/min/kg was defined as VO_{2peak} high response. Univariate and multivariate logistic regression was used to generate a predictive model for training NLR. Predictors of training NLR for univariate logistic regression were selected as follows: sex, age, VO_{2peak} percent predicted at baseline, presence of type 2 diabetes mellitus, and training modality. All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and conducted at the .05 significance level.

RESULTS

Clinical characteristics

The study flowchart is presented in figure 2. In the final analysis, we included a total of 50 patients (LV-HIIT, n = 23, MICET, n = 18, usual care, n = 9). Patients in the HIIT group tended to have lower body mass and lean body mass than patients in the MICET and usual care group. Otherwise, there were no differences with regards to baseline clinical characteristics (table 1).

Proportion of non/low responders in the groups (LV-HIIT, MICET, usual care)

The median value for ΔVO_{2peak} (in mL/min/kg) post and pretraining in the whole cohort was 2.1 mL/min/kg. MICET was associated with a significantly lower proportion of training NLR compared with LV-HIIT and usual care (21% in MICET, 61% in LV-HIIT, and 80% in the usual care group; $P = .004$). Of note, for the LV-HIIT and MICET program, adherence (percentage) was defined as the number of attended sessions divided by the total planned sessions × 100. Patients were only included in the analysis if they attended at least 75% of the training sessions and 1.5 weekly training sessions. Patients completed 2.4 ± 0.5 and 2.4 ± 0.4 weekly training sessions in the LV-HIIT and MICET groups, respectively ($P = .946$). Weekly training duration was 83 ± 12 minutes with LV-HIIT and 80 ± 14 minutes with MICET ($P = .487$). Adherence was 100 (97) in the LV-HIIT and 100 (95) in the MICET group, respectively ($P = .456$).

Cardiopulmonary exercise test parameters in the groups (LV-HIIT, MICET, usual care)

As shown in table 2, VO_{2peak} (normalized for body mass and lean body mass, respectively), predicted VO_{2peak}, and peak workload (absolute and normalized for lean body mass) improved with training in the LV-HIIT and in the MICET group ($P < .05$ for time), while there was no effect in the usual care group. Significant group × time interaction was observed for these parameters ($P < .05$). The oxygen uptake efficiency slope and O_2 pulse

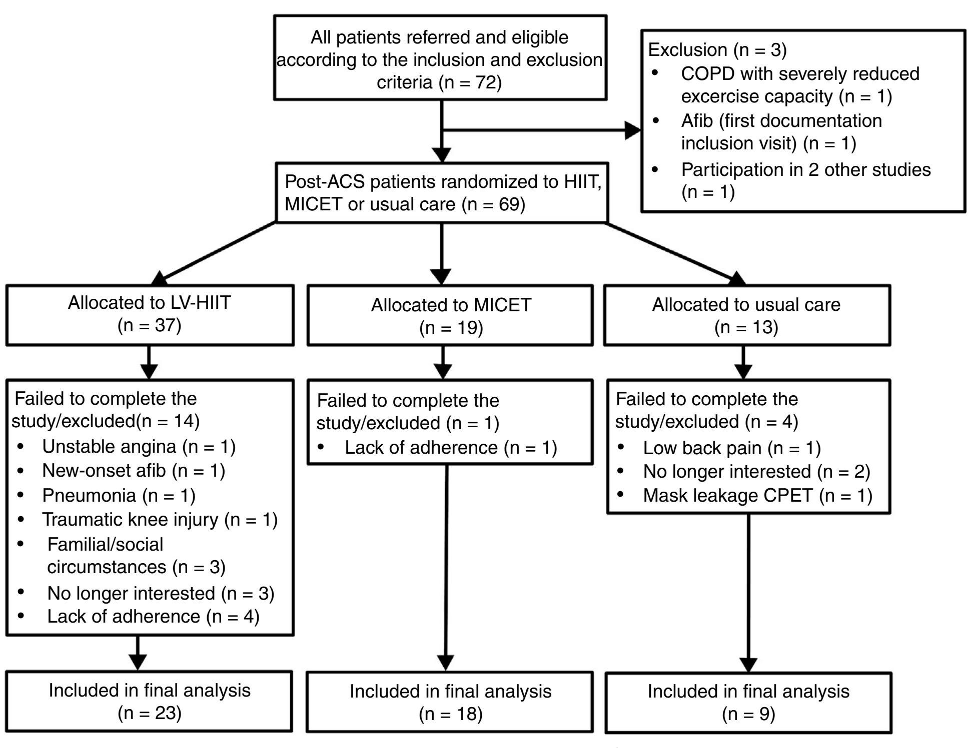

Figure 2. Flowchart of the study. ACS, acute coronary syndrome; Afib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; LV-HIIT, low-volume high-intensity interval training: MICET, moderate-intensity continuous exercise training.

Table 1
Baseline characteristics of post-ACS patients randomized to LV-HIIT, MICET or usual care

Variable	LV-HIIT, n = 23	MICET, n = 18	Usual care, n = 9	*P*
Age, y	63.6 ± 9.0	59.2 ± 9.7	58.7 ± 11.3	.260
Male sex	15 (65)	15 (83)	7 (78)	.405
Height, m	1.68 ± 0.10	1.72 ± 0.09	1.70 ± 0.10	.358
Body mass, kg	76.4 ± 8.2	86.6 ± 17.0	81.4 ± 9.0	.064
LBM, kg	54.5 ± 9.2	62.3 ± 13.3	55.6 ± 10.6	.086
Body mass index, kg/m^2	27.3 ± 3.5	29.1 ± 4.8	28.3 ± 3.5	.364
Periprocedural characteristics				
STEMI	11 (48)	11 (61)	7 (78)	.287
Anterior	5 (45)	5 (45)	3 (43)	
Inferior/posterior	6 (55)	6 (55)	4 (43)	
Lateral	0 (0)	0 (0)	1 (14)	
PCI	23 (100)	18 (100)	9 (100)	NA
LVEF, %	60 ± 8	57 ± 8	60 ± 6	.352
LVEDVi, mL/m^2	53.0 ± 13.0	51.5 ± 13.0	54.1 ± 20.4	.907
LVMI, g/m^2	89.8 ± 25.3	89.0 ± 16.8	74.8 ± 16.4	.190
Cardiovascular risk profile				
Active smoking	1 (4)	4 (22)	2 (22)	.192
Hypertension	15 (65)	10 (56)	5 (56)	.785
Dyslipidemia	17 (74)	15 (83)	9 (100)	.221
Type 2 diabetes	1 (4)	2 (11)	1 (11)	.679
Obesity/overweight	19 (83)	15 (83)	7 (78)	.934
Family history CVD	8 (35)	9 (50)	6 (67)	.243
Baseline medication				
Aspirin	21 (91)	18 (100)	9 (100)	.294
DAPT	23 (100)	17 (94)	9 (100)	.403
Lipid-lowering therapy	22 (96)	18 (100)	9 (100)	.549
RAAS inhibitors	15 (65)	16 (89)	7 (78)	.210
Beta-blockers	18 (78)	16 (89)	8 (89)	.593
CCB	2 (9)	1 (6)	1 (11)	.869

ACS, acute coronary syndrome; CCB, calcium channel blocker; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; LBM, lean body mass; LV-HIIT, low-volume high-intensity interval training; LVEDVi, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MICET, moderate-intensity continuous exercise training; PCI, percutaneous coronary intervention; RAAS, renin angiotensin aldosterone system; STEMI, ST-segment elevation myocardial infarction.
Data are expressed as mean ± standard deviation or No. (%).

improved with LV-HIIT and MICET ($P < .05$ for time), but not in the usual care group. Moreover, the $\Delta VO_2/\Delta$workload slope increased only in the MICET group ($P < .05$ for time), while there was no change in the LV-HIIT and the usual care groups. There was a significant group × time interaction for this variable ($P < .05$). In table 3, initial fitness (expressed as percent-predicted VO_{2peak}) was not related to training NLR either in the univariate or in the multivariate analysis. In the multivariate regression model, age remained a predictor of training NLR ($P < .05$), while there was a trend for LV-HIIT vs MICET ($P = .054$).

DISCUSSION

The main findings of our study can be summarized as follows: *a)* For the first time, we show that optimized LV-HIIT exhibited a higher proportion of NLR to training than isocaloric MICET (61% in the HIIT vs 21% in the MICET group). *b)* VO_{2peak}-dependent variables (ie VO_{2peak}, percent-predicted VO_{2peak}), peak workload, and O_2 pulse were improved after LV-HIIT, but the improvement was more pronounced in the MICET group. *c)* The $\Delta VO_2/\Delta$workload slope increased only in the MICET group. *d)* Age and training group were independent predictors of the non/low response in our patients with a recent ACS.

This is the first study to compare the proportion of responders (non/low vs high) to aerobic exercise training with different modalities in patients with a recent ACS. Contrary to our initial hypothesis, our data revealed a disproportionally higher proportion of VO_{2peak} NLR with LV-HIIT than with isocaloric MICET. Our results disagree with those of the SAINTEX-CAD study in that the proportion of nonresponders (14%) was equivalent after HIIT and MICET.[10] However, the criteria for VO_{2peak} nonresponse were less conservative in this study ($\Delta VO_{2peak} < 1$ mL/min/kg), and the training volume was higher (114 min/wk to 141 min/wk) compared with our study (80 minutes to 83 min).[10] Recently, a multicenter study in adults with different CV status showed that high-volume HIIT led to a lower proportion of nonresponders vs MICET and LV-HIIT.[31] Finally, it has been consistently shown that lower exercise intensity is an independent predictor of training nonresponse in cardiac patients (together with age, initial VO_{2peak}, and comorbidities).[10,11] Therefore, our patient cohort performed an exercise volume at the lower range of current international recommendations, but this reflects common clinical practice in cardiovascular secondary prevention in our center and more generally in our province.[28,29]

The recommendations for exercise prescription based on the FITT principle (FIIT: frequency, intensity, type, and time)[29,32] can influence the proportion of exercise responders, as recently

Table 2

Cardiopulmonary exercise test parameters in post-ACS patients randomized to LV-HIIT, MICET, or usual care

Variable		LV-HIIT n = 23	MICET n = 18	Usual care n = 9	Group × time interaction *P*
VO_{2peak}, mL/min/kg	Pre	20.4 ± 4.6	21.7 ± 5.5	20.2 ± 4.2	.004
	Post	22.1 ± 5.8	25.2 ± 6.8	20.4 ± 4.9	
	Δ (Post-Pre)	1.7 ± 2.5	3.6 ± 2.6	0.2 ± 2.1	
	P-value Δ (Post-Pre)*	.002	< .0001	.767	
VO_{2peak}/LBM, mL/min/kg	Pre	28.2 ± 5.0	29.8 ± 5.3	29.6 ± 4.4	.0005
	Post	30.3 ± 5.5	34.9 ± 7.5	29.6 ± 4.7	
	Δ (Post-Pre)	2.1 ± 3.0	5.1 ± 3.6	?0.0 ± 2.4	
	P-value Δ (Post-Pre)*	.002	< .0001	.995	
VO_{2peak}, % predicted	Pre	86 ± 15	87 ± 16	94 ± 26	.001
	Post	93 ± 17	101 ± 19	92 ± 25	
	Δ (Post-Pre)	6 ± 10	14 ± 10	−1 ± 8	
	P-value Δ (Post-Pre)*	.002	< .0001	.678	
OUES	Pre	1553 ± 382	1853 ± 491	1800 ± 410	.056
	Post	1757 ± 452	2003 ± 503	1772 ± 490	
	Δ (Post-Pre)	149 ± 182	150 ± 203	-28 ± 189	
	P-value Δ (Post-Pre)*	.001	.001	.660	
VE/VCO_2 slope	Pre	30.3 ± 3.5	28.2 ± 4.2	30.6 ± 5.2	.278
	Post	29.2 ± 4.0	28.1 ± 3.7	31.0 ± 3.0	
	Δ (Post-Pre)	−0.8 ± 1.9	−0.1 ± 2.0	0.4 ± 3.1	
	P-value Δ (Post-Pre)*	.072	.874	.571	
$\Delta VO_2/\Delta$workload slope, mL/min/watts	Pre	9.2 ± 1.4	9.2 ± 1.6	10.4 ± 1.2	.022
	Post	9.1 ± 1.1	9.9 ± 1.5	9.7 ± 1.0	
	Δ (Post-Pre)	−0.3 ± 1.4	0.7 ± 1.0	−0.7 ± 1.6	
	P-value Δ (Post-Pre)*	.403	.021	.162	
O_2 pulse, mL/beat	Pre	12.6 ± 3.2	14.3 ± 4.3	12.7 ± 2.2	.050
	Post	14.0 ± 2.8	17.7 ± 5.0	12.9 ± 2.9	
	Δ (Post-Pre)	0.9 ± 1.5	3.4 ± 4.3	0.2 ± 1.8	
	P-value Δ (Post-Pre)*	.005	.003	.725	
VO_2 at VT1, %	Pre	56 ± 16	51 ± 14	63 ± 22	.371
	Post	64 ± 18	55 ± 17	66 ± 21	
	Δ (Post-Pre)	8 ± 10	4 ± 12	3 ± 9	
	P-value Δ (Post-Pre)*	.001	.108	.434	
Peak workload, watts	Pre	109 ± 39	133 ± 43	127 ± 42	.031
	Post	125 ± 43	156 ± 51	135 ± 46	
	Δ (Post-Pre)	17 ± 11	23 ± 16	8 ± 13	
	P-value Δ (Post-Pre)*	< .0001	< .0001	.063	
Peak workload/LBM, watts/kg	Pre	1.97 ± 0.53	2.08 ± 0.49	2.26 ± 0.46	.044
	Post	2.28 ± 0.55	2.49 ± 0.57	2.40 ± 0.45	
	Δ (Post-Pre)	0.31 ± 0.20	0.38 ± 0.27	0.14 ± 0.21	
	P-value Δ (Post-Pre)*	< .0001	< .0001	.653	
Peak RER	Pre	1.19 ± 0.08	1.16 ± 0.10	1.16 ± 0.08	.718
	Post	1.17 ± 0.08	1.16 ± 0.07	1.15 ± 0.05	
	Δ (Post-Pre)	−0.01 ± 0.07	0.00 ± 0.10	0.01 ± 0.05	
	P-value Δ (Post-Pre)*	.282	1.000	.992	
Peak systolic BP, mmHg	Pre	180.5 ± 26.8	183.4 ± 27.4	182.1 ± 25.3	.128
	Post	185.4 ± 25.4	183.1 ± 20.8	171.1 ± 18.5	
	Δ (Post-Pre)	4.9 ± 17.9	−0.3 ± 23.9	−11.0 ± 12.6	
	P-value Δ (Post-Pre)*	.235	.942	.098	
Peak diastolic BP, mmHg	Pre	75.6 ± 9.4	80.4 ± 14.1	77.6 ± 9.6	.205
	Post	75.7 ± 11.6	74.2 ± 10.3	73.8 ± 8.2	
	Δ (Post-Pre)	0.1 ± 9.1	−6.2 ± 13.1	−3.7 ± 11.8	
	P-value Δ (Post-Pre)*	.970	.022	.330	
Peak HR, bpm	Pre	124.7 ± 19.6	127.6 ± 18.7	130.7 ± 22.5	.766
	Post	127.9 ± 21.7	129.5 ± 18.2	130.1 ± 23.8	
	Δ (Post-Pre)	3.2 ± 15.5	1.9 ± 10.8	−0.6 ± 9.0	

Table 2 *(Continued)*
Cardiopulmonary exercise test parameters in post-ACS patients randomized to LV-HIIT, MICET, or usual care

Variable		LV-HIIT n = 23	MICET n = 18	Usual care n = 9	Group × time interaction *P*
	P-value Δ (Post-Pre)*	.247	.540	.898	
HRR after 1 min, bpm	Pre	18.3 ± 6.7	17.2 ± 6.9	19.2 ± 9.0	.473
	Post	18.3 ± 9.5	19.3 ± 6.0	18.7 ± 5.8	
	Δ (Post-Pre)	0 ± 7.3	2.1 ± 4.6	−0.6 ± 8.6	
	P-value Δ (Post-Pre)*	1.000	.076	.851	

ACS, acute coronary syndrome; BP, blood pressure; HR, heart rate; HRR, heart rate recovery; LBM, lean body mass; LV-HIIT, low-volume high-intensity interval training; MICET, moderate-intensity continuous exercise training; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; VE/VCO_2 slope, ventilatory efficiency slope; VO_2, oxygen uptake; VT1, first ventilatory threshold.
Data are expressed as means ± standard deviation.
* *P*-value Δ (Post-Pre) within group

Table 3
Predictors for training non/low response

Variable	Odds ratio	95%CI	*P*
Univariate logistic regression			
Age, y	1.099	1.019-1.184	.0140
Sex	1.882	0.518-6.845	.3369
Type 2 diabetes	1.000	0.130-7.717	1.0000
VO_{2peak} predicted	1.002	0.970-1.034	.9199
Training group			.0152
LV-HIIT vs MICET	5.444	1.354-21.889	.0170
LV-HIIT vs usual care	0.444	0.075-2.637	.3721
Usual care vs MICET	12.250	1.788-83.944	.0107
Multivariate logistic regression			
Age, y	1.122	1.023-1.230	.0141
Training group			.0173
LV-HIIT vs MICET	4.359	0.971-19.562	.0546
LV-HIIT vs usual care	0.175	0.018-1.673	.1302
Usual care vs MICET	24.922	2.366-262.467	.0074
LV-HIIT vs usual care	0.175	0.018-1.673	.1302

95%CI, 95% confidence interval; LV-HIIT, low-volume high-intensity interval training; MICET, moderate-intensity continuous exercise training; VO_2, oxygen consumption.
Univariate and multivariate logistic regression analysis including age, sex, type 2 diabetes (0 = no, 1 = yes), VO_{2peak} predicted and training group.

suggested in young and obese adults.[33,34] In obese adults, Ross et al.[34] showed that, at fixed exercise intensity and frequency, increasing the exercise volume (session duration) reduced the proportion of nonresponders by 50% after 24 weeks. In the same study, for a fixed exercise volume (frequency/duration), increasing training intensity eliminated nonresponders completely. Similarly, in young adults, Montero et al.[33] showed a higher proportion of nonresponders in individuals performing 1 to 3 aerobic exercise training sessions/wk compared with those performing 4 to 5 sessions/wk (6 weeks of training). Training nonresponse was abolished by adding another 120 min/wk to the 4 to 5 sessions for another 6 week training period.[33]

Based on these previous elements, our results with a higher proportion of NLR after LV-HIIT could be explained by several hypotheses: First, our LV-HIIT might not provide a sufficient total exercise duration due to the passive recovery used.[35] Patients in our study effectively pedaled only half of the time during LV-HIIT (9 to 15 minutes for 1 session), whereas exercise was not stopped during MICET (24 minutes for 1 session). Due to the nature of LV-HIIT (very short stage/passive recovery) might have a lower impact on the ventilatory and cardiac function adaptations (ie, ventilation-cardiac output, a major determinant of VO_{2peak}) compared with MICET, as demonstrated acutely.[19,21]

Regarding our CPET variables, we observed substantial training-induced improvements after LV-HIIT and MICET training compared with usual care in our post-ACS patients. Contrary to our initial hypothesis, MICET led to greater improvements with regards to VO_{2peak}-dependent variables (ie, VO_{2peak}, percent-predicted VO_{2peak}) compared with LV-HIIT. Indeed, the mean ΔVO_{2peak} improvement was 1.7 mL/min/kg (or 8.3%) for LV-HIIT and 3.6 mL/min/kg (or 16.1%) in the MICET group. This improvement in our LV-HIIT group is lower than the improvements reported in a recent meta-analysis comparing HIIT and MICET training in CHD patients.[17] Some factors in our LV-HIIT protocol, such as the use of passive recovery, a lower session frequency (2-3/wk) and therefore a lower exercise volume, may have influenced our results, as recently documented in a meta-analysis in cardiac patients.[35] Although previously optimized regarding acute physiological and clinical responses, our LV-HIIT protocol was not equivalent regarding VO_{2peak} improvement compared with isocaloric MICET. However, some clinical benefits have been documented for modest improvements of VO_{2peak} in CHD patients: a VO_{2peak} increase of 1 mL/min/kg confers a 15% mortality reduction and being a lower responder (< 2.5 mL/min/kg) is associated with a better prognosis compared with a nonresponder.[8,36]

Regarding other CPET variables, oxygen uptake efficiency slope improved similarly in the MICET and LV-HIIT group, indicating a similar impact of both modalities on this parameter of ventilatory efficiency. Indeed, the oxygen uptake efficiency slope reflects the efficiency of O_2 extracted by the lungs and used by the peripheral muscle and is also an independent predictor of cardiovascular and total mortality in CHD patients.[37] An increase in the oxygen uptake efficiency slope of 100 can be associated with a 4.4% reduction in cardiovascular mortality in CHD patients. Our patients improved their oxygen uptake efficiency slope by a mean of 150 (table 2) in both groups.[37] We observed an improvement of the ΔVO_2/Δworkload slope only in the MICET group, reflecting an improvement in the adequacy of O_2 transport to the peripheral muscle.[26] Moreover, O_2 pulse was improved to a greater level in the MICET group (table 2) compared with the LV-HIIT group. This suggests an improvement in central cardiac function, because O_2 pulse is an indirect surrogate for stroke volume.[26] Finally, VO_2 at the first ventilatory threshold (VO_2 at VT1) was only improved in the LV-HIIT group, which reflects an improvement in aerobic endurance.

Limitations

In our study, data from 2 prospective randomized control trials were pooled for analysis from a single institution and with the participants composed mainly of men. This explains why a disproportionate number of patients were randomized to the 3 groups. This might have affected our results. However, a carefully selected and highly homogenous population of patients who experienced an ACS in the preceding 6 weeks before inclusion were included and randomized to either HIIT vs MICET or HIIT vs usual care. While our optimized LV-HIIT protocol has been well evaluated regarding the acute responses in CHD patients,[19,21] our protocol is not the most commonly used in clinical research in patients with a recent ACS.[17,31,35] Therefore, the results of our findings cannot be generalized, particularly not to a cohort using a different HIIT protocol.

CONCLUSIONS

In patients with a recent ACS, optimized LV-HIIT resulted in a higher proportion of NLR to training compared with isocaloric MICET. Substantial improvements were observed in both aerobic exercise training groups compared with usual care with a training frequency and duration at the lower range of recommended international guidelines. Key VO_{2peak}-dependent variables and peak workload improved significantly with LV-HIIT, but the improvement was more pronounced with MICET. Other CPET variables related to ventilatory efficiency or aerobic endurance (oxygen uptake efficiency slope, VO_2 VT1) were also improved with LV-HIIT. Based on these findings, we believe that MICET remains an important exercise modality to use in patients with recent ACS during the initiation/improvement phase.[16] Because it is well tolerated, our LV-HIIT protocol could be used during the initiation phase (1 to 2 weeks) to familiarize patients with the HIIT modality. Future research in this field should take into consideration and compare alternative training models such as training periodization (including HIIT and MICET), as recently proposed.[16]

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CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

- Long interval HIIT can be equivalent to isocaloric MICET for VO_{2peak} improvement in CHD patients.
- Long interval HIIT is less well tolerated and its intensity is hard to maintain for CHD patients.
- LV-HIIT is safe, well tolerated by CHD patients, and produces similar acute physiological responses to MICET.

WHAT DOES THIS STUDY ADD?

- LV-HIIT resulted in a higher proportion of NLR to training vs isocaloric MICET.
- In post-ACS patients, key VO_{2peak} variables showed a greater improvement after isocaloric MICET than after LV-HIIT.
- In post-ACS patients, LV-HIIT and MICET similarly improve aerobic endurance and ventilatory efficiency.

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