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Clinical Research

Acute Responses to Intermittent and Continuous Exercise in Heart Failure Patients

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ABSTRACT

Background: The purpose of this study was to compare cardiopulmonary responses, exercise adherence, tolerance, and safety of optimized high-intensity interval exercise (HIIE) compared with moderate-intensity continuous exercise (MICE) in patients with heart failure and reduced ejection fraction (HFREF).

Methods: Twenty patients with HFREF (aged 61 ± 9.9 years) were randomly assigned to HIIE corresponding to 2 × 8 minutes of 30-second intervals at 100% of peak power output and 30-second passive recovery intervals and to a 22-minute MICE corresponding to 60% of peak power output. Gas exchange, electrocardiogram, and blood pressure were measured continuously. Cardiac troponin T (cTnT), C-reactive protein (CRP), and brain natriuretic peptide (BNP) were measured before, 20 minutes after, and 24 hours after HIIE and MICE.

Results: Cardiopulmonary responses did not differ between MICE and HIIE. Higher exercise adherence and efficiency were observed on HIIE with a similar perceived exertion and time spent above 90% of peak oxygen consumption compared with MICE. Neither HIIE nor MICE caused any significant arrhythmias or increased CRP, BNP, or cTnT.

RÉSUMÉ

Introduction : Le but de cette étude était de comparer les réponses cardiopulmonaires, l'observance à l'exercice, la tolérance et la sécurité de l'exercice par intervalles de haute intensité (EIHI) optimisé à l'exercice continu d'intensité modérée (ECIM) chez les patients ayant une insuffisance cardiaque avec fraction d'éjection diminuée (IC-FÉD).

Méthodes : Vingt (20) patients ayant une IC-FÉD (âgés de 61 ± 9,9 ans) ont réalisé de manière aléatoire un EIHI correspondant à 2 × 8 minutes avec des intervalles de 30 secondes à 100 % de la puissance maximale et des intervalles de récupération passive de 30 secondes, et un ECIM de 22 minutes correspondant à 60 % de la puissance maximale. Les échanges gazeux, l'électrocardiogramme et la pression artérielle ont été mesurés de manière continue. La troponine T cardiaque (TnTc), la protéine C réactive (CRP) et le peptide cérébral natriurétique (BNP) ont été mesurés avant, 20 minutes après et 24 heures après l'EIHI et l'ECIM.

Résultats : Les réponses cardiopulmonaires ne diffèrent pas entre l'ECIM et l'EIHI. Une plus grande observance et efficience de l'exercice a été observée lors de l'EIHI avec une perception de l'effort et un temps passé au dessus de 90% du VO2 pic similaires à ceux de l'ECIM.

Exercise training is now accepted as a fundamental part of the clinical management of patients with heart failure and reduced ejection fraction (HFREF).[1,2] Exercise training improves several manifestations of heart failure (HF) through effects on the cardiopulmonary, vascular, and musculoskeletal systems and has a favourable impact on risk of hospitalization and death, functional capacity, and quality of life.[1-6] Continuous exercise training and/or high-intensity interval training (HIIT) can be used in patients with elevated cardiovascular risk, coronary heart disease (CHD), or HFREF.[1,7] Relative to continuous aerobic training, HIIT is generally associated with greater improvements in peak oxygen consumption ($\dot{V}O_2$peak), cardiovascular and muscular function, and quality of life in cardiac

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Conclusions: Compared with MICE, HIIE demonstrated a higher exercise adherence and was well tolerated in patients with HFREF, while still providing a high-level physiological stimulus and leaving indices of inflammation (CRP), myocardial dysfunction (BNP), and myocardial necrosis (cTnT) unaffected.

Ni l'EIHI ni l'ECIM n'ont causé d'arythmies significatives ou d'augmentation de la CRP, du BNP ou de la TnTc.
Conclusions : Comparativement à l'ECIM, l'EIHI a démontré une plus grande observance à l'exercice et a été bien toléré chez les patients ayant une IC-FÉD, tout en fournissant un stimulus physiologique de haut niveau et en laissant les indices d'inflammation (CRP), de dysfonctionnement myocardique (BNP) et de nécrose myocardique (TnTc) inchangés.

and noncardiac subjects alike.[8-14] Among cardiac patients, high-intensity interval exercise (HIIE) also appears to be safe and well tolerated,[8,9,15,16] although larger studies are required to confirm its safety aspects.

Previous HIIT studies in cardiac patients have used various HIIE protocols (with different exercise and recovery intensity and interval duration), including long-stage exercise duration (2-4 minutes) prescribed at a high percentage of maximum heart rate (HR) and employing active recovery intervals.[11,12,14] In particular, a protocol employing 4-minute exercise and active recovery intervals at 90% of maximal HR has recently gained in popularity.[11,14] However, the acute physiological responses to this protocol have never been studied, nor has its rationale been detailed in the scientific literature. Among HFREF patients, only 2 studies evaluated the influence of different HIIE protocols on acute physiological cardiovascular responses and patient tolerance and comfort.[16,17] We recently demonstrated in stable CHD and HFREF patients that an "optimized" HIIE protocol consists of repeated short bouts (15 or 30 seconds) of exercise at 100% of peak power output (PPO) interspersed with passive recovery intervals of equal duration.[9,16] Relative to longer intervals (60-90 seconds) with active recovery, short (15- to 30-second) exercise and recovery intervals with passive recovery were associated with a longer total exercise time, a similar time spent near $\dot{V}O_2$peak, a lower rating of perceived exertion (RPE), greater patient comfort, and a greater likelihood of the patient's completing the prescribed exercise sessions.[9,16] We also showed that compared with moderate-intensity continuous exercise (MICE), an optimized HIIE session is safe and does not induce significant arrhythmias or myocardial injury in stable coronary patients.[18] The acute physiological responses and safety of an optimized HIIE session compared with an isocaloric MICE session have not been studied in patients with HFREF. Therefore, the first objective of this study was to compare the completion rate (percentage of individuals completing the prescribed exercise sessions) and acute cardiopulmonary responses of an optimized HIIE session with those of an isocaloric MICE session in patients with HFREF. Our secondary objectives were to compare RPE, HIIE efficiency, safety (cardiac arrhythmias, myocardial injury), inflammatory parameters, and ventricular mechanical stress (brain natriuretic peptide [BNP]) in response to the same 2 exercise sessions.

Methods

Study design

After an initial screening of 100 patients, we enrolled 20 patients with stable HFREF at the ambulatory HF and cardiac transplantation clinics of the Montreal Heart Institute. On the first visit, anthropometric data, vital signs, and resting electrocardiogram were collected, and all participants underwent a maximal cardiopulmonary exercise test on ergocycle. In a random order, patients performed the 2 single exercise sessions (1 optimized HIIE and 1 MICE) at the Cardiovascular Prevention and Rehabilitation Centre (ÉPIC) of the Montreal Heart Institute, under the supervision of an exercise physiologist and a cardiologist, the single sessions being separated by 1 week. The protocol was accepted by the ethics committee of the Montreal Heart Institute, and written informed consent was obtained from all patients. For details concerning inclusion and exclusion criteria, see Supplementary Material (section A). Demographic and baseline characteristics are presented in Table 1.[19,20]

Maximal cardiopulmonary exercise test

Maximal cardiopulmonary exercise testing was performed according to the current guidelines.[21] A continuous progressive exercise protocol was performed on a cycle ergometer (Ergoline 800S, Bitz, Germany). Pedaling speed was set at 60 revolutions per minute during the entire test. A 2-minute warm-up at 20 W was performed before the test, and the power was increased by 10 W every minute until exhaustion.[21] PPO was defined as the power output reached at the last fully completed stage.[9,16,18] For details on gas exchange and exercise parameters measurement, see Supplementary Material (section B).[9,14,16,22-24]

MICE isocaloric session

This exercise session was performed on the ergocycle (Ergoline 800S) at an intensity of 60% PPO and consistent with current exercise training recommendations in patients with HFREF.[1] Exercise duration was 22 minutes and matched total energy expenditure of the HIIE session according to our previous published methodology in coronary patients.[18] Exercise efficiency defined by gross efficiency of the external work (as a percentage) was calculated by the following formula:[25]

$$[\text{external work (J/s)}/\text{metabolic work (J/s)}] \times 100.$$

Brachial blood pressure was measured manually each 2 minutes.

Optimized HIIE session

The optimized HIIE protocol was also performed on ergocycle and was based on our previous studies in CHD and HFREF patients.[9,16,18] This session consisted of a warm-up for 2 minutes at 50% of PPO, followed by two 8-minute interval training blocks. Each block consisted of repeated bouts of 30 seconds at 100% of PPO, interspersed with 30 seconds of passive recovery. Four minutes of passive recovery was allowed

Table 1. Baseline characteristics of the patients with chronic heart failure

Clinical variables	n = 20
Age (years)	61 ± 9.9
Men	18 (90%)
BMI (kg/m^2)	29.9 ± 6.2
LVEF (%)	26 ± 7
Duration of heart failure (years)	6.1 ± 5
NYHA functional class	
I	5 (25%)
II	12 (60%)
III	3 (15%)
Etiology of heart failure	
Ischemic heart disease	9 (45%)
Idiopathic dilated cardiomyopathy	9 (45%)
LV noncompaction	2 (10%)
Risk factors	
Diabetes mellitus	7 (35%)
Hypertension	13 (65%)
Smoking	1 (5%)
Dyslipidemia	16 (80%)
Obesity (BMI ≥ 30 kg/m^2)	8 (40%)
Medical history	
Previous myocardial infarction	10 (50%)
Previous CABG	1 (5%)
Previous PCI	7 (35%)
Medications	
ACE inhibitors	11 (55%)
ARBs	8 (40%)
β-blockers	20 (100%)
Digoxin	13 (65%)
Furosemide	17 (85%)
Oral hypoglycemic agents	5 (25%)
Insulin	3 (15%)
Spironolactone	10 (50%)
Devices	
ICD	14 (70%)
CRT	3 (15%)

Values are means ± SD or numbers of patients (%).

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; ICD, internal cardioverter-defibrillator; LV, left ventricular; LVEF, LV ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

between the blocks, with 1-minute cooldown at 25% of PPO after the last 30-second exercise bout. The warm-up period and two 8-minute blocks were included in the isocaloric calculation. Exercise efficiency (as a percentage) was also calculated.[25] Brachial blood pressure was measured manually each 2 minutes during the passive recovery period bouts.

Biomarker measurement

Venous blood samples were taken 10 minutes before exercise and 20 minutes and 24 hours after an exercise session. C-reactive protein (CRP), cardiac troponin T (cTnT), and BNP were measured. For more details, see Supplementary Material (section C).[26]

Study end points

Our main end points were (1) percentage of individuals completing the exercise sessions and (2) time spent at high levels of $\dot{V}O_2$peak in each exercise mode (HIIE and MICE). For more details, see Supplementary Material (section D).[9,16,18]

Statistical analysis

Mean and standard deviation were reported for continuous variables. Frequencies and percentages were reported for categorical ones. For more details, see Supplementary Material (section E).

Results

Baseline characteristics

Participants were principally men (90%), aged 45 to 80 years. The majority had a diagnosis of ischemic heart disease, were in New York Heart Association class I and II, and were receiving optimal medical therapy (Table 1).

Maximal cardiopulmonary exercise test

Peak cardiopulmonary variables are presented in Supplemental Table S1. Mean $\dot{V}O_2$peak was 16.9 ± 5.6 mL/min/kg (65% ± 19% of predicted value) corresponding to a mean PPO of 89 ± 37 W.

Effects on primary end points

The proportion of patients completing the exercise session (HIIE, 2 × 8 minutes; MICE, 22 minutes) was significantly higher during HIIE (n = 17, or 85%) compared with MICE (n = 8, or 40%, $P < 0.0075$; Table 2). There was no significant difference in time > 90%, > 95%, or > 100% of $\dot{V}O_2$peak between exercise protocols. Time spent above > 80% and > 85% of $\dot{V}O_2$peak was significantly higher during MICE than during HIIE ($P < 0.05$ and 0.01; Supplemental Table S2).

Table 2. Cardiopulmonary variables measured during MICE and optimized HIIE

Parameters	MICE 22 minutes	HIIE first 8 minutes	HIIE second 8 minutes	ANOVA *P* value
$\dot{V}O_2$ (mL/min)	1092 ± 329	989 ± 253	992 ± 254	0.48
Ventilation (L/min)	37 ± 9	34 ± 8	33 ± 8	0.37
Heart rate (beats/min)	99 ± 18	87 ± 13	90 ± 11	0.16
O_2pulse (mL O_2/beat)	11.2 ± 3.2	11.4 ± 2.4	11.2 ± 2.6	0.95
Mean power (W)	46 ± 20	51 ± 21		0.0188
% $\dot{V}O_2$peak	76 ± 7	71 ± 10*	67 ± 8†	0.0039
Gross efficiency of the external work (%)	12.37 ± 2.85	15.05 ± 3.60		< 0.0001
Cycling exercise time (min)	17 ± 5	7.5 ± 1.5		< 0.0001
Perceived exertion at the end of sessions (Borg scale)	14.4 ± 1.4	13.4 ± 2.7		0.09
n (%) of exercise session completed	8 (40%)	17 (85%)		0.0075

ANOVA, analysis of variance; HIIE, high-intensity intermittent exercise; MICE, moderate-intensity continuous exercise; O_2pulse, $\dot{V}O_2$/heart rate; $\dot{V}O_2$, oxygen consumption.

* $P < 0.05$; † $P < 0.01$ vs MICE.

Effects on secondary end points

Mean cardiopulmonary variables ($\dot{V}O_2$, ventilation [$\dot{V}_E$], HR, and O_2pulse [ie,$\dot{V}O_2$/heart rate]) did not differ during MICE and HIIE (Table 2). Mean percentage of $\dot{V}O_2$peak attained during the 2 blocks of HIIE was lower than during MICE (first block, $P < 0.05$; second block, $P < 0.01$; Table 2). Cycling exercise time was significantly longer during the MICE session ($P < 0.0001$) compared with HIIE (Table 2). RPE measured during HIIE and MICE did not differ (HIIE, 13 ± 3; MICE, 14 ± 1; $P = 0.09$). Gross efficiency of the external work (as a percentage) and mean power output were higher for HIIE vs MICE ($P < 0.0001$ and $P = 0.0188$; Table 2). Time spent > 95% and > 100% of $\dot{V}E$peak was similar during HIIE and MICE but was significantly higher during MICE for time spent > 80%, > 85%, and > 90% of $\dot{V}E$peak. Time spent > 100% and > 95% of HRpeak and O_2pulse peak were similar during HIIE and MICE sessions, but time > 80%, > 85%, and > 90% was significantly higher during MICE (Supplemental Table S2).

No significant ventricular arrhythmias or abnormal blood pressure responses (systolic blood pressure > 250 mm Hg or diastolic blood pressure > 110 mm Hg and/or systolic blood pressure drop > 10 mm Hg during exercise or no return to baseline values during recovery) occurred. Serum concentration of cTnT was < 40 $\mu g/L^{-1}$ in all participants at baseline and did not exceed this value at 20 minutes or at 24 hours after the exercise sessions, thus excluding the presence of any exercise-induced myocardial injury (Supplemental Table S3). There was no significant increase in CRP or BNP (measured after 20 minutes and 24 hours) with either exercise protocol, excluding the presence of an exercise-induced increase of inflammation and ventricular mechanical stress (Supplemental Table S3). One adverse event occurred. The patient was a woman, aged 77 years, with a documented ischemic cardiomyopathy. She underwent the HIIE session on a Wednesday afternoon. The next day (Thursday), she developed signs of aphasia and dyspraxia (duration: 3 hours). A transitory cerebral ischemia was diagnosed, clopidogrel was given to the patient, and she recovered very well. We are uncertain whether the episode was related to the exercise session.

Discussion

This study is the first to compare acute physiological responses and the rate of completion of exercise sessions during an optimized HIIE and an isocaloric MICE in HFREF patients. The optimized HIIE elicited a strong physiological stimulus associated with a greater proportion of subjects completing the prescribed exercise session, and a similar time spent over 90% of $\dot{V}O_2$peak and 95% of $\dot{V}E$peak, HRpeak, and O_2pulse peak. Mean cardiopulmonary responses were similar for both exercise sessions. Despite this fact, total active pedalling time was significantly greater during MICE, while both mean power and external work efficiency were lower, illustrating the optimized HIIE efficiency. Additionally, the optimized HIIE was well tolerated, with similar RPE, compared with MICE. Finally, the optimized HIIE did not induce any significant arrhythmias, abnormal blood pressure responses, or increase in cTnT, BNP, or CRP, even though an adverse event occurred in 1 patient (a transitory cerebral ischemia) the day after the HIIE session. These results add important physiological information relating to the prescription of this aerobic exercise training modality in HFREF patients. Moreover, our results suggest that optimized HIIE could potentially be used to improve exercise training adherence for stable HFREF patients.

We demonstrated that mean cardiopulmonary responses ($\dot{V}O_2$, $\dot{V}E$, HR, and O_2pulse) were equivalent during HIIE and MICE, indicating similar cardiopulmonary stimulus between the 2 exercise modes. However, during HIIE, patients exercised for a shorter cycling exercise time, at a higher power output, and with higher external work efficiency. This illustrates the superior efficiency of optimized HIIE compared with MICE, in accordance with previous published studies of CHD and HFREF patients.[17,18,27,28] In HFREF patients, one principle of HIIE is to improve peripheral muscle power while providing a similar stimulus to the cardiac system.[17,28] This concept was demonstrated in our study by noting that HR and O_2pulse values were similar during MICE and HIIE. Meyer et al.[28] showed that HIIE (30 seconds at 71 W, 60 seconds at 15 W), compared with a MICE session (36 W), was associated with a similar exercise cardiac output, stroke volume, and ejection fraction. Despite a higher exercise power output, patients' RPE was similar for HIIE in association with a significantly higher likelihood of completing the exercise session, indicating that optimized HIIE was very efficient and well tolerated. Several mechanistic explanations can be put forth to explain these findings. First, passive recovery is associated with a slower decline of the muscle oxyhemoglobin signal compared with an active recovery, allowing for a higher rate of myoglobin reoxygenation and a better oxygen-dependent resynthesis of phosphocreatine in healthy people.[29,30] Second, during HIIE, patients exercised at a significantly lower percentage of $\dot{V}O_2$peak associated with nonsignificant lower mean ventilation and HR. Time over 80% to 90% of $\dot{V}E$peak was also significantly lower during HIIE relative to MICE, illustrating a lower solicitation of the ventilatory system. These findings indicate that ventilation and central hemodynamic function were not overloaded by HIIE.[17,28] This is consistent with the lower sensation of breathlessness reported by HFREF patients during HIIE and in accordance with our previous data in coronary patients demonstrating a significant lower RPE, lower mean ventilation, and reduced subjective sensation of breathlessness during HIIE.[18]

Our results on mean cardiopulmonary responses during HIIE are slightly higher than those found previously in patients with HFREF.[17,28] In those studies, patients' $\dot{V}O_2$uptake was approximately 65% of $\dot{V}O_2$peak, with mean HR between 73% and 84% of HRpeak and ventilation of approximately 26 L/minute. The RPE was similar during MICE and HIIE (14.4 and 13.4), in agreement with previous studies,[17,28] and were slightly higher. The lower RPEs observed by Meyer et al.[17,28] are probably due to the longer recovery phase used in their protocol (60 seconds) compared with ours (30 seconds).

We found no evidence of severe or prolonged ischemia, significant arrhythmias, or abnormal blood pressure responses. In addition, cTnT levels did not increase after exercise, excluding any myocardial injury. Furthermore, BNP, an important biomarker of ventricular mechanical stress and prognosis in relation to the severity of ventricular dysfunction,[31] did not increase after HIIE or MICE. These results are consistent with previous data showing the lack of effect of a single maximal exercise on BNP.[32-34] Finally, with respect to CRP, conflicting

data exist on the impact of exercise on this biomarker. Two previous studies in healthy people[35,36] showed no increase in CRP after acute exercise (30%-70% of $\dot{V}O_2$peak). In contrast, in stable coronary patients, Fernandes et al.[37] demonstrated a significant increase in CRP after acute exercise (at 65% of $\dot{V}O_2$peak). No previous studies have evaluated the impact of exercise on CRP in HFREF patients.

A novel finding of our study is that HIIE was associated with a similar time above 90% of $\dot{V}O_2$peak and above 95% of $\dot{V}E$peak, HRpeak, and O_2pulse peak compared with MICE. These results illustrate that our optimized HIIE protocol does not compromise time spent near maximal cardiopulmonary function. However, MICE was associated with a significantly higher time above 80% and 85% of $\dot{V}O_2$peak and above 80% and 90% of $\dot{V}E$peak and HRpeak. It is important that absolute differences were less than 3 minutes for time above 80% of $\dot{V}O_2$peak and $\dot{V}E$peak and less than 6 minutes for time above HRpeak and O_2pulse peak. These differences in our opinion have little clinical significance. In our study, during passive recovery intervals, optimized HIIE allowed patients to stress their cardiopulmonary system without compromising time spent above 90% of $\dot{V}O_2$peak while they were not exercising (not pedaling). This particularity of HIIE is very interesting in less fit HFREF patients, who can have considerable exercise intolerance, particularly during continuous long exercise periods. Although patients were pedaling at higher intensities during the HIIE work phases (100% PPO), they did not perceive the total exercise time as more strenuous (similar RPEs).

This study contributes important clinical information for the cardiac rehabilitation of HFREF patients. **H**eart **F**ailure: **A** **C**ontrolled **T**rial **I**nvestigating **O**utcomes of Exercise Trai**n**ing (HF-ACTION) failed to show significant reduction in mortality with MICE training in HFREF patients.[3,4] Some possible explanations include poor exercise training adherence and the relatively low intensity of the MICE training protocol.[4] In contrast, HIIE training may provide a stronger training stimulus, may be more efficient and motivating, and may help to improve adherence to exercise training in HFREF patients.[38]

This study has several limitations, including a small number of patients and results reported during only 1 HIIE session, which may differ from a prolonged HIIE training program. Additionally, patients were mainly young men with few comorbidities, in class II HF with a mean left ventricular ejection fraction of 26% and a $\dot{V}O_2$peak at 65% of predicted. They were, however, representative of many HFREF patients seen in clinic.

In conclusion, optimized HIIE strongly stimulates cardiopulmonary function in HFREF patients and is associated with a significantly higher exercise session completion rate (thus potentially increasing training adherence), without compromising time spent near peak cardiopulmonary variables. Additionally, optimized HIIE was more efficient, allowing our HFREF patients to exercise at higher power output and similar tolerance, compared with MICE. Finally, a single optimized HIIE session was completed without the occurrence of arrhythmias, myocardial injury, or cardiac decompensation. Larger randomized training studies using our optimized HIIE protocol are needed to confirm the benefits and safety of HIIE in this population.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2012.07.001.

Supplementary Material

A) Inclusion and exclusion criteria

Inclusion criteria were: age ≥ 18 years, left ventricular ejection fraction (LVEF) <40% (measured within 6 months of enrolment by echocardiography, radionuclide ventriculography or cardiac magnetic resonance), New York Heart Association (NYHA) functional class I to III, stable optimal medical therapy including a beta-blocker and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers for at least 6 weeks, ability to perform an maximal cardiopulmonary exercise test and capacity and willingness to sign the informed consent formed. Exclusion criteria included any relative or absolute contraindications to exercise training in chronic HFREF patients according to current recommendations [19,20], fixed-rate pacemaker or internal cardioverter-defibrillator devices with heart rate limits set lower than exercise training target heart rate, major cardiovascular event or procedure within the 3 months preceding enrolment, chronic atrial fibrillation, HF secondary to significant uncorrected primary valvular disease (except for mitral regurgitation secondary to LV dysfunction) and HF secondary to congenital heart disease or obstructive cardiomyopathy.

B) Maximal cardiopulmonary exercise test

Gas exchange variables were measured breath by breath during testing, and then averaged every 15s for minute ventilation (VE, L/min, BTPS), O_2 uptake (VO_2, L/min, STPD), CO_2 production (VCO_2, L/min, STPD), and respiratory frequency (Rf) using an automated gas analyzer system (Oxycon Pro, Jaegger, Germany), which calibration procedure has been described previously [9,16]. All subjects were encouraged to provide a maximal effort. Heart rate, manual brachial blood

pressure and rating of perceived exertion using the Borg scale (level 6 to 20) [22] were recorded before the test and at 2 min intervals during exercise and recovery. Electrocardiographic activity was monitored continuously using an 8-lead ECG (Marquette, Missouri). Criteria for maximal oxygen uptake were the attainment of the primary maximal criteria: a levelling off of oxygen uptake (<150 mL/min) despite increased workload [23], or one of the three secondary maximal criteria: 1) a respiratory exchange ratio >1.05, 2) inability to maintain 60 rpm, 3) patient exhaustion due to fatigue or other clinical symptoms (dyspnea, ECG and/or blood pressure abnormalities) [14]. The average value of the VO_2 recorded during the last 15 seconds of exercise was considered as the peak oxygen uptake (VO_2peak). The ventilatory threshold was determined using a combination of the V-slope, ventilatory equivalents, and end-tidal oxygen pressure methods [24]. Hemodynamic and gas exchange parameters were recorded during the 5 min passive recovery following the test.

C) Biomarker measurement

For each blood sample, 10 ml of venous blood was drawn from the antecubital vein with patients in a sitting position. The samples were then centrifuged and separated serum was stored at -80°C for subsequent analysis. The measurements of CRP, cTnT and BNP were performed in the hospital clinical laboratory using the available commercial assay (Roche Diagnostics, Mannheim, Germany and Biosite, Biosite Incorporated, USA). The decision limit for myocardial injury was set at 0.40 $\mu g.L^{-1}$ [26] for cTnT parameter only.

D) Study endpoint calculation

Time spent at high levels of VO_2peak (>80% and more) was calculated by summing each 5-s VO_2 block above defined thresholds (>80%, >90% and >100% of VO_2peak) as described previously in both CHD patient and patients with HFREF [9,16,18]. Secondary endpoints included rating of perceived exertion (6-20 Borg scale), exercise efficiency (defined above), safety and inflammatory parameter (Hs-CRP). Safety parameters assessed included the occurrence of cardiac arrhythmias, abnormal blood pressure response during exercise (SBP>250 mmHg or DBP>110 mmHg and/or SBP drop>10 mmHg) and recovery (return to baseline values), myocardial injury (serial cTnT measurement), increased LV wall strain (c-BNP), and symptoms or signs of myocardial ischemia or heart failure decompensation. We also evaluated for each exercise mode, the time spent at a high level of peak ventilation (VEpeak), peak heart rate (HRpeak) and peak O_2 pulse (pear oxygen uptake divided by peak heart rate) [16]. Time spent at high levels of VEpeak, HRpeak and O_2 pulse peak (>80% and more) was calculated by summing each 5-s block above defined thresholds (>80%, >85%, >90%, >95% and >100% of peak parameters) [16] .

E) Statistical analysis

For cardiopulmonary responses, p-values were calculated from a one-way Repeated Measure ANOVA with a factor for "group" (2x 8min HIIE and MICE). P-value for the number of exercise session completed was calculated using McNemar's Test. For biomarkers, p-values were calculated from a Two-Way Repeated Measure ANOVA with a factor for "group" (1st 8min HIIE vs MICE) and time point (before, 20 min and 24 hours after the completion of each exercise

session). For acute responses, p-values were calculated from multiple paired comparisons using either a paired T-test for normally distributed data or Paired Wilcoxon Signed Rank test for non-normally distributed data. P-values were calculated, first from multiple paired comparisons using either a paired T-test for Normally distributed data or Paired Wilcoxon Signed Rank test for non-normally distributed data for all variables measuring acute response to 1st 8min HIIE vs. MICE, second from One-way Repeated Measure ANOVA for all but the last variable, measuring cardiopulmonary response repeated on 2 x 8min HIIE and MICE (p-value for the number of exercise session completed was calculated using McNemar's Test) and last from a Two-Way Repeated Measure ANOVA for CRP biomarker measuring cardiac response to 1st 8min HIIE vs. MICE at different time point (before, 20 minutes and 24 hours after the completion of each exercise session). The latter analysis was based on 19 patients. All statistical analyses were performed using SAS, Version 9.2. All statistical tests were two-sided at 5% level of significance.

Supplemental Table S1. Results from the maximal cardiopulmonary exercise test.

Cardiopulmonary and hemodynamic variables	**(n=20)**
Rest	
Resting HR (bpm)	69±10
Resting SBP (mmHg)	113±13
Resting DBP (mmHg)	65±9
Ventilatory threshold	
Exercise time (s)	271±133
Power output (Watts)	57±17
VO_2 (L/min)	1.04±0.29
% of VO_2peak	66±21
VO_2 (mL/min/kg)	12±2.5
Heart rate (bpm)	101±12
Peak exercise level	
VO_2 peak (L/min)	1.45±0.5
% of VO_2peak predicted (%)	65±19
VO_2 peak (mL/min/kg)	16.9±5.6
Metabolic equivalents (METs)	4.78±1.63
VO_2 plateau (n and %) [a]	17 (85%)
Peak ventilation (L/min)	56±20
VE/VCO_2	37±8
RER	1.11±0.11
Peak heart rate (bpm)	118±23
% of maximum heart rate predicted (%)	74±12
Maximal SBP (mmHg)	134±15
Maximal DBP (mmHg)	71±9
Exercise time (s)	503±213
Peak power output (Watts)	89±37

Values are means ± SD. BP: blood pressure, RER: respiratory exchange ratio, VO_2peak: peak oxygen uptake; VE: ventilation, VCO_2, carbon dioxide output. [a]VO_2 plateau criteria: levelling off of oxygen uptake (<150 mL/min) in the last 30 sec of exercise despite increased workload[22].

Supplemental Table S2. Time spent near peak cardiopulmonary values during MICE and optimized HIIE.

	HIIE	MICE	P value
Time above percentages of VO_{2peak}			
Time >100% VO_{2peak} (s)	22 ± 43	38 ± 54	0.1547
Time >95% VO_{2peak} (s)	40 ± 78	77 ± 116	0.1055
Time >90% VO_{2peak} (s)	69 ± 111	141 ± 198	0.1108
Time >85% VO_{2peak} (s)	119 ± 146	232 ± 243	0.0197
Time >80% VO_{2peak} (s)	190 ± 189	374 ± 256	0.0023
Time above percentages of VE_{peak}			
Time >100% VE_{peak} (s)	25 ± 70	41 ± 75	0.1522
Time >95% VE_{peak} (s)	43 ± 93	95 ±143	0.091
Time >90% VE_{peak} (s)	67 ± 110	157 ± 232	0.0169
Time >85% VE_{peak} (s)	101 ± 132	222 ± 273	0.0071
Time >80% VE_{peak} (s)	143 ± 161	284 ± 302	0.0037
Time above percentages of HR_{peak}			
Time >100% HR_{peak} (s)	11 ± 21	57 ± 140	0.1275
Time >95% HR_{peak} (s)	64 ± 124	156 ± 255	0.0662
Time >90% HR_{peak} (s)	151 ± 267	369 ± 381	0.0229
Time >85% HR_{peak} (s)	258 ± 347	619 ± 386	0.0186
Time >80% HR_{peak} (s)	413 ± 331	788 ± 408	0.0063
Time above percentages of O_2pulse_{peak}			
Time >100% O_2pulse_{peak} (s)	215 ± 244	270 ± 292	0.3626
Time >95% O_2pulse_{peak} (s)	296 ± 258	400 ± 326	0.1976
Time >90% O_2pulse_{peak} (s)	388 ± 268	548 ± 334	0.0354
Time >85% O_2pulse_{peak} (s)	488 ± 262	712 ± 317	0.0052
Time >80% O_2pulse_{peak} (s)	578 ± 255	830 ± 315	0.0052

Values are means ± SD. HIIE: high intensity intermittent exercise, MICE: moderate intensity continuous exercise.

Supplemental Table S3. Cardiac and inflammation biomarkers measured during MICE and optimized HIIE.

		Baseline	20 min post	24h post	ANOVA P value
cTnT	**MICE**	<0.40	<0.40	<0.40	-
	HIIE	<0.40	<0.40	<0.40	-
CRP	**MICE**	2.21 ± 1.85	2.16 ± 1.69	2.20 ± 1.72	a : 0.112
	HIIE	2.90 ± 2.17	2.92 ± 2.16	2.71 ± 1.72	b : 0.444 c : 0.664
BNP	**MICE**	161 ± 162	178 ± 194	173 ± 195	a : 0.879
	HIIE	194 ± 215	218 ± 234	179 ± 212	b : 0.721 c : 0.942

cTnT: cardiac tropinin T; CRP: C-reactive protein; BNP: brain natriuretic peptide. a: time effect, b: mode effect, c: interaction effect.