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Original article

Short-term effects of a 3-week interval training program on heart rate variability in chronic heart failure. A randomised controlled trial

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ABSTRACT

Background: Exaggerated sympathetic nervous system activity associated with low heart rate variability (HRV) is considered to trigger cardiac arrhythmias and sudden death. Regular exercise training is efficient to improve autonomic balance.
Objective: We aimed to verify the superiority of high-intensity interval training (HIIT) to enhance HRV, cardiorespiratory fitness and cardiac function as compared with moderate intensity continuous training (MICT) in a short, intense cardiac rehabilitation program.
Methods: This was a prospective, monocentric, evaluator-blinded, randomised (1:1) study with a parallel two-group design. Overall, 31 individuals with voluntary chronic heart failure (CHF) (left ventricular ejection fraction [LVEF] < 45%) were allocated to MICT ($n = 15$) or HIIT ($n = 16$) for a short rehabilitation program (mean [SD] 27 [4] days). Participants underwent 24-hr electrocardiography, echocardiography and a cardiopulmonary exercise test at entry and at the end of the study.
Results: High-frequency power in normalized units (HFnu%) measured as HRV increased with HIIT (from 21.2% to 26.4%, $P < 0.001$) but remained unchanged with MICT (from 23.1% to 21.9%, $P = 0.444$, with a significant intergroup difference, $P = 0.003$). Resting heart rate (24-hr Holter electrocardiography) decreased significantly for both groups (from 68.2 to 64.6 bpm and 66.0 to 63.5 bpm for MICT and HIIT, respectively, with no intergroup difference, $P = 0.578$). The 2 groups did not differ in premature ventricular contractions. Improvement in peak oxygen uptake was greater with HIIT than MICT (+ 21% vs. + 5%, $P = 0.009$). LVEF improved with only HIIT (from 36.2% to 39.5%, $P = 0.034$).
Conclusions: In this short rehabilitation program, HIIT was significantly superior to the classical MICT program for enhancing parasympathetic tone and peak oxygen uptake.
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1. Introduction

The clinical and prognostic implications of exaggerated sympathetic nervous system activity are well documented in chronic heart failure (CHF) [1]. Sympathetic nervous system overactivity is a known trigger for cardiac arrhythmias and sudden death [2]. Low heart rate variability (HRV) likely suggestive of a loss of vagal reflex has been found associated with increased incidence of arrhythmic deaths in CHF [2,3].

Exercise training as become one of the pillars of CHF treatment, with a class I level of evidence A on the latest recommendations [4]; one of the potential targets is to restore the cardiac autonomic balance [3,5]. HRV is a non-invasive electrocardiography (ECG) parameter to evaluate the sympathovagal balance at the sinoatrial level, but the physiological interpretation is still discussed [6–8].

During the last decade, our team has studied and optimized a high-intensity interval training (HIIT) model based on the repetition of very short bouts of high-intensity exercise interspersed by short bouts of passive recovery periods [9–11]. Although the effect of

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exercise training on increasing vagal tone has been discussed [12], we previously found that as compared with a single session of moderate-intensity continuous exercise (MICT), one session of our HIIT protocol was efficient for strengthening vagal tone and decreasing arrhythmias within 24 hr of the session [9]. Nevertheless, the effect of this type of HIIT training performed over several weeks has not been studied in CHF.

The aim of this study was to determine the effectiveness of a short, optimized, supervised HIIT program to improve sympathovagal balance measured by HRV in CHF. We subsequently hypothesized that our optimized HIIT program is superior to MICT training (control) to enhance HRV as measured by high frequency power in normalized units (HFnu%), the main criteria, based on our previous study [9,13]. We also tested changes in cardiorespiratory fitness (peak oxygen uptake [VO_{2peak}] $ml.min^{-1}.kg^{-}1$), cardiac function (left ventricular ejection fraction [LVEF]), and the occurrence of arrhythmias.

2. Materials and methods

2.1. Design

This monocentric, prospective, evaluator-blinded, randomised study with a parallel two-group design investigated 2 exercise training protocols (optimized HIIT and MICT). After inclusion, participants were randomly assigned to HIIT or MICT. At the beginning and end of the rehabilitation program, all patients underwent a complete medical evaluation including 24-hr ECG recording, a cardiopulmonary exercise test and echocardiography. Evaluators and investigators were blinded to the protocol used for training.

The protocol was approved by the *Toulouse Outre-Mer I* Ethics Committee, and the French National Agency for Medicines and Health Products Safety (ANSM: ID-RCB no.: 2015-A00166-43). Written informed consent was obtained from all participants before inclusion. The investigation followed the principles outlined in the Declaration of Helsinki. This study was publicly registered on ClinicalTrials.gov (NCT03603743).

2.2. Participants

CHF patients were recruited from a cardiac rehabilitation unit. Inclusion criteria were stable CHF with New York Heart Association functional class I to III, stable LVEF $< 45\%$ for at least 6 months, stable optimal medical therapy including a beta-blocker and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 6 weeks and ability to perform a maximal cardiopulmonary exercise test. Exclusion criteria were any relative or absolute contraindications to exercise training according to current recommendations [14], fixed-rate pacemaker with HR limits set lower than the exercise training target HR, major cardiovascular event or procedure within the 3 months before enrolment, chronic atrial fibrillation, heart failure secondary to significant uncorrected primary valve disease, and heart failure secondary to congenital heart disease or obstructive cardiomyopathy. A paper case report form was designed to collect patient data and was also approved by the ethics committee.

2.3. Randomisation

After inclusion, participants were randomly assigned to HIIT or MICT. The computer-generated randomisation list (permuted block randomisation with block length 4, allocation ratio 1:1) was provided by the research coordinator before starting the research. The research coordinator gave the individual assignments to the adapted physical education teachers who informed the participants and who conducted the training program.

2.4. Rehabilitation program

The rehabilitation program focused on controlling cardiovascular risk factors, diet monitoring, therapeutic education sessions and psychological support when needed. The rehabilitation program lasted 3 hr/day, 5 days/week, for 3.5 weeks. The daily activity included cycling endurance training (HIIT or MICT), 30 min of gymnastics or muscle strengthening and 45-min outside walking sessions. Each session was monitored by a physiotherapist and was supervised by a cardiologist.

The HIIT included two 8-min blocks of interval training separated by 4 min of passive recovery. Each 8-min block consisted of alternating between 30 sec at 100% of peak power output and 30 sec of passive recovery [11,15]. The MICT training consisted of cycling 30 min at 60% of peak power output. Each mode of training started with 5 min of warm-up and finished with 5 min of cool down at 30% of peak power output.

2.5. Measures

2.5.1. Cardiopulmonary exercise test

The cardiopulmonary exercise test was performed according to current guidelines for CHF patients [14]. A continuous progressive exercise protocol was performed on a cycle ergometer (Ergoline 800S, Ergoline, Bitz, Germany). A 2-min warm-up at 20 W was performed and the power was increased by 10 W/min until exhaustion [14]. Oxygen ($\dot{V}O_2$) and carbon dioxide (CO_2) were registered by a breath-by-breath analysis (PowerCube, Ganshorn Electronic Medizin, Germany). ECG activity was continuously monitored by 12-lead ECG (GE Healthcare Marquette) and was recorded throughout the test and during the 6-min passive recovery period.

2.5.2. 24-hr Holter ECG recording

Monitoring by 24-hr ECG was performed at baseline and at the end of the training by a two-lead 24-hr Holter ECG system (Spiderview, ELA Medical, France). Patients were asked not to consume coffee or tobacco and not to perform any other physical exercise during the 24 hr of recording. An experienced technician, unaware of the randomisation, analysed the recordings (Synescope, ELA Medical, France). HRV analysis was limited to the night time, from 23:00 to 6:00, for stationary signals.

2.5.3. HRV

For the time domain, the following indexes were calculated as recommended [16]: mean N–N interval (SDNN), root mean square difference of successive N–N intervals (RMSSD), and proportion of differences between adjacent N–N intervals of > 50 ms (PNN50). Spectral analysis involved a series of 1024 evenly separated points, sampled at 4 Hz corresponding to 256-sec stationary periods without artefacts or extrasystoles, by using fast Fourier transform and Hanning windowing to reduce the leakage error. The total spectral power (TP, ms^2) and power spectral density of the LF (0.04–0.15 Hz, $ms^2.Hz^{-1}$) and HF (0.15–0.40 Hz, $ms^2.Hz^{-1}$) bands were calculated. LF and HF were also expressed in normalized units (LF% = 100 × LF/(TP–VLF); HF% = 100 × HF/(TP–VLF)) and ratio of LF/HF (ms^2) according to the Task Force recommendation for long-term recordings [6]. The recordings were performed at a 200-Hz sampling rate.

2.5.4. Arrhythmias

The analysis of arrhythmias was computer-assisted (SyneScope, ELA Medical, France) and double-checked visually. Ectopic ventricular and supraventricular beats were classified as isolated premature contractions, bigeminy, and salvos. Rhythmic analysis also revealed conduction blocks or silent ischemia.

2.5.5. Echocardiography

Echocardiography involved using a phased-array transducer (Vivid T8, GE Healthcare). Measurements were in accordance with recommended procedures of the European Association of Cardiovascular Imaging. Measurements included systolic and diastolic LV function and systolic right ventricular function. LV volumes and LVEF were calculated from apical recordings by modified biplane Simpson's method. Stroke volume (SV) and cardiac output (CO) were calculated by Doppler flow measurements.

3. Statistical methods

3.1. Sample size calculation

The primary outcome measure was the change in HFnu% measured at night as a marker of HRV [6,7]. From our first study [9], with a mean (SD) value of the main criterion (HFnu%) of 31.5 (3), statistical power (1-β) 90% and α risk 0.05 in a bilateral hypothesis, we hypothesized that for a ∼11% change in HFnu% (34.96) with HIIT versus MICT, we needed 16 participants per group.

3.2. Statistical analysis

Data are presented as mean (SD) for continuous variables and frequency (%) for categorical variables. Change (post-training minus pre-training value) within each group was evaluated by Student *t* test for one-sample mean comparison (H0: mean = 0). To compare changes between HIIT and MICT groups (comparison named $\Delta_{intergroup}$ with $\Delta = [(post\text{-}pre)_{HIIT}]–[(post\text{-}pre)_{MICT}]$), Student *t* test was used for two-group mean comparison (H0: mean HIIT = mean MICT). The treatment effect ($\Delta_{intergroup}$) was evaluated by using all available data for participants in the treatment group to which they were originally randomly allocated. Given the modest amount of missing data for each examination (Supplementary Material Database), this latter strategy enabled us to work under the intention-to-treat analysis principle [17]. For sensitivity analysis, repeated ANOVA analysis was performed for the primary outcome (HFnu%), cardiorespiratory fitness $\dot{V}O_{2peak}$, and LVEF, estimating a time effect (post- vs. pre-training), group effect (HIIT vs. MICT) and interaction time × group (Supplementary Material. Repeated ANOVA analysis).

$P < 0.05$ was considered statistically significant. No interim analysis was performed. Prior sample size calculation, creating the randomisation list and statistical analyses involved using Stata SE 11.2 (StataCorp LP, College Station, TX, USA).

4. Results

CHF patients were recruited from May 2015 to September 2017. Among the 53 patients screened, 32 were enrolled and randomised to the 2 groups. One patient did not finish the rehabilitation program because of an ankle injury and knee pain (prosthesis) and was excluded from the analysis (Fig. 1). The cardiac rehabilitation program lasted a mean (SD) of 27 (4) days with a mean of 18 (1) sessions (92.9%) for MICT and 19 (2) sessions (93.6%) for HIIT. No adverse events were reported during the program. The baseline characteristics of each group are in Table 1.

5. Effect of training on HRV, HR, and arrhythmias

HFnu% remained unchanged with MICT, from a mean of 23% (12) to 22% (11), but increased with HIIT, from a mean of 21.2% (8) to 26.4% (9) ($P < 0.001$) with a significant inter-group difference ($P_{\Delta intergroup} = 0.003$; Δ=7; 95% confidence interval [CI] 2.46;10.63) (Table 2). Similarly, LFnu% decreased only with HIIT (from a mean of 63.3% to 58.3%, $P = 0.039$) with a significant inter-group difference ($P = 0.037$). PNN50 and RMSSD increased across groups over time ($P = 0.026$ and $P = 0.048$, respectively; Supplementary Material. Repeated-measures ANOVA). Mean 24-hr HR was significantly lower for both groups after training with no inter-group difference (− 3.6 bpm, $P = 0.047$, and − 2.5 bpm, $P = 0.027$, for MICT and HIIT, respectively).

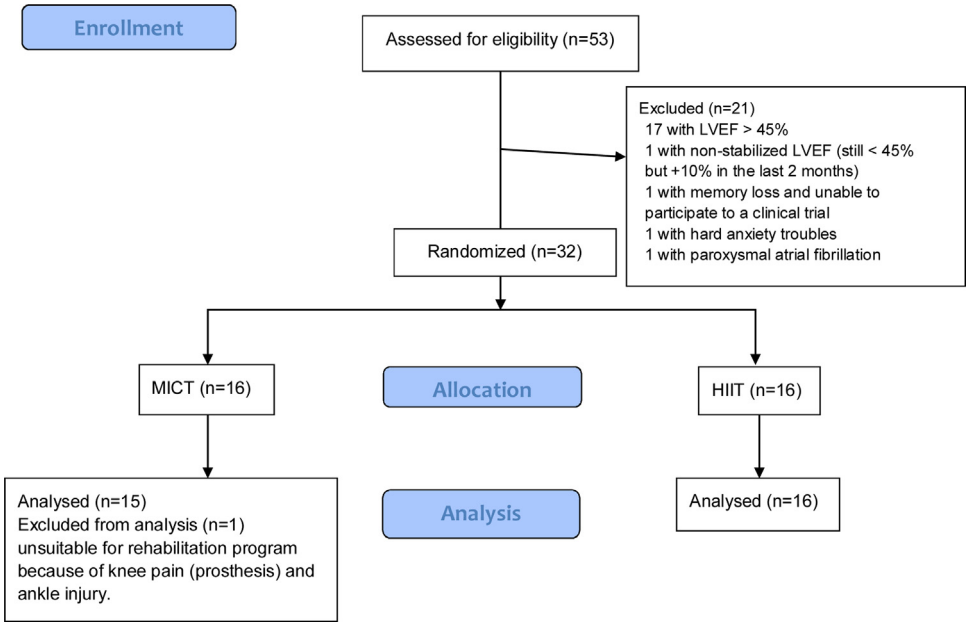

Fig. 1. Flow of participants in the study. HIIT, high-intensity interval training; MICT, moderate intensity continuous training.

Table 1
Baseline inclusion characteristics for high-intensity interval training (HIIT) and moderate intensity continuous training (MICT) groups. MICT and HIIT groups.

	MICT (n = 15)	HIIT (n = 16)
Baseline characteristics		
Sex (male/female)	11/4	11/5
Age (years)	59.5 (12)	59 (13)
BMI (kg/m^2)	28 (5)	25 (5)
Waist size (cm)	102 (9)	93 (15)
New York Heart Association functional class (I/II/III)	6/7/2	8/7/1
LVEF%	36 (7)	36 (8)
NT-proBNP (ng/L)	1232 (1109)	1725 (2526)
Risk factors		
Hypertension	8 (53%)	4 (25%)
Type II diabetes mellitus/prediabetes	3/3 (40%)	1/0 (6%)
Smoking	13 (87%)	12 (75%)
Overweight/obesity	5/6	2/2
Heart disease history		
Etiology of heart failure (ischemic/dilation)	11/4	9/7
Previous myocardial infarction	9 (60%)	7 (44%)
Previous CABG	3 (20%)	1 (6%)
Previous PCI	9 (60%)	8 (50%)
Implantable cardioverter defibrillator	4 (27%)	1 (6%)
Medications		
Beta blockers	13 (87%)	15 (94%)
Angiotensin-converting enzyme inhibitors	10 (67%)	8 (50%)
Angiotensin receptor blockers	2 (13%)	0
Diuretics	11 (73%)	12 (75%)
ARNi	3 (20%)	1 (6%)

Data are mean (SD) or number or as indicated. LVEF%: left ventricular ejection fraction percentage; BMI: body mass index; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; NT-proBNP: N-terminal pro–B-type natriuretic peptide; ARNi: angiotensin receptor-neprilysin inhibitors.

During the night time, SDNN remained unchanged for both groups. Premature ventricular contraction, 24-hr and night, remained statistically unchanged regardless of group (Table 3).

6. Effect of training on cardiopulmonary exercise test and echocardiography

Changes in $\dot{V}O_{2peak}$ (ml.min^{-1}.kg^{-1}) were significantly greater for both groups but were larger with HIIT than MICT regardless of whether $\dot{V}O_2$ was expressed in ml.min^{-1} or in % predicted (+21% vs. +5% for HIIT and MICT, respectively, $P_{\Delta intergroup}$ = 0.009) (Table 4). Vagal rebound after peak exercise measured during passive recovery by HR recovery (HRR) at 1, 2 and 3 min was significantly and exclusively higher with HIIT than MICT, with no inter-group differences.

The only change in echocardiography parameters was observed with HIIT, with decreased end-systolic volume (from 121.7 to 109.8 ml, P = 0.047) and a slight increase in LVEF (from 36.2% to 39.5%, P = 0.034); however, $P_{\Delta intergroup}$ was not significant (Table 5).

Despite significant improvements in HFnu% and cardiorespiratory fitness, we found no association between changes in $\dot{V}O_{2peak}$ and HFnu% or RMSSD nor changes in HFnu% and arrhythmias.

7. Discussion

Most exercise program studies last approximately 8 to 12 weeks [18,19]; we evaluated the efficacy of a short and intense supervised program of 3.5 weeks, which is commonly used in France during phase II cardiac rehabilitation. We previously demonstrated that a single session of HIIT improved the autonomic profile of CHF patients, leading to a significant reduction in HR and arrhythmic events in a 24-hr post-training period [9]. This putative acute cardioprotective effect of HIIT needed confirmation in a chronic setting and comparison with MICT in a larger study, which is what this study represents.

7.1. HRV and arrhythmias

In this randomized study of individuals with CHF, we demonstrated that HIIT is superior to MICT for improving HRV as assessed by an increase in HFnu% and a decrease in LFnu% and LF/HF ratio. This finding is consistent with a previous study from our group [9]. The only study of HRV comparing HIIT to MICT in CHF revealed no changes (whatever the group) in LF/HF ratio or SDNN index after 12 weeks of training or after 24 weeks [20]. Nevertheless, other markers of autonomic nervous system (ANS) modulation such as HFnu%, RMSSD, or HR recovery were not reported and the HIIT program was different from ours. Several studies revealed increased HF and reduced LF/HF in CHF patients after resistance exercise training [21] or MICT [3,22,23]. Nevertheless, the duration of these trials (between 8 and 24 weeks) was at least 2 to 7 times longer than in our study without the HIIT mode, so comparison of results is difficult.

Regular exercise training can improve cardiovascular ANS by reducing both peripheral and central levels of angiotensin II, nitric oxide and catecholamine [24–26]. Baroreflex function is also improved with exercise training in CHF patients [27] and helps enhance sympathovagal balance and rhythmic profile [28]. In our study, the simultaneous significant evolution of HF (+26.2%) and LF/HF ratio (−36%) with HIIT suggested improved vagal

Table 2
Time and spectral domain parameters measured during night time.

	MICT			HIIT			HIIT-MICT		
	Pre-training	Post-training	P	Pre-training	Post-training	P	Δ	$P_{\Delta\ inter\ group}$	[95% CI]
HR (bpm)	68.2 (10.7)	64.6 (9.6)	0.047	66.0 (5.5)	63.5 (5.9)	0.027	1.06	0.578	[−2.82;4.95]
PNN50 (%)	7.8 (8.7)	11.9 (10.7)	0.228	8.5 (10.8)	14.0 (14.5)	0.048	1.40	0.733	[−6.96;9.77]
RMSSD (ms)	32.4 (20.3)	46.5 (31.7)	0.179	40.3 (39.6)	49.2 (31.7)	0.123	−5.25	0.641	[−28.1;17.6]
SDNN	86.8 (37.0)	96.3 (37.4)	0.302	100.9 (46.2)	112.3 (42.6)	0.081	1.83	0.865	[−20.0;23.7]
Total power (ms^2)	2753 (2259)	3869 (4083)	0.197	5013 (6405)	5103 (5570)	0.855	−1025	0.283	[−2947;895]
VLF (ms^2)	1847 (1429)	2484 (2530)	0.178	2758 (2507)	2942 (2282)	0.537	−454	0.396	[−1533;625]
LF (ms^2)	517 (526)	1022 (1452)	0.122	1532 (3139)	1432 (2665)	0.539	−605	0.084	[−1297;87]
LFnu%	56.5 (13.5)	61.3 (17.3)	0.227	63.3 (13.6)	58.3 (13.9)	0.039	−9.80	0.037	[−19.0;−0.6]
HF (ms^2)	189 (240)	231 (236)	0.594	485 (997)	563 (826)	0.400	36.0	0.763	[−207;280]
HFnu%	23.1 (11.9)	21.9 (10.6)	0.444	21.2 (7.8)	26.4 (9.1)	< 0.001	6.5	0.003	[2.46;10.63]
LF/HF	3.0 (1.4)	3.8 (2.5)	0.097	3.8 (2.8)	2.6 (1.4)	0.021	−2.05	0.004	[−3.42;−0.7]

Data are mean SD. Change within each group: Student t test for one-sample mean comparison (H0: mean = 0). Change between HIIT and MICT: Student t test for two-group mean comparison (H0: mean HIIT: mean MICT). Comparison named $\Delta_{\ inter\ group}$ with Δ = [(post-pre)$_{HIIT}$]−[(post-pre)$_{MICT}$]). PNN50: measure of the number of adjacent NN intervals which differ by more than 50 ms; RMSSD: root mean square difference of successive R-R intervals; SDNN: standard deviation of normal to normal R-R intervals; VLF: very low frequency, a band of power spectrum from 0.0033 to 0.04 Hz; LF: low frequency, a band of power spectrum from 0.04 to 0.15 Hz; HF: high frequency, a band of power spectrum from 0.15 to 0.4 Hz.

Table 3
Premature ventricular contraction (*n*/24 hr).

	MICT			HIIT			HIIT-MICT		
	Pre-training	Post-training	*P*	Pre-training	Post-training	*P*	Δ	$P_{\Delta \text{ inter group}}$	[95% CI]
Isolated	548 (920)	517 (910)	0.474	850 (1620)	691 (1273)	0.584	−128	0.669	[−735;479]
Doublet	118 (330)	81 (216)	0.242	25 (64)	9 (14)	0.376	22	0.525	[−48;92]
Salvos	106 (326)	26 (69)	0.266	1 (64)	1 (2)	0.464	80	0.239	[−56;216]
Total	1165 (2676)	776 (1576)	0.263	903 (1706)	665 (1116)	0.468	151	0.746	[−794;1096]
Bigeminy	378 (1091)	284 (217)	0.507	1755 (5079)	813 (2985)	0.179	−848	0.237	[−2286;589]
Trigeminy	217 (634)	242 (600)	0.763	603 (1719)	292 (889)	0.476	−336	0.457	[−1250;577]

Data are mean (SD). Change within each group: Student *t* test for one-sample mean comparison (H0: mean = 0). Change between HIIT and MICT: Student *t* test for two-group mean comparison (H0: mean HIIT: mean MICT). Comparison named $\Delta_{\text{inter group}}$ with $\Delta = [(\text{post-pre})_{\text{HIIT}}] - [(\text{post-pre})_{\text{MICT}}]$).

Table 4
Cardiopulmonary exercise test.

	MICT			HIIT			HIIT-MICT		
	Pre-training	Post-training	*P*	Pre-training	Post-training	*P*	Δ	$P_{\Delta \text{ inter group}}$	[95% CI]
Rest									
Weight (kg)	81.5 (19.3)	81.0 (18.9)	0.139	71.8 (13.2)	71.5 (12.9)	0.297	0.2	0.639	[−0.7;1.1]
SAP (mmHg)	112.1 (15.0)	112.3 (10.9)	0.934	112.9 (14.7)	110.5 (11.2)	0.321	−2.6	0.442	[−9.4;4.2]
DAP (mmHg)	67.9 (9.5)	62.8 (6.3)	0.129	63.1 (8.0)	64.0 (7.9)	0.679	5.9	0.125	[−1.7;13.6]
HRrest (bpm)	63.1 (7.5)	60.8 (7.3)	0.149	61.5 (9.3)	57.2 (8.0)	0.015	−1.9	0.393	[−6.3;2.5]
Exercise									
HRmax (bpm)	125.7 (22.9)	125.9 (25.8)	0.949	117.5 (18.3)	125.1 (18.5)	0.011	7.3	0.079	[−0.9;15.6]
$\dot{V}O_{2peak}$ ($ml.min^{-1}$)	1244 (547)	1302 (598)	0.045	1243 (440)	1459 (521)	< 0.001	158	0.010	[41;276]
$\dot{V}O_{2\ peak}$ ($ml.min^{-1}.kg^{-1}$)	15.0 (4.6)	15.7 (5.1)	0.037	17.2 (4.5)	20.2 (5.8)	< 0.001	2.3	0.009	[−0.6;3.9]
$\dot{V}O_{2peak}$ (% predicted)	57.0 (15.6)	59.3 (16.1)	0.140	58.1 (13.1)	68.1 (17.6)	< 0.001	12.9	0.021	[−2.1;23.9]
RER	1.2 (0.1)	1.2 (0.1)	0.965	1.2 (0.1)	1.2 (0.1)	0.696	0.0	0.755	[−0.07;0.09]
Power output (watts)	99.0 (40.8)	111.8 (43.1)	< 0.001	93.7 (29.5)	116.0 (39.4)	< 0.001	9.5	0.074	[−1;20]
SAP_{max} (mmHg)	153.0 (23.8)	148.2 (24.5)	0.367	148.4 (24.0)	153.9 (23.2)	0.327	10.1	0.179	[−4.9;25.2]
$\dot{V}O_2/FC$ ($ml.beat^{-1}$)	10.0 (4.2)	10.5 (4.4)	0.033	10.5 (3.1)	11.8 (3.5)	0.005	0.8	0.104	[−0.2;1.7]
$\dot{V}_E/\dot{V}CO_2$	40.1 (8.6)	37.4 (7.2)	0.285	34.1 (6.8)	34.7 (6.5)	0.542	2.3	0.214	[−1.4;6.0]
VT_1 ($ml.min^{-1}$)	658 (282)	770 (341)	< 0.001	669 (232)	845 (250)	< 0.001	64	0.121	[−18;145]
VT_1 ($ml.min^{-1}.kg^{-1}$)	8.0 (2.4)	9.3 (2.9)	< 0.001	9.3 (2.5)	11.8 (3.0)	< 0.001	1.2	0.043	[0.03;2.3]
$\dot{V}O2/W$ ($ml.min^{-1}.W^{-1}$)	10.1 (2.4)	9.0 (2.3)	< 0.01	10.2 (1.8)	9.6 (1.5)	0.200	−1.7	0.450	[−2.4;0.5]
Peak circulatory power ($mmHg.ml^{-1}.min^{-1}.kg^{-1}$)	2268 (694)	2343 (837)	0.418	2533 (732)	3116 (1092)	0.005	508	0.015	[106;910]
HR reserve (bpm)	62.6 (21.5)	65.1 (24.8)	0.462	56.1 (22.8)	71.7 (26.8)	0.007	13.1	0.038	[0.8;25.4]
Passive recovery									
t 1/2 $\dot{V}O_2$ (s.)	118.6 (28.4)	125.7 (26.7)	0.230	103.9 (22.5)	105.7 (28.1)	0.859	5.3	0.431	[−27.1;11.9]
HRR 1 min	−20.9 (9.1)	−22.9 (8.8)	0.349	−18.1 (10.5)	−21.7 (9.3)	0.018	1.6	0.522	[−3.5;6.7]
HRR 2 min	−34.5 (11.6)	−37.9 (14.2)	0.186	−28.5 (12.4)	−34.3 (13.8)	0.003	2.3	0.430	[−3.6;8.3]
HRR 3 min	−41.7 (13.3)	−43.5 (15.6)	0.515	−33.5 (13.3)	−39.5 (14.4)	0.002	4.2	0.180	[−2.1;10.5]

Data are mean (SD). Change within each group: Student *t* test for one-sample mean comparison (H0: mean = 0). Change between HIIT and MICT: Student *t* test for two-group mean comparison (H0: mean HIIT: mean MICT). Comparison named $\Delta_{\text{inter group}}$ with $\Delta = [(\text{post-pre})_{\text{HIIT}}] - [(\text{post-pre})_{\text{MICT}}]$). SAP: systolic arterial pressure; DAP: diastolic arterial pressure; HR: heart rate; RER: respiratory exchange ratio; VT_1: first ventilatory threshold; HRR: heart rate recovery.

Table 5
Echocardiography findings.

	MICT			HIIT			HIIT-MICT		
	Pre-training	Post-training	*P*	Pre-training	Post-training	*P*	Δ	$P_{\Delta \text{ inter group}}$	[95% CI]
Systolic left ventricular function									
LVED (mm)	62.7 (9)	63.8 (10.1)	0.087	62.2 (8.7)	61.6 (7.8)	0.667	−1.2	0.379	[−3.9;1.5]
LVES (mm)	51.1 (9.4)	51.3 (9.7)	0.958	51.5 (10.3)	49.5 (10)	0.448	−1.2	0.536	[−5.3;2.8]
LV septal thickness (mm)	10.4 (1.8)	9.8 (1.7)	0.099	10.6 (2)	9.9 (2.6)	0.910	0.7	0.401	[−1.1;2.5]
LV posterior wall thickness (mm)	9.6 (2.9)	9.3 (2.4)	0.926	9.9 (2)	9.2 (1.6)	0.782	−0.1	0.947	[−2.5;2.3]
LVED volume (ml)	171.3 (85.6)	161.1 (79.6)	0.713	160.7 (76.5)	161.2 (60.7)	0.354	9.7	0.895	[−39.4;34.7]
LVES volume (ml)	119 (74.6)	106.9 (66.5)	0.324	121.7 (54.8)	109.8 (25.3)	0.047	−0.3	0.888	[−27.3 23.8]
LVEF%	35.6 (7.4)	36.9 (8)	0.513	36.2 (7.4)	39.5 (8.5)	0.034	2.0	0.355	[−2.3;6.2]
LV mass (g/m^2)	131.4 (31)	128.6 (31.2)	0.448	141.5 (35.7)	130.1 (25.7)	0.818	1.8	0.853	[−18.9;22.6]
Left atrial size (cm^2)	22 (5)	22.4 (6.1)	0.278	24.3 (8.2)	24.1 (6.8)	0.928	0.6	0.738	[−3.1;4.2]
Diastolic left ventricular function									
A	77.1 (17.9)	72.7 (18.5)	0.267	78.9 (44.9)	89.4 (32.5)	0.872	6.7	0.406	[−10.1;23.5]
E/A	0.9 (0.3)	0.9 (0.4)	0.798	1 (0.6)	0.8 (0.3)	0.238	0.1	0.659	[−0.25;0.38]
E (cm/s)	72.7 (20.8)	65.7 (22.4)	0.649	72.6 (27.4)	65.8 (30.3)	0.624	−11	0.905	[−20.1;17.9]
E/Ea	11.3 (4.8)	10.3 (4.3)	0.423	11.2 (4.9)	9.2 (2.7)	0.348	−0.5	0.775	[−4.1;3.1]
Systolic right ventricular function									
Shortening fraction	32.2 (16.5)	32.2 (13.6)	0.997	31.2 (17.8)	32.9 (15.8)	0.851	0.6	0.903	[−8.8;9.9]
TAPSE (mm)	19 (5)	20.3 (4.2)	0.231	18.4 (6.9)	20.7 (5.3)	0.078	2.5	0.274	[−2.1;7.1]
S' (cm/s)	11.9 (2.9)	11.5 (4.2)	0.816	11.6 (2.8)	11.6 (2.1)	0.732	0.5	0.692	[−2.1;3.1]

Data are mean SD. Change within each group: Student *t* test for one-sample mean comparison (H0: mean = 0). Change between HIIT and MICT: Student *t* test for two-group mean comparison (H0: mean HIIT: mean MICT). Comparison named $\Delta_{\text{inter group}}$ with $\Delta = [(\text{post-pre})_{\text{HIIT}}] - [(\text{post-pre})_{\text{MICT}}]$). LVED: left ventricular end diastolic; LVES: left ventricular end systolic; LVEF: left ventricular ejection fraction; E/A: mitral early diastolic velocity/atrial diastolic velocity ratio; E/Ea: diastolic velocity/transmitral E-wave; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; S': right systolic velocity.

modulation of HR. Nevertheless, other markers of vagal tone did not show a significant intergroup difference (RMSSD, pNN50, HF ms^2, resting HR and HRR at 1, 2, 3 min), which suggests caution with our interpretation. Moreover, despite the altered HFnu% and the mathematically associated parameters LFnu% and LF/HF [29], we found no difference in the other spectral or temporal components of vagal activity, possibly because of low sample size. However, independent of the controversial debate concerning the links between ANS modulation (parasympathetic and/or sympathetic branch) and HRV [7,8], most of the spectral components of HRV, including LF/HF ratio, have been associated with all causes of mortality and sudden death in CHF [30–32]. Conversely, the improvements in these parameters after HIIT that we observed are of interest.

Nevertheless, unlike our first study [9], we did not note any significant reduction in total premature ventricular contraction/24 hr whatever the group. This finding could be explained by the large inter-individual responses in a small sample. However, with HIIT, arrhythmias were not worse, which agrees with Rognmo et al. [33], who analysed the risk of cardiovascular events during HIIT and MICT among 4,846 patients with coronary heart disease and 175,820 exercise training hours. The results indicate that the risk is low after both HIIT and MICT in a cardiovascular rehabilitation setting.

7.2. Cardiorespiratory fitness

$\dot{V}O_{2\ peak}$ is one of the most powerful and independent predictors of cardiac mortality. Although the typology of training is discussed [34], our results confirm those from a meta-analysis of $\dot{V}O_{2peak}$ improvement [19,35]. With only 20 sessions, our HIIT training mode was efficient to increase the $\dot{V}O_{2peak}$ by 21% versus 5% with MICT. In CHF, exercise capacity is inversely correlated with sympathetic tone as measured by microneurography [36]. Also, in healthy sedentary people and athletes, change in $\dot{V}O_{2max}$ is associated with increased parasympathetic tone [37,38]. Unfortunately, although we found greater improvements in $\dot{V}O_{2\ peak}$ and HFnu% with HIIT, we found no correlation with changes in these values.

7.3. Cardiac function

HIIT but not MICT significantly increased LVEF (+9%) and reduced end systolic volume (with no intergroup difference, $P = 0.355$). LVEF improvement was less than in the study by Wisloff et al. over 12 weeks (+35%) [39]. Thus, the ratio of LVEF improvement/weeks of training is promising with HIIT and should be tested in a longer study. Our HIIT led to both increased contractility and afterload, resulting in decreased LVES volume. End-systolic volume is an indicator of remodelling after myocardial necrosis, and resting LVES volume and LVEF are associated with mortality and incident heart failure [40].

All together, we demonstrated that HIIT leads to better and earlier results as compared with MICT in terms of the main variables predicting sudden cardiac death ($\dot{V}O_{2peak}$, vagal tone, HR reserve, LVEF) (Fig. 2). HIIT training with passive recovery may play an important role as a "vagal training stimulation" each 30 sec and, as such, should be studied in larger and longer clinical trials. Benefits for ANS associated with HIIT are intensity- and/or range-dependent (difference between P_{peak} and $P_{recovery}$).

7.4. Limitations

The small sample size allowed us to highlight a greater effect of HIIT on HFnu% but not other parasympathetic markers. Moreover, we found no correlation between the improvement in cardiorespiratory fitness, HRV index, and arrhythmias. The beneficial effects of HIIT in CHF patients need to be confirmed in a larger and multicentre clinical trial. Because of an increase in cardiac events with a high dose of exercise training (> 7 MET/hr/week) [41], a longer follow-up should be also studied. The functional benefits of a short rehabilitation program are very encouraging, but we do not have the necessary hindsight to know its effectiveness in maintaining the benefits in the medium to long term. The effects of HIIT on ANS outcomes measured with HRV could have been characterized more extensively by using extensive biological assessment or muscle sympathetic nerve activity or baroreflex sensitivity. Renin–angiotensin system activity or nitric oxide bioavailability could be measured. The main limitation of our study concerns the number of type II diabetic and prediabetic patients in the MICT group ($n = 6$) versus the HIIT group ($n = 1$) ($P = 0.037$). For further research on exercise training and HRV in heart failure, randomization could be stratified on type II diabetes mellitus presence. Chronic hyperglycemia limits the improvement of $\dot{V}O_{2\ peak}$ and changes in ANS activity after rehabilitation, so our results are debatable. However, in our study, mean (SD) haemoglobin A1c level was rather low in diabetic/prediabetic patients (6.8% [1.1]). Furthermore, 3 patients with MICT did not receive

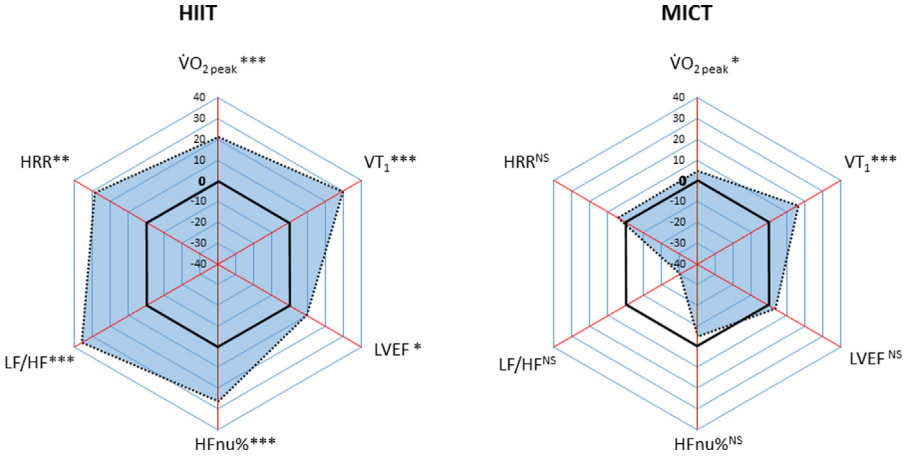

Fig. 2. Improvements after HIIT and MICT. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ comparing post- to pre-training. NS, non-significant. HRR, heart rate reserve; VT_1, first ventilatory threshold; LVEF, left ventricular ejection fraction; HFnu%, high frequency power in normalised units; LF/HF, low-frequency/high-frequency ratio; VO_{2peak}, peak oxygen uptake. The black bold line indicates the baseline values "0". For visual consistency, a decrease in LF/HF ratio with HIIT is illustrated by a + 36% improvement ($P < 0.001$). Conversely, an increase in LF/HF ratio with MICT is illustrated by a − 30% decrease (ns). The objective of this figure is not statistical but educational. The only 2 statistically significant criteria for inter-group comparisons are HFnu% and VO_{2peak}.

pharmacological treatment but only lifestyle advice. Finally, post-hoc analysis excluding these 7 diabetic/prediabetic patients confirmed our first findings concerning HFnu% for MICT, from a mean (SD) of 18% (4) to 16.5% (7) ($P = 0.397$), and HIIT, from a mean of 20.2% (7) to 25.4% (8) ($P = 0.001$) with $P_{\Delta intergroup} = 0.004$.

8. Conclusions

The beneficial effects of HIIT are still debated, especially with recent publications [42]. Our results highlight the positive benefit/risk ratio with HIIT in CHF patients and suggest that short and intensive HIIT using passive recovery confers cardioprotective effects by increasing vagal modulation and cardiorespiratory fitness. Further studies should clarify whether HIIT interventions are effective over the long term for restoring ANS in CHF patients.

Authors' contributions

Conceived and designed the experiments: FB TG ML JMS. Performed the experiments: FB LR LS MB JLG HK. Analyzed the data: FB FF ML TG. Wrote the paper: FB TG ML CG JMS AP.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/10.1016/j.rehab.2019.06.013.

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