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

3
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24

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26

27 **Abstract**

28 **Background.** Exaggerated sympathetic nervous system activity associated with low heart rate
29 variability (HRV) is considered to trigger cardiac arrhythmias and sudden death. Regular
30 exercise training is efficient to improve autonomic balance.

31 **Objective.** We aimed to verify the superiority of high-intensity interval training (HIIT) to
32 enhance HRV, cardiorespiratory fitness and cardiac function as compared with moderate
33 intensity continuous training (MICT) in a short, intense cardiac rehabilitation program.

34 **Methods.** This was a prospective, monocentric, evaluator-blinded, randomised (1:1) study
35 with a parallel two-group design. Overall, 31 individuals with voluntary chronic heart failure
36 (CHF) (left ventricular ejection fraction [LVEF] < 45%) were allocated to MICT (n=15) or
37 HIIT (n=16) for a short rehabilitation program (mean [SD] 27 [4] days). Participants
38 underwent 24-hr electrocardiography, echocardiography and a cardiopulmonary exercise test
39 at entry and at the end of the study.

40 **Results.** High-frequency power in normalized units (HFnu%) measured as HRV increased
41 with HIIT (from 21.2% to 26.4%, $p < 0.001$) but remained unchanged with MICT (from 23.1%
42 to 21.9%, $p = 0.444$, with a significant intergroup difference, $p = 0.003$). Resting heart rate (24-
43 hr Holter electrocardiography) decreased significantly for both groups (from 68.2 to 64.6 bpm
44 and 66.0 to 63.5 bpm for MICT and HIIT, respectively, with no intergroup difference,
45 $p = 0.578$). The 2 groups did not differ in premature ventricular contractions. Improvement in
46 peak oxygen uptake was greater with HIIT than MICT (+21% vs +5%, $p = 0.009$). LVEF
47 improved with only HIIT (from 36.2% to 39.5%, $p = 0.034$).

48 **Conclusions.** In this short rehabilitation program, HIIT was significantly superior to the
49 classical MICT program for enhancing parasympathetic tone and peak oxygen uptake.

50

51 **Keywords:** exercise training; cardiovascular; rehabilitation; chronic heart failure;
52 parasympathetic; cardiorespiratory fitness

53

54 **Introduction**

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

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

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

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

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

80

81 **Materials and methods**

82 *Design*

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

89 The protocol was approved by the Toulouse Outre-Mer I Ethics Committee, and the
90 French National Agency for Medicines and Health Products Safety (ANSM: ID-RCB no.:
91 2015-A00166-43). Written informed consent was obtained from all participants before
92 inclusion. The investigation followed the principles outlined in the Declaration of Helsinki.
93 This study was publicly registered on ClinicalTrials.gov (NCT03603743).

94

95 *Participants*

96 CHF patients were recruited from a cardiac rehabilitation unit. Inclusion criteria were stable
97 CHF with New York Heart Association functional class I to III, stable LVEF < 45% for
98 at least 6 months, stable optimal medical therapy including a beta-blocker and an angiotensin-
99 converting enzyme inhibitor or angiotensin receptor blocker for at least 6 weeks and ability to
100 perform a maximal cardiopulmonary exercise test. Exclusion criteria were any relative or
101 absolute contraindications to exercise training according to current recommendations [14],

102 fixed-rate pacemaker with HR limits set lower than **the** exercise training target HR, major
103 cardiovascular event or procedure within the 3 months **before** enrolment, chronic atrial
104 fibrillation, heart failure secondary to significant uncorrected primary valve disease, and heart
105 failure secondary to congenital heart disease or obstructive cardiomyopathy. A paper case
106 report form was designed to collect patient data and was also approved by the ethics
107 committee.

108

109 **Randomisation**

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

115

116 *Rehabilitation program*

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

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

128

129 *Measures*

130 Cardiopulmonary exercise test

131 **The cardiopulmonary** exercise test was performed according to current guidelines for CHF
132 patients [14]. A continuous progressive exercise protocol was performed on a cycle ergometer
133 (Ergoline 800S, Ergoline, Bitz, Germany). A 2-min warm-up at 20 W was performed and the
134 power was increased by 10 W/min until exhaustion [14]. Oxygen ($\dot{V}O_2$) and carbon dioxide
135 (CO_2) were registered by a breath-by-breath analysis (PowerCube, Ganshorn Electronic

136 Medizin, Germany). ECG activity was continuously monitored by 12-lead ECG (GE
137 Healthcare Marquette) and was recorded throughout the test and during the 6-min passive
138 recovery period.

139

140 24-hr Holter ECG recording

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

147

148 HRV

149 For the time domain, the following indexes were calculated as recommended [16]: mean N–N
150 interval (SDNN), root mean square difference of successive N–N intervals (RMSSD), and
151 proportion of differences between adjacent N–N intervals of > 50 ms (PNN50). Spectral
152 analysis involved a series of 1024 evenly separated points, sampled at 4 Hz corresponding to
153 256-sec stationary periods without artefacts or extrasystoles, by using fast Fourier transform
154 and Hanning windowing to reduce the leakage error. The total spectral power (TP, ms^2) and
155 power spectral density of the LF (0.04–0.15 Hz, $\text{ms}^2 \cdot \text{Hz}^{-1}$) and HF (0.15–0.40 Hz, $\text{ms}^2 \cdot \text{Hz}^{-1}$)
156 bands were calculated. LF and HF were also expressed in normalized units ($\text{LF}\% = 100 \times$
157 $\text{LF}/(\text{TP}-\text{VLF})$; $\text{HF}\% = 100 \times \text{HF}/(\text{TP}-\text{VLF})$) and ratio of LF/HF (ms^2) according to the Task
158 Force recommendation for long-term recordings [6]. The recordings were performed at a 200-
159 Hz sampling rate.

160

161 Arrhythmias

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

166

167 Echocardiography

168 Echocardiography involved using a phased-array transducer (Vivid T8, GE Healthcare).
169 Measurements were in accordance with recommended procedures of the European

170 Association of Cardiovascular Imaging. Measurements included systolic and diastolic LV
171 function and systolic right ventricular function. LV volumes and LVEF were calculated from
172 apical recordings by modified biplane Simpson's method. Stroke volume (SV) and cardiac
173 output (CO) were calculated by Doppler flow measurements.

174

175 **Statistical methods**

176 *Sample size calculation*

177 The primary outcome measure was the change in HFnu% measured at night as a marker of
178 HRV [6, 7]. From our first study [9], with a mean (SD) value of the main criterion (HFnu%)
179 of 31.5 (3), statistical power (1-β) 90% and α risk 0.05 in a bilateral hypothesis, we
180 hypothesized that for a ~11% change in HFnu% (34.96) with HIIT versus MICT, we needed
181 16 participants per group.

182

183 *Statistical analysis*

184 Data are presented as mean (SD) for continuous variables and frequency (%) for categorical
185 variables. Change (post-training minus pre-training value) within each group was evaluated
186 by Student *t* test for one-sample mean comparison (H0: mean = 0). To compare changes
187 between HIIT and MICT groups (comparison named $\Delta_{\text{intergroup}}$ with $\Delta = [(post-pre)_{HIIT}] -$
188 $[(post-pre)_{MICT}]$), Student *t* test was used for two-group mean comparison (H0: mean HIIT =
189 mean MICT). The treatment effect ($\Delta_{\text{intergroup}}$) was evaluated by using all available data for
190 participants in the treatment group to which they were originally randomly allocated. Given
191 the modest amount of missing data for each examination (Supplementary Material. Database),
192 this latter strategy enabled us to work under the intention-to-treat analysis principle [17]. For
193 sensitivity analysis, repeated ANOVA analysis was performed for the primary outcome
194 (HFnu%), cardiorespiratory fitness $\dot{V}O_{2\text{peak}}$, and LVEF, estimating a time effect (post- vs pre-
195 training), group effect (HIIT vs MICT) and interaction time x group (Supplementary Material.
196 Repeated ANOVA analysis).

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

200

201 **Results**

202 CHF patients were recruited from May 2015 to September 2017. Among the 53 patients
203 screened, 32 were enrolled and randomised to the 2 groups. One patient did not finish the

204 rehabilitation program because of an ankle injury and knee pain (prosthesis) and was excluded
205 from the analysis (Fig. 1). The cardiac rehabilitation program lasted a mean (SD) of 27 (4)
206 days with a mean of 18 (1) sessions (92.9%) for MICT and 19 (2) sessions (93.6%) for HIIT.
207 No adverse events were reported during the program. The baseline characteristics of each
208 group are in Table 1.

209

210 **Effect of training on HRV, HR, and arrhythmias**

211 HFnu% remained unchanged with MICT, from a mean of 23% (12) to 22% (11), but
212 increased with HIIT, from a mean of 21.2% (8) to 26.4% (9) ($p < 0.001$) with a significant
213 inter-group difference ($p_{\Delta\text{intergroup}} = 0.003$; $\Delta = 7$; 95% confidence interval [CI] 2.46;10.63)
214 (Table 2). Similarly, LFnu% decreased only with HIIT (from a mean of 63.3% to 58.3%,
215 $p = 0.039$) with a significant inter-group difference ($p = 0.037$). PNN50 and RMSSD increased
216 across groups over time ($p = 0.026$ and $p = 0.048$, respectively; Supplementary Material).
217 Repeated-measures ANOVA). Mean 24-hr HR was significantly lower for both groups after
218 training with no inter-group difference (-3.6 bpm, $p = 0.047$, and -2.5 bpm, $p = 0.027$, for MICT
219 and HIIT, respectively).

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

222

223 **Effect of training on cardiopulmonary exercise test and echocardiography**

224 Changes in $\dot{V}O_{2\text{peak}}$ ($\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) were significantly greater for both groups but were larger
225 with HIIT than MICT regardless of whether $\dot{V}O_2$ was expressed in $\text{ml}\cdot\text{min}^{-1}$ or in % predicted
226 (+21% vs +5% for HIIT and MICT, respectively, $p_{\Delta\text{intergroup}} = 0.009$) (Table 4). Vagal rebound
227 after peak exercise measured during passive recovery by HR recovery (HRR) at 1, 2 and 3
228 min was significantly and exclusively higher with HIIT than MICT, with no inter-group
229 differences.

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

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

236

237 **Discussion**

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

245

246 *HRV and arrhythmias*

247 In this randomized study of individuals with CHF, we demonstrated that HIIT is superior to
248 MICT for improving HRV as assessed by an increase in HFnu% and a decrease in LFnu%
249 and LF/HF ratio. This finding is consistent with a previous study from our group [9]. The only
250 study of HRV comparing HIIT to MICT in CHF revealed no changes (whatever the group) in
251 LF/HF ratio or SDNN index after 12 weeks of training or after 24 weeks [20]. Nevertheless,
252 other markers of autonomic nervous system (ANS) modulation such as HFnu%, RMSSD, or
253 HR recovery were not reported and the HIIT program was different from ours. Several studies
254 revealed increased HF and reduced LF/HF in CHF patients after resistance exercise training
255 [21] or MICT [3, 22, 23]. Nevertheless, the duration of these trials (between 8 and 24 weeks)
256 was at least 2 to 7 times longer than in our study without the HIIT mode, so comparison of
257 results is difficult.

258 Regular exercise training can improve cardiovascular ANS by reducing both
259 peripheral and central levels of angiotensin II, nitric oxide and catecholamine [24-26].
260 Baroreflex function is also improved with exercise training in CHF patients [27] and helps
261 enhance sympathovagal balance and rhythmic profile [28]. In our study, the simultaneous
262 significant evolution of HF (+26.2%) and LF/HF ratio (-36%) with HIIT suggested improved
263 vagal modulation of HR. Nevertheless, other markers of vagal tone did not show a significant
264 intergroup difference (RMSSD, pNN50, HF ms², resting HR and HRR at 1, 2, 3 min), which
265 suggests caution with our interpretation. Moreover, despite the altered HFnu% and the
266 mathematically associated parameters LFnu% and LF/HF [29], we found no difference in the
267 other spectral or temporal components of vagal activity, possibly because of low sample size.
268 However, independent of the controversial debate concerning the links between ANS
269 modulation (parasympathetic and/or sympathetic branch) and HRV [7, 8], most of the
270 spectral components of HRV, including LF/HF ratio, have been associated with all causes of

271 mortality and sudden death in CHF [30-32]. Conversely, the improvements in these
272 parameters after HIIT that we observed are of interest.

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

280

281 *Cardiorespiratory fitness*

282 $\dot{V}O_{2\text{ peak}}$ is one of the most powerful and independent predictors of cardiac mortality.
283 Although the typology of training is discussed [34], our results confirm those from a meta-
284 analysis of $\dot{V}O_{2\text{ peak}}$ improvement [19, 35]. With only 20 sessions, our HIIT training mode was
285 efficient to increase the $\dot{V}O_{2\text{ peak}}$ by 21% versus 5% with MICT. In CHF, exercise capacity is
286 inversely correlated with sympathetic tone as measured by microneurography [36]. Also, in
287 healthy sedentary people and athletes, change in $\dot{V}O_{2\text{ max}}$ is associated with increased
288 parasympathetic tone [37, 38]. Unfortunately, although we found greater improvements in
289 $\dot{V}O_{2\text{ peak}}$ and HFnu% with HIIT, we found no correlation with changes in these values.

290

291 *Cardiac function*

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

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

305

306 **Limitations**

307 The small sample size allowed us to highlight a greater effect of HIIT on HFnu% but not
308 other parasympathetic markers. Moreover, we found no correlation between the improvement
309 in cardiorespiratory fitness, HRV index, and arrhythmias. The beneficial effects of HIIT in
310 CHF patients need to be confirmed in a larger and multicentre clinical trial. Because of an
311 increase in cardiac events with a high dose of exercise training (> 7 MET/hr/week) [41], a
312 longer follow-up should be also studied. The functional benefits of a short rehabilitation
313 program are very encouraging, but we do not have the necessary hindsight to know its
314 effectiveness in maintaining the benefits in the medium to long term. The effects of HIIT on
315 ANS outcomes measured with HRV could have been characterized more extensively by using
316 extensive biological assessment or muscle sympathetic nerve activity or baroreflex sensitivity.
317 Renin-angiotensin system activity or nitric oxide bioavailability could be measured. The main
318 limitation of our study concerns the number of type II diabetic and prediabetic patients in the
319 MICT group (n = 6) versus the HIIT group (n = 1) (p =0.037). For further research on
320 exercise training and HRV in heart failure, randomization could be stratified on type II
321 diabetes mellitus presence. Chronic hyperglycemia limits the improvement of $\dot{V}O_2$ peak and
322 changes in ANS activity after rehabilitation, so our results are debatable. However, in our
323 study, mean (SD) haemoglobin A1c level was rather low in diabetic/prediabetic patients
324 (6.8% [1.1]). Furthermore, 3 patients with MICT did not receive pharmacological treatment
325 but only lifestyle advice. Finally, post-hoc analysis excluding these 7 diabetic/prediabetic
326 patients confirmed our first findings concerning HFnu% for MICT, from a mean (SD) of 18%
327 (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
328 $p_{\Delta intergroup} = 0.004$.

329

330 **Conclusions**

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

336

337 **Authors' contributions.** Conceived and designed the experiments: FB TG ML JMS.
338 Performed the experiments: FB LR LS MB JLG HK. Analyzed the data: FB FF ML TG.
339 Wrote the paper: FB TG ML CG JMS AP.

340

341 **Conflict of interest.** None declared.

342

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352

353 **Legends**

354 **Figure 1.** Flow of participants in the study. HIIT, high-intensity interval training; MICT,
355 moderate intensity continuous training

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

365

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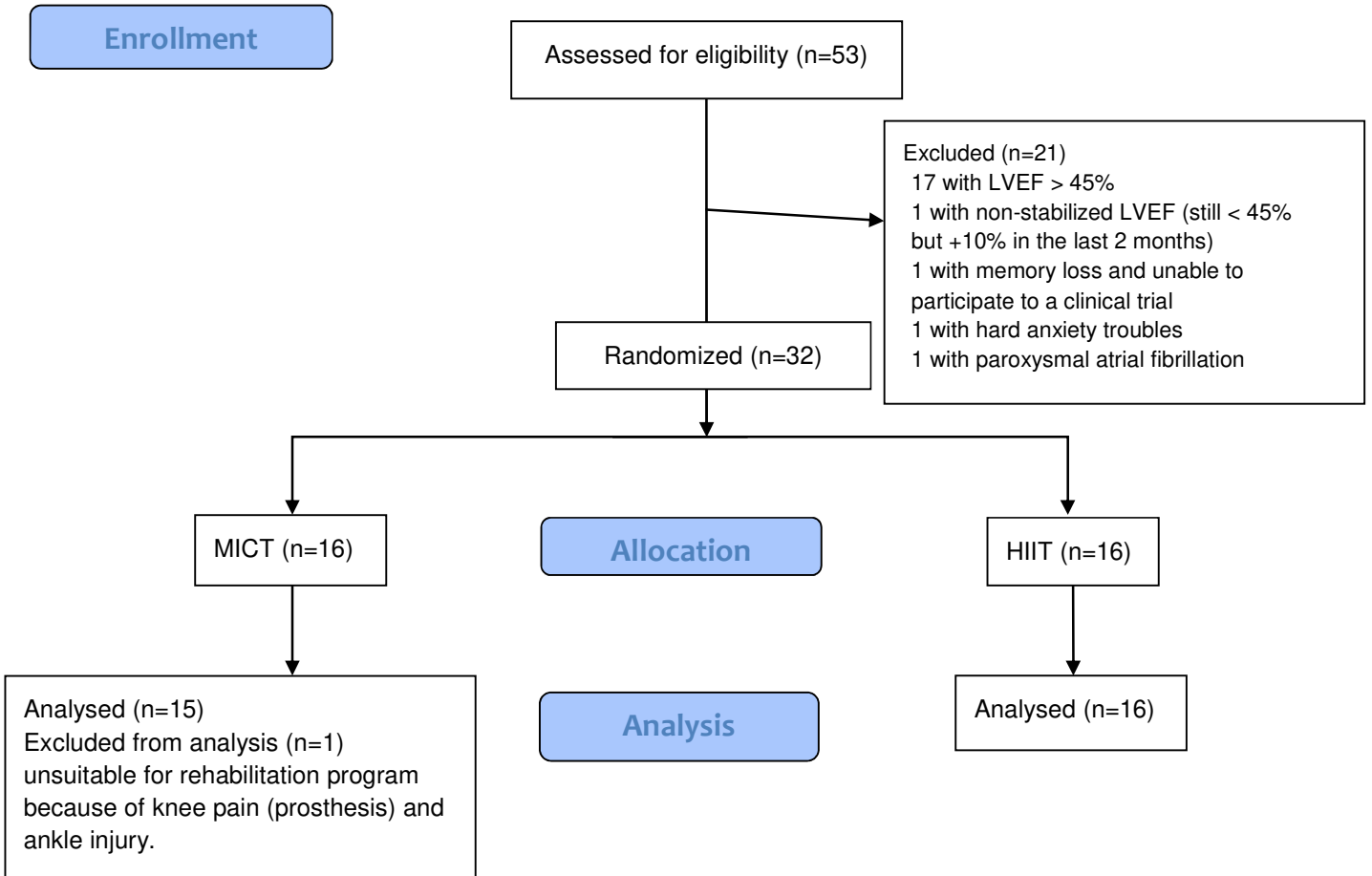
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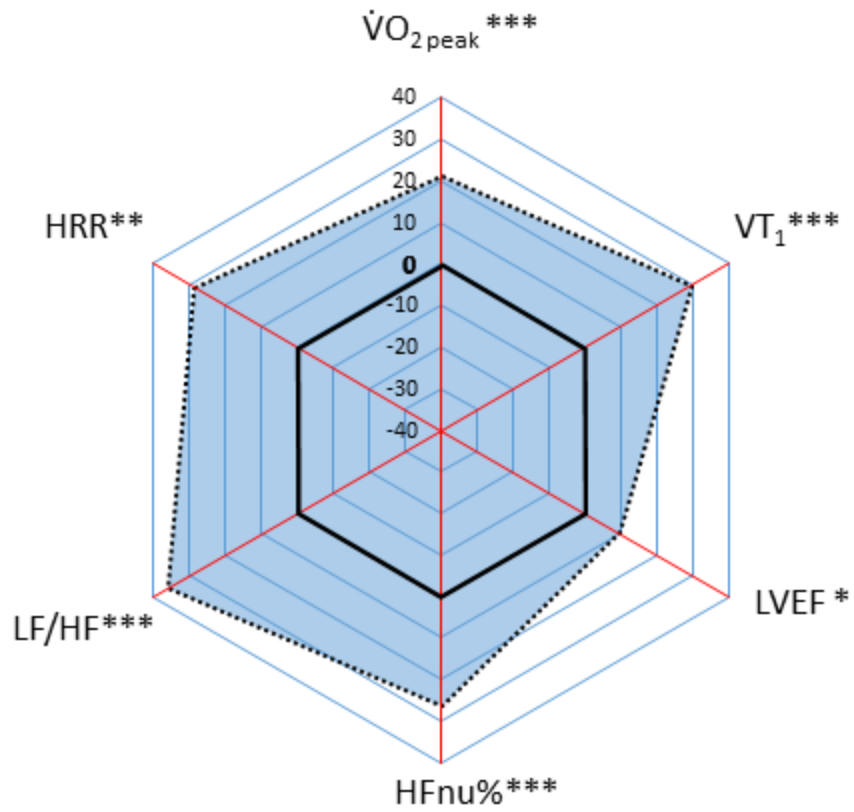
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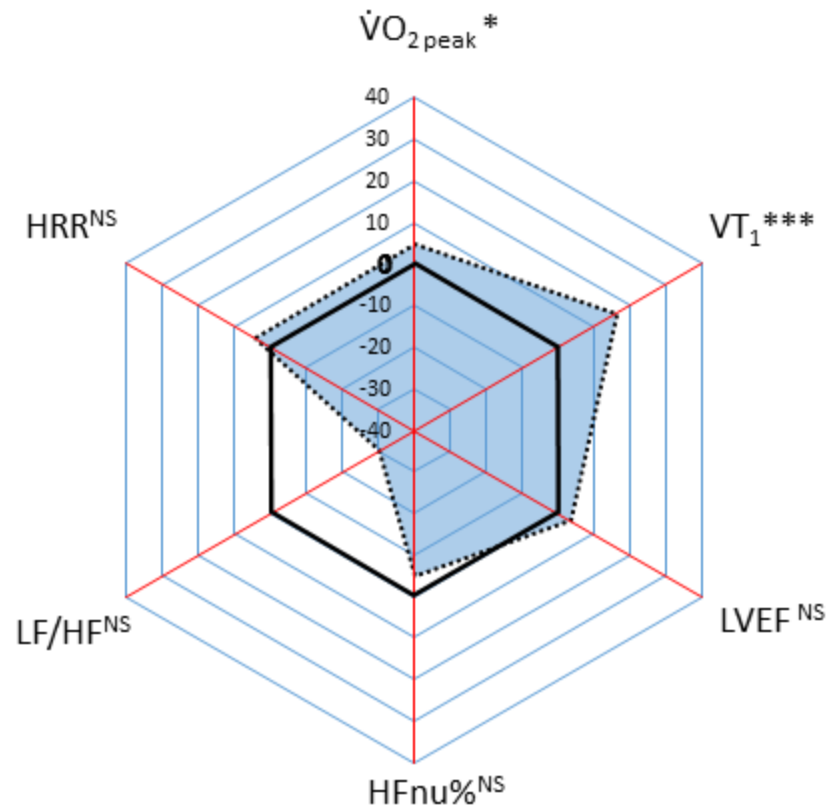
Fig. 1



HIIT



MICT



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

3 **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%)

4 **Data are mean (SD) or number or as indicated. LVEF%, left ventricular ejection fraction**
 5 **percentage; BMI, body mass index; PCI, percutaneous coronary intervention; CABG,**

6 coronary artery bypass graft surgery; NT-proBNP, N-terminal pro-B-type natriuretic peptide;

7 ARNi, angiotensin receptor-neprilysin inhibitors

8

9

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

	MICT			HIIT			HIIT-MICT		
	Pre-training	Post-training	<i>p</i>	Pre-training	Post-training	<i>p</i>	Δ	<i>p</i> $\Delta_{inter\ group}$ [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]	

11 Data are mean SD. Change within each group: Student *t* test for one-sample mean comparison (H0: mean = 0). Change between HIIT and MICT:
 12 Student *t* test for two-group mean comparison (H0: mean HIIT = mean MICT). Comparison named $\Delta_{inter\ group}$ with $\Delta = [(post-pre)_{HIIT}] - [(post-$
 13 $pre)_{MICT}]$. PNN50, measure of the number of adjacent NN intervals which differ by more than 50 ms; RMSSD, root mean square difference of
 14 successive R-R intervals; SDNN, standard deviation of normal to normal R-R intervals; VLF, very low frequency, a band of power spectrum
 15 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
 16 0.15 to 0.4 Hz

17
 18

19 **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 (2)	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]

20 Data are mean (SD). Change within each group: Student *t* test for one-sample mean comparison (H0: mean = 0). Change between HIIT and
 21 MICT: Student *t* test for two-group mean comparison (H0: mean HIIT = mean MICT). Comparison named $\Delta_{\text{inter group}}$ with $\Delta = [(post-pre)_{HIIT}] -$
 22 $[(post-pre)_{MICT}]$.

23 **Table 4. Cardiopulmonary exercise test.**

	MICT				HIIT				HIIT-MICT		
	Pre-training	Post-training		<i>p</i>	Pre-training	Post-training		<i>p</i>	Δ	<i>p</i> Δ 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]
$\dot{V}O_{2peak}$ (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]
$\dot{V}O_2/W$ (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]

24 Data are mean (SD). Change within each group: Student *t* test for one-sample mean comparison (H0: mean = 0). Change between HIIT and MICT:

25 Student *t* test for two-group mean comparison (H0: mean HIIT = mean MICT). Comparison named $\Delta_{\text{inter group}}$ with $\Delta = [(\text{post-pre})_{\text{HIIT}}] - [(\text{post-pre})_{\text{MICT}}]$.

26 SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; RER, respiratory exchange ratio; VT_1 , first ventilatory threshold; **HRR**,

27 **heart rate recovery**

Table 5. Echocardiography findings.

	MICT			HIIT			HIIT-MICT		
	Pre-training	Post-training	p	Pre-training	Post-training	p	Δ	p Δ 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 $\Delta = [(post-pre)_{\text{HIIT}}] - [(post-pre)_{\text{MICT}}]$. 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