High-Intensity Interval Exercise Improves Vagal Tone and Decreases Arrhythmias in Chronic Heart Failure

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ABSTRACT

GUIRAUD, T., M. LABRUNEE, K. GAUCHER-CAZALIS, F. DESPAS, P. MEYER, L. BOSQUET, C. GALES, A. VACCARO, M. BOUSQUET, M. GALINIER, J.-M. SÉNARD, and A. PATHAK. High-Intensity Interval Exercise Improves Vagal Tone and Decreases Arrhythmias in Chronic Heart Failure. *Med. Sci. Sports Exerc.*, Vol. 45, No. 10, pp. 1861–1867, 2013. **Purpose**: Autonomic dysfunction including sympathetic activation and vagal withdrawal has been reported in patients with chronic heart failure (CHF). We tested the hypotheses that high-intensity interval exercise (HIIE) in CHF patients would enhance vagal modulation and thus decrease arrhythmic events. **Methods**: Eighteen CHF patients underwent a baseline assessment (CON) and were then randomized to a single session of HIIE and to an isocaloric moderate-intensity continuous exercise (MICE). We evaluated the HR, HR variability parameters, and arrhythmic events by 24-h Holter ECG recordings after HIIE, MICE, and CON sessions. **Results**: We found that HR was significantly decreased after HIIE (68 ± 3 bpm, $P < 0.01$) when compared with CON and MICE values (71.1 ± 2 and 69 ± 3 bpm, respectively). HIIE led to a significant increase in normalized high-frequency power (35.95% ± 2.83% vs 31.56% ± 1.93% and 24.61% ± 2.62% for CON and MICE, respectively, $P < 0.01$). Both exercise conditions were associated with an increase in very low frequency power comparative to CON. After HIIE, premature ventricular contractions were significantly decreased (531 ± 338 vs 1007 ± 693 and 1671 ± 1604 for CON and MICE, respectively, $P < 0.01$). An association was found between the changes in premature ventricular contraction and the changes in low-frequency/high-frequency ratio ($r = 0.66$, $P < 0.01$) in patients exposed to HIIE. **Conclusion**: We demonstrate that a single session of HIIE improves autonomic profile of CHF patients, leading to significant reductions of HR and arrhythmic events in a 24-h posttraining period. Cardioprotective effects of HIIE in CHF patients need to be confirmed in a larger study population and on a long-term basis. **Key Words:** INTERVAL, HIGH INTENSITY, HR VARIABILITY, HEART FAILURE

Patients with chronic heart failure (CHF) are prone to elevated mortality and occurrence of arrhythmic events potentially leading to sudden cardiac death. Autonomic nervous system (ANS) abnormalities as assessed by 24-h HR variability (HRV) indexes were found to be predictive of this outcome. Galinier et al. (12) reported that CHF patients with an SD of all N–N intervals (SDNN) of less than 67 ms were at a 2.5-fold increased risk for all-cause mortality and progressive heart failure death. In addition, lower daytime low-frequency (LF) power, short-term controlled breathing LF power, and LF to high-frequency (HF) power ratio were also found to have independent prognostic value among individuals with CHF (29). Altogether, a decreased vagal tone and a relative or absolute increase in sympathetic activity are autonomic patterns predictive of an unfavorable prognosis. Although most of the treatment strategies (beta blockers, renin–angiotensin system blockers, cardiac resynchronization therapy, etc.) used in the management of CHF patients have been shown to reduce sympathetic activation, less is known about the effect of current care on vagal modulation. Yet, experimental studies indicate that increased parasympathetic activity using vagal stimulation may reduce mortality in animal models of postinfarction sudden cardiac death and of CHF (31). More recently, a first-in-man study performed in patients with CHF suggests

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that vagus nerve stimulation was associated with significant improvements (i.e., New York Heart Association (NYHA) class, quality of life, or ejection fraction). This type of approach used in patient with refractory epilepsia or depression is invasive and still under investigation in the field of heart failure (9). In this context, exercise appears as a nonpharmacological tool able to enhance vagal modulation, because exercise training has been found to have beneficial effects on HRV in CHF patients (29). Malfatto et al. (20) reported greater restoration of ANS responsiveness to vagal and sympathetic stimulation in CHF patients who completed 3 months of low-intensity exercise therapy. Improvements in HRV among CHF patients have also been observed in supervised aerobic exercise programs, supervised resistance training programs, and home-based training programs (29). These findings suggest that a variety of exercise therapy program may be used to improve HRV in the CHF population (4,30). However, the effect of high-intensity interval training (HIIT) on HRV in CHF patients has never been investigated.

Moreover, any type of intervention (such as HIIT) able to reduce premature ventricular contraction (PVC) could potentially be associated with a reduction of life-threatening arrhythmias.

HIIT appears to have superior effect on maximal oxygen uptake, endothelial function, cardiac and muscular function and quality of life in healthy subjects, CHD, metabolic syndrome, and CHF patients (8,14,17,38,39) than moderate-intensity continuous exercise (MICE). We recently optimized a high-intensity interval exercise (HIIE) protocol in stable CHD and CHF patients (13,24). However, these studies have never assessed the effect of this type of exercise on ANS activity (15,26,39). We therefore compared the effect of HIIE protocol and MICE on ANS activity and arrhythmias in CHF patients. We hypothesized that HIIE would restore the sympathovagal balance and thus lead to a reduction in HR and in the occurrence of arrhythmias. This in turn could be of importance to explain how CHF patients benefit from HIIE (13,23).

METHOD

Study design. This was a randomized crossover study investigating two different exercise protocols (an optimized HIIE and an isocaloric MICE session). At the first visit, anthropometric data, vital signs, resting ECG, and a 24-h Holter ECG (CON) were collected, and patients performed a cardiopulmonary exercise test (CPET). At the second and third visit (each separated by a 1-wk period), every patient performed in random order HIIE and MICE sessions under the supervision of an exercise physiologist and a cardiologist. After every exercise session, a 24-h Holter ECG was connected to the patients for HRV analysis to determine the frequency of arrhythmias (Fig. 1). The protocol was accepted by the Ethics Committee for the Protection of Human (University of Toulouse), and written informed consent was

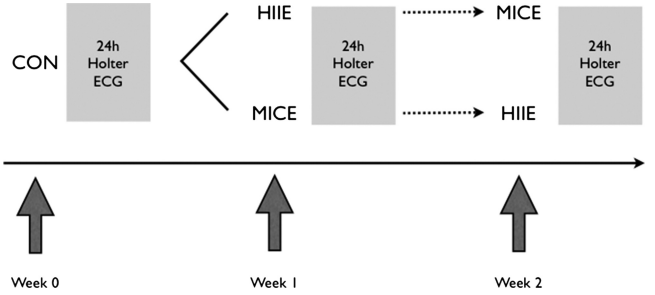

FIGURE 1—Study design.

obtained from all patients. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Participants. A minimum of 17 patients per condition was calculated to show a reduction in HR. After an initial screening of 30 patients, we enrolled 18 patients with stable CHF. Inclusion criteria were as follows: age ≥18 yr, left ventricular ejection fraction <40% (measured within the last month of enrollment by echocardiography, radionuclide ventriculography, or cardiac magnetic resonance), NYHA functional class I to III, stable optimal medical therapy including a beta blocker and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) for at least 6 wk, ability to perform a maximal CPET, and capacity and willingness to sign the informed consent form. Exclusion criteria included any relative or absolute contraindications to exercise training in CHF patients according to current recommendations (27), fixed-rate pacemaker with HR limits set lower than exercise training target HR, major cardiovascular event or procedure within the 3 months preceding enrollment, chronic atrial fibrillation, heart failure secondary to significant uncorrected primary valvular disease (except for mitral regurgitation secondary to left ventricular dysfunction), and heart failure secondary to congenital heart disease or obstructive cardiomyopathy.

CPET. CPET was performed according to current guidelines for CHF patients (27). A continuous progressive exercise protocol was performed on a cycle ergometer (Ergoline 800S, Ergoline, Bitz, Germany). The pedaling speed was settled at 60 rpm during the entire test. A 2-min warm-up at 20 W was performed before the test, and the power was increased by 10 $W \cdot min^{-1}$ depending on the functional capacity of the patient until exhaustion (27). Peak power output (PPO) was defined as the power output reached at the last fully completed stage (13). All subjects were encouraged to provide a maximal effort. HR, manual brachial blood pressure, and RPE using the Borg scale (level 6 to 20) (27) were recorded before the test and at 2-min intervals during exercise and recovery. Electrocardiographic activity was monitored continuously using a 12-lead ECG (GE Healthcare Marquette) and was recorded throughout the test and during the 5-min passive recovery after the test.

MICE and HIIE session. MICE consisted of 22 min of exercise at 60% of PPO on the basis of current recommendations of the American Heart Association (28). The

optimized HIIE session consisted of a warm-up for 2 min at 50% of PPO, followed by two sets of 8-min intervals at 100% of PPO. Each interval block was composed of repeated bouts of 30 s at 100% of PPO interspersed by 30 s of passive recovery in the seated position (24). Four minutes of passive recovery were allowed between the two sets, as well as a 1-min cool down at 25% of PPO after the last 30-s exercise bout. Both protocols were estimated to be isocaloric on the basis of previous research (26).

24-h Holter ECG recording. Ambulatory 24-h ECG monitoring was performed at the baseline visit and at the end of each exercise session. The ambulatory recordings were acquired using a two-lead 24-h Holter ECG system (Spiderview; Medsource, LLC, Stillwater, MN). Patients were requested to undertake their usual daily activities and to avoid caffeinated beverages, smoking, and certain activity such as going on a walk during the 24 h of recording. An experienced technician blinded to randomization analyzed the recordings.

HRV. The recordings were performed at a 200-Hz sampling rate. The ELATEC Holter analysis HRV and QT software (ELA Medical, Montrouge, France) was used for analysis. Recordings were excluded if they lasted <20 h, if they were of poor quality, if atrial fibrillation or a paced rhythm was present, or if T wave amplitude was <0.15 mV. Time domain HRV was analyzed, and the following indexes were calculated (21): Mean N–N interval, the SDNN, root mean square of differences of successive N–N intervals, and proportion of differences between adjacent N–N intervals of more than 50 ms were computed. Spectral analysis was performed for 256-s periods with a fast Fourier transform to quantify the total spectral power (TP), the power spectral density of the LF (0.04–0.15 Hz), and the HF (0.15–0.40 Hz) bands. Additional calculations included LF and HF expressed in normalized units [LF% = 100 LF/(TP − very low frequency (VLF))], HF in normalized units [HF% = 100 HF/(TP − VLF)], and the ratio of LF (ms^2)/HF (ms^2) according to the Task Force recommendation for short-term recordings (21). The computation was done only if there were more than 100 normal beats and 80% normal complexes within the 256 s. Because a 50% overlapping function was applied on the 256-s buffer, the analysis was computed every 128 s and the spectra were averaged. The 256-s tachograms were sampled at a 4-Hz frequency to obtain equidistant sampling. A Hanning window was applied to reduce the leakage error. All the parameters were computed from normal-to-normal RR values (QRS complexes of sinus origin) and determined for 24 h. The power spectral density of the preprocessed signal was computed, and the results were expressed in natural logarithm of the square of milliseconds per hertz. The areas under the spectral density curve between the limits of the spectral bands of HF and LF were then integrated to obtain values for HF and LF power.

Arrhythmias. The analysis of arrhythmias was computer assisted (SyneScope, Medsource, LLC) and visually double-checked. Ectopic ventricular and supraventricular beats were classified as isolated premature contractions, bigeminy, and salves. Analysis also stated the occurrence of atrial and ventricular arrhythmias, as conduction blocks or silent ischemia.

Statistical analysis. Descriptive statistics were reported for demographics, baseline clinical characteristics, and CPET (Table 1). They were also reported by exercise mode, i.e., 2 × 8 min of HIIE and MICE and baseline (Tables 2 and 3). Mean and SD (or SEM) were reported for continuous variables. Frequencies and percentages were reported for categorical ones. For the 24-h electrophysiological responses, *P* values were calculated using a one-way repeated ANOVA with a factor for "condition." Logarithmic transformation has been performed before ANOVA if data were not normally distributed. If ANOVA was significant and to know the difference between two conditions, *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 nonnormally distributed data. Furthermore, to verify if the effects were persistent in all variables, we performed additional analyses in the 24th hour, i.e., a one-way repeated ANOVA with a factor for "condition" and then a paired *t*-test for normally distributed data or paired Wilcoxon signed-rank test for nonnormally distributed data, to know the difference between the two conditions. Spearman correlations were also generated to verify the relation between changes in parameters. All statistical analyses were based

TABLE 1. Patient's characteristics.

Clinical variables	*n* = 18
Gender (male/female)	12/6
Age (yr)	53 ± 12.0
BMI ($kg \cdot m^{-2}$)	26.9 ± 7.1
LVEF (%)	33 ± 10.7
NYHA functional class (I/II/III)	2.0 ± 0.9 (4/10/4)
BNP ($pg \cdot dL^{-1}$)	612.88 ± 385
Etiology of heart failure (ischemic heart disease/nonischemic)	12/6
Risk factors	
Diabetes mellitus	0
Hypertension	6 (33%)
Smoking	3 (16%)
Obesity (BMI ≥30 $kg \cdot m^{-2}$)	2 (11%)
Medical history	
Previous myocardial infarction	12 (64%)
Previous CABG	8 (44%)
Previous PCI	6 (32%)
Medications	
ACE inhibitors	14 (87.5%)
Beta blockers	18 (100%)
Digoxin	0
Furosemide	9 (50%)
Spironolactone	4 (22%)
Devices	
CRT/ICD	0/2 (0/11%)
Cardiopulmonary maximal testing variables	
HR_{rest} (bpm)	55.4 ± 8.5
HR_{max} (bpm)	112.1 ± 10.4
PPO (W)	118.49 ± 38.7
METs	6.2 ± 1.67

Data are presented as mean ± SD except BNP, which is presented as mean ± SEM.
BMI, body mass index; LVEF, left ventricular ejection fraction; BNP, brain natriurectic peptide; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator.

TABLE 2. Time domain parameters.

n = 18	CON	MICE	HIIE
HR_{24h} (bpm)	71.1 ± 2.7	69 ± 3*,***	68 ± 3.2*,**
PVC (N/24 h)	1671 ± 1604	1007 ± 693***	531 ± 338*,**
Bigeminy (N/24 h)	2.5 ± 1.5	7.4 ± 4.81	0.389 ± 0.33
Salves (N/24 h)	38.39 ± 17.72	115.94 ± 87.88***	11.61 ± 3.03**
SVPC (N/24 h)	301 ± 747	306 ± 286	322 ± 348
SDNN (ms)	68.5 ± 9.0	75.6 ± 6.2*	76.9 ± 11.5*
RMSSD (ms)	36.43 ± 4.54	29.95 ± 1.60	30.14 ± 3.89
pNN50 (%)	16.36 ± 1.81	12.25 ± 1.13	11.66 ± 1.04

Data are presented as mean ± SD, except PVC and SVPC, which are presented as mean ± SEM.
*Significantly different from CON values ($P < 0.05$).
**Significantly different from MICE values ($P < 0.05$).
***Significantly different from HIIE values.
RMSSD, root mean square of differences of successive N–N intervals; pNN50, proportion of differences between adjacent N–N intervals of more than 50 ms; SVPC, supraventricular premature contraction.

on 18 patients and performed using SAS, Version 9.2. A P value <0.05 was considered as significant.

RESULTS

Baseline characteristics. Three patients were excluded because of poor quality of 24-h Holter ECG or change of their treatment. Participants were mainly men (66%) with a mean age of 53 ± 12.0 yr. Most patients had ischemic heart disease (64%). Mean NYHA was 2.0 ± 0.9, and all patients were on optimal medical therapy. Demographic, baseline characteristics and maximal CPET variables are presented in Table 1.

Effects on HR, HRV, and PVC. Average HR was significantly lower after HIIE compared with CON (−2.1 bpm, $P < 0.01$) and MICE (−1 bpm, $P < 0.01$) values. Compared with CON, both exercise sessions significantly increased SDNN ($P < 0.01$). When compared with CON and MICE values, HF power was significantly higher after HIIE ($P < 0.01$) in the 24-h period. LF was significantly higher after MICE (54.07% ± 2.99%, $P < 0.01$) compared with CON and HIIE values (48.33% ± 3.17% and 47.90% ± 2.47%, respectively). When compared with MICE, HF power values remained higher after HIIE in the 24th hour (37.2% ± 29.1% and 22.6% ± 12.2%, respectively, $P = 0.06$).

When compared with CON and MICE, the number of PVC was significantly decreased in patients undergoing HIIE ($P < 0.01$).

TABLE 3. Spectral domain parameters.

Spectral Domain Parameters—24 h	CON	MICE	HIIE
HF power (ms^2)	155 ± 9	118 ± 11*,***	145 ±12*,**
LF power (ms^2)	238 ± 14	258 ± 15*,***	196 ± 11**
VLF (ms^{-2})	1434 ± 346	1804 ± 372*	1710 ± 372*
TP (ms^{-2})	1930 ± 289	2281 ± 484*,***	2118 ± 421**
LF/HF ratio	1.54 ± 0.13	2.22 ± 0.24*,***	1.34 ± 0.11*,**
HF power (nu, %)	31.56 ± 1.93	24.61 ± 2.62*,***	35.95 ± 2.83*,**
LF power (nu, %)	48.33 ± 3.17	54.07 ± 2.99*,***	47.90 ± 2.47**

*Significantly different from CON values ($P < 0.05$).
**Significantly different from MICE values ($P < 0.05$).
***Significantly different from HIIE values. nu, normalized units.

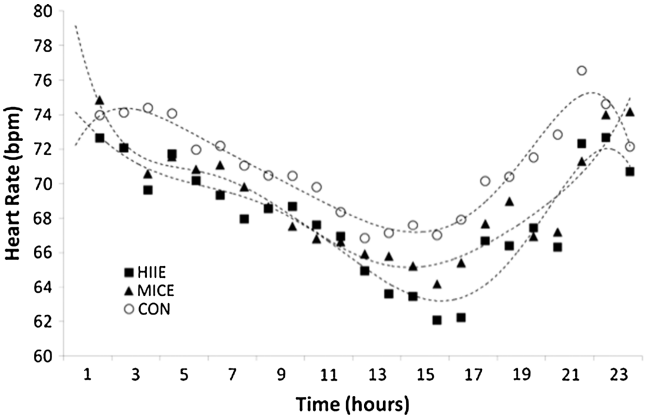

FIGURE 2—HR after the MICE, HIIE, and CON.

The only significant association was between the changes in PVC and the changes in LF/HF ratio ($r = 0.66$; $P < 0.01$) after HIIE and MICE, suggesting that the decrease in PVC was strongly related to the decrease in LF/HF ratio (Tables 2 and 3, Figs. 2 and 3).

DISCUSSION

Major finding. The present study was designed to provide insights into the change in ANS activity, as assessed by HRV, achieved by HIIE in CHF patients. We also planned to describe the effect of this nonpharmacological therapy in patients with CHF on HR and arrhythmias to assess the benefit/risk ratio of HIIE in the setting of CHF. To our knowledge, this study is the first to assess the effects of HIIE on HRV-derived parameters and subsequently on the occurrence of arrhythmias. In this randomized controlled study, we were able to demonstrate that HIIE is safe and beneficial through an increase of the parasympathetic tone associated with a decrease in HR and ventricular susceptibility as shown by a significant decrease (more than threefold) in PVC frequency. Compared with MICE and CON, HIIE induces an early and larger improvement of HRV-derived

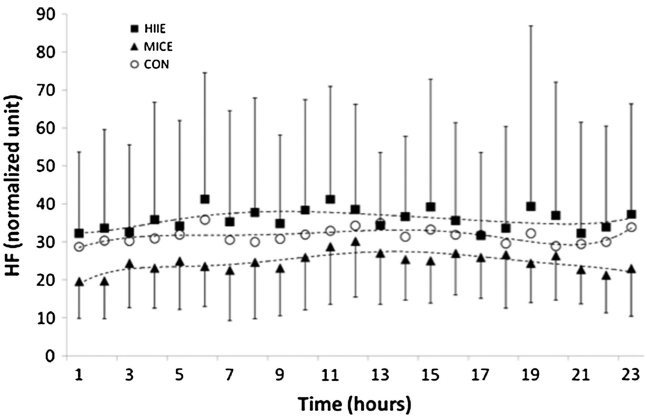

FIGURE 3—HF after the HIIE, MICE, and CON.

parameters, and these effects lasted for at least 24 h after a single session of exercise. HIIE leads also to enhancement of VLF power. Finally, according to patients, HIIE was the most preferred protocol, associated with a lower perceived exertion compared with MICE, and no adverse event was reported by health care providers or patients (data not shown). Altogether, these results highlight the positive benefits/risk ratio associated with HIIE in CHF patients and suggest that this type of intervention could reduce the cardiovascular risk of CHF patients.

Effects of HIIE on HRV parameters. Different types of exercise have been shown to improve HRV in CHF population (29). Our study further adds to this concept, showing for the first time that HIIE has the same global effect on the autonomic tone as that of other programs. The major finding of this study is that HR reduction post-HIIE exercise is directly correlated to vagal modulation enhancement as assessed by an increase in HF power. Although the underlying mechanisms by which exercise training improves vagal modulation are speculative at present, angiotensin II and nitric oxide (NO) are potential mediators. Angiotensin II is known to inhibit cardiac vagal activity (36). One theory is that exercise training suppresses angiotensin II expression (5). It has been shown that plasma renin activity levels are lower in long-distance runners than that in untrained individuals or nonathletes and sedentary individuals (10). This finding is important given that athletes with lower plasma renin activity would presumably have lower angiotensin II and higher associated levels of cardiac vagal activity. Therefore, it is possible that the suppression of angiotensin II via exercise may, to some extent, mediate enhancement of cardiac vagal tone (5). NO may also play a role in increasing cardiac vagal control and, in doing so, may indirectly inhibit sympathetic influences (7). Exercise training, particularly HIIE, has been found to improve endothelial function and NO bioavailability among individuals with coronary atherosclerosis (25,37). Moreover, in experimental models, overexpression of nitric oxide synthase-3 (NOS3) in murine cardiomyocytes potentiates vagal modulation of heart function (22). Other mechanisms can also be responsible for parasympathetic activation. We have shown that adrenomedullin, a peptide increased in CHF patient and also during exercise (33), can up-regulate muscarinic receptors in cardiomyocytes (6). These data illustrate how endogenous ligands can possibly modulate autonomic control of the heart and potentially influence exercise-mediated cardiac vagal tone increase.

In our study, HIIE is associated with an increase in VLF power. The latter is known to reflect in part thermoregulatory mechanisms, fluctuation in activity of the renin–angiotensin system, and the function of peripheral chemoreceptors. Akselrod et al. (2) reported that ACE blockade increases very low frequency RR interval spectral power. HIIE as another mode of exercise is associated with angiotensin II decrease, consequently leading to VLF rise. Taylor et al. (34) showed that atropine nearly abolished very low frequency RR interval power in healthy volunteers, suggesting that VLF improvement post-HIIE could mainly reflect vagal modulation improvement. Irrespective of mechanisms, this effect is clinically relevant because depressed VLF power has been identified as an independent risk predictor in patients with CHF (16). However, we remain cautious about our results since the large discussion on the limitations of spectral analysis in HRV (35). Concerning the time domain analysis, we found a significant improvement of SDNN after HIIE when compared with MICE and CON. This suggests a decrease in the risk for all-cause mortality (12).

Effects of HIIE on HR and PVC. The effects of HIIE on HRV parameters (both HF and VLF increases) have a direct clinical effect because HR and PVC are reduced after a single session of exercise. HR reduction is considered as a key target in the management of CHF. Randomized clinical trials from the beta blocker era have shown that morbidity and mortality reduction is partly related to HR reduction (1). In addition, recent trial with ivabradine emphasized the role of reducing HR on the top of beta blockade therapy (32). We hypothesized that HF and VLF (i.e., reflecting vagal modulation for some authors) increases are the major trigger for HR reduction in this patient population. In experimental and clinical model, it has been described that vagal modulation enhancement, for example, through nerve stimulation, could restore baroreflex sensitivity, suppress proinflammatory cytokines, and thus contribute to both HR reduction and antiarrhythmic effects through other mechanisms. Surprisingly, we have noted a significant discrepancy between MICE and HIIE; although the first was associated with a reduction in HF, the second was inducing the opposite effect, suggesting that beneficial effects on HRV are probably related to the mode and intensity of HIIE.

We noticed that patients exposed to HIIE had a significant decrease in arrhythmic event, as assessed by the PVC number reduction. This can directly ($r = 0.66$, $P < 0.01$) be related to HRV modification (i.e., both HF and VLF increase). In experimental models, exercise training enhances baroreflex control of HR by a vagal mechanism (19), suggesting a sympathovagal balance resetting in postexercise period. The clinical importance of reducing PVC in CHF patients has been recently emphasized. Le et al. (18) showed after 6.2 yr of follow-up that the presence of PVC is a powerful predictor of cardiovascular mortality in CHF. Indeed, after adjustment, PVC was associated with a 5.5-fold increased of cardiovascular mortality ($P = 0.004$).

HRV modifications were observed at an early stage. Interestingly, it has been suggested that CHF patients may require more time to achieve modulation of autonomic tone and responsiveness than myocardial infarction patients. This may be due, in part, to the chronic nature of heart failure, which may contribute to greater autonomic impairment (20). In this case, it can be hypothesized that repeated periods of exercise and recovery through vascular mechanisms such as ischemic preconditioning could have led to these early autonomic modifications. It cannot be excluded that benefits associated with HIIE are intensity dependent.

Limitations. Several limitations of this study need to be outlined. We included a relatively small number of patients. Our study was based on a single session of exercise, and a beneficial effect observed with HIIE in CHF patients needs to be confirmed in a larger study population and for a longer follow-up. The effect of HIIE on ANS outcomes could have been characterized more extensively using direct nerve recording (muscle sympathetic nerve activity) or extensive biological assessment (11) for the sympathetic tone. We have not measured renin–angiotensin system activity, NO bioavailability, or other surrogate marker for neurohumoral modulation such as endothelial function. Finally, although Holter recordings permit analysis of RR interval fluctuations, they do not allow for control of common factors known to affect heart period variability such as posture, physical activity, breathing frequency, and tidal volume (3).

CONCLUSION

The beneficial effects of HIIE are still a matter of debate, because it is usually assumed that training in ischemic range could increase the risk of events. Our study shows, for the first time, that in CHF patients, this mode of training is safe and leads to significant clinical improvement. We provide evidence that HIIE in CHF patients exerts an influence on HRV via increasing vagal modulation. This is associated with an increase in VLF power. Overall, these findings translate into an HR reduction and a significant decrease of PVC number. Knowing that enhanced cardiac vagal modulation may not only offer a survival advantage but also reduce the risk of frequently lethal ventricular dysrhythmias including ventricular fibrillation, it could be hypothesized that HIIE may reduce the cardiovascular risk of CHF patients. In this context, there is a need to identify the exercise regimen (i.e., duration and intensity) that produces optimal improvements in HRV. Further studies should clarify whether HIIE interventions are effective long-term therapies for ANS recovery associated with meaningful improvements in outcomes of CHF patients.

Thibaut Guiraud and Marc Labrunee contributed equally to this work. The authors have no conflict of interest to declare.
The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Abraham WT. Beta-blockers: the new standard of therapy for mild heart failure. *Arch Intern Med*. 2000;160(9):1237–47.
2. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981; 213(4504):220–2.
3. Arai Y, Saul JP, Albrecht P, et al. Modulation of cardiac autonomic activity during and immediately after exercise. *Am J Physiol*. 1989;256(1 Pt 2):H132–41.
4. Barretto AC, Santos AC, Munhoz R, et al. Increased muscle sympathetic nerve activity predicts mortality in heart failure patients. *Int J Cardiol*. 2009;135(3):302–7.
5. Buch AN, Coote JH, Townend JN. Mortality, cardiac vagal control and physical training–what's the link? *Exp Physiol*. 2002; 87(4):423–35.
6. Buys S, Smih F, Pathak A, et al. Adrenomedullin upregulates M2-muscarinic receptors in cardiomyocytes from P19 cell line. *Br J Pharmacol*. 2003;139(6):1219–27.
7. Chowdhary S, Townend JN. Role of nitric oxide in the regulation of cardiovascular autonomic control. *Clin Sci (Lond)*. 1999; 97(1):5–17.
8. Cornish AK, Broadbent S, Cheema BS. Interval training for patients with coronary artery disease: a systematic review. *Eur J Appl Physiol*. 2011;111(4):579–89.
9. De Ferrari GM, Crijns HJ, Borggrefe M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J*. 2011;32(7):847–55.
10. Fagard R, Grauwels R, Groeseneken D, et al. Plasma levels of renin, angiotensin II, and 6-ketoprostaglandin F1 alpha in endurance athletes. *J Appl Physiol*. 1985;59(3):947–52.
11. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol*. 2009;54(5):375–85.
12. Galinier M, Pathak A, Fourcade J, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. *Eur Heart J*. 2000; 21(6):475–82.
13. Guiraud T, Juneau M, Nigam A, et al. Optimization of high intensity interval exercise in coronary heart disease. *Eur J Appl Physiol*. 2010;108(4):733–40.
14. Guiraud T, Nigam A, Gremeaux V, Meyer P, Juneau M, Bosquet L. High-intensity interval training in cardiac rehabilitation. *Sports Med*. 2012;42(7):587–605.
15. Guiraud T, Nigam A, Juneau M, Meyer P, Gayda M, Bosquet L. Acute responses to high-intensity intermittent exercise in CHD patients. *Med Sci Sports Exerc*. 2011;43(2):211–7.
16. Hadase M, Azuma A, Zen K, et al. Very low frequency power of heart rate variability is a powerful predictor of clinical prognosis in patients with congestive heart failure. *Circ J*. 2004;68(4):343–7.
17. Helgerud J, Hoydal K, Wang E, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc*. 2007;39(4):665–71.
18. Le VV, Mitiku T, Hadley D, Myers J, Froelicher VF. Rest premature ventricular contractions on routine ECG and prognosis in heart failure patients. *Ann Noninvasive Electrocardiol*. 2010;15(1):56–62.
19. Liu JL, Kulakofsky J, Zucker IH. Exercise training enhances baroreflex control of heart rate by a vagal mechanism in rabbits with heart failure. *J Appl Physiol*. 2002;92(6):2403–8.
20. Malfatto G, Branzi G, Riva B, Sala L, Leonetti G, Facchini M. Recovery of cardiac autonomic responsiveness with low-intensity physical training in patients with chronic heart failure. *Eur J Heart Fail*. 2002;4(2):159–66.
21. Malik M. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J*. 1996;17(3):354–81.
22. Massion PB, Dessy C, Desjardins F, et al. Cardiomyocyte-restricted overexpression of endothelial nitric oxide synthase (NOS3) attenuates beta-adrenergic stimulation and reinforces vagal inhibition of cardiac contraction. *Circulation*. 2004;110(17):2666–72.
23. Meyer K, Samek L, Schwaibold M, et al. Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. *Med Sci Sports Exerc*. 1997; 29(3):306–12.

24. Meyer P, Normandin E, Gayda M, et al. High-intensity interval exercise in chronic heart failure: protocol optimization. *J Card Fail*. 2012;18(2):126–33.
25. Munk PS, Staal EM, Butt N, Isaksen K, Larsen AI. High-intensity interval training may reduce in-stent restenosis following percutaneous coronary intervention with stent implantation A randomized controlled trial evaluating the relationship to endothelial function and inflammation. *Am Heart J*. 2009;158(5): 734–41.
26. Normandin E, Nigam A, Meyer P, et al. Acute responses to intermittent and continuous exercise in heart failure patients. *Can J Cardiol*. 2013;29(4):466–71.
27. Piepoli MF, Conraads V, Corra U, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail*. 2011; 13(4):347–57.
28. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation*. 2003;107(8): 1210–25.
29. Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL. Improvements in heart rate variability with exercise therapy. *Can J Cardiol*. 2011;26(6):303–12.
30. Roveda F, Middlekauff HR, Rondon MU, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. *J Am Coll Cardiol*. 2003;42(5):854–60.
31. Sabbah HN, Ilsar I, Zaretsky A, Rastogi S, Wang M, Gupta RC. Vagus nerve stimulation in experimental heart failure. *Heart Fail Rev*. 2011;16(2):171–8.
32. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875–85.
33. Tanaka M, Kitamura K, Ishizaka Y, et al. Plasma adrenomedullin in various diseases and exercise-induced change in adrenomedullin in healthy subjects. *Intern Med*. 1995;34(8):728–33.
34. Taylor JA, Carr DL, Myers CW, Eckberg DL. Mechanisms underlying very-low-frequency RR-interval oscillations in humans. *Circulation*. 1998;98(6):547–55.
35. Taylor JA, Studinger P. Counterpoint: cardiovascular variability is not an index of autonomic control of the circulation. *J Appl Physiol*. 2006;101(2):678–81; discussion 81.
36. Townend JN, al-Ani M, West JN, Littler WA, Coote JH. Modulation of cardiac autonomic control in humans by angiotensin II. *Hypertension*. 1995;25(6):1270–5.
37. Vona M, Rossi A, Capodaglio P, et al. Impact of physical training and detraining on endothelium-dependent vasodilation in patients with recent acute myocardial infarction. *Am Heart J*. 2004;147(6):1039–46.
38. Wisloff U, Ellingsen O, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc Sport Sci Rev*. 2009;37(3):139–46.
39. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study *Circulation*. 2007;115(24):3086–94.