

## Optimization of high intensity interval exercise in coronary heart disease

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**Abstract** High intensity interval training has been shown to be more effective than moderate intensity continuous training for improving maximal oxygen uptake ( $VO_{2max}$ ) in patients with coronary heart disease (CHD). However, no evidence supports the prescription of one specific protocol of high intensity interval exercise (HIIE) in this population. The purpose of this study was to compare the acute cardiopulmonary responses with four different single bouts of HIIE in order to identify the most optimal one in CHD patients. Nineteen stable CHD patients (17 males, 2 females,  $65 \pm 8$  years) performed four different bouts of HIIE, all with exercise phases at 100% of maximal aerobic power (MAP), but which varied in interval duration (15 s

for mode A and B and 60 s for mode C and D) and type of recovery (0% of MAP for modes A and C and 50% of MAP for modes B and D). A passive recovery phase resulted in a longer time to exhaustion compared to an active recovery phase, irrespective of the duration of the exercise and recovery periods (15 or 60 s,  $p < 0.05$ ). Time to exhaustion also tended to be higher with mode A relative to mode C ( $p = 0.06$ ). Despite differences in time to exhaustion between modes, time spent at a high percentage of  $VO_{2max}$  was similar between HIIE modes except for less time spent above 90 and 95% of  $VO_{2max}$  for mode C when compared with modes B and D. When considering perceived exertion, patient comfort and time spent above 80% of  $VO_{2max}$ , mode A appeared to be the optimal HIIE session for these coronary patients.

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### Introduction

Physical activity is a recognized non-pharmacological intervention recommended for both the primary and secondary prevention of coronary heart disease (CHD) (Fletcher et al. 2001). Current guidelines encourage the participation in moderate- to vigorous-intensity aerobic exercise of 20- to 30-min duration on most, and preferably all, days of the week to promote or maintain health (Balady et al. 2007; Giannuzzi et al. 2003; Haskell et al. 2007). If the benefits of exercise-based cardiac rehabilitation are now undeniable (Taylor et al. 2004), the question of the form of exercise that should be prescribed to CHD patients is still unresolved. In the meta-analysis by Taylor et al. (2004) which showed the benefits of exercise-based rehabilitation

on mortality in CHD patients, most of the included randomized trials used moderate-intensity continuous training (MCT) ranging from 40 to 80% of maximal oxygen uptake ( $VO_{2max}$ ). High-intensity interval training (HIT), which involves repeated 30–300-s bouts of aerobic exercise at an intensity ranging from 85 to 100% of  $VO_{2max}$  interspersed by recovery periods of equal or shorter duration (Daniels and Scardina 1984), is another form of exercise that is only occasionally used in rehabilitation programs. Although first described in the 1950s as a mode of training by the German cardiologist Hans Reindell (Reindell and Roskamm 1959), HIT has largely been used by elite athletes for training purposes (Billat 2001). Only recently has HIT been studied as a potential mode of cardiac rehabilitation (Rognmo et al. 2004; Warburton et al. 2005; Wisloff et al. 2007). In the only two studies performed in CHD patients, interval training was shown to be superior to MCT for improving  $VO_{2max}$  (Rognmo et al. 2004; Warburton et al. 2005). According to Wenger and Bell (1986), HIT protocols should be designed to allow the maintenance of a high percentage of  $VO_2$  for a long duration in order to improve aerobic power. In this regard, the HIT protocols used in previous studies suffered from several limitations. First, the acute cardiopulmonary responses of these protocols were not studied prior to their implementation into training programs. In healthy subjects, manipulating exercise/recovery intensity has been shown to alter time to exhaustion and time spent at a high percentage of  $VO_2$  independently of bout duration (Billat 2001; Dupont et al. 2003a; Thevenet et al. 2007). In the absence of this specific information, it is difficult to determine whether the HIT protocols used by Rognmo et al. (2004), Warburton et al. (2005), and Wisloff et al. (2007) induced a cardiovascular response that was optimal for improving  $VO_{2max}$ . Second, it is now accepted that prescribing and monitoring exercise intensity with heart rate, as done by Warburton et al. (2005) and Wisloff et al. (2007) is imprecise. In fact, manipulating walking or running velocity to maintain heart rate in the target zone may lead to a decreased  $VO_2$  as a result of cardiovascular drift (Fritzsche et al. 1999). Furthermore, heart rate generally begins to plateau at approximately 85–90% of  $VO_{2max}$  while metabolic work can still increase with increasing exercise intensity (Davies 1968). The overshoot concerning heart rate response that is occasionally observed at the end of a short high intensity exercise period may also result in the imprecise estimation of energy expenditure. Finally, the difficulty of the interval training protocols proposed in these studies (i.e. 2–4 min of exercise at approximately 90% of peak heart rate, interspersed by 2–3 min of recovery at approximately 70% of peak heart rate) could represent a significant challenge to patients with respect to heart rate monitoring, which might lead to difficulties with long-term adherence to exercise training.

In summary, the interval training protocols used in prior studies suffered from several limitations, including (1) use of arbitrary protocols without knowledge regarding the acute cardiopulmonary responses elicited, (2) long exercise intervals which could be difficult or unsafe for certain individuals leading to non-compliance with the training protocol, and (3) use of percentage of heart rate reserve or percentage of  $VO_{2max}$  for prescription of exercise intensity. The objective of the present study was therefore to compare four different single bouts of high intensity interval exercise (HIIE) which differed in duration of exercise and recovery periods (15 vs. 60-s intervals) and type of recovery (active vs passive), in order to identify the most optimal protocol with respect to time to exhaustion, time spent near  $VO_{2max}$ , patient comfort and safety in a stable CHD sample. As suggested by data in healthy individuals (Dupont and Berthoin 2004; Dupont et al. 2002), we hypothesized that a HIIE protocol with short exercise intervals and passive recovery periods would result in a longer time to exhaustion, without altering the time spent at high percentage of  $VO_{2max}$ .

## Materials and methods

### Participants

Twenty patients with stable CHD providing written informed consent were recruited at the cardiovascular prevention centre of the Montreal Heart Institute. Inclusion criteria were a history of  $\geq 70\%$  arterial diameter narrowing of at least one major coronary artery and/or documented prior myocardial infarction and or/perfusion defect on Sesta MIBI exercise testing. Exclusion criteria were recent acute coronary syndrome ( $\leq 3$  months), significant resting ECG abnormality, history of ventricular arrhythmias or congestive heart failure, uncontrolled hypertension, recent bypass surgery intervention  $< 3$  months, recent percutaneous transluminal coronary angioplasty  $< 6$  months, left ventricular ejection fraction  $\leq 45\%$ , pacemaker or implantable cardioverter defibrillator, recent modification of medication  $< 2$  weeks, and musculoskeletal conditions making exercise on ergocycle difficult or contra-indicated. Demographic and characteristics are presented in Table 1. The protocol was reviewed and approved by the local Research Ethics Board.

### Experimental design

Subjects underwent a complete medical evaluation which included measurement of height, body mass, body composition and resting ECG. Subsequently, all subjects performed a maximal continuous graded exercise test, followed by four, randomly-ordered, single HIIE sessions. Training sessions were separated by  $\geq 72$  h, and were

**Table 1** Patient characteristics and medication use

Anthropometrics	
Age (years)	65 ± 8
Men	17 (89%)
Body mass index (kg/m <sup>2</sup> )	28 ± 4
Waist circumference (cm)	97 ± 12
Body fat (%)	27 ± 8
Risk factors	
Diabetes mellitus	4 (21%)
Hypertension	7 (36%)
Dyslipidemia	13 (68%)
Smoking	0 (0%)
Medical history	
Symptoms of angina pectoris	3 (16%)
Myocardial ischemia	4 (21%)
Ejection fraction (%)	59 ± 6
Previous myocardial infarction	11 (58%)
PCI	8 (42%)
CABG	5 (26%)
Medications	
Anti platelet agents	18 (95%)
Betablockers	12 (63%)
Calcium channel blockers	3 (16%)
ACE inhibitors	4 (21%)
Angiotensin receptor antagonist	8 (42%)
Statins	15 (79%)
Nitrates	2 (10%)

Results are reported as mean ± SD or row value (% of the sample)

PCI percutaneous coronary intervention, CABG coronary artery bypass grafting surgery, ACE angiotensin-converting enzyme

conducted over a 3-week period. Participants were asked to arrive fully hydrated to the laboratory, at least 3 h after their last meal. No attempt was made to control meal size or content. All sessions were supervised by an exercise physiologist, a nurse, and a cardiologist.

## Exercise testing

### Ergometer

This test was performed on an electro-mechanically braked bicycle ergometer (Ergoline 800S, Bitz, Germany). Cycling position, which is known to affect energy expenditure, was standardized by adopting a top bar position. Saddle height was adjusted according to the participant's inseam leg length, as measured from the point of the pubic symphysis palpation to the floor. Toe-clips were used and participants were instructed to stay seated during the test. Subjects were required to maintain a constant pedal cadency between 60 and 80 revolutions per minute.

### Maximal continuous graded exercise test

The test began immediately after a 3-min warm-up phase at 20 W. Initial workload was set at 60 W and increased by 15 W every minute until exhaustion. Strong verbal encouragement was given throughout the test. The power of the last completed stage was considered as the maximal aerobic power (MAP). Oxygen uptake ( $\dot{V}O_2$ ) was determined continuously on a breath-by-breath basis using an automated cardiopulmonary exercise system (Oxycon Alpha, Jaeger, Germany). Gas analyzers were calibrated before each test, using a gas mixture of known concentration (15% O<sub>2</sub> and 5% CO<sub>2</sub>) and ambient air. Participants breathed through a facemask attached to a one-way valve with low resistance and small dead space. The turbine was calibrated before each test using a 3-l syringe at several flow rates. Electrocardiographic activity was monitored continuously using a 12-lead ECG (Marquette, Missouri) and blood pressure was measured manually every 2 min using a sphygmomanometer.

### HIIE sessions

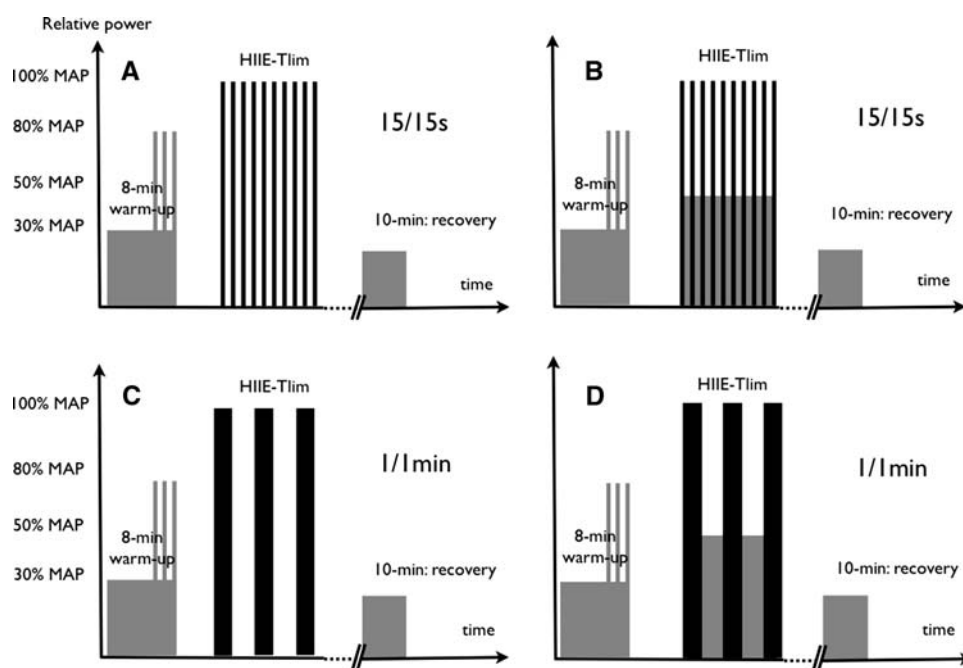
Each HIIE session was preceded by a standardized warm-up consisting of a 5-min bout at 50% of MAP followed by a set of three 10-s bouts at 80% of MAP interspersed by 1 min of active recovery at 50% of MAP. A 5-min passive recovery phase separated the warm-up from the HIIE session. After each HIIE session, a 3-min active recovery phase (30 W) was employed to prevent vagal reactions, followed by a 7-min passive recovery phase with patients seated on a chair, during which time blood pressure was measured at 2-min intervals and ECG monitored continuously. The characteristics of each HIIE session are presented in Fig. 1 and described in Table 2. Each HIIE session lasted a maximum of 35 min or was terminated prematurely due to patient exhaustion, significant cardiac arrhythmias, or abnormal blood pressure response. Strong verbal encouragement was given throughout the session, as well as feedback on elapsed time. Perceived exertion using the Borg scale (level 6–20) was determined every 3 min.  $\dot{V}O_2$  and related gas exchange measures were determined breath-by-breath using the same automated cardiopulmonary exercise system after calibration of the metabolic cart and turbine.

### Data analysis

#### Determination of maximal oxygen uptake ( $\dot{V}O_{2max}$ )

Mean values of  $\dot{V}O_2$  were displayed every 15 s during the test. The primary criterion for the attainment of  $\dot{V}O_{2max}$  was a plateau in  $\dot{V}O_2$  (change < 2.1 ml min<sup>-1</sup> kg<sup>-1</sup>) despite an increase in power output (Duncan et al. 1997). In the

**Fig. 1** Schematic illustration of the four HIIE modes. Each HIIE session was preceded by an 8-min standardized warm-up followed by a 5-min passive recovery. The duration of exercise periods was either 15 s (**a, b**) or 60 s (**c, d**). The recovery (same duration than exercise) was either passive recovery (0% of MAP; **a**) and **(c)** or active (50% of MAP; **b**) and **(d)**. HIIE high intensity interval exercise, MAP maximal aerobic power, Tlim time limit



**Table 2** Descriptive characteristics of each HIIE mode

	A	B	C	D
Phase duration	(15/15 s)	(15/15 s)	(60/60 s)	(60/60 s)
Type of recovery (%)	Passive (0)	Active (50)	Passive (0)	Active (50)
Mean intensity (%)	50	75	50	75
Amplitude (%)	200	67	200	67
Ratio	1:1	1:1	1:1	1:1

Mean intensity represents the average power output. The ratio is the ratio between exercise and recovery phase duration. Amplitude is the difference between exercise and recovery intensities, expressed as a percentage of mean intensity (Saltin et al. 1976)

absence of a plateau, attainment of  $VO_{2max}$  was based upon the presence of a respiratory exchange ratio of 1.10 or greater, or the inability to maintain the required pedal cadence (i.e. 60 revolutions per minute).

#### Determination of time spent at a high percentage of $VO_2$

Mean values of  $VO_2$  were displayed every 5-s during the HIIE session. Time spent above 80% (T80), 90% (T90) and 95% (T95) of was computed by summing each 5-s block that satisfied the criterion (Dupont et al. 2003b).

#### Statistical analysis

Results are expressed as mean  $\pm$  standard deviation for continuous variables and as frequency (%) for categorical variables. Normal Gaussian distribution of the data was verified by the Shapiro–Wilk test. Since none of the variables met this condition, a non-parametric procedure was used. A Friedman ANOVA by ranks was performed to test

the null hypothesis that there was no difference between HIIE sessions. Multiple comparisons were made with a Wilcoxon matched-pairs test. The proportion of patients completing each 35-min HIIE session was compared using a chi-square test. All analyses were performed using Statistica 6.0 (Statsoft, Tulsa, USA). A  $p$  level  $< 0.05$  was considered statistically significant.

#### Results

One participant did not complete the protocol due to an injury that occurred during a recreational activity. Consequently, his results were withdrawn from the analyses. Two participants had a vagal reaction following HIIE mode C. No patients developed significant ventricular arrhythmias during the maximal exercise test or any of the HIIE sessions. Four subjects presented myocardial ischemia during maximum exercise testing. Three of them presented myocardial ischemia and developed mild angina (maximal

**Table 3** Results from the maximal continuous graded exercise test

$VO_{2max}$ (ml min <sup>-1</sup> kg <sup>-1</sup> )	27.1 ± 6.7
$VO_{2max}$ (ml min <sup>-1</sup> )	2,239 ± 631
Exercise tolerance (METs)	8.2 ± 2
Maximal aerobic power (W)	173 ± 41
Resting heart rate (bpm)	64 ± 10
Maximal heart rate (bpm)	135 ± 21
Heart rate reserve (bpm)	70 ± 24
Heart rate at 1 min recovery (bpm)	113 ± 23
Delta heart rate at 1 min recovery (bpm)	23 ± 13
Resting systolic blood pressure (mmHg)	125 ± 15
Maximal systolic blood pressure (mmHg)	170 ± 22

Results are presented as mean ± SD

intensity 2/10) during the four HIIE sessions. Maximal ST segment depressions were 1.1 ± 0.3, 1.1 ± 0.3, 1.6 ± 0.6, 1.5 ± 0.5 for modes A, B, C, and D, respectively. However, ST-segment depression never exceeded 2 mm, and both anginal symptoms and ST-segment depression would resolve during the passive recovery periods in modes A and C (Table 4).

Cardiopulmonary data from the maximal exercise test are presented in Table 3. The occurrence of the primary criterion for the determination of  $VO_{2max}$  (i.e. the plateau) was 84%. All participants who did not reach a plateau satisfied the secondary criteria (i.e. RER > 1.1 or the inability to maintain pedal cadence). We therefore considered that  $VO_{2max}$  was reached in all participants.

Exercise tolerance in the sample was superior relative to age-based predicted values. Data on time to exhaustion, time spent near  $VO_{2max}$ , and rating of perceived exertion during each of the 4 HIIE sessions are presented in Table 4. Sixty-three percent of participants were able to complete 35-min of exercise in mode A, while only 16, 42, and 0% completed 35-min HIIE sessions in modes B, C and D, respectively (A > B, C and D;  $p < 0.05$ ). A passive recovery phase (modes A and C) resulted in a longer time to

exhaustion compared to an active recovery phase, irrespective of the duration of the exercise and recovery phases (15 or 60 s,  $p < 0.05$ ). Time to exhaustion also tended to be higher with mode A relative to mode C ( $p = 0.06$ ). Despite differences in time to exhaustion between modes, time spent at a high percentage of  $VO_{2max}$  was similar between HIIE modes except for less time spent above 90 and 95% of  $VO_{2max}$  for mode C when compared with modes B and D. We found that 13 (68%), 17 (89%), 15 (79%), and 14 (73%) of subjects reached  $VO_{2max}$  in mode A, B, C, and D. Finally, 18 participants rated mode A as their preferred one, which was also considered to be the least difficult (RPE presented in Table 4,  $p < 0.05$ ). This observation is not based on objective measurement of these parameters, but on indirect indices such as RPE and the open question. The  $VO_2$  responses of one participant to the four HIIE sessions are presented in Fig. 2.

## Discussion

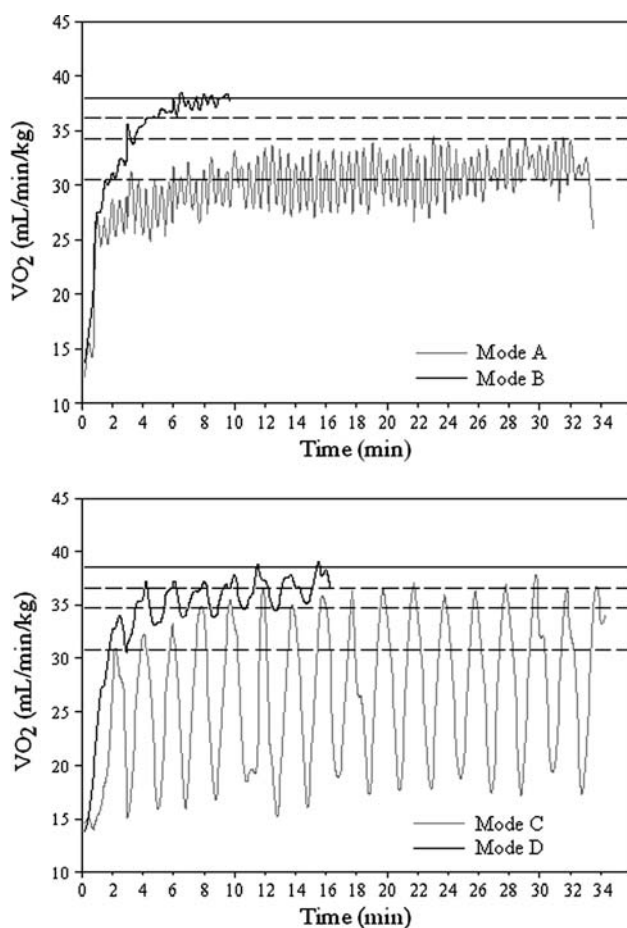
The purpose of this study was to compare the time to exhaustion, the time spent at a high percentage of  $VO_2$ , patient comfort and adherence, and safety of four different single HIIE sessions in order to identify the optimal HIIE session to be incorporated in future HIT training studies in fit patients with stable CHD. Our findings indicate that mode A, consisting of 15-s phases of exercise and recovery, and a passive recovery period, was the optimal mode among the four tested. Time to exhaustion was longest, patient comfort was maximized, and the time spent near  $VO_{2max}$  was also similar to modes using longer (60-s) intervals or an active (50% MAP) recovery phase. Finally, all four modes were considered safe.

To the best of our knowledge, this is the first study in CHD patients to use a HIIE session in which exercise periods were prescribed at 100% of MAP. As a consequence, certain patients necessarily performed exercise at or above their ischemic threshold. Current guidelines arbitrarily

**Table 4** Acute responses to the 4 HIIE modes

	A	B	C	D
Time to exhaustion (s)	1,724 ± 482 <sup>§</sup>	733 ± 490*	1,525 ± 533 <sup>§</sup>	836 ± 505*
Time above 95% $VO_{2max}$ (s)	274 ± 410	337 ± 319	223 ± 258 <sup>§</sup>	307 ± 309
Time above 90% $VO_{2max}$ (s)	433 ± 486	441 ± 335	329 ± 308 <sup>§</sup>	429 ± 336
Time above 80% $VO_{2max}$ (s)	819 ± 578	635 ± 443	585 ± 370	654 ± 366
Rating perceived exertion at the end of sessions	15 ± 2*	17 ± 2	17 ± 2	18 ± 0.6
Angina (%)	3 (16)	3 (16)	3 (16)	3 (16)
ST-depression (%)	3 (16)	3 (16)	3 (16)	3 (16)
n at 35 min	12 (63)*	3 (16)	8 (42)	0

<sup>§</sup> Significantly different from B and D ( $p < 0.05$ ); \*Significantly different from all others ( $p < 0.05$ )



**Fig. 2** Typical  $\text{VO}_2$  response of a participant during each HIIE mode. The solid line represents  $\text{VO}_{2\text{max}}$  and dashed lines represent 80, 90, and 95% of  $\text{VO}_{2\text{max}}$

recommend a training intensity at 10 bpm below the ischemic threshold (Gibbons et al. 1999). Despite this fact, no patients in our study experienced significant ventricular arrhythmias or abnormal blood pressure responses. As noted previously, three subjects developed myocardial ischemia and mild angina (maximal intensity 2/10) during the four HIIE sessions. However, both ST-segment depression and angina would disappear during the passive recovery periods in modes A and C, and ST-segment depression never exceeded 2 mm during any test. Importantly, two recent studies showed that continuous training above the ischemic threshold is safe and well tolerated without evidence of myocardial damage, significant arrhythmias, or left ventricular dysfunction (Juneau et al. 2008; Noel et al. 2007). In theory, HIIE could be safer than continuous aerobic training above the ischemic threshold, resulting in intermittent rather than prolonged periods of ischemia. Furthermore, intermittent periods of ischemia might lead to ischemic preconditioning as is witnessed during warm-up angina (Tomai 2002; Tomai et al. 1996). Brief, repetitive episodes of ischemia have also

been shown to promote collateral formation in animals (Duncker and Bache 2008).

In accordance with our hypothesis, passive recovery (modes A and C) resulted in a longer time to exhaustion than active recovery (modes B and D). This effect was independent of exercise duration (i.e. 15 or 60 s), although mode A tended to be associated with a longer time to exhaustion compared with mode C ( $p = 0.06$ ). Dupont et al. (2003a) measured the time to exhaustion of a HIIE session involving intermittent runs of 15 s at 120% of maximal aerobic speed (MAS), interspersed with 15 s of either active (50% MAS) or passive (0% MAS) recovery. They found a longer time to exhaustion when recovery was passive ( $745 \pm 171$  vs.  $445 \pm 79$  s,  $p < 0.001$ ). Thevenet et al. (2007) reported similar results following a HIIE session involving intermittent runs of 30 s at 105% of MAS interspersed with 30 s of either active (50% MAS) or passive (0% MAS) recovery ( $2,145 \pm 829$  vs.  $1,072 \pm 388$  s,  $p < 0.01$ ). Our results are therefore in agreement with the existing literature on healthy subjects. Among the factors that have been proposed to explain this phenomenon is the phosphocreatine (PCr) hypothesis. Dupont et al. (2004) assessed  $\text{HbO}_2$  changes in the vastus lateralis muscle of healthy subjects during a HIIE session similar to the one used in their 2003 protocol (Dupont et al. 2003a). They observed a lower decline in  $\text{HbO}_2$  during passive recovery, suggesting a higher oxygen saturation of myoglobin and hemoglobin. Since the re-synthesis of PCr is dependent on oxygen availability during rest periods of intermittent exercise (Haseler et al. 1999), it would be expected that its rate of recovery would differ between interval training protocols using active or passive recovery periods. This hypothesis is supported by the work of Yoshida et al. (1996). These authors measured PCr kinetics with  $^{31}\text{P}$ -nuclear magnetic resonance spectroscopy during the recovery from a high-intensity exercise, and reported a higher rate of re-synthesis of PCr during passive recovery relative to active recovery (Yoshida et al. 1996).

Despite a longer time to exhaustion in modes A and C, we found no major difference in the time spent at a high percentage of  $\text{VO}_2$ . The single difference that was evident was a shorter time spent above 90 and 95% of  $\text{VO}_{2\text{max}}$  during mode C, which can be explained by a larger  $\text{VO}_2$  decline during the longer recovery period (Fig. 2). Consistent with the findings of Dupont and Berthoin (2004), time spent near  $\text{VO}_{2\text{max}}$  was longer using an active recovery phase (i.e. modes B and D) when normalized for time to exhaustion. In other words, use of a passive recovery phase prevents the maintenance of  $\text{VO}_2$  near  $\text{VO}_{2\text{max}}$  during each bout of exercise because of a lower  $\text{VO}_2$  at the beginning of each subsequent exercise phase. However, the time to exhaustion is long enough to compensate for this phenomenon in mode A, but not in mode C. This nuance has

important practical implications. If we accept the premise that the time spent near  $VO_{2max}$  is one of the main stimuli for improving  $VO_{2max}$ , then the number of repetitions during a HIIE session should always be adjusted to the type of recovery (active or passive).

The primary aim of this study was to develop a HIIE model on the basis of its metabolic demands, in an effort to maximize cardiovascular and other potential health benefits. According to our results, HIIE modes A, B, and D were physiologically similar. Importantly, however, a majority of patients rated mode A as the easiest and most preferred despite a longer time to exhaustion. Since the metabolic demands imposed by mode A were equivalent to those of modes B and D, provided the number of repetitions is sufficient, we conclude that mode A represents the best compromise between physiological and psychological considerations.

Limitations of the current study include the small, predominantly male, sample. However, we have no reason to believe that our results would have differed in women. In addition, the sample was selected among a cohort of CHD patients who are followed closely and perform exercise on a regular basis. We did not measure troponin T levels following HIIE sessions to exclude any myocardial injury; however, once again, all training sessions were very well tolerated and free of severe, prolonged ischemia or significant ventricular arrhythmias. Furthermore, as mentioned previously, continuous aerobic exercise training above the ischemic threshold has been shown to be safe according to two recent studies (Juneau et al. 2008; Noel et al. 2007).

## Conclusion

We conclude that a HIIE session employing exercise phases at 100% MAP is feasible and appears safe in stable, fit, well-selected CHD patients. A passive recovery period provides for significantly longer total exercise duration prior to reaching exhaustion (modes A and C). Mode A with 15-s exercise and recovery phases, and passive recovery, represents a balance between patient comfort and safety on the one hand, and maintenance of  $VO_2$  near  $VO_{2max}$  during the recovery phase on the other hand, yet still providing a metabolic expenditure similar to that observed with HIIE modes using active recovery periods. Future studies in this domain will require ensuring the safety of our optimized HIIE mode in a larger CHD sample, not to mention comparative studies with continuous aerobic training, studying various biological and physiological parameters influenced by exercise that also impact on prognosis.

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**Conflict of interest statement** None.

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