`Research article`

Acute Physiological Responses to Short- and Long-Stage High-Intensity Interval Exercise in Cardiac Rehabilitation: A Pilot Study

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Abstract

Despite described benefits of aerobic high-intensity interval exercise (HIIE), the acute responses during different HIIE modes and associated health risks have only been sparsely discovered in heart disease patients. Therefore, the aim of this study was to investigate the acute responses for physiological parameters, cardiovascular and inflammatory biomarkers, and catecholamines yielded by two different aerobic HIIE protocols compared to continuous exercise (CE) in phase III cardiac rehabilitation. Eight cardiac patients (7 with coronary heart disease, 1 with myocarditis; 7 males, 1 female; age: 63.0 ± 9.4 years; height: 1.74 ± 0.05 m; weight: 83.6 ± 8.7 kg), all but one treated with ß-blocking agents, performed a maximal symptom-limited incremental exercise test (IET) and three different exercise tests matched for mean load (P_{mean}) and total duration: 1) short HIIE with a peak workload duration (t_{peak}) of 20 s and a peak workload (P_{peak}) equal to the maximum power output (P_{max}) from IET; 2) long HIIE with a t_{peak} of 4 min, P_{peak} was corresponding to the power output at 85 % of maximal heart rate (HR_{max}) from IET; 3) CE with a target workload equal to P_{mean} of both HIIE modes. Acute metabolic and peak cardiorespiratory responses were significantly higher during long HIIE compared to short HIIE and CE ($p < 0.05$) except HR_{peak} which tended to be higher in long HIIE than in short HIIE ($p = 0.08$). Between short HIIE and CE, no significant difference was found for any parameter. Acute responses of cardiovascular and inflammatory biomarkers and catecholamines didn't show any significant difference between tests ($p > 0.05$). All health-related variables remained in a normal range in any test except NT-proBNP, which was already elevated at baseline. Despite a high P_{peak} particularly in short HIIE, both HIIE modes were as safe and as well tolerated as moderate CE in cardiac patients by using our methodological approach.

Key words: intermittent exercise, exercise prescription, acute effects, health-related markers, heart disease patients.

Introduction

Exercise training is accepted as a fundamental non-pharmacological intervention strategy in cardiac rehabilitation (Normandin et al., 2013). For training therapy, extensive research looking at the individual dose-effect relationship should be standard practice as it is for pharmacological interventions (Church and Blair, 2009). The participation of vigorous-intensity aerobic exercise (Haskell et al., 2007) as well as high- to severe-intensity aerobic interval exercise (Mezzani et al., 2012) is encouraged by current guidelines and recommendations. The various beneficial effects yielded by aerobic high-intensity interval training in heart disease patients are well documented (Juneau et al., 2014; Warburton et al., 2005). In particular, maximal oxygen uptake (VO_{2max}), which has been noted as the best single predictor of death among cardiac patients (Kavanagh et al., 2002), was found to be improved through high-intensity interval exercise (HIIE). These improvements were observed to be similar (Conraads et al., 2015) or even greater compared to moderate continuous exercise training (Arena et al., 2013; Haykowsky et al., 2013; Wisloff et al., 2007). Therefore, aerobic high-intensity interval training has been reported to be an effective alternate to conventional continuous endurance training in cardiac rehabilitation (Gibala et al., 2012; Guiraud et al., 2012).

However, since the peak workload in aerobic HIIE is usually higher than in moderate continuous exercise (moderate CE), the acute physiological responses and, consequently, the potential risk of adverse events, may be increased during HIIE (Arena et al., 2013; Rognmo et al., 2012; Keteyian, 2012; Thompson et al., 2007). Though Rognmo et al. (2012) found low event rates during both moderate CE (1 event per 129456 exercise hours) and HIIE (1 event per 23182 exercise hours), Keteyian (2012) argued that an exploratory interpretation of these data might be that moderate CE is safer than HIIE. As emphasized by Arena et al. (2013) and our own working group (Tschakert and Hofmann, 2013), both the adverse event risk and the achieved beneficial effects may vary between different HIIE protocols (Mezzani et al., 2012). More precisely, health risks and training adaptations are caused by the acute physiological responses yielded by particular interval protocols depending on the setting of the single HIIE determinants (intensity and duration of the peak workload and recovery phases and the resulting mean load, respectively). Therefore, it is highly relevant to discover which HIIE prescription is most suitable for cardiac patients with respect to both safety and efficiency (Arena et al., 2013; Gibala et al., 2012).

With respect to the particular setting of HIIE, the

fundamental findings of Astrand et al. (1960) and Saltin et al. (1976) revealed that a great amount of work at high intensities can be obtained with clear submaximal circulatory and respiratory load by an appropriate application of short work periods. These findings were supported by recent investigations in healthy individuals (Tschakert et al., 2015) and patients with type 1 diabetes mellitus (Moser et al., 2015).

The number of studies investigating the acute response to aerobic HIIE in cardiac patients, however, is rather small. The impact of different HIIE protocols on the acute physiological response was investigated in chronic heart failure (CHF) patients (Meyer et al., 1996; 2012) and in subjects with stable coronary heart disease (CHD) (Guiraud et al., 2010). Meyer et al. (1996) did not find essential differences in the acute metabolic, cardiac, and hormonal response between the HIIE modes, whereas Guiraud et al. (2010) and Meyer et al. (2012) found short HIIE to be more effective with respect to the time to exhaustion, the time spent near VO_{2max}, and rating of perceived exertion (RPE) compared to long intervals. Cardiac risk markers such as cardiac troponin T (cTnT) and creatine phosphokinase MB (CK MB) which are biomarkers of cardiac injury, and B-type natriuretic peptide (NT-proBNP), a marker for cardiomyocyte stress (heart failure), as well as Lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$), a platelet-activating factor, were not measured.

Few studies have investigated the acute physiological response yielded by certain HIIE protocols compared to CE in cardiac patients. No significantly different response for cardiac biomarkers (Benda et al., 2015; Normandin et al., 2013), endothelial microparticles (Guiraud et al., 2012; 2013), hemodynamic markers and arteriovenous O_2-difference (Gayda et al., 2012; Meyer et al., 1998), respiratory markers (Normandin et al., 2013), C-reactive protein (Normandin et al., 2013), and RPE (Normandin et al., 2013) were observed between HIIE and CE, despite markedly higher peak intensities in HIIE. In these studies, HIIE and CE were isocaloric (Benda et al., 2015; Guiraud et al., 2012; 2013; Normandin et al., 2013) or matched for mean load (Meyer et al., 1998). However, no HIIE protocols with peak workload durations longer than 1 min were applied in these investigations. Meyer et al. (2012) used longer peak workload durations of 90 s for intermittent exercise but did not compare HIIE vs. CE.

The question arises which HIIE protocol is most convenient for cardiac patients. Guiraud et al. (2010) and Meyer et al. (2012) suggested HIIE protocols with short t_{peak} and passive recovery to be more convenient than HIIE with long t_{peak} and active recovery. Benda et al. (2015) and Guiraud et al. (2011, 2012) suggested highly intense exercise stimuli to the peripheral muscles without great cardiovascular stress to be possible by using intermittent exercise with short bouts of work followed by short recovery periods. In line with that, Meyer et al. (2012) and Conraads et al. (2015) suggested long intervals, such as the 4 x 4 min model, to be problematic since patients can hardly sustain 4 min intervals at high intensities. In contrast, Arena et al. (2013) favors HIIE with long t_{peak} similar to the "Norwegian" model which is frequently

applied in scientific studies and practice in patients suffering from different chronic diseases (Helgerud et al., 2010; Rognmo et al., 2004; Tjonna et al., 2008; Wisloff et al., 2007). However, as emphasized by Normandin et al. (2013), the acute physiological responses to the 4 x 4 interval mode, or to similar HIIE protocols applying a longer t_{peak} (Warburton et al., 2005), were not published.

Therefore, the aim of our study was to investigate the acute response for metabolic, cardiorespiratory, and plasma parameters such as cardiovascular and inflammatory markers and catecholamines, in patients undergoing phase III cardiac rehabilitation. The test protocols which were applied in the study included short (20 s) and long (4 min) HIIE and moderate CE matched for mean load and total duration.

We hypothesized that during short HIIE, mean and peak values for lactate (La) as well as peak values for heart rate (HR) and oxygen uptake (VO_2) will be similar to CE but significantly lower compared to long HIIE despite a markedly higher P_{peak} in short HIIE. However, we hypothesized that the exercise-induced changes in the concentration of cardiovascular biomarkers, catecholamines, and inflammatory markers will not significantly differ between CE, short HIIE, and long HIIE, indicating that all three exercise tests can be performed safely.

Table 1. Baseline clinical characteristics and medication (n = 8). Results are presented as row values (% of the sample).

Cardiac etiology	
CHD	7 (87.5 %)
Bypass	1 (12.5 %)
PCI	3 (37.5 %)
Myocardial infarction	1 (12.5 %)
Myocarditis	1 (12.5 %)
Medication	
Beta blocker	7 (87.5 %)
ACE inhibitors	7 (87.5 %)
Statins	6 (75 %)
Anti platelet agents	7 (87.5 %)
Proton pump inhibitors	7 (87.5 %)

CHD, coronary heart disease; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme.

Methods

Eight patients undergoing phase III cardiac rehabilitation (7 males, 1 female; age: 63.0 ± 9.4 years; height: 1.74 ± 0.05 m; weight: 83.6 ± 8.7 kg; VO_{2max}: 21.6 ± 7.6 ml·kg^{-1}·min^{-1}) participated in this study. Preceding coronary incidences (> 8 weeks) included coronary heart disease (CHD; n = 7) and myocarditis without CHD (n = 1). Left ventricular ejection fraction (LVEF) was ≥ 45 % in all subjects. Seven of eight patients were treated with ß-blocking agents during the study (Table 1). The experimental protocol was approved by the ethics commission of the Medical University of Graz, Austria (EK decision number 23-397 ex 10/11). The test design, and potentially associated health risks, were explained to all subjects who gave their written informed consent before participating in the study. They were familiar with the cycle ergometer exercise in the cardiac rehabilitation center (ZARG, Graz, Austria) where all tests were performed within the rehabilitation program under medical supervision.

Experimental design

At the beginning of the study, the subjects performed a maximal symptom-limited incremental exercise test (IET) in order to assess the maximum aerobic power output (P_{max}), VO_{2max}, and maximum heart rate (HR_{max}), as well as the first and second lactate turn point (LTP_1, LTP_2) referring to the three phase model of metabolism (Hofmann and Tschakert, 2011) and to the Lactate Shuttle Theory by Brooks (Brooks, 2009). LTP_1 and LTP_2 were accordant with the first (VT_1) and second ventilatory threshold (VT_2) and were used for exercise intensity prescription for HIIE and CE.

Then, the participants performed three specific exercise tests: short HIIE (A), long HIIE (B), and CE (C). Importantly, all exercise tests were matched for mean load (P_{mean}) and total exercise duration. The testing sessions were randomly assigned and interspersed by at least 2 days.

Incremental Exercise Test (IET)

The IET started with a resting period of 1 min (0 W) and a subsequent warm-up phase at 10 Watt (W) also for 1 min. Then, the power output was increased by 10 W per minute until (symptom-limited) exhaustion according to the standard protocol of the Austrian Society of Cardiology (Wonisch et al., 2008). A 3 min cool-down period at 10 W finalized the IET.

LTP_1 and LTP_2 were determined by means of computer-aided linear regression break point analysis. LTP_1 was defined as the first increase of La above baseline level, and LTP_2 was defined as the second abrupt increase of La between LTP_1 and P_{max}.

Short and long High-Intensity Interval Exercise (HIIE) and Continuous Exercise (CE)

After the IET, the participants performed three specific exercise tests (short HIIE, long HIIE, and CE) in randomized order. For each of these exercise tests, the periods for rest (0 W for 3 min), warm-up (consisting of 3 workload steps of 1 min each with increasing intensity until P_{LTP2} was reached), and cool-down (5 min passive recovery, 0 W) were the same. The specific exercise protocols were matched for mean load, which was purposefully set at 80 % of the power output at LTP_2, and for total exercise duration (28 min). The other exercise components were prescribed as follows (Figure 1): A) short HIIE with a t_{peak} of 20 sec, a P_{peak} at 100 % of P_{max} from IET, a recovery workload (P_{rec}) 10 % below the power output at LTP_1, and a calculated recovery duration (t_{rec}) (39 ± 6 s); B) long HIIE (according to Wisloff et al. (2007) but modified) with a t_{peak} of 4 min, a P_{peak} corresponding to the power output at 85 % of HR_{max} (74 % of P_{max}) from IET, a t_{rec} of 3 min, and a calculated P_{rec} (95 $\pm$ 20 % of P_{LTP1}); and C) CE with a target workload equal to P_{mean} of both HIIE protocols (80 % of P_{LTP2} equating to 57 % of P_{max} from IET). The participants were permitted to cycle at a cadence of 70 - 90 revolutions per minute (rpm), and each subject completed all tests with the same rpm.

The equation $P_{mean} = (P_{peak} \cdot t_{peak} + P_{rec} \cdot t_{rec}) / (t_{peak} + t_{rec})$ (Tschakert and Hofmann, 2013) was used and transformed in order to calculate t_{rec} for short HIIE and P_{rec} for long HIIE.

Measurements

An electrocardiogram (Cardiosoft v6.51 GE Healthcare, GE Healthcare, UK) was obtained from each subject during all tests and supervised by an experienced physician. Pulmonary gas-exchange variables were collected continuously during all tests by breath-by-breath measurement and were averaged over 5 s periods (MetaMax 3B, Cortex, Germany). The maximum oxygen uptake (VO_{2max}) was defined as the highest mean value for VO_2 over 30 s. Heart rate data, averaged over 5 s periods, were also obtained during all tests via chest belt telemetry (PE 4000, Polar Electro, Kempele, Finland). Blood lactate concentrations were obtained from capillary blood samples taken from ear lobes during all tests. For IET, capillary blood samples were taken at the end of rest and warm-up, at the end of each workload step, and at the end of the cool-down period. For each of the three exercise tests, capillary blood samples were taken at rest and at the end of the warm-up phase, after 4, 7, 11, 14, 18, 21, 25, and 28 min of the specific exercise protocol, and after the 5 min cool-down phase.

Venous blood withdrawal from the cubital vein was done before each test and directly after the specific exercise protocol. The blood samples were collected in specific blood tubes and centrifuged (~3000 rpm, 10 min) to separate the plasma, which was immediately frozen in aliquots at -80° C for longer storage and subsequent analysis.
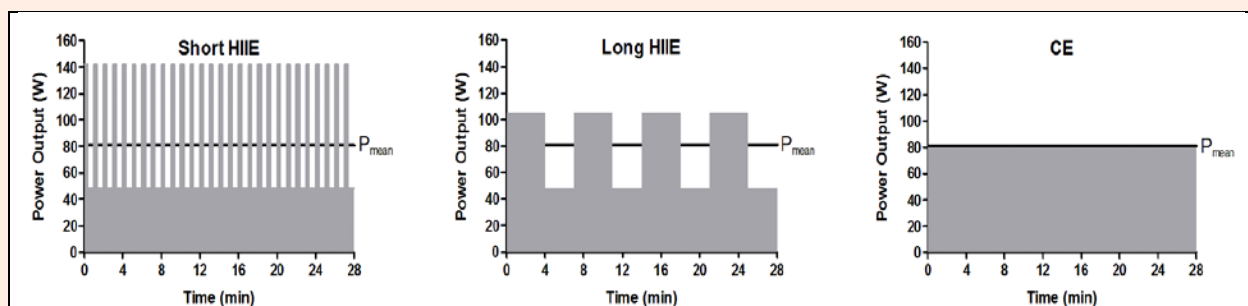
Figure 1. Prescription of the three specific exercise protocols (short HIIE, long HIIE, and CE) matched for mean load and exercise duration. Consequently, the total work performed during the 28 min (dark area) was also equal between tests, but P_{peak} was markedly higher in short HIIE. HIIE, high-intensity interval exercise; CE, continuous exercise.

Data analysis procedures

The determination of individual turn points during IET (LTP$_1$, LTP$_2$, VT$_1$, VT$_2$) was accomplished by means of a computer-supported linear regression turn point model within defined regions of interest (ROI) (Hofmann and Tschakert, 2011). ROI for LTP$_1$ (and VT$_1$) was between La (and VE) at first workload and La (and VE) at 70 % of P$_{max}$, ROI for LTP$_2$ (and VT$_2$) was between La (and VE) at LTP$_1$ and La (and VE) at P$_{max}$ (Hofmann et al., 2001).

The concentrations of capillary blood lactate were evaluated via the fully enzymatic-amperometric method (Biosen S-line, EKF diagnostics, Barleben, Germany).

Plasma concentrations of the following markers were determined and compared with reference values by the Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz: creatine phosphokinase (CK) was measured enzymatically (Roche Diagnostics, Mannheim, Germany) on a cobas® 8000 modular analyzer from Roche. C-reactive protein (CRP) was measured by immunoturbidimetry (Roche Diagnostics, Mannheim, Germany) on a cobas® 8000 modular analyzer from Roche. N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and interleukin 6 (IL-6) were determined by electrochemiluminescence (Roche Diagnostics, Mannheim, Germany). Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) activity was measured with the PLAC® test (diaDexus Inc., South San Francisco, USA) on an Olympus AU640 (Olympus Diagnostika, Hamburg, Germany). Adiponectin (Immundiagnostik AG, Bensheim, Germany) and leptin (DRG Instruments GmbH, Marburg, Germany) were measured by ELISA according to the manufacturer's instructions. Homoarginine (hArg), asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) were measured by high-performance liquid chromatography (HPLC). The concentrations of free noradrenaline (NA), adrenaline (ADR), and dopamine (DOP) were detected using an amperometrical detector (RECIPE, Munich, Germany) and specialized software (ClarityTM, DataApex, Prague, Czech Republic).

Statistical analysis

All data are presented as mean ± standard deviation (SD) and were analyzed by means of SPSS (IBM SPSS Statistics 23). Normal distribution of variables and variables' paired differences were assessed by the Kolmogorov-Smirnov test.

A one-way ANOVA with repeated measures (within factors) was conducted in order to determine the effects of the different exercise regimes on the acute response of La, HR, and gas exchange variables. When the analysis revealed a significant difference, post-hoc paired t-tests with least significant difference (LSD) were used to locate the origin of the significant difference.

A two-way repeated measures ANOVA design (2x3) was used to test the differences in the increase (or decrease) of plasma parameters during exercise (factor time: pre, post) between the three test protocols (factor test: CE, short HIIE, and long HIIE). The interaction between both factors was taken into account. If an overall significance could be detected for one or both of the factors, post-hoc t-tests with LSD were conducted for clarification. A p-value < 0.05 was considered as significant.

Results

Incremental exercise test

Figure 2 shows the performance curves for lactate and heart rate during the incremental exercise test. The lactate performance curve showed three phases of blood lactate appearance and two corresponding turn points (LTP$_1$, LTP$_2$). The first and second lactate turn point was significantly related to the first (VT$_1$) and second ventilatory threshold (VT$_2$) with no significant difference in power output (LTP$_1$: 51.8 ± 10.4 W; VT$_1$: 52.3 ±13.8 W; LTP$_2$: 101.1 ± 30.1 W; VT$_2$: 99.8 ± 31.2 W).
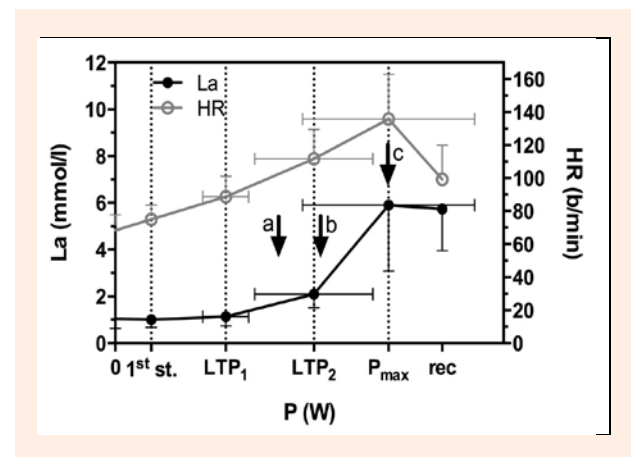
Figure 2. **Performance curves for lactate and heart rate during the incremental exercise test (IET). The three phases of lactate metabolism are separated by the first (LTP$_1$) and second lactate turn point (LTP$_2$). Values are means ± SD. Exercise intensities for both HIIE modes and CE were set with respect to P$_{LTP1}$, P$_{LTP2}$, and P$_{max}$ from IET. Arrow a represents P$_{mean}$ for all three exercise protocols; arrow b represents P$_{peak}$ for long HIIE; arrow c represents P$_{peak}$ for short HIIE.** La, blood lactate; HR, heart rate; 1st st., first workload step; P$_{max}$, maximum power output; rec, recovery.

CE, short HIIE, and long HIIE
*Metabolic and cardiorespiratory parameters:*
All subjects completed each exercise session. As shown in Table 2, mean and peak lactate values were significantly higher during long HIIE than during short HIIE and CE (p < 0.05). A lactate steady state (LaSS) (no La increase higher than 1.0 mmol·l^{-1} for the last 20 min of the specific exercise protocol) was reached in each test (Figure 3A).

In long HIIE, HR$_{peak}$ was significantly higher than in CE (p < 0.05) and tended to be higher than in short HIIE (p = 0.08). HR$_{peak}$ during long HIIE was also markedly higher compared to the heart rate at LTP$_2$ in the IET (111.7 ± 17.7 b/min). Peak VO$_2$ values were significantly higher in long HIIE compared to short HIIE and CE (p < 0.05). As expected, no significant differences for HR$_{mean}$ and VO$_{2mean}$ were found between CE, short HIIE, and long HIIE.

Table 2. Mean and peak values for P, La, HR, and VO_2 during CE, short HIIE (20 s), and long HIIE (4x4 min) compared to the according values at P_{max} or LTP_2 and VT_2 from IET. Values are means (±SD).

Peak values	CE	HIIE 20s	HIIE 4x4min	at P_{max} (IET)	
P (W)	80.9 (24.0)	142.4 (44.9)*	105.3 (51.8)*‡	142.4 (44.9)	
La (mmol·l^{-1})	3.63 (1.73)	3.90 (1.98)	5.54 (2.93)*‡	5.90 (2.82)	
HR (b·/min^{-1})	111.3 (18.0)	116.3 (22.8)	124.0 (24.9)*	135.8 (27.1)	
VO_2 (l·min^{-1})	1.53 (.25)	1.63 (.36)	1.87 (.61)*‡	1.78 (.60)	
Mean values	**CE**	**HIIE 20s**	**HIIE 4x4min**	**at LTP_2 (IET)**	**at VT_2 (IET)**
P (W)	80.9 (24.0)	80.9 (24.0)	80.9 (24.0)	101.1 (30.1)	99.8 (31.2)
La (mmol·l^{-1})	3.20 (1.58)	3.35 (1.74)	4.80 (2.55)*‡	2.39 (.98)	2.34 (1.03)
HR (b·min^{-1})	103.6 (17.2)	106.2 (20.8)	109.1 (20.5)	111.7 (17.8)	110.7 (18.5)
VO_2 (l·min^{-1})	1.40 (.24)	1.46 (.34)	1.48 (.34)	1.36 (.28)	1.36 (.29)

P, power output; La, blood lactate concentration; HR, heart rate; VO_2, oxygen uptake; CE, continuous exercise; HIIE, high-intensity interval exercise; LTP_2, second lactate turn point; VT_2, second ventilatory threshold; P_{max}, maximum power output; IET, incremental exercise test. *, significant difference to CE. ‡, significant difference to short HIIE.
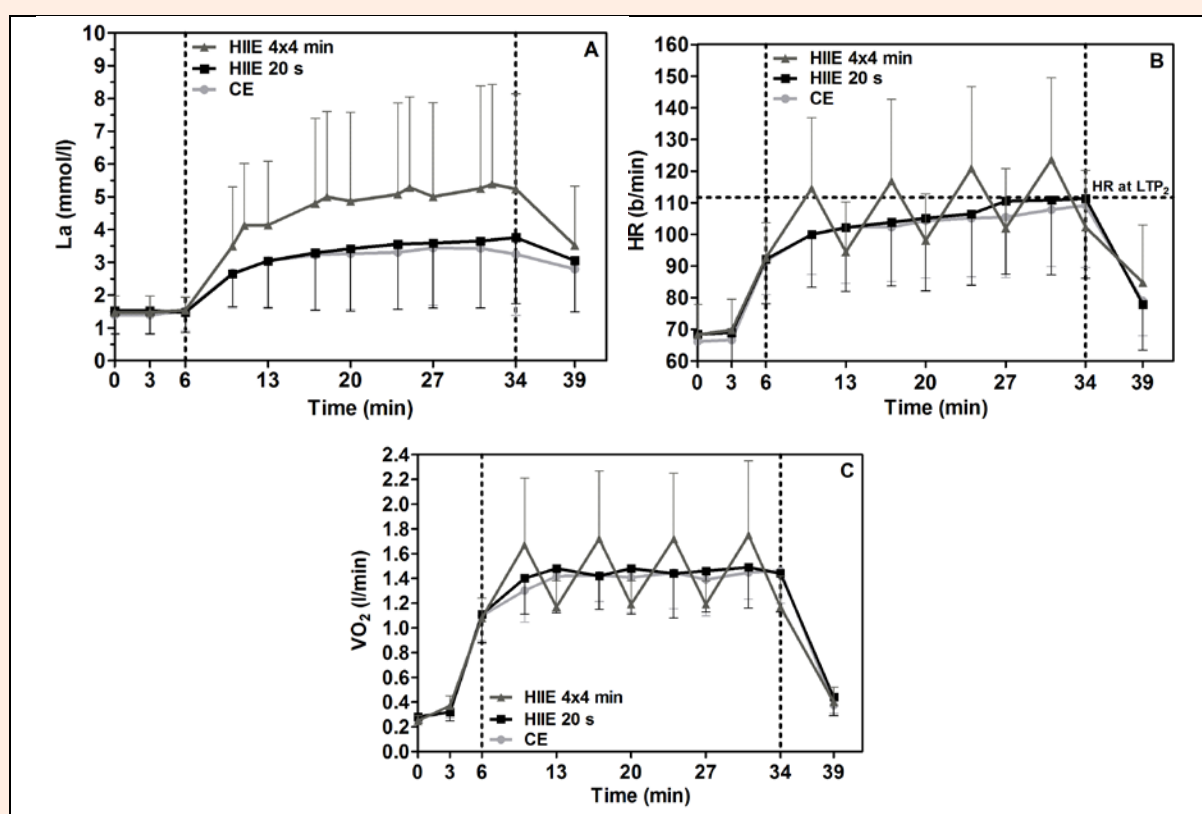
Figure 3. Acute response for La (A), HR (B), and VO_2 (C) to CE, short HIIE, and long HIIE. Values are means ± SD. The specific exercise modes were conducted from min 6 to min 34 after a standardized warm up phase. La, blood lactate; HR, heart rate; VO_2, oxygen uptake; HIIE, high-intensity interval exercise; CE, continuous exercise; LTP_2, second lactate turn point from the incremental exercise test.

Between short HIIE and CE, no significant difference was found for any physiological parameter (Table 2).

Plasma parameters:
Cardiac biomarkers: Between CE, short HIIE, and long HIIE, no significant differences were found in the exercise-induced increase (or decrease) of NT-proBNP, hs-cTnT, CK MB, and Lp-PLA$_2$ (p > 0.05) (Figure 4A-D).

The differences between pre- and post-exercise values for each single exercise protocol are presented in Figure 4A-D.

Catecholamines: The increase (or decrease) of the free catecholamines NA, ADR, and DOP during exercise was not significantly different between CE, short HIIE, and long HIIE (p > 0.05) (Table 3).

Significant differences (p < 0.05) between pre-exercise vs. post-exercise values were found for NA and ADR in all tests (Table 3).

Other plasma parameters: Between CE, short HIIE, and long HIIE, no significant differences were found in the increase (or decrease) of CK, vascular parameters such as ADMA, SDMA, and hArg, both inflammatory markers CRP and IL-6, and leptin (p > 0.05).
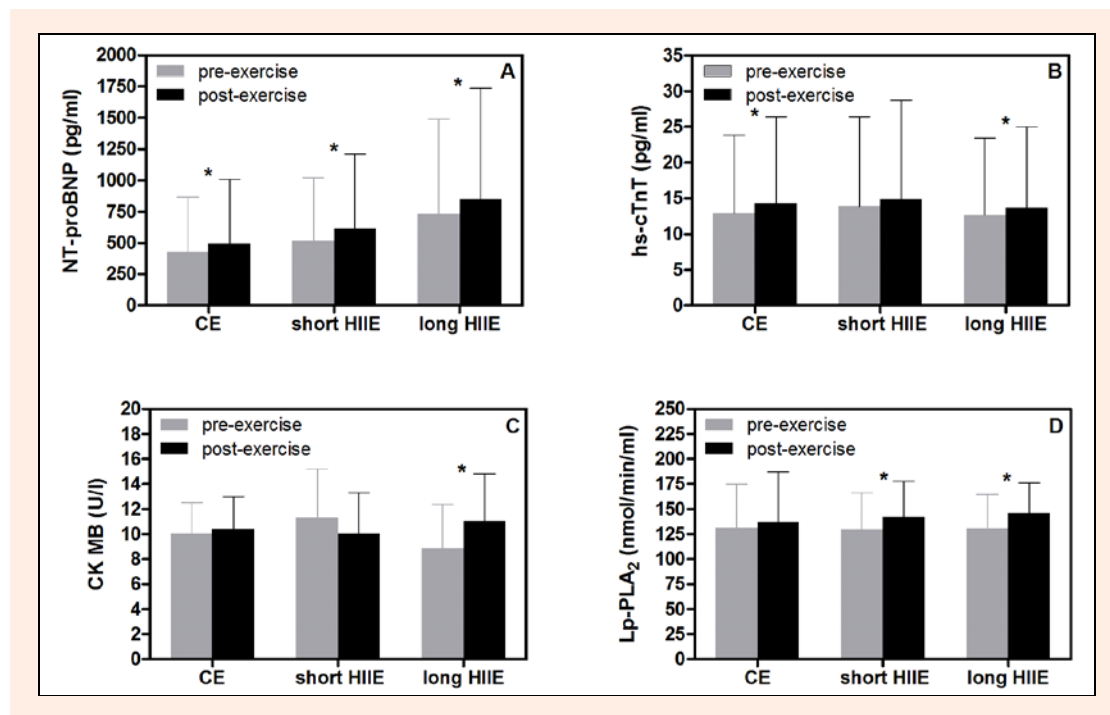
Figure 4. Comparison of baseline vs. post-exercise values of cardiac biomarkers NT-proBNP (A), hs-cTnT (B), CK MB (C), and Lp-PLA$_2$ (D) for CE, short HIIE, and long HIIE. Between test protocols, no significant difference was found for the exercise-induced increase (or decrease, respectively) of cardiac biomarkers. HIIE, high-intensity interval exercise; CE, continuous exercise; NT-proBNP, N-terminal pro B-type natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; CK MB, creatine phosphokinase MB; Lp-PLA$_2$, Lipoprotein-associated phospholipase A$_2$. *, significant difference between pre- vs. post-exercise value (p < 0.05).

Only adiponectin showed a significantly higher increase during short HIIE compared to CE and long HIIE (p < 0.05) (Table 3).

Between pre- and post-exercise values, a significant difference (p < 0.05) in each test was found for CK, CRP, IL-6, and adiponectin (Table 3).

Discussion

In this study, we investigated the acute response for health-related variables such as cardiac biomarkers, inflammatory parameters, and catecholamines induced by moderate CE vs. short and long HIIE in patients with CHD or myocarditis undergoing phase 3 cardiac rehabilitation.

The major finding of our study was that although the acute metabolic and peak-cardiorespiratory responses were higher during long HIIE compared to short HIIE and CE, the exercise-induced increase (or decrease, respectively) of any health-related plasma parameters was not significantly different between the three test protocols, and all exercise modes were performed safely. The methodological approach for exercise prescription may be a critical factor in this population.

Methodological approach

Exercise should be prescribed individually and as accurately as possible. Homogeneous relative exercise stimuli as well as acute physiological responses across subjects should be induced. Therefore, exercise intensities are recommended to be prescribed with respect to objective and individual submaximal (LTP$_1$, LTP$_2$ or VT$_1$, VT$_2$) and maximal markers (P$_{max}$) assessed during an incremental exercise test (Hofmann and Tschakert, 2011; Mezzani et al., 2012). Intensity prescriptions by means of fixed percentages of HR$_{max}$ or VO$_{2max}$ have been shown to result in heterogeneous relative exercise stimuli and, consequently, in a wide range of acute physiological responses across subjects (Mezzani et al., 2012; Scharhag-Rosenberger et al., 2010). In our study, all exercise intensities were prescribed with respect to LTP$_1$, LTP$_2$, or P$_{max}$ except for P$_{peak}$ for long HIIE which was set at the power output at 85 % of HR$_{max}$ according to the original Norwegian 4x4 HIIE mode (Wisloff et al., 2007).

Second, CE and both HIIE protocols were matched for mean load and total duration in our study (Figure 1). This allows a consistent comparison and interpretation of obtained results (Moser et al., 2015; Tschakert and Hofmann, 2013; Tschakert et al., 2015) as it is when isocaloric exercise modes are applied (Benda et al., 2015; Normandin et al., 2013).

Since the mean load determines the average cardiorespiratory response and strongly influences the acute metabolic response as well (Tschakert and Hofmann, 2013; Tschakert et al., 2015), P$_{mean}$ was set consciously in order to allow for better control and regulation of the acute physiological response (Tschakert and Hofmann, 2013). P$_{mean}$ was set moderately (at 80 % of P$_{LTP2}$) to avoid high cardiac and metabolic stress. In the original Norwegian 4x4 min model (Helgerud et al., 2007; Rognmo et al., 2004; Wisloff et al., 2007), the mean load has not been considered.

Table 3. Pre- and post-exercise values for different plasma parameters in CE, short HIIE (20 s), and long HIIE (4x4 min). Values are means (±SD).

Plasma Parameters	CE pre-exercise	CE post-exercise	HIIE 20s pre-exercise	HIIE 20s post-exercise	HIIE 4x4min pre-exercise	HIIE 4x4min post-exercise
CK (U·l^{-1})	109.3 (48.1)	117.1 (51.1)*	128.3 (77.4)	139.4 (77.5)*	124.6 (64.2)	135.3 (67.2)*
CRP (mg·l^{-1})	3.6 (3.4)	3.8 (3.5)*	2.8 (2.5)	3.0 (2.6)	2.8 (1.6)	3.0 (1.7)*
IL-6 (pg·ml^{-1})	4.5 (2.2)	5.4 (2.2)*	4.5 (1.7)	5.8 (2.3)*	5.2 (3.2)	6.6 (4.0)*
Adiponectin (µg·ml^{-1})	7.5 (5.1)	7.8 (5.3)*	7.2 (5.4)	7.8 (5.8)*†	7.1 (4.6)	7.3 (4.6)*
Leptin (ng·ml^{-1})	7.2 (4.6)	6.9 (3.8)	5.2 (2.1)	5.3 (2.1)	5.9 (2.5)	6.0 (2.4)
hArg (µmol·l^{-1})	1.7 (.7)	1.7 (.7)	1.8 (.7)	1.8 (.7)	1.6 (.6)	1.6 (.6)
ADMA (µmol·l^{-1})	.7 (.2)	.7 (.2)	.7 (.2)	.7 (.2)	.7 (.2)	.7 (.2)
SDMA (µmol·l^{-1})	.8 (.3)	.7 (.3)	.8 (.3)	.9 (.5)	.8 (.3)	.8 (.3)
ADR (pg·ml^{-1})	84.7 (54.9)	127.7 (46.9)*	102.1 (93.5)	166.4 (87.6)*	83.6 (38.2)	139.4 (67.5)
NA (pg·ml^{-1})	1011.3 (438.8)	1764.2 (947.9)*	955.8 (602.8)	2057.2 (1488.0)*	892.0 (395.8)	1723.8 (888.1)*
DOP (pg·ml^{-1})	302.9 (207.1)	300.1 (188.4)	370.8 (218.4)	371.6 (119.4)	332.1 (241.8)	360.2 (256.0)

CK, creatine phosphokinase; CRP, C-reactive protein; IL-6, interleukin 6; hArg, homo arginine; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; ADR, free adrenaline; NA, free noradrenaline; DOP, free dopamine; CE, continuous exercise; HIIE, high-intensity interval exercise. *, significant difference to pre-exercise value. †, significantly higher increase from baseline to post-exercise value compared to CE and long HIIE.

Acute metabolic and cardiorespiratory responses

If the power output is above the second lactate turn point (LTP$_2$) and the second ventilatory threshold (VT$_2$) respectively, the blood lactate concentration increases with exercise duration (Beneke et al., 2011). In patients treated with beta blockers, who typically show a non-regular heart rate performance curve, a peak power output at 85% of HR$_{max}$ might correspond to workloads above LTP$_2$ (Hofmann et al., 2001, 2005; Wonisch et al., 2003). With respect to that, the acute metabolic response (La$_{mean}$, La$_{peak}$) in this study was significantly higher during long HIIE compared to short HIIE and CE, despite a markedly higher P$_{peak}$ and a significantly shorter t$_{rec}$ in short HIIE. A LaSS was reached in each exercise protocol, even in long 4x4 HIIE. However, the LaSS during long HIIE was probably facilitated by the moderate P$_{mean}$ but was still near the maximal LaSS (Figure 3A).

The acute mean cardiorespiratory response (HR$_{mean}$, VO$_{2mean}$) did not significantly differ between CE, short HIIE, and long HIIE since P$_{mean}$ for each test was equal. However, during the 4x4 min HIIE, the HR markedly oscillated between work and recovery phases (Figure 3B) reflecting a temporarily elevated cardiac stress during the peak workload periods. In short HIIE, the HR oscillation was clearly smaller due to the short t$_{peak}$ of 20 s resulting in peak HR values similar to those during CE. This is remarkable given the high P$_{peak}$ in short HIIE (corresponding to P$_{max}$ from IET). As a consequence, the peak cardiorespiratory response (HR$_{peak}$, VO$_{2peak}$) was significantly higher during long HIIE compared to short HIIE and CE. Our results are in accordance with the fundamental findings of Astrand et al. (1960) and Saltin et al. (1976) and support the results of Meyer et al. (1997), who have successfully applied HIIE in clinical populations.

Plasma parameters

We measured hs-cTnT and CK MB, which are risk markers of cardiac damage, NT-proBNP, a risk factor of cardiac insufficiency, and Lp-PLA$_2$, a platelet-activating factor reported to be associated with many traditional risk factors for cardiovascular disease such as cardiac death, myocardial infarction, acute coronary syndromes and ischemic stroke. None of these biomarkers showed significantly different acute increases (or decreases) between short and long HIIE and CE (Figure 4A-D). This is in accordance with the studies of Benda et al. (2015), Normandin et al. (2013), and Guiraud et al. (2011).

Importantly, during all tests the post-exercise concentrations of hs-cTnT, CK MB, and Lp-PLA$_2$ were not clinically relevant excluding myocardial injuries during any exercise test. The levels of NT-proBNP clearly exceeded the normal range (up to 150 pg·ml^{-1} for females and up to 100 pg·ml^{-1} for males) already at baseline and further increased during exercise (Figure 4A). However, the NT-proBNP levels remained below the age-specific cut-off value of 900 pg·ml^{-1} for 50-75 years of age (Gaggin and Januzzi, 2013).

In addition, no significantly different increase (or decrease) between the three exercise regimes was found for all other plasma parameters such as free catecholamines (NA, ADR, and DOP), inflammatory markers (CRP, IL-6), vascular markers (ADMA, SDMA, hArg), a marker for overall muscle damage (CK), and a metabolic parameter (leptin). Only the acute response of adiponectin, another metabolic marker regulating insulin sensitivity and glucose homeostasis, was shown to depend on exercise mode as it was significantly higher during short HIIE compared to CE and long HIIE. None of these biomarkers showed exercise-induced levels which were clinically relevant (Table 3). This shows that no elevated risks, such as inflammatory reactions (Pedersen, 2009), atherosclerotic processes (Kayacelebi et al., 2015), or myocardial/skeletal muscle damage, were induced.

Our results are in line with findings of several other authors. Meyer et al. (1996; 1997) did not find significantly different increases for catecholamines between different HIIE protocols, and between CE and HIIE, in patients with chronic heart failure. However, in these studies, P$_{mean}$ was not matched. A recent study by Moser et al. (2015), in patients with type 1 diabetes mellitus, also

revealed a similar catecholamine response during aerobic short HIIE and P_{mean}-matched CE. Studies by Guiraud et al. (2012, 2013) in CHD patients revealed no significant increases of endothelial microparticles (EMP) during short HIIE and isocaloric CE, which are specific biological markers associated with endothelial dysfunction. Most importantly, our findings support the results of other studies which revealed that aerobic HIIE was well tolerated and did not induce significant arrhythmias, severe or prolonged ischemia, or abnormal blood pressure responses in cardiac patients (Guiraud et al., 2011; Gayda et al., 2012; Meyer et al., 1996; 1997; 1998; Meyer et al., 2012; Normandin et al., 2013).

However, in most of these HIIE studies, peak workload durations were no longer than 15 s up to a maximum of 60 s except the HIIE protocol used by Meyer et al. (2012) which included a t_{peak} of 90 s. In contrast, the 4x4 HIIE model, which is frequently applied in both healthy individuals (Helgerud et al., 2007) and patients (Rognmo et al., 2004; 2012; Wisloff et al., 2007), includes long work phases of 4 min. However, studies of Laursen et al. (2005), Helgerud et al. (2007), and Ronnestad et al. (2015) revealed similar or even superior training effects yielded by short vs. long HIIE in healthy subjects. Additionally, HIIE with long work phases up to 4 min was clearly shown to induce significantly higher acute metabolic and peak cardiorespiratory responses compared to P_{mean}-matched short HIIE and CE in healthy subjects (Astrand et al., 1960; Saltin et al., 1976; Tschakert et al., 2015; Wiewelhove et al., 2015). Similar results were recently found by Peake et al. (2014). Meyer et al. (2012), Conraads et al (2015), and Keteyian (2012) suggested that the 4x4 HIIE may be highly demanding, even more so for heart disease patients, especially if P_{peak} is set at 90 or even 95 % of HR_{max} (Wisloff et al., 2007). Furthermore, Normandin et al. (2013) and Keteyian (2012) critically noted that the acute physiological response to this protocol was not investigated.

Another aspect of HIIE prescription that has to be considered is the setting of P_{rec}. Guiraud et al. (2010) and Meyer et al. (2012) found passive recovery to be more convenient than active recovery in patients with CHD and chronic heart failure, respectively. However, HIIE protocols with passive vs. active recovery were not matched by total work or mean load. In our study, we incorporated active recovery phases during both HIIE modes since we wanted to adopt the original 4 x 4 min HIIE protocol (including active recovery) as far as possible. Blood lactate clearance was found to be greater during active recovery compared to passive recovery (Bangsbo et al. 1994); however, this topic is controversially discussed. In addition, passive instead of active recovery phases with the same mean load results in markedly shorter recovery phases. In short-stage HIIE, t_{rec} may be too short to allow a sufficient resynthesis of creatine phosphate leading to a more pronounced anaerobic lactic metabolism (Tschakert and Hofmann, 2013). A comparison of HIIE protocols with passive vs. active recovery phases matched for mean load and total duration is required.

By using our methodological approach for exercise prescription, we could clearly show that even long HIIE with a t_{peak} of 4 min (and a P_{peak} corresponding to the power output at 85 % of HR_{max} from IET) as well as short HIIE with a P_{peak} according to P_{max} from IET were as safe and as well tolerated as moderate CE in patients with CHD or myocarditis.

Future perspectives

Further methodological studies are required to determine if aerobic HIIE is also safe for heart disease patients (CHD patients as well as chronic heart failure patients) when P_{peak} (of long HIIE) or P_{mean} (of long and short HIIE) is higher than in our study. Mechanistic HIIE studies with a consistent methodological approach are also necessary in patients with other chronic diseases such as diabetes mellitus type 1 and type 2, the metabolic syndrome, chronic obstructive pulmonary disease (COPD), or cancer. By all means, we recommend prescribing the P_{mean} consciously for a better control and prediction of acute cardiorespiratory and metabolic responses.

On the basis of methodological studies looking at the acute responses, training intervention studies are highly relevant to investigate the short- and long-term effects of different HIIE modes vs. P_{mean}-matched CE. If short intervals lead to similar training adaptations as long intervals, short HIIE is suggested to be the preferable HIIE mode since it is associated with lower metabolic and peak cardiorespiratory demands. In addition, it is still unclear to what extent systemic adaptations and peripheral muscular adaptations contribute to the overall aerobic training effect (increase of VO_{2max}) yielded by different HIIE regimes.

Limitations

A limit of this study was that plasma parameters were measured only before and at the end of exercise but not over a period of 24 or 48 hours after exercise. Another limit of the study was the small number of participants (n = 8). However, an a-priory power analysis revealed the statistical power to be sufficient for our experimental design. Furthermore, since our small sample was composed only of patients with CHD or myocarditis, our results are not generalizable to all heart disease patients. It is unknown if the obtained results also apply to patients with lower functional capacity, particularly in the long intervals.

Conclusion

Our study revealed that, in cardiac rehabilitation, the acute metabolic and peak-cardiorespiratory response was higher during long HIIE compared to short HIIE and CE. However, both HIIE regimes did not yield significantly higher acute responses for cardiac and cardiovascular biomarkers, inflammatory markers, and catecholamines compared to conventional moderate CE. In addition, the exercise-induced levels of health-related markers remained within a normal range except for NT-proBNP which was already elevated at baseline. Despite markedly higher peak workloads during the intervals, long and short HIIE were as safe as moderate CE in patients with CHD or myocarditis by using our methodological approach for

exercise prescription. However, subjects with lower functional capacity may not tolerate HIIE with long intervals and active recovery. Exercise prescription needs to be personalized taking this fact into account.

Both the acute responses for health related markers and training adaptations induced by different HIIE protocols are of high relevance for cardiac patients as well as those suffering from other chronic diseases. Therefore, in the field of intermittent exercise, further methodological investigations and training intervention studies, with a consistent approach to the exercise prescription, are required.

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Key points

- High-intensity interval exercise (HIIE) with short peak workload durations (t_{peak}) induce a lower acute metabolic and peak cardiorespiratory response compared to intervals with long t_{peak} despite higher peak workload intensities and identical mean load. No significant difference for any physiological parameter was found between short HIIE and CE.

- Between short HIIE, long HIIE, and CE, no significant difference was found in the increase (or decrease, respectively,) of health related markers such as cardiovascular biomarkers, catecholamines, or inflammatory parameters during exercise.

- During all exercise modes, all risk markers remained in a normal range except for NT-proBNP which was, however, already elevated at baseline.

- Short HIIE, long HIIE, and CE were safely performed by patients with CHD or myocarditis in cardiac rehabilitation by using our methodological approach to exercise prescription. This approach included the prescription of exercise intensities with respect to LTP_1, LTP_2, and P_{max} as well as a conscious setting of P_{mean} at a moderate level (80 % of P_{LTP2}). Importantly, all exercise modes were matched for P_{mean} and exercise duration in order to enable a comparison of the three protocols.

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