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Current Aspects of High-Intensity Interval Training for Patients with Cardiac Disease

Ito S*

Division of Cardiology, Sankuro Hospital, 7-80 Kosaka-cho, Toyota-shi, Aichi-ken, 471-0035, Japan

***Corresponding author:** Ito S, Division of Cardiology, Sankuro Hospital, 7-80 Kosaka-cho, Toyota-shi, Aichi-ken, 471-0035, Japan, Tel: 81-565-32-0282; Fax: 81-565-35-2570; E-mail: shigeito918@gmail.com

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Abstract

As an exercise training protocol in comprehensive cardiac rehabilitation, time-efficient high-intensity interval training (HIIT) has been investigated other than guideline based moderate-intensity continuous training. The scientific background of this protocol is that higher intensity exercise works to yield more improvement in aerobic and metabolic function by giving more stimuli to cardiopulmonary system and skeletal muscle. Among many combination of work interval, (active) rest, and frequency, most popular and evidence-based HIIT is 4 × 4 min. This protocol is the first one that has been investigated by multi center randomized controlled trials (RCT). In this mini-review, we discussed the current status and potential of HIIT for cardiac patients by commenting on the results of recently published multi center RCT and review articles.

Keywords: Cardiac rehabilitation; High-intensity interval training; Chronic heart failure; Coronary artery disease; Lifestyle-related disease

Introduction

Exercise training is a cornerstone in cardiac rehabilitation (CR); however, there is still controversy regarding the exercise characteristics that are most effective for improving peak oxygen consumption (VO_{2peak}) and cardiac/metabolic parameters in cardiac patients. Historic training programs in cardiac rehabilitation include endurance training, however, recently resistance training has been also been recognized as an essential training to be added. Acanfora et al. [1] showed that a specific four-week exercise program (closed-chain resistive activities and abdominal exercises) improves cardiac performance indexes and pulmonary function in both middle-aged and elderly heart failure patients early after an acute episode of cardiac decompensation. In the meantime, proof-of-concept studies comparing high-intensity interval training (HIIT) and moderate-intensity continuous training (MCT) were conducted in small sample sizes and findings were inconsistent and heterogeneous [2-19]. Table 1 shows the randomized controlled trials comparing improvement of VO_{2peak} after exercise between HIIT and MCT in patients with coronary artery disease (CAD) or congestive heart failure (CHF. The HIIT protocols and number of studies showing superiority of HIIT over MCT for each protocol are shown [2-19]. The 4 × 4 min protocol was most frequently used showing a positive rate of 70.2% in the CAD group and 60% in the CHF group. The other protocols with 30 s, 2 min, and 3 min exercise duration were also effective in a limited number of studies.

Recently, two multicenter randomized controlled trials (RCT) [18,20] were performed and the results did not show superiority of HIIT to MCT. In this mini-review, we discuss about the latest data of HIIT for cardiac patients focusing on the effective implementation of HIIT.

Golden standard of exercise protocol in cardiac rehabilitation

MCT is well known as an effective exercise strategy for patients with cardiac disease such as CAD and CHF to improve VO_{2peak}, cardiac and metabolic function, and subsequently long-term prognosis. There is much evidence to reveal this fact including RCT [21]. The current guidelines on CR/exercise training recommend endurance exercise with a moderate intensity at 50-85% (mostly 70-85%)of the peak heart rate (HR_{peak}) or anaerobic threshold (AT) level for CAD and CHF patients [22-25].

Studies Showing Superiority of HIIT			
	Protocol	**No. of studies**	
Coronary artery disease	10 × 1 min	1	0/1 (0%)
	8 × 2 min	1	1/1 (100%)
	7 × 3 min	1	0/1 (0%)
	4 × 4 min	7	5/7 (70.2%)
Chronic heart failure	40 × 30 sec	3	1/3 (33.3%)
	30 × 1 min	1	0/1 (0%)
	5 × 3 min	1	1/1 (100%)
	4 × 4 min	6 (1 study in progress)	3/5 (60%)

Table 1: HIIT Protocol and VO_{2peak} Improvement.

Indication and potential effects of exercise training with high intensity for cardiac patients

As a potential alternative exercise protocol in CR, HIIT has emerged to be investigated and practiced in some limited institutions. A certain

number of single center studies have revealed superiority of HIIT compared with MCT in the improvement of VO_{2peak} as well as cardiac and metabolic function since 10 years ago [3,2,6]. In patients with severe left ventricular dysfunction in acute phase, interval training with low- to moderate-intensity would be used if they could not tolerate even MCT. However, in this mini-review, we discuss only HIIT in which high-intensity of 90-95% of HR_{peak} is adopted.

Although there might be worries about "high intensity" exercise for cardiac patients, individualized protocol for each patient should be prepared based on the exact exercise tolerance. Thus, cardiac patients could implement the HIIT protocol except for those with contraindications which is shown in Table 2. We previously summarized clinical and metabolic parameters which favor HIIT compared with MCT in RCT 21 (Table 3).

Unstable angina pectoris
Uncompensated heart failure
Recent myocardial infarction (<4 weeks)
Significant arrhythmia or >1 mm of horizontal or down sloping ST depression during cardiorespiratory exercise test
Recent coronary artery bypass graft or percutaneous coronary intervention*
Heart disease that limits exercise (valvular, congenital, ischemic and hypertrophic cardiomyopathy
Complex ventricular arrhythmias or heart block
Severe chronic obstructive pulmonary, cerebrovascular disease or uncontrolled peripheral vascular disease
Uncontrolled diabetes mellitus
Hypertensive patients with blood pressure>180/110 (or uncontrolled)
Severe neuropathy

Table 2: Suggested contraindications to High-intensity Interval Training (HIIT) in cardiac rehabilitation.

Representative HIIT protocols

Training programs using interval exercises are expected to be a highly effective, time-efficient strategy for public health [26]. HIIT is divided into two main categories: sprint and aerobic types. Previous studies indicated that sprint-type interval training (SIT) improves maximal oxygen consumption (VO_{2max}) mainly through increased oxidative capacity in peripheral muscles [27], whereas aerobic-type interval training improves VO_{2max} mainly through cardiac function [6,28]. We mean SIT as Wingate [29] and Tabata protocols [30,31]. Exercise interval of Wingate and Tabata protocols was 30 seconds and 20 seconds, respectively. These protocols need physically demanding intensity. On the other hand, in aerobic type HIIT exercise duration is usually between 30 seconds and 4 min. Among aerobic HIIT, low-volume HIIT [32,33] is defined as short exercise protocol with total exercise duration of within 30 min including warming-up, and intervals exercise with interspersed rests, and cool down.

SIT protocols have been frequently investigated for subjects with obesity and lifestyle-related disease. In contrast SIT protocols lack evidence about application for patients with cardiac disease, because SIT is physically demanding. Potential candidates with cardiac disease of SIT could be patients with coronary artery disease who have preserved left ventricular function without significant coronary ischemia. Meanwhile, most popular and evidence-based protocol of HIIT for cardiac disease would be 4 × 4 min HIIT.

Parameters	Target
insulin sensitivity (HOMA index) HbA1C	skeletal muscle
IR β subunit in skeletal muscle (peripheral insulin sensitivity)	
PGC-1α	
re-uptake of Ca^{2+} into the salcoplasmic reticulum	
fatty acid transporter in the vastus lateralis and FAS (a key lipogenic enzyme)	
mitochondrial function in lateral vastus	
frequency of metabolic syndrome	risk factor
endothelial dysfunctionFMD	vasculature
improvement of ventilatory efficiency (increased value of $PETCO_2$)	respiration
oxygen consumption at the first ventilator threshold	
parasympathetic activity (HR recovery)	autonomic nerve
reversed LV re-modelling (LV end diastolic and systolic volumes)	cardiac function
E_a, E/A ratio, S_a	
diastolic function (e′, E, E/ e′, E/A ratio, higher proportion of e ′>8cm/sec, E improvement during exercise), systolic function after 12 weeks at rest and during exercise)	
E reductiondeceleration time increaseleft atrial volume	
oxygen pulse reduced-plasma BNP	
duration of exercise time distance walked during the 6-min walk	exercise capacity
interleukin-6 high-sensitivity CRP level myeloperoxidase	inflammation
increased Short Form-36 physical/mental component scores and decreased Minnesota Living with Heart Failure questionnaire score	quality of life
HOMA: homeostasis model assessment, HbA1c: hemoglobin A1c, IR: insulin receptor, PGC: peroxisome-proliferator activated receptor γ co-activator, FMD: flow mediated dilation, FAS: fatty acid synthase, PETCO2: end-tidal carbon dioxide pressure, HR: heart rate, LV: left ventricular, E_a: peak early diastolic tissue Doppler velocity, E: trans mitral peak early diastolic velocity, A: trans mitral late diastolic velocity, S_a: peak systolic tissue Doppler velocity, BNP: brain natriuretic peptide, CRP: C-reactive protein.	

Table 3: Parameters Improved More in High-Intensity Interval Training than Moderate-Intensity Continuous Training for Cardiac patients in Randomized Controlled Trials.

The other protocols of HIIT using short exercise bouts

The other unique protocols were also reported to improve VO_{2max} and cardiac/metabolic parameters for sedentary subjects with obesity and/or lifestyle-related diseases, which could be potentially applied to the cardiac disease. Little et al. [32] shortened the work-out duration to 1 min. Durability for work-out might improve by this protocol.

However, effectiveness remains still controversial [3,33,34]. I suspect that it would be a little difficult to raise target HR to target %HR_{peak} during only 1 min. Alvarez et al. [35] used a progressive 16-week HIIT program in a RCT comparing HIIT and MCT for young patients with type 2 diabetes. This program starts from 8 jogging/running intervals of ~30 seconds interspersed with ~120 seconds of low-intensity walking. To promote sufficient workload for eliciting improvements throughout the follow-up, there was a 7-10% increase in high-intensity interval duration and a 4% decrease in the recovery duration every two weeks. There was also an increase of two exercise intervals every 4 weeks. With the exercise intensity/volume progression, total working duration ranged from 4 to 13.5 min (week 1-16), total recovery duration from 18 to 24 min (week 1-16) and numbers of intervals ranged from 8 to 14 (week 1-16). Thus, the exercise session duration ranged from 22 min to 37.5 min. Improvement in fasting glucose, HbA1C, triglyceride, systolic blood pressure, endurance performance (2 km walking test), and body weight etc. were found after HIIT program. Matsuo et al. [36,37] also developed a unique and shorter work-out (3 × 3 min interspersed with 2 min active rest), in which exercise intensity is meticulously programmed using cardiopulmonary exercise test (CPX) data. They tested this protocol, named "high-intensity aerobic training (HIAT)", comparing three exercise training protocols in a RCT for forty-two healthy but sedentary male subjects (mean age 26.5 y) who underwent an 8 week, five times per week, supervised exercise intervention. Because this protocol is developed considering the potential application for exercise in international space station, they used a substantially shorter duration and at a lower volume compared with moderate-intensity continuous exercise and 4 × 4 min protocol. HIAT composed of three intervals of 3 min (85%–90% VO_{2max}, 70–80 rpm) interspersed with 2 min (50% VO_{2max}, 60 rpm) active rest. During the third stage of our HIAT, intensity (80%–85% VO_{2max}) was lower than the first and second stages (85%–90% VO_{2max}) because they consider a lower intensity during third stage to be crucial in daily exercise for sedentary individuals. To determine each subject's exercise intensity during the exercise session, they used the VO_{2max} measurement data. Exercise protocols were sprint interval training (SIT, 5 min, 100 kcal), HIAT (13 min, 180 kcal), and continuous aerobic training (CAT, 40 min, 360 kcal). They tested the hypothesis that despite the exercise volumes of SIT and HIAT being 30% and 50% of CAT, respectively, SIT and HIAT would have more impact than CAT on VO_{2max}. VO_{2max} and left ventricular mass (3T-MRI) were also measured. Significant increases in VO_{2max} were observed in all three groups, and the effect of the HIAT was the greatest of the three (SIT, 16.7% ± 11.6%; HIAT, 22.5% ± 12.2%; CAT, 10.0% ± 8.9%; P=0.01). These protocols using shorter exercise-bout than 4 × 4 min could be more easily completed and feasible even for cardiac patients especially without exercise experience.

Potential of 4 × 4 min HIIT protocol

4 × 4 min HIIT would be most popular and evidence-based exercise protocol for cardiac disease and consists of 4 bouts of 4 min exercise at intensity of 90-95% HR_{peak} interspersed with 3 min active rests at intensity of 60-70% HR_{peak}. Thus, total work-out time is less than 40 minutes including warm-up and cool-down. This protocol is time-efficient compared with MCT to improve VO_{2peak}/cardiac and metabolic function [3,7,8]. Although the results of multiple small single-center RCT and meta-analyses [38-40] , comparing 4 × 4 min HIIT and MCT for patients with cardiac disease, favored 4 × 4 min HIIT, recently published two multicenter RCT [18,20] failed to reveal positive results. By the analysis and interpretation of these studies, we may understand the way of future practice using 4 × 4 min HIIT and limitations.

Pivotal RCT comparing 4 × 4 min HIIT and MCT for cardiac disease

The first RCT was a multi-center study for CAD (The SANITEX-CAD study) that showed a similar improvement in the VO_{2peak} in a comparison between the HIIT and MCT protocols [12,18]. In this study, two-hundred CAD patients (LVEF>40%, 90% men, mean age 58.4 years) were randomized to a supervised 12-week CR program of three weekly sessions of either HIIT (90–95% of HR_{peak}) or MCT (70–75% of HR_{peak}) on a bicycle. Primary outcome was VO_{2peak}; secondary outcomes were peripheral endothelial function, cardiovascular risk factors, quality of life and safety. The HIIT training protocol was like those reported in the previous studies [3]. VO_{2peak} increased significantly in both groups (HIIT 22.7 ± 17.6% *vs.* MCT 20.3 ± 15.3%). In addition, flow-mediated dilation (HIIT+34.1% *vs.* MCT +7.14%), quality of life and some other cardiovascular risk factors including resting diastolic blood pressure and HDL-C improved significantly after training. Improvements were equal for both training interventions. The authors noted that the absence of a difference in the VO_{2peak} was due to the low feasibility of 4 × 4 min at 90-95% HR_{peak} in the HIIT group, and the higher average HR than prescribed (80% HR_{peak}) in the MCT group. Mean training intensity for the HIIT group was around 88% of HR_{peak} and for the MCT group around 80% of HR_{peak} during the 12 week intervention. The second multicenter RCT regarding HIIT compared 12 weeks of supervised interventions of 4 × 4 min HIIT, MCT, or a recommendation of regular exercise (RRE) for patients with heart failure The SMARTEX (Study of Myocardial Recovery After Exercise Training in Heart Failure) Heart Failure Study [20]. Two hundred sixty-one patients from 9 European sites with left ventricular ejection fraction ≤ 35% and New York Heart Association class II to III were randomly assigned to HIIT at 90% to 95% of HR_{peak}, MCT at 60% to 70% of HR_{peak}, or RRE. Thereafter, patients were encouraged to continue exercising on their own. Primary endpoint was a between-group comparison of change in left ventricular end-diastolic diameter from baseline to 12 weeks. Change in left ventricular end-diastolic diameter from baseline to 12 weeks was not different between HIIT and MCT. There was also no difference between HIIT and MCT in VO_{2peak}, but both were superior to RRE. However, none of these changes was maintained at follow-up after 52 weeks. Serious adverse events were not statistically different during supervised intervention or at follow-up at 52 weeks (HIIT, 39%; MCT, 25%; RRE, 34%; P=0.16). Training records showed that 51% of patients exercised below prescribed target during supervised HIIT and 80% above target in MCT. Average relative training intensity (percentage of maximal heart rate) was estimated as for heart rate during study: HIIT, 90% (88%–92%); MCT, 77% (74%–82%); difference, 10% (8%–13%; P<0.001). The authors suggested that some of the variability in estimated training intensity probably results from variation in maximal heart rate. HIIT was not superior to MCT in changing left ventricular remodeling or aerobic capacity, and its feasibility remains unresolved in patients with heart failure. In the discussion, the authors described that given that HIIT was not superior to MCT in reversing remodeling or improving second endpoints, and considering that adherence to the prescribed exercise intensity based on heart rate may be difficult to achieve, even when supervised and performed in centers experienced in cardiac rehabilitation, MCT remains the standard exercise modality for patients with CHF.

Nevertheless, I still insist on the importance of high intensity rather than the mode of exercise in the training program menu. Even if very short-term exercise, high-intensity exercise added in the daily life would be beneficial as shown in sedentary and obesity subjects. Two RCT suggest that MCT with %HR more than study prescription or guideline recommendation might show superior results in VO_{2peak} (20.3-25.0% increase), which are similar data in HIIT groups in these RCT and the other single study RCT3.

Practical tips to implement HIIT effectively

Both multi center RCT did not show the superiority of 4 × 4 min HIIT for patients with CHD and CHF with reduced left ventricular systolic dysfunction compared with MCT. However, it is still inconclusive whether 4 × 4 min HIIT is more effective than MCT to improve VO_{2peak}, cardiac function etc., because adherence to exercise intensity was not adequate in both HIIT and MCT groups despite the supervised training. In both RCT, training intensity during exercise evaluated by HR was lower in HIIT and higher in MCT group than prescription. We speculate there might have been inter-sites variability in adherence to exercise intensity, which subsequently led to the negative primary and secondary outcomes. In the other words, tips may exist to perform 4 × 4 min HIIT with sufficient intensity adherence to the protocol. Karlsen et al. from a Norwegian cardiac exercise research group [41] published a review article regarding HIIT for maximizing health outcomes very recently. It is worthy of special mention that they discussed the key practical considerations for successful HIIT in addition to the epidemiological and clinical evidence of HIIT. This group is one of the pioneers that have applied HIIT for cardiac disease. Adherence to work intensity could improve by understanding their detailed methodology, with which they perform 4 × 4 min HIIT as workout in daily cardiac rehabilitation or as a procedure of clinical studies, about warm-up, work load, and HR_{peak}. The followings are the tips of successful 4 × 4 min HIIT implementation [41].

Appropriate warm-up

Patients with CAD perform 10-15 min of aerobic exercise training at light to moderate intensity before the first bout of HIIT. With proper warm-up, the risk of arrhythmias and ischemia is minimized [42,43]. The ability to reach target HR within two-three minutes is facilitated by exercising somewhat hard (approaching 85% of HR_{peak}) during the last minutes of warm up reducing the time to reach target HR in the first exercise bout.

Adjustments of exercise workload

The first exercise session(s) should be used to find the correct exercise training workload that will result in prescribed relative intensity ($\%HR_{peak}$). A rule of the thumb is that after two-three minutes, the patient should be close to 90% of HR_{peak}. If not, workload should be increased if the HR is too low, or decreased if the HR is too high. Reaching target HR too fast may result in accumulation of lactate, making the person not able to finish the four-minute bout. Keeping the intensity at ~70% between the bouts reduce the time to reach target HR in the subsequent bout.

Use of the Borg scale as adjunct of %HR to evaluate exercise intensity

Correct measurement of HR_{peak}

The prerequisite to prescribe relative exercise intensity is a correct HR_{peak} measurements obtained from CPX. To achieve near maximal effort in this test, a proper warm-up is crucial. Walking/running rather than cycling would be recommended to obtain submaximal values because cycle tests may give about 10-20% lower VO_{2peak} compared to treadmill walking/running. Cycling is less feasible to reach the target HR in patients not familiar with cycling.

Conclusions

Taking previous single-center RCT and meta analyses, which showed superiority of HIIT in VO_{2peak} and the other cardiac and metabolic parameters improvement, into consideration, we should not deny the 4 × 4 min HIIT protocol for CR even after the negative results revealed in two multi center RCT. These trials denoted that it would be arduous to perform HIIT with expected adherence to the high intensity for cardiac patients. Investigations on the feasibility and merits of HIIT for cardiac disease are still on the way. Future research is expected to focus on 1) the comparison of HIIT and MCT performed at representative and feasible intensities satisfying the adherence to exercise intensity in multicenter studies, 2) the underlying mechanisms responsible for VO_{2peak} improvements, 3) feasibility and safety of long-term HIIT for cardiac disease in not only laboratory setting but also in a real-world setting

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