Review Article

Review of High-intensity Interval Training in Cardiac Rehabilitation

Shigenori Ito, Tatsuya Mizoguchi and Tomoaki Saeki

Abstract

For the secondary prevention of cardiovascular disease, comprehensive cardiac rehabilitation is required. This involves optimal medical therapy, education on nutrition and exercise therapy, and smoking cessation. Of these, efficient exercise therapy is a key factor. A highly effective training protocol is therefore warranted, which requires a high rate of compliance. Although moderate-intensity continuous training has been the main training regimen recommended in cardiac rehabilitation guidelines, high-intensity interval training has been reported to be more effective in the clinical and experimental setting from the standpoint of peak oxygen uptake and central and peripheral adaptations. In this review, we illustrate the scientific evidence for high-intensity interval training. We then verify this evidence and discuss its significance and the remaining issues.

Key words: high-intensity, interval training, heart failure, coronary artery disease, maximal oxygen uptake, cardiac rehabilitation

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Introduction

Of all established risk factors, a low aerobic exercise capacity appears to be the strongest predictor of mortality (1). Given the worldwide heart disease pandemic and inadequate strategies currently employed to prevent and treat heart disease, there is a need to investigate management strategies that are effective and affordable. In the field of cardiac rehabilitation, moderate-intensity continuous training (MCT) has been the gold standard for patients with cardiac disease for many years (2). The current guidelines on cardiac rehabilitation (CR)/exercise training (ET) recommend endurance exercise with a moderate intensity at 50-85% (mostly 70-85%) of the peak heart rate (HRpeak) or anaerobic threshold (AT) level for cardiovascular disease (CVD) and chronic heart failure (CHF) patients (3-6). However, more efficient forms of exercise might be necessary to improve exercise efficacy.

Nearly all cardiac rehabilitation teams adopt MCT as endurance training in the cardiac rehabilitation program. However, several European and North American teams have adopted high-intensity interval training (HIIT), which would be a potential candidate for more efficient forms of exercise, as considerable evidence of its short-term effects has been reported for patients with coronary artery disease (CAD), CHF, and metabolic syndrome. HIIT can be broadly defined as repeated bouts of short to moderate duration exercise (i.e., 10 seconds to 5 minutes) completed at an intensity that is greater than the anaerobic threshold (7). Exercise bouts are separated by brief periods of low-intensity work or inactivity that allows a partial, but often not a full, recovery (7). Although grading of the exercise intensity (low, moderate, high) slightly varies according to the studies, it is generally considered that a low intensity is below the AT level [<45% peak oxygen uptake (VO2peak) or <80% HR at the AT level], moderate is around the AT level (50-60% VO2peak or 50-75% HRpeak), and high includes an anaerobic level over the AT level (80-90% VO2peak or 85-95% HRpeak). The purpose of HIIT is to repeatedly stress the physiological system (7). In 2010-2014, several reviews and meta-analyses of HIIT for CAD and CHF were published (8-14), reflecting its increasing interest in the field of cardiac rehabilitation. One of these studies (11) involving more than 260 patients, the superiority of HIIT in patients with CAD was demonstrated. The latest evidence for HIIT was shown in two recently published studies (15, 16) describing its effects even on left...
ventricular (LV) diastolic dysfunction that had not been treated with effective drugs. In this review, we aim to examine the latest advances in HIIT in terms of the maximal/peak VO₂ (VO₂max/peak) improvement and central and peripheral adaptations.

## Materials and Methods

We conducted a literature review in April 2015, from the earliest time available to March 31, 2015, limited to the English language, using computerized databases including the PubMed and Medline databases. The search combined key words related to cardiac disease (i.e., ischemic heart disease, myocardial infarction, angina pectoris, heart failure), cardiac rehabilitation (i.e., exercise rehabilitation, training, sports, physical activity) and interval training (i.e., interval training, aerobic interval training, anaerobic interval training, HIIT). Articles retrieved were examined for further relevant references. Clinical randomized controlled trials (RCTs) and meta-analyses comparing HIIT and MCT including aerobic capacity data were used to evaluate the VO₂peak and other clinical variables which indicated central and peripheral adaptations. Non-randomized, non-prospective studies were also used to describe and discuss the exercise protocol, adherence, and risk of HIIT at our discretion. Abstracts and case reports were excluded.

## Results

### Benefits of HIIT

#### RCTs comparing the VO₂peak in HIIT versus MCT (Table 1, 2)

Tables 1 and 2 summarize the 21 previously reported RCTs with the VO₂peak data. They involved assessments of HIIT versus MCT for patients with CAD, including metabolic syndrome (n=10) (17-27), and CHF, including diastolic dysfunction (n=11) (15, 16, 28-36). In the studies shown in Tables 1 and 2, although the VO₂peak was not necessarily the primary endpoint, we presented the VO₂peak at baseline and the percentage increase in the VO₂peak during the exercise period in order to compare the two groups. In 12 out of 19 studies, the VO₂peak improvement was greater in the HIIT group than in the MCT group (two studies are currently ongoing). Of these, 10 studies, four for CHF (mean VO₂peak 13.0-19.2) and six for CAD (mean VO₂peak 21.8-32.2), adopted a 4x4 minutes HIIT mode, which produced better results in terms of an increase in the VO₂peak in eight studies (80.0%). The baseline VO₂peak was lower in the CHF group than the CAD group, partially reflecting the cardiac function before training. The VO₂peak increased by 9.4% to 46.0% in the HIIT group, compared to an increase of 0-22% in the

<table>
<thead>
<tr>
<th>Reference Number</th>
<th>Sample</th>
<th>n</th>
<th>HIIT</th>
<th>MCT</th>
<th>Duration</th>
<th>Mode</th>
<th>VO₂peak pre</th>
<th>VO₂peak %increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>CAD</td>
<td>17</td>
<td>(HIIT=8)</td>
<td>3 wk 4x4 min @ 80-90%VO₂peak</td>
<td>total 33 min</td>
<td>3 wk 41 min @ 50-60%VO₂peak</td>
<td>10 wks</td>
<td>TM</td>
</tr>
<tr>
<td>27</td>
<td>CAD</td>
<td>14</td>
<td>(HIIT=7)</td>
<td>2 wk 2 min @ 95%VO₂peak, 2 min recovery, 30 min total</td>
<td>2 wk 3 min @ 85%VO₂peak</td>
<td>16 wks</td>
<td>TM</td>
<td>32.1</td>
</tr>
<tr>
<td>26</td>
<td>Metabolic syndrome</td>
<td>18</td>
<td>(HIIT=9)</td>
<td>3 wk 4 x 4 min @ 70%HRmax, 3 min active recovery</td>
<td>5 wk 4x4 min @ 70%HRpeak</td>
<td>10 wks</td>
<td>TM</td>
<td>33.6</td>
</tr>
<tr>
<td>23</td>
<td>CAD</td>
<td>59</td>
<td>(HIIT=28)</td>
<td>4 x 4 min @ 90%HRmax</td>
<td>4 wks</td>
<td>TM</td>
<td>36.0</td>
<td>16%</td>
</tr>
<tr>
<td>22</td>
<td>post MI</td>
<td>89</td>
<td>(HIIT=30)</td>
<td>2 wk 4 x 4 min @ 85-95%HRmax</td>
<td>3 min recovery</td>
<td>12 wks</td>
<td>TM</td>
<td>31.6</td>
</tr>
<tr>
<td>24</td>
<td>CAD</td>
<td>37</td>
<td>(HIIT=17)</td>
<td>3 wk 7x3 min @ RCP</td>
<td>total 42 min</td>
<td>3 wk 5 min @ VAT</td>
<td>3 months</td>
<td>TM</td>
</tr>
<tr>
<td>19</td>
<td>recent event</td>
<td>22</td>
<td>(HIIT=11)</td>
<td>2 wk 10x1 min @ 80-100% PPO, 1 min recovery</td>
<td>10% PPO</td>
<td>12 wks</td>
<td>bike</td>
<td>19.8</td>
</tr>
<tr>
<td>20</td>
<td>Stable CAD</td>
<td>28</td>
<td>(HIIT=15)</td>
<td>3 wk 4x4 min @ 80-90%HRmax</td>
<td>3 min recovery</td>
<td>10 wks</td>
<td>TM</td>
<td>22.4</td>
</tr>
</tbody>
</table>
| 21               | CAD with stents | 36 | (HIIT=16) | 3 wk 4 x 4 min @ 85-95%HRmax | 3 min active recovery | 12 wks | TM | 31.2 | 10.8%
| 17               | CAD    | 173 | (HIIT=85) | 3 wk 4 x 4 min @ 90-95%HRmax | 3 min active recovery | 12 wks | TM | 29.8 | 6.7% |


Reference 27: * data shown is VO₂ at anaerobic threshold

Data is shown in figure without exact value at VO₂peak (30+ in HIIT 30 in MCT), and %increase at peak exercise is similar.

TM etc. means TM or stair climber, upper leg ergometer

Reference 25: There was no difference at 4 wks. Increase of VO₂peak between 4 wks and 6 mons was significant within HIIT and between HIIT and MCT. The participant attended additional sessions with various intensity at the center with their choice. Exercise was performed at center for 4 wks and at home for 6 months, Reference 22: TM means TM or aerobic exercise
Table 2. Mode, Intensity, and VO2peak Increment in High-Intensity Interval Training Versus Moderate-Intensity Continuous Training (congestive Heart Failure or Diastolic Dysfunction) in Randomized Controlled Trials.

<table>
<thead>
<tr>
<th>Reference Number</th>
<th>Sample</th>
<th>n</th>
<th>HIIT</th>
<th>MCT</th>
<th>Duration</th>
<th>Mode</th>
<th>VO2peak pre</th>
<th>VO2peak %increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>CHF</td>
<td>24</td>
<td>HIIT=10</td>
<td>MCT</td>
<td>3 d/wk, 30 seconds@100% Wr</td>
<td>3 d/wk, 40 mins@50% Wr</td>
<td>36 sessions</td>
<td>bike</td>
</tr>
<tr>
<td>31</td>
<td>CHF</td>
<td>30</td>
<td>HIIT=9</td>
<td>MCT</td>
<td>3 d/superintensity@4x4 min</td>
<td>3 d/2 superintensity@wk</td>
<td>12 wks</td>
<td>TM</td>
</tr>
<tr>
<td>32</td>
<td>HFpEF</td>
<td>26</td>
<td>HIIT=12</td>
<td>MCT</td>
<td>3 d/4x4 sec@70% Vpeak</td>
<td>3 d/4x4 sec@70% Vpeak</td>
<td>5 sessions</td>
<td>bike</td>
</tr>
</tbody>
</table>

**Table 2: Mode, Intensity, and VO2peak Increment in High-Intensity Interval Training Versus Moderate-Intensity Continuous Training (congestive Heart Failure or Diastolic Dysfunction) in Randomized Controlled Trials.**

**Reference Number**
- 28: CHF
- 31: CHF
- 32: HFpEF

**Sample**
- CHF
- HFpEF

**n**
- 24
- 30
- 26

**HIIT**
- 3 d/superintensity@4x4 min
- 3 d/4x4 sec@70% Vpeak

**MCT**
- 3 d/4x4 sec@50% Vpeak

**Duration**
- 36 sessions
- 12 wks
- 5 sessions

**Mode**
- bike
- TM

**VO2peak pre**
- HIIT
- MCT

**VO2peak %increase**
- 7.8%
- 5.8%
- 13.0%

**Table 2: Mode, Intensity, and VO2peak Increment in High-Intensity Interval Training Versus Moderate-Intensity Continuous Training (congestive Heart Failure or Diastolic Dysfunction) in Randomized Controlled Trials.**

**Reference Number**
- 28: CHF
- 31: CHF
- 32: HFpEF

**Sample**
- CHF
- HFpEF

**n**
- 24
- 30
- 26

**HIIT**
- 3 d/superintensity@4x4 min
- 3 d/4x4 sec@70% Vpeak

**MCT**
- 3 d/4x4 sec@50% Vpeak

**Duration**
- 36 sessions
- 12 wks
- 5 sessions

**Mode**
- bike
- TM

**VO2peak pre**
- HIIT
- MCT

**VO2peak %increase**
- 7.8%
- 5.8%
- 13.0%
conducted a pivotal study of post-infarction CHF patients (31). They found that in addition to a greater increase in the VO2peak in the HIIT group, the cardiac, endothelial, and mitochondrial function endpoints favored HIIT (Table 3). In addition, a study by Tjønna et al. revealed a reversal in the risk factors of metabolic syndrome, improved insulin action in muscle and fat tissues, and reduced lipogenesis in fat in addition to the VO2max and other factors detected in the report conducted in the vastus lateralis and FAS (a key lipogenic enzyme) (26).

There have been a number of published studies examining the dose and frequency of HIIT training in healthy, but sedentary or overweight individuals (44-48). Although the current public health or cardiac rehabilitation guidelines recommend a frequency of moderate-intensity exercise at least five times per week, other protocols have also been reported. For instance, a single weekly bout of exercise may reduce car-

Table 3. Variables Improved More in High-Intensity Interval Training than Moderate-Intensity Continuous Training in Randomized Controlled Trials.

<table>
<thead>
<tr>
<th>Variables [references]</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>insulin sensitivity (HOMA index) [26]</td>
<td>skeletal muscle</td>
</tr>
<tr>
<td>IR β subunit in skeletal muscle (peripheral insulin sensitivity) [26]</td>
<td></td>
</tr>
<tr>
<td>PGC-1α [26, 31]</td>
<td></td>
</tr>
<tr>
<td>re-uptake of Ca2+ into the sarcoplasmic reticulum [26, 31]</td>
<td></td>
</tr>
<tr>
<td>fatty acid transporter in the vastus lateralis and FAS (a key lipogenic enzyme) [26]</td>
<td></td>
</tr>
<tr>
<td>mitochondrial function in lateral vastus [31]</td>
<td></td>
</tr>
<tr>
<td>frequency of metabolic syndrome [26]</td>
<td>risk factor</td>
</tr>
<tr>
<td>endothelial dysfunction [26, 31]</td>
<td>vasculature</td>
</tr>
<tr>
<td>improvement of ventilatory efficiency (increased value of PETCO₂) [24]</td>
<td>respiration</td>
</tr>
<tr>
<td>oxygen consumption at the first ventilator threshold [31]</td>
<td></td>
</tr>
<tr>
<td>parasympathetic activity (HR recovery) [28]</td>
<td>autonomic nerve</td>
</tr>
<tr>
<td>reversed LV re-modeling (LV end diastolic and systolic volumes) [31]</td>
<td>cardiac function</td>
</tr>
<tr>
<td>Ea, E/A ratio, Sa [31]</td>
<td></td>
</tr>
<tr>
<td>diastolic function (e’, E/ e’, E/A ratio, higher proportion of e’&gt;8cm/sec, E improvement during exercise), systolic function after 12 weeks at rest and during exercise [16]</td>
<td></td>
</tr>
<tr>
<td>left atrial volume [15]</td>
<td></td>
</tr>
<tr>
<td>oxygen pulse [32]</td>
<td></td>
</tr>
<tr>
<td>reduced-plasma BNP [31, 34]</td>
<td></td>
</tr>
<tr>
<td>duration of exercise time [32]</td>
<td>exercise capacity</td>
</tr>
<tr>
<td>distance walked during the 6-minute walk [32]</td>
<td></td>
</tr>
<tr>
<td>increased Short Form-36 physical/mental component scores and decreased Minnesota Living with Heart Failure questionnaire score [34]</td>
<td>quality of life</td>
</tr>
</tbody>
</table>

diovascular mortality in older populations (49). Additionally, a single bout of HIIT for four minutes at 90% HRpeak (1×4 minutes HIIT) yielded similar improvements in the VO₂max to 4×4 minutes HIIT bouts in healthy men (46). On the other hand, higher frequency training (24 high-intensity sessions per 3 weeks) showed a similar improvement in the VO₂max compared to moderate frequency training (24 high-intensity sessions per 8 weeks) in healthy subjects, although cardiovascular adaptation was delayed in the high-frequency group (44).

**Exercise period**

In studies with positive results in favor of HIIT, the training period is often 8-12 weeks (Table 1, 2). According to Moholdt et al., after four weeks of center-based training and six months of home-based training, HIIT showed a greater improvement than MCT in VO₂peak between 4 weeks and 6 months. This implies that longer periods of more than four weeks of exercise, along with compliance to exercise, could yield better results.

**Safety issue of HIIT**

Although no complications have been reported in previous RCTs, the total number of patients is small (320 patients in the HIIT group). One report by Rognmo et al. indicated that HIIT is safe (50). They examined the risk of cardiovascular events during HIIT and MCT organized for 4,846 patients with CAD. In a total of 175,820 exercise training hours, during which all patients performed both types of training, they recorded one fatal cardiac arrest during MCT (129,456 exercise hours) and two non-fatal cardiac arrests (46,364 exercise hours) during HIIT. There were no myocardial infarctions observed in their study. Because the number of high-intensity training hours was 36% of the number of moderate-intensity hours, the rates of complication regarding the number of patient-exercise hours were one per 129,456 hours of MCT and one per 23,182 hours of HIIT.

**Adherence and long-term effects**

A continuation of exercise habit is necessary to improve the long-term prognosis of cardiovascular patients. Moholdt et al. reported improved long-term exercise adherence after cardiac rehabilitation with HIIT compared with hospital-based group exercise at moderate-to-high intensity (22). The difference in aerobic capacity 30 months after cardiac rehabilitation cessation could be due to not only a greater improvement during HIIT programme duration, but also a higher self-reported physical activity in the HIIT group than in the usual care group. Aamot et al. also revealed excellent self-reported adherence after a 12-month HIIT program (51). The majority of participants (>90%) met the recommended daily level of 30 minutes of moderate physical activity. On the contrary, these reports did not demonstrate precise adherence to the HIIT protocol.

**Discussion**

**Rationale and potential working mechanisms of HIIT**

The rationale for HIIT usage is that it allows for rest periods which make it possible for patients with CHF or CAD to work for short periods of time at a higher intensity. This challenges the heart’s pumping ability beyond that possible during continuous exercise (26, 31). The mechanisms involved in the superiority of HIIT to MCT have not been clearly elucidated. However, there are several potential mechanisms. First, it has been shown that increased peroxisome proliferator activated receptor-γ-coactivator-1α (PGC-1α), regarded as the master regulator of mitochondrial biogenesis in muscle, is related to the enzyme activity of 5’-AMP-activated protein kinase (AMPK), which is activated proportionally to the exercise intensity (10, 52). The reason for the improvement in the aerobic capacity in HIIT can be explained by the following intracellular signaling sequence (53): muscular stimulus by HIIT→increase in AMPK activity in muscle cells→increase in PGC-1α mRNA and protein→increase in the mRNA of the mitochondrial oxygenation enzyme→increase in mitochondrial oxygenation protein→improvement in physical fitness (aerobic capacity) (54). Second, it is reasonable to speculate that higher shear stress in HIIT patients during exercise bouts may trigger greater responses at the cellular and molecular levels, leading to a partial recovery from endothelial dysfunction. Third, Hanssen et al. recently reported another potential reason for the benefits of HIIT (55). They showed the acute effects of interval versus continuous-endurance training on pulse wave reflection in healthy young men. Although initially higher after HIIT, the augmentation index at a set HR declined in the 24-hour follow-up period, indicating favorable effects on pulse-wave reflection compared to MCT. This may result in substantial positive chronic training effects on arterial stiffness in health and cardiovascular disease (55). The training protocol for this study was nearly the same as previously mentioned pivotal studies (25, 26, 31).

**Limitations in previous HIIT studies**

There are some limitations associated with the previous HIIT studies. First, some studies on exercise interventions with HIIT in patients with chronic diseases such as CHF and CAD may involve a self-selected (relatively fit and motivated) sample of participants. Few trials have reported a randomization procedure in sufficient detail to determine whether selection bias may have influenced the study outcomes (11). Second, in nearly all RCTs on HIIT versus MCT, the sample sizes were small. However, a few meta-analyses have been reported (11-14) yielding positive results. In contrast, a recent multicenter RCT (17) did not show an improvement in the VO₂peak with HIIT. There was low adherence to the intensity of HIIT. Thus, when comparing the VO₂peak and other clinical variables between two
groups, it is important that the participants exercise precisely at the prescribed intensities. In addition, one should be very cautious in evaluating the results of RCTs comparing HIIT and MCT on physical fitness and central (cardiac and circulation) and peripheral (skeletal muscle and endothelium) adaptations. Generally, in order to show the superiority of one exercise protocol to another, the two protocols should adjust for total calories. In contrast, there are two schools of thought on how to evaluate the exercise protocol. One important method is to evaluate HIIT efficacy by adjusting for total calories (work load) between HIIT and MCT. Another method (19) is to show the equivalence of the effects of HIIT to MCT at a smaller work load. As such, the method used for calculating the dose of exercise could affect the results (29). For instance, shorter intervals of 30 s and 60 s failed to show any further improvement in the VO2peak when comparing HIIT to MCT. However, this could be related to a lower total dose of exercise. This means that, optimistically, even low doses of HIIT yield a similar improvement in the VO2peak. On the other hand, recent positive HIIT data would be a realistic way to begin HIIT in patients with cardiac disease who are not quite ready for high-intensity exercise. Furthermore, the frequency of high-intensity sessions per week could be gradually increased from one to three times per week. The knowledge of how a short and intensified period of HIIT influences the progression of the VO2peak is not well elucidated. Fewer than four weeks could be too short of a period to obtain differences in the VO2peak and other variables between groups, according to studies shown in Tables 1 and 2. Finally, HIIT could become an element in evidence-based care for patients with cardiovascular disease, and most cardiac rehabilitation programs are likely to utilize programs which incorporate both HIIT and MCT into the exercise regimen. Safety issues, adherence after the exercise period and hard clinical endpoints remain to be examined in future long-term RCTs.

**Conclusion**

Although MCT has been the main training regimen recommended in the guidelines for cardiac rehabilitation, HIIT has been shown to be more effective than MCT with regard to short-term effects from the standpoint of central and peripheral adaptations.

The authors state that they have no Conflict of Interest (COI).

**References**


