High Intensity Interval Training in Patients With Cardiovascular Disease: A Brief Review of Physiologic Adaptations and Suggestions for Future Research

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INTRODUCTION

Over the past 100 years, performance records for many track events have steadily improved—two of which are shown in Table 1—with similar record-breaking trends observed for competitive swimming, cycling, and cross-country skiing. One of the many factors contributing to this consistent improvement in human performance is enhanced training techniques, not the least of which is the use of high-intensity interval training (HIIT). Interval training was systematically formalized and applied to elite athletes some 80 years ago by Drs. Woldemar Gershler and Herbert Reindel, a professor of physical education and a physician, respectively (24). As the name implies, interval training is a series of repeated bouts of higher intensity work intervals alternated with periods of relief (light or mild intensity exercise).

Among athletes, the intermittent nature of HIIT allows for less fatigue because of the relief periods, which leads to the achievement of a higher intensity of effort during the work interval. As a result, the adenosine triphosphate phosphocreatine (ATP-PC) and glycolysis energy systems are used over and over, promoting an increase in the energy capacity of the skeletal muscles (13). Additionally, the multiple recovery or relief bouts associated with HIIT allow stroke volume to reach its highest levels multiple times during a single bout of exercise rather than just one time with a continuous bout of exercise. These repeated bouts may provide a better stimulus for improving maximal stroke volume (4,13).

In addition to HIIT being associated with less fatigue, the higher intensity training stimulus results in more total work being accomplished during a training session and greater improvements in exercise capacity (as measured by maximal or peak oxygen uptake [$\dot{V}O_2$]). The magnitude of physiologic benefit appears to be associated with the accumulated amount of time spent in the higher intensity intervals (8). Based on this, to this day, coaches continue to incorporate HIIT into the training regimens of their athletes, regardless of whether they are training the 800 m athlete involved in high school track or the marathon runner competing in the Olympics.

TABLE 1. Progression of selected world records in men and women.

Men		Women	
Year	**Time**	**Year**	**Time**
The Marathon Run (h:min:s)			
1908	2:55:18	1926	3:40:22
1920	2:32:35	1964	3:27:45
1952	2:20:42	1967	3:07:27
1960	2:15:16	1970	3:02:53
1970	2:09:28	1980	2:30:27
1988	2:06:50	1985	2:21:06
2002	2:05:38	2001	2:19:46
2011	2:03:38	2003	2:15:25
The 1500-Meter Run (min:s)			
1912	3:55.8	—	—
1930	3:49.2	—	—
1941	3:47.6	1967 (June)	4:17.3
1952	3:43.0	1967 (October)	4:15.6
1967	3:31.1	1969	4:10.7
1983	3:30.77	1972	4:01.4
1995	3:27.37	1980	3:52.47
1998	3:26.00	1993	3:50.46

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Given the favorable effects of HIIT on physical performance in athletes, it should come as no surprise that this same method of training found its way into the care of patients at risk for or presenting with a clinically manifest disease. In fact, HIIT was evaluated in the clinical setting more than 25 years ago, when Meyer and coworkers (14) employed an interval method consisting of 30 s work phases and 60 s recovery phases and observed improvements in peak $\dot{V}O_2$, total power output, and training work rate among patients with chronic heart failure.

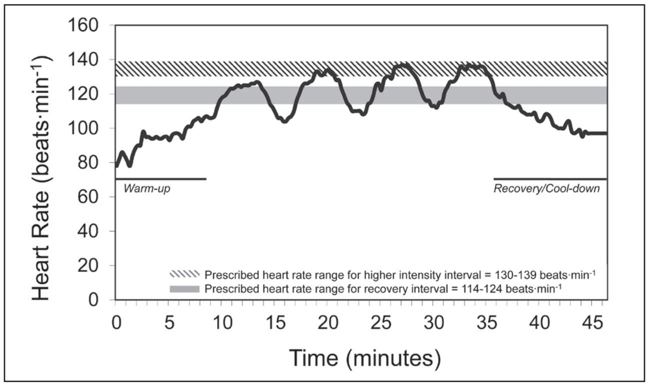
This paper briefly reviews and summarizes the application of HIIT among patients with cardiovascular disease (CVD), with a special focus on physiologic adaptations and programming methods. It also highlights areas that are in need of future research, which is especially true if HIIT is to be considered for incorporation into clinical practice guidelines.

HIIT: THE METHOD

When the rehabilitation of patients with coronary heart disease (CHD) first began to formalize in the mid-1960s through the early 1970s, the intensity, duration, and frequency of exercise were typically prescribed at 70 to 85% of measured peak heart rate, 20 to 60 min, and 3 to 4 $d \cdot wk^{-1}$, respectively (2). Although some mild refinements in this approach to prescribing exercise have evolved over the last 40 years (e.g., intensity is now typically prescribed at 50 to 80% of heart rate reserve [HRR]) (1,3), in general, the method of moderate intensity continuous training (MCT) remains today as the guideline-based recommendation for patients with CHD.

As mentioned earlier, HIIT consists of a series of repeated bouts of higher intensity exercise or work intervals alternated with periods of low to moderate intensity recovery or relief intervals. Figure 1 provides an example of the heart rate response during a single HIIT training session. Although the duration of the work interval and recovery intervals have varied from one study to another, a common model for HIIT prescribes four to five bouts of work for 3 to 4 min each, during which exercise intensity is set as high as 85 to 90% of HRR. These work bouts are interspersed with recovery bouts of similar duration, prescribed at 50 to 70% of HRR. Other HIIT protocols that are less common but still under investigation include work and relief phases that range between 30 s and 90 s (15). Regardless of the prescribed durations for the work and recovery intervals, like all exercise training programs, the interval period should be preceded by a minimum 5 min period of warm-up and followed by a minimum 5 min period of cooldown. In addition to walking and running, HIIT can be used with other modes of exercise, including swimming, cycling, and cross-country skiing.

FIGURE 1. Example of the heart rate (HR) response during high intensity interval training in a patient participating in cardiac rehabilitation.



High intensity interval with a training HR of 130 to 139 $beats \cdot min^{-1}$ corresponds to 80 to 90% of HR reserve. Recovery or relief interval with a training HR of 114 to 124 $beats \cdot min^{-1}$ corresponds to 65 to 75% of HR reserve.

Training Adaptations: High Intensity Interval vs. Moderate Continuous Training

Among patients with a metabolic disorder (e.g., hypertension, metabolic syndrome, and obesity), HIIT often results in a twofold greater mean increase in peak $\dot{V}O_2$ when compared with MCT (Table 2). Similarly, other adaptations in patients with metabolic disorders may also occur and include a greater improvement in brachial artery flow-mediated dilation with HIIT (versus MCT) (18,23,29) and improvement in resting heart rate, body composition, and ventilatory threshold (25).

Most of the research to date addressing the impact of HIIT in people with clinically manifest disease involves patients with CVD. Table 3 summarizes exercise intensity programming and benefits from select studies involving patients with heart failure or CHD. Most programs were 8 wk to 6 mo in duration and many yielded a greater than twofold mean increase in peak $\dot{V}O_2$ with HIIT versus MCT. Despite the relatively small sample sizes in these trials, the single center nature of each trial, and the fact that several of the trials were conducted at the same center, the totality of the evidence to date suggests that among patients with CVD, HIIT improves exercise capacity to a greater extent than MCT. Likewise, other observations that report on the potential effects of HIIT on other physiologic parameters include an increase in ejection fraction (32), improved brachial artery flow-mediated dilation (19,32), and improved peak oxygen pulse (5).

One important subgroup of patients with CVD that has undergone much needed investigation relative to the impact of HIIT involves patients with chronic heart failure. Among the trials conducted in these patients to date, several studies by Wisloff and colleagues provide insight into the programming options and training adaptations associated with HIIT. In 2007, they reported a study (32) in which they randomized 27 patients to either MCT, no exercise control, or HIIT, with the latter group undergoing 12 wk of training three times per week at an intensity during four work intervals of 4 min each that was equivalent to 95% of peak HR. Patients in the HIIT group showed a greater than 6 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in peak $\dot{V}O_2$, whereas no change and a 1.9 $mL \cdot kg^{-1} \cdot$

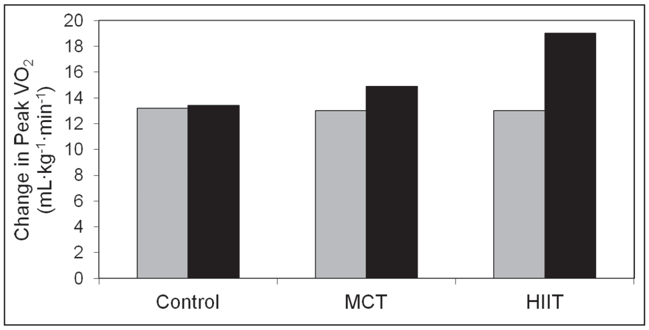
TABLE 2. Characteristics of selected exercise trials involving higher intensity interval training in patients with a metabolic disorder.

First Author, Year (reference)	Metabolic Disorder	Mean Age Men/Women (n)	Exercise Intensity	Key Findings
Tjonna et al., 2008 (29)	Metabolic syndrome	53 yr 13/15	HIIT = 4×4 min work intervals at 90% of peak HR MCT = 70% of peak HR Control = usual care advice	• Twofold greater increase in peak $\dot{V}O_2$ with HIIT vs. MCT; peak O_2 pulse also improved • Risk factors comprising metabolic syndrome improved
Schjerve et al., 2008 (23)	Obesity	40 yr 8/32	HIIT = 4×4 min work intervals at 85 to 95% of peak HR MCT = 60 to 70% of peak HR ST = 4 sets of 5 repetitions at 90% 1 repetition maximum	• 33% increase in peak $\dot{V}O_2$ with HIIT was 2 to 3-fold greater than other groups • Greater increase in flow mediated dilation with HIIT
Wallman et al., 2009 (30)	Overweight, obesity	42 yr 6/18	HIIT = 1 min at 90 to 105% of peak $\dot{V}O_2$ MCT = 50 to 65% of peak $\dot{V}O_2$ Control = no exercise	• Both exercise groups similarly improved peak $\dot{V}O_2$ and time to exhaustion • HIIT group showed larger reduction in fat mass
Stensvold et al., 2010 (26)	Metabolic syndrome	50 yr 26/17	HIIT = 4×4 min work intervals at 90 to 95% of peak HR ST = 3 sets of 8 to 12 repetitions at 80% of 1 repetition maximum HIIT + ST = HIIT 2 $d \cdot wk^{-1}$; ST 1 $d \cdot wk^{-1}$ Control = no prescribed exercise	• Peak $\dot{V}O_2$ increased >10% with HIIT and HIIT + ST • Endothelial function improved in all 3 exercise groups
Molmen-Hansen et al., 2011 (18)	Hypertension	52 yr 49/39	HIIT = 85 to 90% of peak $\dot{V}O_2$ MCT = 60% of peak $\dot{V}O_2$ Control = no exercise	• Peak $\dot{V}O_2$ improved 15% with HIIT versus 5% with MCT • Systolic and diastolic ambulatory blood pressures both reduced more with HIIT versus MCT
Sijie et al., 2012 (25)	Overweight	19-20 yr 0/60	HIIT = work intervals at 85% of peak $\dot{V}O_2$ MCT = 50% of peak $\dot{V}O_2$ Control = no exercise	• Resting HR, peak $\dot{V}O_2$, and ejection fraction improved with training; effect was greater with HIIT than MCT

HIIT = high intensity interval training; MCT = moderate intensity continuous training; HR = heart rate; $\dot{V}O_2$ = oxygen uptake; ST = strength training

min^{-1} increase were observed among patients randomized to the control group and MCT, respectively (Figure 2). Greater improvements in flow mediated dilation and measures of skeletal muscle histochemistry were also noted with HIIT versus either MCT or a control.

FIGURE 2. Change (baseline to follow-up at 12 wk) in peak oxygen uptake ($\dot{V}O_2$) among patients randomized to no exercise control, moderate continuous training (MCT), and high intensity interval training (HIIT).



Adapted from Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, Tjønna AE, Helgerud J, Slørdahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen Ø, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115:3086-94.

Exercise Programming Using HIIT

An important question concerning the utilization of HIIT pertains to which patients are eligible; specifically, are there subgroups of patients (e.g., atrial fibrillation, patients with pacemakers and/or implantable cardiac defibrillators, patients with exercise-induced ischemia, and patients with moderate to severe aortic stenosis) in whom HIIT should not be used? At present, this issue is not well addressed in the literature. Most exercise trials employing HIIT to date have used relatively younger patients (Tables 2 and 3) and most of these studies predominately involved men. Additionally, all trials have prescribed exercise intensity as a percentage of a peak parameter (e.g., heart rate, $\dot{V}O_2$), which means a symptom-limited exercise test is needed before HIIT is initiated to ensure that exercise intensity is properly prescribed. This also means that the not uncommon practice of prescribing exercise intensity in cardiac rehabilitation in the absence of a previously completed symptom-limited exercise test must be avoided if HIIT is deployed (1). In addition to an interest and willingness of patients to participate in HIIT, they should also be free of exercise-induced ischemia, exercise-induced arrhythmias, and complicating musculoskeletal or metabolic disorders.

Until the use of HIIT becomes part of guideline recommendations for patients with CVD or in those patients in whom HIIT should not be undertaken are better defined, a similar but alternate model to employ is moderate intensity

TABLE 3. Characteristics of selected exercise trials involving higher intensity interval training in patients with cardiovascular disease.

First Author, Year (reference)	Cardiovascular Disorder	Mean Age Men/Women (n)	Exercise Intensity	Key Findings
Rognmo et al., 2004 (21)	Coronary heart disease	62 yr 14/3	HIIT = 4×4 min work intervals at 80 to 90% of peak $\dot{V}O_2$ MCT = 50 to 60% of peak $\dot{V}O_2$	• Greater than twofold increase in peak $\dot{V}O_2$ among HIIT versus MCT subjects
Warburton et al., 2005 (31)	Coronary heart disease	56 yr 14/0	HIIT = 7×2 min work intervals at 85 to 95% of HR reserve MCT = 30 min at 65% of HR reserve	• Both groups equally improved peak $\dot{V}O_2$ and anaerobic threshold was improved to a greater extent with HIIT
Wisloff et al., 2007 (32)	Heart failure	76 yr 20/7	HIIT = 4×4 min work intervals at 90 to 95% of peak HR MCT = 70 to 75% of peak HR Control = usual care plus 47 min of walking once every 3 wk at 70% of peak HR	• Peak $\dot{V}O_2$ increased 6.0, 1.9, and 0.2 $mL \cdot kg^{-1} \cdot min^{-1}$ in HIIT, MCT, and control, respectively • LV function, endothelial function, and mitochondrial function improved more with HIIT
Moholdt et al., 2009 (16)	Coronary heart disease	61 yr 48/11	HIIT = 4×4 min work intervals at 90% of peak HR MCT = 70% of peak HR	• 18.8% and 8.8% increase in peak $\dot{V}O_2$ in HIIT and MCT, respectively • No difference between groups for quality of life or biomarkers
Munk et al., 2009 (19)	Coronary heart disease	59 yr 33/7	HIIT = 4 min work intervals at 80 to 90% of peak HR Control = usual care	• No difference in coronary artery minimal luminal diameter; net luminal gain and late luminal loss improved with HIIT • Peak $\dot{V}O_2$,ventilatory threshold, power output, and resting HR all improved with HIIT
Hermann et al., 2011 (7)	Cardiac transplant	50 yr 25/5	HIIT = repeated blocks of 4 min/2 min/30 s work intervals at 80%, 85%, and 90% of peak $\dot{V}O_2$, respectively Control = no exercise training	• Peak $\dot{V}O_2$ increased 4.4 $mL \cdot kg^{-1} \cdot min^{-1}$ with HIIT and decreased 1.2 $mL \cdot kg^{-1} \cdot min^{-1}$ in controls • Flow mediated dilation improved with HIIT; few differences between group in biomarkers
Moholdt et al., 2011 (17)	Myocardial infarction	57 yr 85/17	HIIT = 4×4 min work intervals at 90% of peak HR MCT = moderate to high intensity	• Greater improvements in peak $\dot{V}O_2$ at 12 wk, 6 mo, and 30 mo with HIIT versus control; at 30 mo, increase in $\dot{V}O_2$ among HIIT was 7% • No differences observed between for quality of life
Nytroen et al., 2012 (20)	Cardiac transplant	51 yr 29/19	HIIT = 4×4 min work intervals at 85 to 95% of peak HR Control = usual care	• HIIT resulted in a 3.6 $mL \cdot kg^{-1} \cdot min^{-1}$ greater increase in peak $\dot{V}O_2$ versus control • Resting and peak HR and HR reserve also improved with HIIT versus control
Freyssin et al., 2012 (5)	Heart failure	54 yr 13/13	HIIT = 3 sessions × 12 repetitions of 30 s at estimated 80 to 120% of peak power output MCT = HR at ventilatory threshold	• Peak $\dot{V}O_2$, exercise duration, and peak O_2 pulse improved more with HIIT than MCT • Scores evaluating anxiety and depression improved similarly in both groups

HIIT = high intensity interval training; MCT = moderate intensity continuous training; HR = heart rate; $\dot{V}O_2$ = oxygen uptake; ST = strength training

interval training (MIIT). This method of training is used often at Henry Ford Hospital and includes the same frequency (one to three times per week) and duration (four work bouts of 4 to 5 min each, interspersed with 3 min recovery or relief bouts) of training employed with HIIT. However, instead of training patients using work intervals at 85 to 90% of HRR, we use 70 to 80% of HRR. During the recovery intervals for MIIT, training intensity is set at 60 to 70% of HRR.

We have observed that using this approach in routine patients participating in our cardiac rehabilitation program accomplishes three things. First, it incorporates the intermittent and the potentially more favorable effects of interval work without having patients exceed current guidelines for prescribing exercise. Second, it helps "force" patients to spend a portion of their aerobic training at the upper end of their training range, which at times can be an issue because some patients set a pace near the lower to middle levels of their training range and stay there for the entire bout of exercise. In contrast, MIIT provides a structured sequence that patients follow—one that systematically and periodically takes them up to as high as 80% of HRR. Third, anecdotally, we observe that patients using MIIT (or using HIIT in one of our research trials) report that they "enjoy" their workouts better. They often report getting a "better" workout with interval training regardless if they used HIIT or MIIT. Like HIIT, the use of MIIT in patients with CVD should only be employed if results from a recently completed symptom-limited exercise test are available.

Future Research

Although the use of HIIT in patients with CVD holds promise, especially as it pertains to inducing greater gains in exercise capacity, three well-defined areas of research remain: clinical integration, safety, and impact on clinical endpoints. Concerning clinical integration, the process by which HIIT is inserted into the care of patients with CVD requires additional investigation, such as testing the incorporation of this method of training into the typical cardiac rehabilitation setting (5,22,31). One possible reason for the absence of abundant research that tests the application of HIIT in cardiac rehabilitation is that most trials to date have involved an isocaloric model that dictates differences in exercise duration. Specifically, exercise time is typically less in the HIIT group due to the increase in intensity during the work intervals, and when matched for caloric expenditure, exercise duration is longer in the MCT group. Such an approach allows for the direct comparison of training adaptations when the training stimulus (e.g., total kilocalorie expenditure) is equalized. Clearly, more work is needed that tests the efficacy and how to best incorporate HIIT into the typical phase 2 cardiac rehabilitation model—that being a model in which patients undergo three supervised sessions per week, with most receiving a fixed duration of usually only 30 min for aerobic training, that is proceeded by a 5 min period of warm-up and followed by a 5 min cooldown period.

Although many of the exercise trials to date involving HIIT report few, if any, safety issues, all of them included a sample size that is insufficient to assess the safety of this method of training. A recent report by Rognmo and colleagues (22) begins to address the issue of safety by using a retrospective analysis involving 4,846 patients with CVD (mean age: 58 yr). They report on more than 175,000 exercise training hours gathered from three different rehabilitation units in Norway. On average, each patient completed 37 cardiac rehabilitation sessions, with the majority of these sessions being MCT and the balance HIIT. An event was defined as a cardiac arrest or myocardial infarction during exercise or within 1 h afterward. They observed one fatal cardiac arrest per 129,456 exercise hours of MCT and two nonfatal cardiac arrests per 46,364 HIIT sessions (1 per 23,182 exercise hours). Based on the "low events rates" observed in both groups, the authors recommended that HIIT be considered in the rehabilitation of patients with CVD.

Although promising, in the aforementioned study aimed at assessing the safety of HIIT, the calculated power is only 23%. More importantly, a close look at the authors' safety data suggests that MCT might be safer than HIIT (MCT: 1 event per 129,456 h of exercise versus HIIT: 1 event per 23,182 h of exercise). Supporting this potential concern is the 2005 paper by Leon et al. (12), who estimated the rate for major cardiovascular events in cardiac rehabilitation programs, which traditionally use MCT, to be between approximately 1 per 50,000 to 1 per 120,000 patient-hours. Realizing the difficulty associated with securing funding for and conducting a trial sufficiently powered to assess safety, investigators can indirectly get at the issue of safety by first conducting more randomized trials that assess the effect of HIIT on other endpoints of interest (e.g., cardiovascular characteristics, the pathophysiology of the disease, and clinical outcomes). From these studies, safety data should also be collected and subsequently combined for a better determination of safety by using a meta-analytic approach. One such trial that is presently under way at seven centers in Europe but is underpowered to determine safety ($N = 200$ subjects) is SMART-HF (Controlled Study of Myocardial Recovery after Interval Training in Heart Failure). The primary aim of SMART-HF is to evaluate the effects of HIIT on left ventricular end-diastolic diameter (27).

A final vital area of research that is needed for HIIT relative to its acceptance and incorporation into routine patient care pertains to its impact on subsequent clinical endpoints, a line of study that has not undergone any investigation to date. Using surrogate logic, one might hypothesize that because peak $\dot{V}O_2$ is related to mortality in patients with CVD (9) and given that HIIT likely provides greater improvements in this measure of exercise capacity than MCT, then HIIT might result in a greater reduction in risk for mortality or other clinical endpoints. Tempting as it might be, such logic does not always pan out. The clinical benefit of MCT in patients with CVD is well appreciated, equating to a 15 to 25% reduction in risk for clinical events (6,10,11,28). Simply, before deciding to incorporate HIIT into clinical practice guidelines, randomized trials would be helpful to determine the effects of HIIT on mortality and other meaningful clinical endpoints. At minimum, data are needed to ensure that the clinical benefits derived from HIIT are at least equivalent to those observed with MCT.

SUMMARY

The role of exercise in the care of patients with CVD has now enjoyed more than four decades of research and practice. Although most of this work has utilized MCT, several recent studies now also suggest a potential role for HIIT. Specifically, the totality of the data to date indicate that HIIT improves exercise capacity to a greater extent than MCT alone. In addition, other physiologic training effects (e.g., resting heart rate, endothelial function) also appear to improve more so with HIIT than MCT. However, much work remains relative to (a) the application of HIIT in older patients and women; (b) the proper methods for incorporating HIIT into the cardiac rehabilitation setting; (c) the safety of HIIT; and (d) the equivalency of clinical benefits between HIIT and MCT. Systematically addressing these issues will allow us to better appreciate how and to what extent HIIT should be incorporated into guideline-based care recommendations for patients with CVD.

Keywords: physiologic adaptations, safety, clinical outcomes

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REVIEWS