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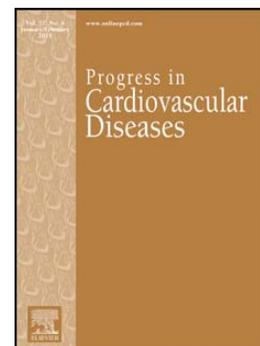
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High Intensity Interval Training For Maximizing Health Outcomes

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Abstract

Regular physical activity or exercise training are important actions to improve cardiorespiratory fitness and maintain health throughout life. There is solid evidence that exercise is an effective preventative strategy against at least 25 medical conditions, including cardiovascular disease, stroke, hypertension, colon and breast cancer, and type 2 diabetes. Traditionally, endurance exercise training (ET) to improve health related outcomes has consisted of low- to moderate ET intensity. However, a growing body of evidence suggests that higher exercise intensities may be superior to moderate intensity for maximizing health outcomes. The primary objective of this review is to discuss how aerobic high-intensity interval training (HIIT) as compared to moderate continuous training may maximize outcomes, and to provide practical advices for successful clinical and home-based HIIT.

Key Words: HIIT, Physical activity, exercise training, cardiorespiratory fitness, exercise intensity, interval training

Alphabetical list of abbreviations:

BP – blood pressure

CHD – coronary heart disease

CPET – cardiopulmonary exercise testing

CR – cardiac rehabilitation

CRF – cardiorespiratory fitness

CV – cardiovascular

CVD – cardiovascular disease

DBP – diastolic blood pressure

EF – ejection fraction

ET – exercise training

HF – heart failure

HFpEF – heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

HIIT – high intensity interval training

HR – heart rate

HR_{max} – maximal heart rate

HR_{peak} – peak heart rate

HTN - hypertension

LV – left ventricle

LVEF – left ventricular ejection fraction

MET – metabolic equivalent

MICT – moderate intensity continuous training

PA – physical activity

RCTs – randomized controlled trials

SIT – sprint interval training

SBP – systolic blood pressure

T2D – type 2 diabetes

VO_{2peak} – peak oxygen uptake

Epidemiological Evidence of the Importance of High Exercise Intensity for Mortality Reduction

Epidemiological evidence on all-cause and disease-specific mortality demonstrates that low- and moderate intensity exercise is associated with protection against chronic diseases, especially cardiovascular (CV) disease (CVD),¹⁻³ and that risk reduction can be achieved at quite low volumes of exercise.⁴ For instance, the Nurses' Health Study found that moderate intensity activity, even as little as once a week, was sufficient to reduce mortality risk by 22%.⁵ Another study involving 55 137 healthy adults found that running, even as little as 5 to 10 minutes per day, was associated with markedly reduced risks of death from all causes and from CVD.⁶ In addition, "weekend warrior" and other physical activity (PA) patterns characterized by one or two sessions per week may be sufficient for significantly reducing all-cause-, CVD-, and cancer mortality risks.^{7, 8} A meta-analysis of prospective cohort studies on leisure time PA found marked risk reduction in all-cause mortality in active subjects compared to sedentary persons.⁹ Specifically, a dose-response curve was found, especially from sedentary subjects to those with mild and moderate PA level. A growing body of evidence however suggest that exercise involving high-intensity may induce larger health benefits relative to the time spent on PA, and that even small amounts of vigorous PA increases the benefits of moderate PA alone.^{10, 11} A recent Australian study found an inverse dose-response relationship between proportion of vigorous PA and mortality,¹² leading to the conclusion that "vigorous activities should be endorsed in clinical and public health activity guidelines to maximize the benefits of PA". To this end, a large study from Taiwan demonstrated that 15 minutes of daily vigorous intensity PA resulted in similar all-cause mortality risk reduction (~25%) as 60 minutes of daily PA at moderate intensity.¹³ Similarly, our research group found that one single weekly bout of high intensity (~90% of peak heart rate) exercise was associated with a similar or higher protection against premature all-cause and CVD mortality compared to several hours of moderate intensity exercise.⁸ Finally, a meta-analysis involving 459 833 participants free from CVD at baseline concluded that walking pace was a stronger independent predictor of overall mortality risk compared with walking volume (48% versus 26% risk reductions, respectively),¹⁴ indicating the impact of high exercise intensity to promote mortality risk reduction.

Exercise Intensity in Coronary Heart Disease (CHD) Risk Reduction

Substantial evidence has established the significance of high levels of PA, exercise training (ET), and overall cardiorespiratory fitness (CRF), not only for mortality benefits, but also for prevention and treatment of CHD.¹⁵ Two studies found an inverse association between the relative intensity of PA and risk of developing CHD, independent of the amount of total PA performed.^{16, 17} Long-term aerobic ET conducted at higher intensities is associated with a reduced risk of future CVD compared to lower intensities, suggesting that the former may confer greater cardioprotective benefits.^{18, 19} Swain and Franklin examined the role that ET intensity has on the risk factors for and incidence of CHD;²⁰ they included both epidemiologic studies that evaluated the benefits of PA of varying intensity levels, and clinical trials with ET at different intensities, while controlling for the total energy expenditure. The epidemiological findings showed greater reduction in risk of CHD with high- compared to moderate intensity PA and more favorable risk profiles for individuals engaged in high-, as opposed to moderate intensity PA.²⁰ The clinical trials generally reported greater improvements after high- compared to moderate intensity ET for diastolic blood pressure (BP; DBP), glucose control, and aerobic capacity, but reported no intensity effect on improvements in systolic BP (SBP), lipid profile, or body fat loss. The authors concluded that, if the total energy expenditure of ET is held constant, ET performed at high intensity appears to induce greater cardioprotective effects than exercise at moderate intensity.²⁰ A recent study found that high intensity ET had greater influence on most of the components of the metabolic syndrome compared to equivalent energy expenditure of moderate intensity ET.²¹

Cardiorespiratory fitness and Exercise Intensity

Although PA levels are strongly associated with reduced all-cause mortality,²² the association appears to disappear after adjustment for CRF.^{23, 24} There are clear indications that low CRF is a CVD risk factor distinctly from PA,²⁵ that higher levels of CRF protects against CVD- and all-cause mortality,²⁶⁻²⁸ and that positive changes in CRF reduces CVD risk factors,²⁹ as well as all-cause mortality.³⁰ In fact, CRF is found to be a more powerful predictor of mortality than traditional risk factors, such as hypertension (HTN), smoking, obesity, hyperlipidemia, and type 2 diabetes (T2D).³¹ Peak oxygen consumption (VO_{2peak}) measured objectively during a cardiopulmonary exercise test (CPET) to exhaustion, is considered the gold-standard measure of CRF, because it is an integrated measure of

the body's ability to take in, transport and utilize oxygen to fuel aerobic work.³² Directly measured VO_{2peak} is a strong independent predictor of mortality,^{33, 34} and improving VO_{2peak} is found to improve prognosis. Vanhees et al.³⁵ measured VO_{2peak} before and after a 3-month ET period in 417 CHD patients and followed them for a mean duration of 6.2 years. Oxygen uptake increased by 33% after the training period. During the total follow-up of 2,583 patient-years, 37 patients died; CVD mortality was inversely related with changes in CRF, with a 1% increase in VO_{2peak} after ET associated with a 2% decrease in CVD mortality.³⁵ Given the prognostic value of changes in VO_{2peak} , it would be important to know how to effectively improving CRF. There is epidemiological evidence that PA at high intensity is associated with substantially higher VO_{2peak} . For instance, Norwegian men reporting ~49 minutes/week of very-vigorous intensity (defined as >90% of VO_{2peak}) measured almost 6 $ml \cdot kg^{-1} \cdot min^{-1}$ higher VO_{2peak} compared to those exercising at moderate intensities (~70% of VO_{2peak}).³⁶ Moderate intensity exercise performed for more than 216 minutes/week resulted in VO_{2peak} levels that were about 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (1 metabolic equivalent, MET) lower than 49 minutes of weekly very-vigorous PA. Similar findings were observed in women. A recent meta-analysis of 55 randomized controlled trials among CHD and heart failure (HF) patients showed that trials with higher average exercise intensity achieved greater improvements in VO_{2peak} .³⁷ Specifically, each 10% increase in exercise intensity was associated with a 1 $ml \cdot kg^{-1} \cdot min^{-1}$ improvement in VO_{2peak} . There was no strong evidence to support any other intervention-, patient- or trial factors to be predictive of the heterogeneity in the CRF response. Altogether, this points to exercise intensity rather than duration or frequency of exercise, as the most important variable in determining CRF.

Essentials of High Intensity Interval Training (HIIT)

Interval ET with HIIT may be a particularly effective way for increasing VO_{2peak} and improve CV health compared to moderate intensity continuous training (MICT). The terminology used to describe HIIT unfortunately varies across research groups. Here we use the definition suggested recently using HIIT when the intervals' are of aerobic character and the target intensity is between 85-95% of peak heart rate (HR_{peak}),³⁸ with a distinction to more sprint interval training (SIT), using low-volume supramaximal (i.e. all-out performance) ET.³⁹ The principle of HIIT is based upon high intensity aerobic ET bouts (but still at an intensity below VO_{2peak}) that are separated by periods of lower intensities that allow for recovery, making an individual able to reengage in high-intensity ET (Figure 1). Typically, HIIT is

performed in activities involving dynamical work with large muscle mass (such as brisk uphill walking, running or cycling), at intensities close to peak heart rate (HR_{peak} : 85-95%) or VO_{2peak} (80-90%) for 4 minutes. The recovery periods consist of walking or “jogging” at considerably lower intensities (60-70% of HR_{peak} of the intensity during the high-intensity interval) for approximately 2-3 minutes.³⁸ It is important to note that the ET intensity is relative to the individual's VO_{2peak} and HR_{peak} and that every participant needs to be tailored individually such that two subjects exercising next to each other may look very different, one running very fast and the other walking, although they both are exercising at the same relative intensity. The differences stem from different CRF levels, but they would be experiencing the same relative exercise stress. This is illustrated in Figure 2 where two individuals with different CRF levels and HR_{peak} (Olympic athlete and CHD patient) have performed 4x4 minutes HIIT with the aim of reaching 90-95% of HR_{peak} . They possess widely different absolute heart rates (beats/min) and energy consumptions; however, they exercise at identical relative intensity (percentage of HR_{peak}). This also raises the point that HR_{peak} (preferably as close as possible to the individual's true maximal heart rate HR_{max}) ideally should be measured for each individual before engaging with HIIT, in order to control the relative ET intensity properly. The training HR could then be monitored during the course of the HIIT program in order to adjust the absolute workload so that the relative exercise intensity remains constant as exercise capacity improves. However, if exercise testing prior to interval training is not possible, a rule of thumb is that the relative strain during the work-bouts should be perceived as 16-18 on the Borg scale,⁴⁰ i.e. heavy breathing without getting too stiff in the legs. In addition, one should aim to maintain the chosen workload during all the repeated intervals during a HIIT session. If unable to maintain exercise intensity throughout the exercise session, a too high starting workload has been chosen. If a fifth or sixth interval is easily manageable after having completed the prescribed 4x4 minute intervals, a too low exercise intensity has been chosen. In addition, if the 3 minutes active recovery period feels very short, exercise intensity is likely too high and may interfere with the ability to complete a 4x4 minute HIIT session. If the three-minute active brake feels too long, a too low exercise intensity has been chosen. A typical HIIT session consists of 4x4 minutes interval, but HIIT can well be performed as 4x5 minutes, 3x5 minutes, 5x3 minutes, or something similar. Importantly, as illustrated in Figure 1 & 2, the increase in HR during HIIT occurs gradually during the first 1-3 minutes of the intervals. Typically, it takes longer time to reach 90% of HR_{peak} during the first interval. Reaching 90% of HR_{peak} at the end of the first 4-minute

interval is normal, and an acceptable performance. In the continuation of the interval session, the aim is to reach higher in the target heart rate zone, 1-3 minutes into the intervals (as illustrated by the gradual increase in heart rate from intervals 1 – 4 in figures 1 and 2). It is crucial to avoid “sprinting” exercise to reach target intensity exercise zone as soon as possible and allow for good dynamic working conditions. The ET mode used during HIIT may thus be important. Uphill walking or running facilitate good dynamical work for most individuals, and the pace is actually rather slow. It is noteworthy that peak exercise during stationary biking normally produces 10-15% lower VO_{2peak} compared to treadmill walking or running.⁴¹ If a CPET is performed before training, it is therefore crucial to test HR_{peak}/VO_{2peak} in the specific exercise mode used during ET. However, testing of VO_{2peak} is not of vital importance before performing interval training. It is more desirable to test HR_{peak} , but also that is not a prerequisite. One may instead reach the targeted intensity zone of 85-95% HR_{peak} guided by that one should be breathing heavily without being able to hold a conversation going, but still be able to continue for the whole 4-minute period, and 16-18 on the Borg scale of perceived exertion.

HIIT for Improving CRF in Health and Disease

In a clinical setting, HIIT is found to be an effective way of performing high intensity ET and developing a high level of CRF.⁴² In most cases, the studies have shown that ET using HIIT compared to MICT is more effective for improving health outcomes (VO_{2peak} , ventricular function, endothelial function, quality of life).⁴³ A meta-analysis of 28 trials confirmed that both MICT and HIIT elicit large improvements in VO_{2peak} of healthy, young to middle-aged adults with the effects being greater for the less fit⁴². Importantly, when comparing the two modes of training, the gains in VO_{2peak} were greater following HIIT. In most single center studies, HIIT has been found more beneficial for improving VO_{2peak} in healthy individuals,^{44, 45} HF,^{43, 46-49} CHD,^{43, 50, 51} heart transplant recipients,⁵² individuals with the metabolic syndrome,⁵³ HTN,⁵⁴ obese individuals,⁵⁵ and in patients with T2D.⁵⁶ On the other hand, a recent randomized study found that HIIT was not superior to other forms of endurance ET during cardiac rehabilitation (CR).⁵⁷ Two larger multicenter studies in CHD⁵⁸ and HF patients with reduced left ventricle (LV) ejection fraction (EF) (HFREF)⁵⁹ that were unable to reproduce the intensity difference outcomes found in single center studies supported this finding. However, a systematic review and meta-analysis including 10 randomized controlled trials (RCTs) in patients with lifestyle-induced cardiometabolic disease identified that HIIT gave larger adaptations than MICT.³⁸ HIIT significantly

improved VO_{2peak} by almost double that of MICT (19.4% vs 10.3%). The results also showed a variety of CVD risk factors adaptations occurring significantly more with HIIT compared with MICT including: BP; high density lipoproteins, triglycerides and fasting glucose, oxidative stress and inflammation, body weight, adiponectin, insulin sensitivity and β -cell function.³⁸ The authors stated that this should translate into greater decreases in risks of morbidity and all-cause mortality (due to the power of CRF as a predictor of death). They further claimed that incorporation of HIIT into a CR program would be a more achievable way for people with chronic disease to reach a level of ET that promotes health-enhancing benefits. In addition, from a practical point of view, it has been pointed out that in severely deconditioned patients, as for instance those with HF, normal PA of daily living actually corresponds to high intensity ET.⁶⁰ Hence, using the same intensity during structured ET may in a short period of time increase these patients' CRF level, making daily tasks less strenuous. Improvements in VO_{2peak} have also been studied in two meta-analyses in CHD patients, where HIIT was found to be more effective than MICT for the improvement of both VO_{2peak} ^{61, 62} and the anaerobic threshold,⁶¹ although MICT was associated with a more pronounced numerical decline in patients' resting HR and body weight.⁶² No difference related to exercise intensity was however, found regarding CHD patients' metabolic health.⁶² In a systematic review and meta-analysis in HF patients with preserved and/or reduced LV ejection fraction (EF) (LVEF), HIIT was found superior to MICT for improving VO_{2peak} , while MICT was more effective in reducing body weight.⁶³ Also among patients with HF, it seems that as ET intensity increases, so does the magnitude of improvement in CRF.^{64, 65} A meta-analysis involving seven studies in clinically stable HFrEF patients concluded that HIIT was more effective than MICT for improving VO_{2peak} .⁴⁹

CV Adaptations to HIIT

The observation that HIIT gives about twice the benefit of MICT regarding improvement of VO_{2peak} ^{38, 66, 67} may be of importance since VO_{2peak} constitutes an important prognostic parameter for CVD morbidity and mortality.^{35, 68, 69} HIIT may also be required for a positive effect to occur on LV structure and function. Two studies in young, healthy individuals found HIIT effective for improving maximal stroke volume.^{44, 70} A study in patients with HTN found significantly improved stroke volume, LV end-diastolic volume and EF, as well as HTN⁵⁴ after HIIT compared to MICT. Our research group has previously identified several different patterns of response to programs utilizing HIIT or MICT in

patients with established CVD or dysfunction. In patients with CHD, HF and T2D, an attenuation of LV remodeling and systolic- and diastolic function were observed only after high-intensity ET.^{46, 56, 66, 67, 71} In these RCTs, both strain rate and myocardial tissue imaging echocardiographic evaluation of ventricular function suggest that high-, but not moderate-intensity, ET improves parameters related to both systolic and diastolic LV function.^{46, 56, 71} In fact, 36 sessions of HIIT in HF patients reduced LV volume and diameter, increased LVEF and systolic and diastolic blood flow, as well as several systolic and diastolic motion parameters.⁴⁶ Supportive to this, Fu et al.⁴⁷ demonstrated improved pumping function with enhanced peak cardiac power index in HFrEF patients after HIIT [but not in HF patients with preserved EF (HFpEF)]. On the other hand, Iellamo et al.⁷² saw no difference in cardiac output, stroke volume, LVEF or VO_{2peak} in HFrEF patients after HIIT and MICT, despite a 22% increase in VO_{2peak} in both ET groups. No exercise HR or workload data was presented making comparison of exercise intensity and workload with other studies challenging. These findings were supported by a meta-analysis involving seven studies in clinically stable patients with HFrEF, which concluded that HIIT was not more effective than MICT for improving LVEF at rest.⁴⁹ In the multicenter SMART-EX-HF study, LV end-diastolic diameter was significantly reduced after HIIT compared to the control group after 12 weeks of supervised ET; however, there was no difference between the HIIT and the MICT group.⁵⁹ A key adaptation to HIIT in comparison to MICT is an increased maximal stroke volume.^{48, 73, 74} In HFrEF patients, ET-induced increase in maximal stroke volume is associated with reduced resting LV end-diastolic volume,⁷⁵ and increased LVEF and reduced total peripheral resistance.⁴⁷ Peak oxygen pulse, a surrogate measure of peak stroke volume, and an important prognostic marker in HFrEF,⁷⁶ did not change after ET in the SMART-EX-HF (Baseline to 12-weeks median values; HIIT, 11.6 to 12.3 ml·beats⁻¹ and MICT, 11.0 to 12.3 ml·beats⁻¹). As with VO_{2peak} , there were no group differences in peak oxygen pulse.⁵⁹ In the multicenter SAINT-EX-CAD study, peak oxygen pulse increased in both the HIIT (14.8 to 16.6 ml·beats⁻¹) and the MICT group (14.7 to 16.2 ml·beats⁻¹) from baseline to 12 weeks; however there was no difference between groups.⁵⁸ These two studies confirm a moderate central adaptation to ET, independent of ET intensity^{58, 59} as to be expected from comparable studies in HFrEF patients.^{47, 48} In these studies, it is unknown if peripheral limitations to ET, such as high degree of muscle wasting, limited patient's ability to exercise at high intensity,⁶⁰ however, a large overlap in ET intensity between groups was seen in both studies and could be a key factor explaining no difference between groups.^{58, 59}

Feasibility of ET Prescription of HIIT

The few multicenter studies having compared HIIT against MICT in patients with CVD have highlighted the challenges of practical feasibility of HIIT in CR. In particular, adherence to ET intensity and continuously increasing ET workload throughout the ET period may seem challenging in multicenter studies, possibly also reflecting daily clinical practice.

Importance of ET Intensity

In the SAINTEX-CAD study, mean ET intensity was 88% in the HIIT group and 80% in the MICT group.⁵⁸ In the SMARTEX-HF study, the median ET intensity was 90% of HR_{peak} in HIIT and 77% of HR_{peak} in MICT; however, in the HIIT group, 51% trained at lower intensity, whereas in the MICT group 80% trained at higher intensity than prescribed and there were a large intensity crossover between groups and variability within groups.⁵⁹ In comparison, Wisløff et al. report no challenges concerning adherence to target ET intensity (HIIT; 92-93% of HR_{peak} and MCT; 73-74% of HR_{peak}).⁴⁶ The importance of ET intensity on exercise response is well documented in high- versus moderate intensity ET,⁵⁰ but also within the HIIT zone.⁷⁷ A recent analysis showed that CHD patients performing HIIT above 92% HR_{peak} had a $\sim 2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ larger increase in VO_{2peak} compared to patients exercising below 92% after 12 weeks of exercise. The study further showed that higher intensity induced larger improvement in VO_{2peak} , both with VO_{2peak} as a categorical and a continuous variable.⁷⁷ The low feasibility to ET intensity prescription in HIIT could be due to the patients' ability and/or motivation to exercise at high intensity,⁷⁸ or the challenges to implement the ET program in a multicenter setting. In CHD patients, coaching in combination with use of HR monitors were necessary to achieve exercise within target HIIT intensity zone. Without active coaching, patients chose to exercise below 85% of HR_{peak} , despite use of HR monitors and knowledge of target intensity.⁷⁸ This may indicate that the implementation of HIIT might be more difficult than previously predicted. In addition, several of the previous single center studies have been performed using treadmill exercise, while a majority of the patients in the multicenter studies have been performed using biking as the mode of ET. The effect of biking versus walking or running exercise during HIIT thus needs to be further addressed, with potential differences in societies with a population more familiar with bicycling, as opposed to less trained with cycle exercise (e.g. European vs. United States).

Importance of Increasing Exercise Workload

A key factor for any exercise response to occur over time is the principle of increasing exercise workload as training adaptation progresses. In the SAINTEX-CAD study, 12 weeks of ET increased peak workload by 38 watts in the HIIT group and 35 watts in the MICT group, respectively.⁵⁸ In the SMARTEX-HF study, mean exercise workload increased from baseline to the end of the 12-week exercise intervention from 76 to 97 watts in HIIT, and 47 to 62 watts in MICT, while the control group increased workload from 52 to 62 watts. In comparison, Wisløff et al.⁴⁶ reported an increase from 40 to 135 and from 40 to 70 watts in HIIT and MICT, respectively. Similarly, Iellamo et al.⁷² reported an increase from 50 to 120 and from 45 to 95 watts after HIIT and MICT, respectively. This corresponds to an increase in exercise workload (watts) per exercise session in the SMARTEX-HF study of 0.28 and 0.42 watts in MICT and HIIT⁵⁹ and 0.97 and 1.05 watts in MICT and HIIT, respectively in the SAINTEX-CAD study,⁵⁸ in comparison to 0.83 and 2.6 watts in Wisløff et al.⁴⁶ and 1.2 and 1.7 watts in Iellamo et al.,⁷² respectively. Thus, the low increase in ET load in the SMARTEX-HF study, particular in the HIIT group, could explain the moderate exercise response, as well as no difference between MICT and HIIT.⁵⁹ The lack of difference between groups regarding change in peak workload in the SAINTEX-CAD study supports this as well.⁵⁸ All four studies trained patients for 12-weeks, with 3-5 exercise session per week, and both Wisløff et al.,⁴⁶ Iellamo et al.⁷² and Conraads et al.⁵⁸ reported to systematically increase workload weekly to ensure training at prescribed workload throughout the study; however, a large variability in watt-increase is seen between the studies. The importance of systematical increase in ET workload was further illustrated in both the SMARTEX-HF and the SAINTEX-CAD studies by no added exercise response beyond expectations despite higher than prescribed ET intensity in the MICT groups.^{46, 58} The practical implications of the findings may be to keep a combined focus on both target ET intensity⁷⁷ and a continuous progress in ET workload to secure sufficient relative exercise intensity as VO_{2peak} improves throughout the exercise period.

Key Practical Considerations for Successful HIIT

Despite the challenges seen in multicenter studies to reach target ET intensity, HIIT is found to be feasible and effective for clinically stable CHD-patients across different modes of ET settings, even ET at home.⁷⁹ Eighty-three participants (74 men/9 women, mean age 57) completed 12 weeks of HIIT twice a week, performed as either treadmill exercise, group-based exercise or home-based ET. The

preferred ET mode in the home-based group was uphill walking. Target exercise intensity was set to 85-95% of HR_{peak} . The home-based ET program was unsupervised, and therefore started with two initial sessions with personal instruction where the patients learned how to perform HIIT and to use the HR monitors, including how to perform proper warm-up, execution of the high-intensity exercise bouts, and how to keep target HR during the intervention (adjustment of work load). The patients themselves administrated the HR-monitors for intensity guidance and documentation of ET. The results showed that, independent of group allocation, all participants achieved target HR with a mean ET intensity of 90% of HR_{peak} during the last two minutes of each high-intensity bout in every ET session.⁷⁹ What is then the key to successful clinical and home-based HIIT? Based on our clinical experience, we emphasize the importance of appropriate warm-up, adjustment of exercise workload, use of the Borg scale and correct measurement of HR_{peak} .

Warm-up

Warm-up is the period of preparatory exercise to enhance performance,⁸⁰ and in patients with CHD and HF (and probably endothelial dysfunction), sufficient time for warm-up is crucial. Myocardial oxygen demand prevents arrhythmias, increases HR, and stimulates vasodilation. In our clinic, patients with CHD perform 10-15 minutes of aerobic ET at light to moderate intensity before the first bout of HIIT. With proper warm up, the risk of arrhythmias and ischemia is minimized^{81, 82} and the ability to reach target HR within two-three minutes is facilitated. Additionally, we have experienced that exercising somewhat hard (approaching 85% of HR_{peak}) during the last minutes of warm up reduces the time to reach target HR in the first exercise bout.

Workload

The exercise workload is set according to the patient's HR_{peak} . Instead of extrapolating exercise workload from the cardiopulmonary exercise test, the first exercise session(s) should be used to find the correct ET 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. Normally, it takes two-three minutes to reach the target HR in the first bout (in some patients up to four, and

thereafter the HR increases more rapidly for every bout performed (illustrated in Figure 2). The ET intensity during the pauses is aiming at 60-70% of HR_{peak} , an intensity where lactate removal is found effective, compared to passive breaks.⁸³ Keeping the intensity at ~70% between the bouts also reduces the time to reach target HR in the subsequent bout. The last bout of HIIT is normally followed by a cool-down period. The purpose of cool-down is not only lactate removal but also to control for the decrease in HR and BP, thus reducing the risk of hypotension. Normally, this phase lasts 3-5 minutes.

HR_{peak}

Achieving a target HR of 90-95% during the last two minutes in the ET bouts is associated with improvement in VO_{2peak} .⁷⁷ However, the prerequisite to prescribe relative exercise intensity is a correct HR_{peak} -measurement obtained from a cardiopulmonary exercise test. To achieve near maximal effort, a proper warm-up is crucial, and exercise using large muscle groups is required, such as walking, running or cycling. Bicycle testing has a long tradition in the assessment of patients with CHD. However, cycle tests may give about 10-20% lower VO_{2peak} (corresponding to ~5-15% lower HR_{peak}) compared to treadmill walking/running.⁸⁴ In addition, if the test person is not familiar with cycling, local muscle fatigue will impair the test results. Hence, submaximal values are often used to prescribe ET intensity and the calculated exercise load is often too low. Figure 3 shows a CHD-patient performing three separate HIIT as cycling, treadmill walking and outdoor uphill walking, respectively, and demonstrate that cycling is less feasible to reach the target HR in patients not familiar with cycling.

Safety of HIIT

Even if ET is considered relatively safe,⁸⁵ also for CVD patients,⁸⁶ HIIT transiently elevates the risk of a CVD event in both young subjects with inherited CVD and adults with occult or diagnosed CHD.⁸⁷ However, no evidence suggests that the risks of exercise outweigh the benefits. Indeed, the converse appears to be true.⁸⁷ In a prospective study of over 12 000 U.S. male physicians who were healthy at baseline, it was found that habitual vigorous ET diminished the risk of sudden death during vigorous exertion.⁸⁸ Although the safety profile of HIIT has not been fully established yet, there is data demonstrating that in stable and selected patients, such ET can be performed with relatively low risk. Our research group examined the risk of CVD events during organized HIIT and MICT among 4846 CHD patients in four Norwegian CR centers.⁸⁹ Of a total of 175 820 ET hours, where all patients

performed both types of training in separate sessions, we found one fatal CVD arrest during MICT (129 456 hours of exercise) and two non-fatal cardiac arrests during HIIT (46 364 hours of exercise). There were no myocardial infarctions associated with exercise in the data material. As the number of HIIT hours was 36% of the number of MICT hours, the rates of events to the number of patient-exercise hours were 1 per 129 456 from MICT and 1 per 23 182 from HIIT. The absolute event rates were thus very low after exposure to both types of ET. Even if the low event rates after exposure to both types of ET modes may give a glimpse regarding the risk, we believe that larger RCTs are needed to further evaluate the risk of HIIT among CHD patients. Still, due to the more extensive use of HIIT in CR worldwide, we believe that this study gives an indication about the risk of such ET for secondary CR. A recently published systematic review also evaluated the safety of HIIT.⁹⁰ The investigators included 11 HIIT studies with 156 patients with cardiometabolic disease and found the incidence of adverse responses during or within 24 hours post exercise to be around 8%, 'mild in nature' and only 'somewhat higher compared to the previously reported risk during MICT'. They concluded based on this that: "caution must be taken when prescribing HIIT to patients with cardiometabolic disease". A review assessed the efficacy and safety of HIIT for HF patients.⁹¹ Despite documented benefits of HIIT in patients with CVD, including CHD and HF, the authors stated that currently there is still insufficient evidence to supplant a MICT approach with HIIT.

Future Perspectives

Most clinical HIIT studies yielding good results have been short-term and performed in a laboratory setting. The feasibility of longer-term HIIT in a real-world setting requires that important aspects essential for this type of ET are followed, so that it can be carried out in a simple and effective way, not only in small clinical trials but also in a broader scale. More studies regarding safety must be established before HIIT can be fully adapted as therapy for those with elevated cardiometabolic risk. In addition, RCTs showing that ET to improve VO_{2peak} will lead to more and/or healthier years with social engagement are yet to be established. Such studies are demanded, and at least one has been initiated, involving more than 1500 elderly that are exercised using either MICT or HIIT, where the primary outcome is mortality.⁹² We believe that for over 2 billion physically inactive adults worldwide,⁹³ HIIT may constitute an effective and more efficient way of improving health and reducing mortality, particularly since a commonly cited barrier to PA is lack of time.⁹⁴

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Figure texts**Figure 1**

Figure 1 shows the principle of high intensity interval training (HIIT), that facilitates the execution of repeated high intensity aerobic work. The work-bouts are separated by 'pauses' of lower intensity exercise that allow for recovery, making an individual able to reengage in HIIT. Moderate intensity continuous training (MICT) on the other hand, is performed continuously over longer time, at lower exercise intensities.

Figure 2

Figure 2 shows two individuals performing high intensity interval training (HIIT). They have different absolute peak heart rate (HR_{peak}) and energy consumptions, but they exercise at identical relative intensity (% of HR_{peak}). Red line: HIIT performed as 4x4 minutes rollerski training by a highly trained Olympic athlete with a HR_{peak} of 188. Target HR zone is 169-179 beats/min (90-95% of HR_{peak}). Blue line: HIIT performed as 4x4 minutes outdoors uphill walking by a patient with coronary artery disease (CAD) with a HR_{peak} of 130. Target HR zone is 117-124 beats/min (90-95% of HR_{peak}).

Figure 3

Figure 3 shows one coronary heart disease (CHD) patient performing three separate high intensity interval training (HIIT) sessions as outdoor uphill walking, treadmill walking, and cycling, respectively. Cycling seems less feasible concerning reaching the target heart rate (HR) in patients not familiar with cycling.

Case: Man, 56 years of age, BMI 26, undergone coronary artery bypass graft surgery (CABG), Blood pressure: 121/70 mmHg; Resting HR: 53 beats per minute (beats/min); Medication: Zelosok, Cordarone, Albyl E. On a preliminary testing day, cardiopulmonary exercise testing (CPET) took place on a treadmill, using an individualized walking ramp protocol, starting at 6.1 km/h with 5% inclination. After 2 minutes, workload was increased every minute with 3% increase in inclination, until exhaustion. Peak oxygen uptake (VO_{2peak}) was $36 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and peak heart rate (HR_{peak}) was 130 beats/min. Target HR of 90-95% of HR_{peak} was calculated to 117-124 bpm. He had one supervised outdoor exercise session (walking/jogging uphill) where he was taught how to use the heart rate monitor (Polar 400) and how to reach target HR. Then the patient performed unsupervised HIIT in three different modes with at least three days apart: uphill walking (outdoors), treadmill walking, and cycling on a bike. Figure 3 shows the different HR-curves during the HIIT sessions. Walking resulted in significantly more minutes in the target exercise intensity zone (outdoor equally feasible as treadmill walking) compared to cycling. This example shows the importance of using the same exercise mode

at all centers in multi-center studies, and at the same time bear in mind, that cycling is less feasible to reach target HR in patients not familiar with cycling.

Total time in target heart rate zone during each exercise session:

Inside the intensity zone of 90-95% of HR_{peak}:

Uphill walking: 6:45 min

Treadmill: 7:00 min

Cycling: 3:10 min

Inside the intensity zone of 85-95% of HR_{peak}:

Uphill walking: 12:10 min

Treadmill: 11:50 min

Cycling: 8:05 min

References

1. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil*. 2008;15:239-246.
2. Anderson L, Thompson DR, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2016:CD001800.
3. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev*. 2014:CD003331.
4. Warburton DE, Bredin SS. Reflections on Physical Activity and Health: What Should We Recommend? *Can J Cardiol*. 2016;32:495-504.
5. Manson JE, Hu FB, Rich-Edwards JW, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *N Engl J Med*. 1999;341:650-658.
6. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol*. 2014;64:472-481.
7. O'Donovan G, Lee IM, Hamer M, Stamatakis E. Association of "Weekend Warrior" and Other Leisure Time Physical Activity Patterns With Risks for All-Cause, Cardiovascular Disease, and Cancer Mortality. *JAMA internal medicine*. 2017.
8. Wisloff U, Nilsen TI, Droyvold WB, Morkved S, Slordahl SA, Vatten LJ. A single weekly bout of exercise may reduce cardiovascular mortality: how little pain for cardiac gain? 'The HUNT study, Norway'. *Eur J Cardiovasc Prev Rehabil*. 2006;13:798-804.
9. Löllgen H, Böckenhoff A, Knapp G. Physical Activity and All-cause Mortality: An Updated Meta-analysis with Different Intensity Categories. *International journal of sports medicine*. 2009;30:213-224.
10. Rankin AJ, Rankin AC, MacIntyre P, Hillis WS. Walk or run? Is high-intensity exercise more effective than moderate-intensity exercise at reducing cardiovascular risk? *Scott Med J*. 2012;57:99-102.
11. Shiroma EJ, Sesso HD, Moorthy MV, Buring JE, Lee IM. Do moderate-intensity and vigorous-intensity physical activities reduce mortality rates to the same extent? *J Am Heart Assoc*. 2014;3:e000802.
12. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of Moderate to Vigorous Physical Activity on All-Cause Mortality in Middle-aged and Older Australians. *JAMA internal medicine*. 2015;175:970-977.
13. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet*. 2011;378:1244-1253.
14. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. *British journal of sports medicine*. 2008;42:238-243.
15. Lavie CJ, Arena R, Swift DL, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. *Circulation research*. 2015;117:207-219.
16. Lee IM, Sesso HD, Oguma Y, Paffenbarger RS, Jr. Relative intensity of physical activity and risk of coronary heart disease. *Circulation*. 2003;107:1110-1116.
17. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *Jama*. 2002;288:1994-2000.
18. Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med*. 2002;347:716-725.
19. Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation*. 2000;102:975-980.
20. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. *Am J Cardiol*. 2006;97:141-147.
21. Janssen I, Ross R. Vigorous intensity physical activity is related to the metabolic syndrome independent of the physical activity dose. *International journal of epidemiology*. 2012;41:1132-1140.

22. Paffenbarger RS, Jr., Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med*. 1986;314:605-613.
23. Lee DC, Sui X, Ortega FB, et al. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *British journal of sports medicine*. 2011;45:504-510.
24. DeFina LF, Haskell WL, Willis BL, et al. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? *Prog Cardiovasc Dis*. 2015;57:324-329.
25. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc*. 2001;33:754-761.
26. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*. 1989;262:2395-2401.
27. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation*. 2003;108:1554-1559.
28. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis*. 2015;57:306-314.
29. Lee DC, Sui X, Church TS, Lavie CJ, Jackson AS, Blair SN. Changes in fitness and fatness on the development of cardiovascular disease risk factors hypertension, metabolic syndrome, and hypercholesterolemia. *J Am Coll Cardiol*. 2012;59:665-672.
30. Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA*. 1995;273:1093-1098.
31. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793-801.
32. Bassett DR, Jr., Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc*. 2000;32:70-84.
33. Keteyian SJ, Brawner CA, Savage PD, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *American heart journal*. 2008;156:292-300.
34. Vanhees L, Fagard R, Thijs L, Staessen J, Amery A. Prognostic significance of peak exercise capacity in patients with coronary artery disease. *J Am Coll Cardiol*. 1994;23:358-363.
35. Vanhees L, Fagard R, Thijs L, Amery A. Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. *Am J Cardiol*. 1995;76:1014-1019.
36. Nes BM, Janszky I, Aspenes ST, Bertheussen GF, Vatten LJ, Wisloff U. Exercise patterns and peak oxygen uptake in a healthy population: the HUNT study. *Med Sci Sports Exerc*. 2012;44:1881-1889.
37. Uddin J, Zwisler AD, Lewinter C, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis. *European journal of preventive cardiology*. 2016;23:683-693.
38. Weston KS, Wisloff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *British journal of sports medicine*. 2014;48:1227-1234.
39. Gibala MJ, Little JP, van Essen M, et al. Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *The Journal of Physiology*. 2006;575:901-911.
40. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377-381.
41. Åstrand P-O, Rodahl K. *Textbook of work physiology - physiological bases of exercise, third edition*: McGraw-Hill International Editions; 1986.
42. Milanovic Z, Sporis G, Weston M. Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO₂max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. *Sports medicine*. 2015;45:1469-1481.

43. Guiraud T, Nigam A, Gremeaux V, Meyer P, Juneau M, Bosquet L. High-intensity interval training in cardiac rehabilitation. *Sports medicine*. 2012;42:587-605.
44. Helgerud J, Høydal K, Wang E, et al. Aerobic High-Intensity Intervals Improve V̇O₂max More Than Moderate Training. *Medicine & Science in Sports & Exercise*. 2007;39:665-671
610.1249/mss.1240b1013e3180304570.
45. Baekkerud FH, Solberg F, Leinan IM, Wisloff U, Karlsen T, Rognmo O. Comparison of Three Popular Exercise Modalities on V̇O₂max in Overweight and Obese. *Med Sci Sports Exerc*. 2016;48:491-498.
46. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115:3086-3094.
47. Fu TC, Wang CH, Lin PS, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. *International journal of cardiology*. 2013;167:41-50.
48. Freyssin C, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. *Archives of physical medicine and rehabilitation*. 2012;93:1359-1364.
49. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. *Am J Cardiol*. 2013;111:1466-1469.
50. Rognmo O, Hetland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2004;11:216-222.
51. Moholdt TT, Amundsen BH, Rustad LA, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *American heart journal*. 2009;158:1031-1037.
52. Dall CH, Snoer M, Christensen S, et al. Effect of high-intensity training versus moderate training on peak oxygen uptake and chronotropic response in heart transplant recipients: a randomized crossover trial. *Am J Transplant*. 2014;14:2391-2399.
53. Tjonna AE, Lee SJ, Rognmo O, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*. 2008;118:346-354.
54. Molmen-Hansen HE, Stolen T, Tjonna AE, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *European journal of preventive cardiology*. 2012;19:151-160.
55. Schjerve IE, Tyldum GA, Tjonna AE, et al. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. *Clinical science*. 2008;115:283-293.
56. Hollekim-Strand SM, Bjorgaas MR, Albrektsen G, Tjonna AE, Wisloff U, Ingul CB. High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: a randomized controlled trial. *J Am Coll Cardiol*. 2014;64:1758-1760.
57. Tschentscher M, Eichinger J, Egger A, Droese S, Schonfelder M, Niebauer J. High-intensity interval training is not superior to other forms of endurance training during cardiac rehabilitation. *European journal of preventive cardiology*. 2016;23:14-20.
58. Conraads VM, Pattyn N, De Maeyer C, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. *International journal of cardiology*. 2015;179:203-210.
59. Ellingsen O, Halle M, Conraads VM, et al. High Intensity Interval Training in Heart Failure Patients with Reduced Ejection Fraction. *Circulation*. 2017.
60. Haykowsky MJ, Daniel KM, Bhella PS, Sarma S, Kitzman DW. Heart Failure: Exercise-Based Cardiac Rehabilitation: Who, When, and How Intense? *Can J Cardiol*. 2016;32:S382-S387.

61. Elliott AD, Rajopadhyaya K, Bentley DJ, Beltrame JF, Aromataris EC. Interval training versus continuous exercise in patients with coronary artery disease: a meta-analysis. *Heart Lung Circ.* 2015;24:149-157.
62. Liou K, Ho S, Fildes J, Ooi SY. High Intensity Interval versus Moderate Intensity Continuous Training in Patients with Coronary Artery Disease: A Meta-analysis of Physiological and Clinical Parameters. *Heart Lung Circ.* 2016;25:166-174.
63. Pattyn N, Coeckelberghs E, Buys R, Cornelissen VA, Vanhees L. Aerobic interval training vs. moderate continuous training in coronary artery disease patients: a systematic review and meta-analysis. *Sports medicine.* 2014;44:687-700.
64. Meyer P, Gayda M, Juneau M, Nigam A. High-intensity aerobic interval exercise in chronic heart failure. *Curr Heart Fail Rep.* 2013;10:130-138.
65. Ismail H, McFarlane JR, Nojournian AH, Dieberg G, Smart NA. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. *JACC Heart Fail.* 2013;1:514-522.
66. Wisloff U, Ellingsen O, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? *Exercise and sport sciences reviews.* 2009;37:139-146.
67. Kemi OJ, Wisloff U. High-intensity aerobic exercise training improves the heart in health and disease. *J Cardiopulm Rehabil Prev.* 2010;30:2-11.
68. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation.* 2002;106:666-671.
69. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol.* 2003;42:2139-2143.
70. Astorino TA, Edmunds RM, Clark A, et al. High-Intensity Interval Training Increases Cardiac Output and V O₂max. *Med Sci Sports Exerc.* 2017;49:265-273.
71. Amundsen BH, Rognmo O, Hatlen-Rebhan G, Slordahl SA. High-intensity aerobic exercise improves diastolic function in coronary artery disease. *Scand Cardiovasc J.* 2008;42:110-117.
72. Iellamo F, Manzi V, Caminiti G, et al. Matched dose interval and continuous exercise training induce similar cardiorespiratory and metabolic adaptations in patients with heart failure. *International journal of cardiology.* 2013;167:2561-2565.
73. Fu TC, Yang NI, Wang CH, et al. Aerobic Interval Training Elicits Different Hemodynamic Adaptations Between Heart Failure Patients with Preserved and Reduced Ejection Fraction. *Am J Phys Med Rehabil.* 2016;95:15-27.
74. Helgerud J, Hoydal K, Wang E, et al. Aerobic high-intensity intervals improve VO₂max more than moderate training. *Med Sci Sports Exerc.* 2007;39:665-671.
75. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *JAMA.* 2000;283:3095-3101.
76. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *European heart journal.* 2012;33:2917-2927.
77. Moholdt T, Madssen E, Rognmo O, Aamot IL. The higher the better? Interval training intensity in coronary heart disease. *Journal of science and medicine in sport / Sports Medicine Australia.* 2014;17:506-510.
78. Aamot IL, Forbord SH, Karlsen T, Stoylen A. Does rating of perceived exertion result in target exercise intensity during interval training in cardiac rehabilitation? A study of the Borg scale versus a heart rate monitor. *Journal of science and medicine in sport / Sports Medicine Australia.* 2014;17:541-545.
79. Aamot IL, Forbord SH, Gustad K, et al. Home-based versus hospital-based high-intensity interval training in cardiac rehabilitation: a randomized study. *European journal of preventive cardiology.* 2014;21:1070-1078.

80. Fradkin AJ, Zazryn TR, Smoliga JM. Effects of warming-up on physical performance: a systematic review with meta-analysis. *Journal of strength and conditioning research / National Strength & Conditioning Association*. 2010;24:140-148.
81. Bogaty P, Poirier P, Boyer L, Jobin J, Dagenais GR. What induces the warm-up ischemia/angina phenomenon: exercise or myocardial ischemia? *Circulation*. 2003;107:1858-1863.
82. Tuomainen P, Hartikainen J, Vanninen E, Peuhkurinen K. Warm-up phenomenon and cardiac autonomic control in patients with coronary artery disease. *Life sciences*. 2005;76:2147-2158.
83. Menzies P, Menzies C, McIntyre L, Paterson P, Wilson J, Kemi OJ. Blood lactate clearance during active recovery after an intense running bout depends on the intensity of the active recovery. *Journal of sports sciences*. 2010;28:975-982.
84. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128:873-934.
85. Whang W, Manson JE, Hu FB, et al. Physical exertion, exercise, and sudden cardiac death in women. *JAMA*. 2006;295:1399-1403.
86. Pavy B, Iliou MC, Meurin P, et al. Safety of exercise training for cardiac patients: results of the French registry of complications during cardiac rehabilitation. *Arch Intern Med*. 2006;166:2329-2334.
87. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation*. 2007;115:2358-2368.
88. Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med*. 2000;343:1355-1361.
89. Rognmo O, Moholdt T, Bakken H, et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation*. 2012;126:1436-1440.
90. Levinger I, Shaw CS, Stepto NK, et al. What Doesn't Kill You Makes You Fitter: A Systematic Review of High-Intensity Interval Exercise for Patients with Cardiovascular and Metabolic Diseases. *Clinical Medicine Insights. Cardiology*. 2015;9:53-63.
91. Arena R, Myers J, Forman DE, Lavie CJ, Guazzi M. Should high-intensity-aerobic interval training become the clinical standard in heart failure? *Heart Fail Rev*. 2013;18:95-105.
92. Stensvold D, Viken H, Rognmo O, et al. A randomised controlled study of the long-term effects of exercise training on mortality in elderly people: study protocol for the Generation 100 study. *BMJ open*. 2015;5:e007519.
93. Hallal PC, Andersen LB, Bull FC, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet*. 2012;380:247-257.
94. Justine M, Azizan A, Hassan V, Salleh Z, Manaf H. Barriers to participation in physical activity and exercise among middle-aged and elderly individuals. *Singapore Med J*. 2013;54:581-586.

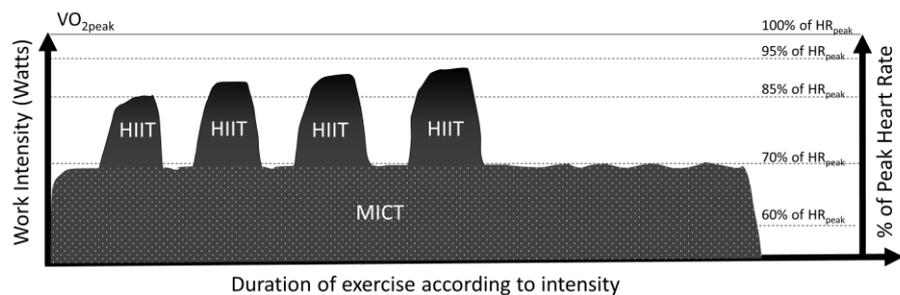


Fig. 1

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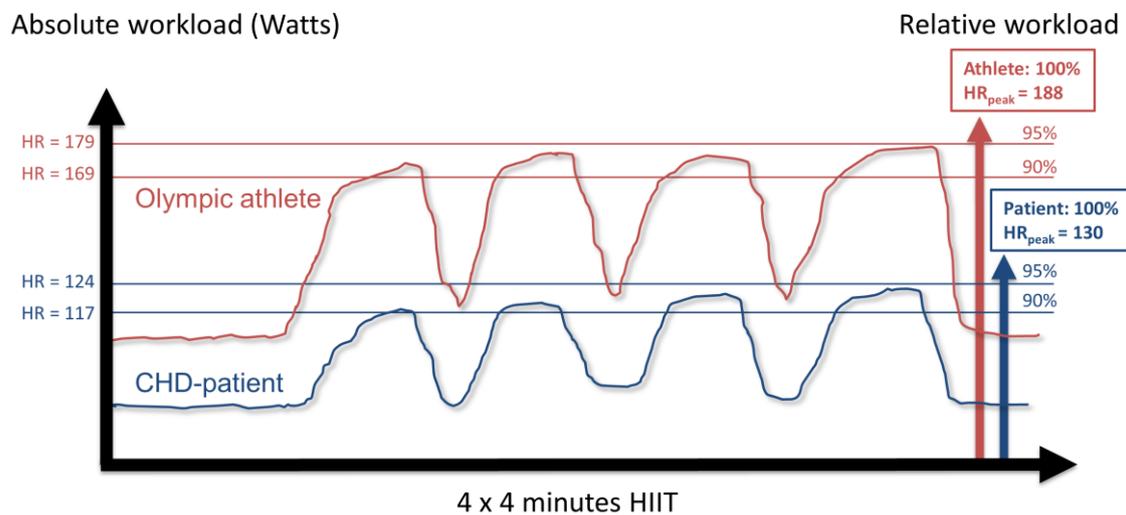


Fig. 2

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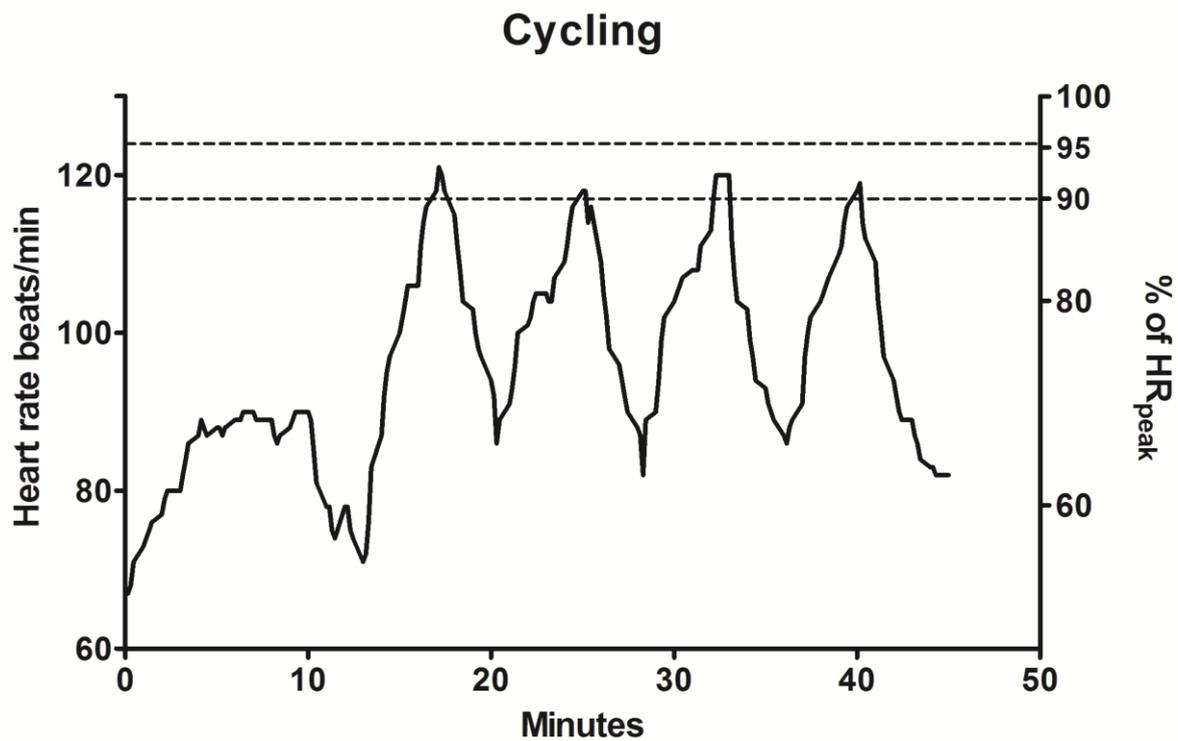


Fig. 3

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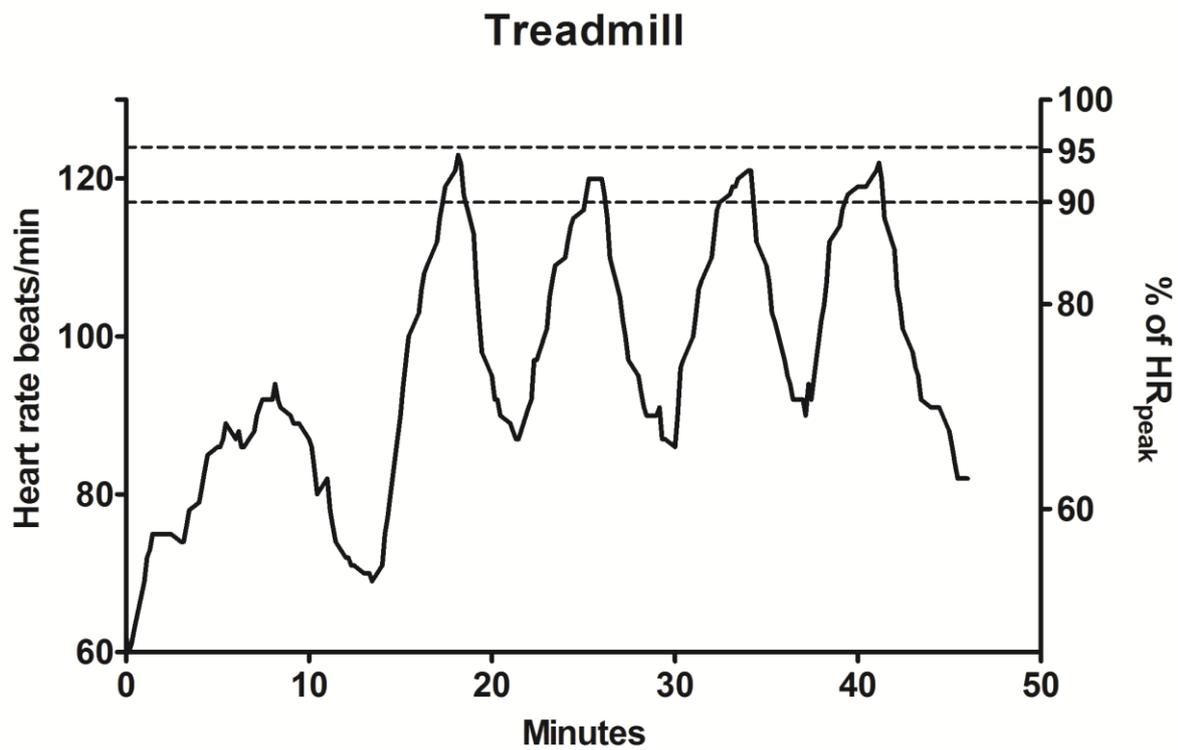


Fig. 3

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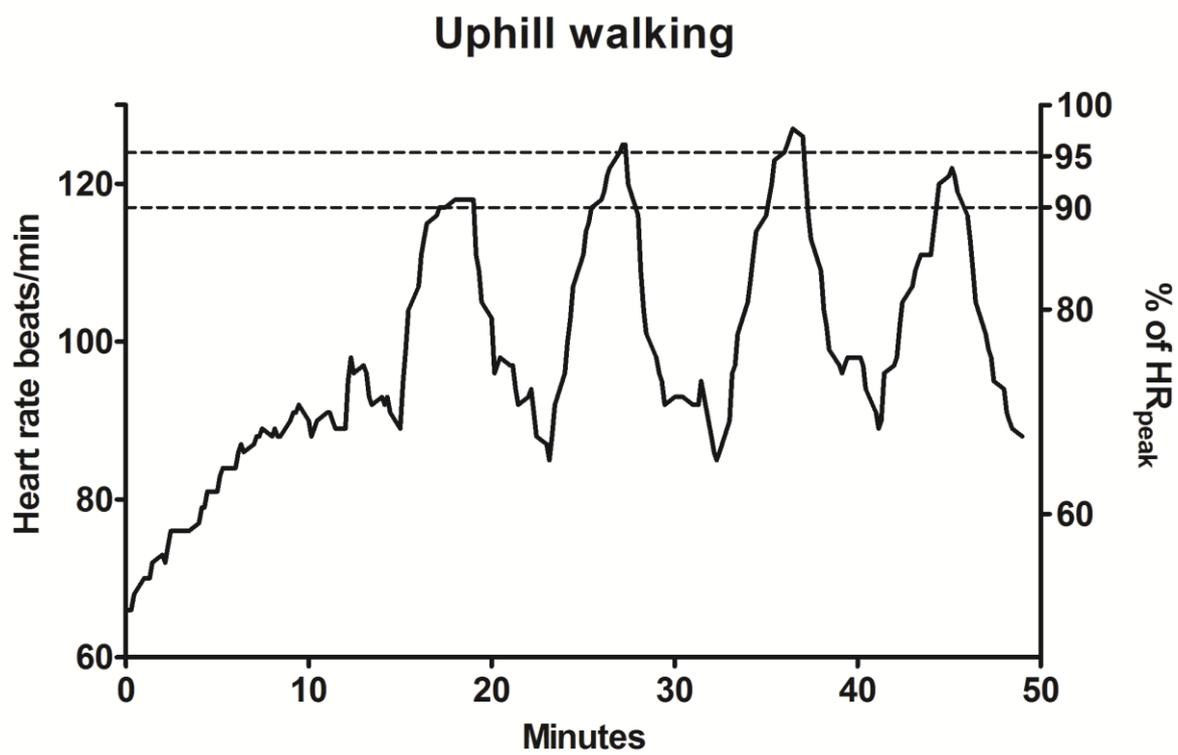


Fig. 3

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