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Review

Provocative Issues in Heart Disease Prevention

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ABSTRACT

In this article, new areas of cardiovascular (CV) prevention and rehabilitation research are discussed: high-intensity interval training (HIIT) and new concepts in nutrition. HIIT consists of brief periods of high-intensity exercise interspersed by periods of low-intensity exercise or rest. The optimal mode according our work (15-second exercise intervals at peak power with passive recovery intervals of the same duration) is associated with longer total exercise time, similar time spent near peak oxygen uptake (VO2 peak) VO_2 peak, and lesser perceived exertion relative to other protocols that use longer intervals and active recovery periods. Evidence also suggests that compared with moderate-intensity continuous exercise training, HIIT has superior effects on cardiorespiratory function and on the attenuation of multiple cardiac and peripheral abnormalities. With respect to nutrition, a growing body of evidence suggests that the gut microbiota is influenced by lifestyle choices and might play a pivotal role in modulating CV disease development. For example, recent evidence linking processed (but not unprocessed) meats to increased CV risk pointed to the gut microbial metabolite trimethylamine N-oxide as a potential culprit. In addition, altered

RÉSUMÉ

Dans cet article, nous examinerons les nouveaux axes de recherche en réadaptation cardiaque et en prévention des maladies cardiovasculaires (CV) : l'entraînement par intervalles à haute intensité (EIHE) et les nouveaux concepts en nutrition. L'EIHE consiste en de brèves périodes d'effort de haute intensité entrecoupées de périodes d'effort de faible intensité ou de repos. Le mode optimal selon notre travail (intervalles d'effort de 15 secondes à la puissance maximale suivis d'intervalles de récupération active de la même durée) est associé à une durée totale d'effort plus longue, une durée similaire près de la consommation maximale d'oxygène (VO_2 max) et une perception de l'effort moindre par rapport à d'autres protocoles qui utilisent des intervalles et des périodes de récupération active plus longs. Les données scientifiques indiquent également que comparativement à l'entraînement continu à intensité modérée, l'EIHE a des effets supérieurs sur le fonctionnement cardiorespiratoire et sur l'atténuation de multiples anomalies cardiaques et périphériques. En ce qui concerne la nutrition, des données de plus en plus nombreuses indiquent que le microbiote intestinal est influencé par les choix relatifs au mode de vie et qu'il pourrait jouer un rôle pivot dans la modulation du

Healthy lifestyle choices including a high-quality diet and performing regular exercise continue to play a vital role in the primary, secondary, and even tertiary prevention of cardiovascular (CV) disease. Unequivocally, a large body of evidence shows that conventional nutritional and exercise interventions are associated with substantial reductions in cardiac and total mortality. Despite this fact, and most relevantly for subjects with pre-existing heart disease, considerable residual CV risk exists despite optimal pharmacological and nonpharmacological treatment. In this light, not only is it important to continuously reassess current medical approaches, but also to reassess our understanding of how diet and exercise can be beneficial and harmful in the optics developing innovative and more efficacious strategies to further improve short- and long-term CV outcomes. The purpose of this focus article is to summarize provocative issues in CV disease prevention that we believe will continue to garner considerable attention at the general public and scientific levels and have a major effect on heart health.

High-Intensity Interval Training Should Be Recommended for Aerobic Exercise Training in Heart Disease Prevention

High-intensity interval training (HIIT) has a long tradition and was used empirically in the beginning of the 20th century by European elite athletes to improve athletic performance.[1] In 1959, the first article on HIIT was published in a Swiss scientific journal[2] and the first data on the acute physiological responses during different HIIT protocols in healthy adults was published

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gut microbiota could also mediate the proinflammatory and cardiometabolic abnormalities associated with excess added free sugar consumption, and in particular high-fructose corn syrup. Substantially more research is required, however, to fully understand how and which alterations in gut flora can prevent or lead to CV disease and other chronic illnesses. We conclude with thoughts about the appropriate role for HIIT in CV training and future research in the role of gut flora-directed interventions in CV prevention.

développement de la maladie CV. Par exemple, des données récentes liant les viandes transformées (mais non les viandes non transformées) à l'augmentation du risque CV ont désigné la triméthylamine N-oxyde produite par le microbiote intestinal comme étant un responsable potentiel. De plus, la modification du microbiote intestinal pourrait également intervenir dans les anomalies pro-inflammatoires et cardiométaboliques associées à l'excès de consommation de sucres ajoutés et en particulier le sirop de maïs à haute teneur en fructose. Cependant, davantage de recherches sont nécessaires pour bien comprendre quelles modifications dans la flore intestinale et de quelle manière elles peuvent prévenir ou mener à la maladie CV et à d'autres maladies chroniques. Nous concluons par des réflexions sur le rôle approprié de l'EIHE dans l'entraînement CV et sur la recherche future concernant le rôle des interventions orientées sur la flore intestinale dans la prévention des maladies CV.

in 1960.[3] In the 1990s, Meyer et al. studied the acute and chronic CV adaptations after HIIT in patients with coronary heart disease (CHD) and heart failure (HF).[4-7] Recently, clinical interest has emerged for this training modality in individuals with high CV risk (HCVR)[8-10] and/or cardiac patients[11-14] (Supplemental Tables S1-S3). Notably, HIIT was mentioned for the first time in the American Heart Association recommendations for exercise prescription in 2007.[15] We will next review the general principles of HIIT prescription, the acute and chronic adaptations of HIIT, and safety and future perspectives in the heart disease context.

HIIT: General Principles and Exercise Prescription in a Heart Disease Prevention Context

The main principle of HIIT is to perform brief periods of high-intensity exercise interspersed by periods of low-intensity exercise or rest. HIIT permits individuals to accumulate greater time at a higher intensity than they would otherwise with continuous exercise.[8,11,16] Therefore, HIIT can be considered as a time-efficient substitute and/or alternative to traditional moderate-intensity continuous exercise training (MICET). The aerobic stimulus of HIIT, or improvement in peak oxygen uptake (VO2 peak) VO_2 peak,[11] has been demonstrated in athletes[17,18] and in cardiac patients,[19,20] and is related to time spent near VO_2 peak ($\geq$90%). Different HIIT protocols (intensity, stage duration, nature of recovery, and number of intervals) have been tested and used in individuals with HCVR and in cardiac patients. Furthermore, HIIT can be performed during cycling, running, walking, rowing, swimming, or other activities. Three different categories of HIIT have been previously described[11,16]: (1) long intervals: 3-15 minutes at 85%-90% of VO_2 peak; (2) moderate intervals: 1-3 minutes at 95%-100% of VO_2 peak; and (3) short intervals: 10 seconds to 1 minute at 100%-120% of VO_2 peak. Exercise intensity can be prescribed according to percentage of VO_2 peak, percentage of maximal heart rate, percentage of maximal aerobic power, percentage of maximal short exercise capacity or subjective rate of perceived exertion (RPE; Borg scale). The choice with respect to exercise intensity, duration of intervals, and the use of active or passive recovery has a profound influence on acute physiological responses, exercise tolerance, and RPE.[11,16]

Is There an Optimal HIIT Protocol for Cardiac Patients?

The acute physiological responses to different HIIT protocols have been studied in patients with CV disease.[5,19-27] However, protocols have varied considerably and have generally been chosen empirically. To bring some clarity to this issue, we performed "optimization" studies to identify the optimal protocols that allow patients to spend more time near to VO_2 peak in combination with a longer total exercise time and a lower subjective feeling of fatigue and dyspnea.[19,20] In coronary patients, an HIIT protocol consisting of 15-second exercise intervals at peak power, interspersed with passive recovery intervals of the same duration was found to be the best[19] (see Supplemental Table S2 for details). Furthermore, compared with a single isocaloric MICET session, the optimized HIIT protocol was associated with a lower mean VO_2, lower ventilation, lower RPE, longer total exercise duration, and was preferred by patients.[28] Similarly, in HF patients, we identified 30-second intervals at peak power interspersed by passive recovery intervals of similar duration to be superior to longer intervals and the use of active recovery, leading to a longer total exercise time, a similar time spent near VO_2 peak, a lower RPE, greater patient comfort, and a greater likelihood of the patient completing the prescribed exercise session.[20] A subsequent study that compared an isocaloric MICET session with our optimized HIIT session demonstrated that HIIT was associated with: (1) a similar time spent near VO_2 peak; (2) a trend toward a lower RPE; (3) a higher exercise session completion rate; and (4) a higher external power work (Watts) performed during exercise.[25] Finally, compared with a single MICET session, our optimized HIIT protocol also elicited similar central hemodynamics (cardiac output) and muscle substrate oxidation in patients with HF.[22,27] A recent study by Tomczak et al. also demonstrated improved biventricular cardiac function after 1 HIIT session in patients with HF[26] (see Supplemental Table S3 for studies of HIIT in HF).

High-Intensity Training Vs HIIT: Survival, Safety Aspects, and Adherence

Epidemiological data suggest that higher exercise intensity during physical activity might provide an additional survival benefit relative to isocaloric moderate-intensity training.[29] This benefit might be in part because of the superior effects

of high-intensity exercise on improving VO_2 peak. Furthermore, high-intensity exercise also results in a greater improvement in cardiometabolic parameters in HCVR individuals[30,31] and in those with established CHD.[32] In parallel, data on the health benefits of HIIT are emerging. Although prospective clinical trials designed to assess the potential survival benefit of HIIT are ongoing, this training modality has been shown to be superior to MICET for improving cardiometabolic parameters,[33] ambulatory blood pressure,[34,35] endothelial function,[12,33,34,36,37] inflammation,[38] sympathovagal balance,[34,35,39] left ventricular remodelling,[12,34,40] and brain natriuretic peptide levels.[12,41] A recent study also demonstrated that HIIT is superior to MICET for improving VO_2 peak among heart transplant patients.[42] Taken together, available evidence indicates that compared with MICET, HIIT appears to have superior effects on cardiorespiratory function and on the attenuation of various cardiac and peripheral abnormalities found in individuals with CV disease and those at risk. As expected, patients with the greatest abnormalities at baseline appear to achieve the greatest benefit.

The Achilles heel of exercise training without a doubt remains adherence. In this respect, we believe HIIT can also play a significant role. In the **H**eart **F**ailure: **A** **C**ontrolled **T**rial **I**nvestigating **O**utcomes of Exercise Trai**n**ing (HF-ACTION) trial, which randomized patients with class II-IV systolic HF and to either MICET or usual care, exercise training was not associated with a decreased incidence of the primary end point of all-cause mortality or hospitalization.[43] Importantly, only approximately 40% of patients in the exercise group reported weekly training volumes $\geq$ recommended values. As a consequence, smaller than expected improvements in VO_2 peak (median of 0.6 mL/kg/min) and 6-minute walking distance (median, 20 m) were observed after 3 months.[44] In the same trial, the longest event-free survival was witnessed among those with the greatest improvement in VO_2 peak.[44] These data highlight the importance of developing training strategies that improve adherence to exercise training, particularly among HF patients, knowing that increasing exercise intensity permits a stepwise increase in VO_2 peak in this population.[45,46] Because HIIT might be associated with superior improvements in VO_2 peak, and is preferred by patients over MICET because of a decreased subjective feeling of fatigue, breathlessness, and monotony, and is concretely associated with decreased minute-ventilation, a longer total exercise time, and a high level of VO_2,[11,47,48] we believe a larger place should be reserved for this type of training in cardiac rehabilitation (CR).

HIIT: Recommendations and Future Perspectives

HIIT is increasingly used in CR and prevention programs across Canada. The Canadian cardiology community has contributed significantly to expanding the literature on the benefits of HIIT in various populations.[11,13,16,19-22,24,25,27,28,49-52] HIIT is now incorporated into the latest CR guidelines of the Canadian Association of Cardiac and Pulmonary Rehabilitation.[53] The most recent Canadian Cardiovascular Society Heart Failure Management Guidelines Update[54] has also incorporated HIIT into the recommendations for exercise training, stating that HIIT be "considered and initiated in a supervised setting and considered for all stable HF patients who are already undergoing moderate-intensity continuous aerobic training." Although sometimes acknowledging the benefits of HIIT, other societies have stopped short of providing specific recommendations.[55-62] This hesitancy is likely based on the belief that continuous training provides an adequate CV stimulus,[63,64] that only young fit individuals can tolerate HIIT, and that high-intensity training might be associated with inordinate risk.[65] Importantly, we and others have prospectively demonstrated the short- and longer-term safety of high-intensity exercise among individuals with CHD (exercise > the ischemic threshold)[66,67] and the short-term safety of HIIT among individuals with CHD.[11,24,68] and HF.[11,12] Furthermore, a retrospective analysis of 4846 CHD patients participating in CR and undergoing MICET or HIIT revealed a rate of major adverse cardiac events of 1 event per 129,456 hours of MICET and 1 event per 23,182 hours of HIIT.[69] Thus, although vigorous or intense physical activity might be associated with an increase in risk, the absolute event rate is exceedingly low with questionable clinical relevance in light of the significant improvements in CV function and improvement in risk factors. At the Montreal Heart Institute, HIIT has been used in routine phase II and III CR programs since 2009.[70-72] Currently, HIIT is considered for all individuals at our CV disease prevention centre, and is used in approximately 1000 cardiac patients annually undergoing phase III-IV CR.

In addition to improving CV fitness and the CV risk profile, HIIT is increasingly being studied in other noncardiac conditions, including the elderly with mobility and gait problems,[73] post-stroke patients,[74] chronic pulmonary disease,[75] cancer,[76,77] and to improve cognitive function.[78] Data from our own group have shown that a 4-month HIIT program improves several executive cognitive functions including short-term memory and attention span among obese subjects and correlates with the improvement in cardiometabolic and fitness parameters.[79] The CV and non-CV effects of HIIT are listed in Table 1.

In conclusion, we are convinced that HIIT is superior to MICET and results in greater improvements in exercise capacity, a chief determinant of mortality and CV events. Furthermore, HIIT elicits superior physiological responses and has a more beneficial effect on the CV and cardiometabolic risk profile. In addition, a growing body of data suggest it is safe, better tolerated, and preferred by patients,

Table 1. Cardiac and noncardiac effects of high-intensity interval training

Cardiac effects
Improved VO_2 peak
Improved endothelial function
Improved blood pressure
Improved sympathovagal balance
Improved cardiac remodelling
Improved natriuretic peptide levels
Improved cardiometabolic profile
Improved adherence to exercise training?
Noncardiac effects
Improved mobility and gait
Improved functional capacity
Improved quality of life
Improved cognitition

VO_2, oxygen uptake.

thus potentially resulting in improved adherence to exercise training. For these reasons, we and other groups believe HIIT should be considered in all patients enrolled in a CR program.[48,69] Ongoing clinical trials by others[80] and us should help confirm the longer-term safety and efficacy of this training modality.

Nutritional Controversies in CV Disease Prevention

The World Health Organization (WHO) and the United Nations released a joint report outlining the epidemiological evidence linking changes in worldwide dietary patterns with the increase in chronic illnesses including CV diseases and cancer.[81] This report highlighted the emergence of an affluent diet abundant in processed foods and rich in energy, sodium, saturated fats, and refined sugars that were shown to mirror the increase in death rates from coronary artery disease and stroke, and was associated with childhood and adult obesity. Experimental data now point toward inflammation as a major driver of diet-induced chronic diseases.[82] Several examples of important and provocative issues in nutrition seem to highlight the importance of the gut microbiota, the "forgotten organ," for the maintenance of health and prevention of diseases and will be highlighted next.[83]

The Intestinal Microbiota

Humans are covered and inhabited by microbiota. The human gut contains the most diverse and abundant microbiota with over 100 trillion organisms representing $>$ 1000 unique species and a collective of $>$ 5 million genes, the gut microbiome.[84] The gut microbiota can act in symbiosis with the host and modulate biological and metabolic processes such as appetite and energy balance, glucose and lipid metabolism, and inflammation.[85] For example, microbial fermentation of nondigestible carbohydrates leads to the formation of short-chain fatty acids such as butyrate that might have beneficial anti-inflammatory and anorexigenic properties.[85]

An important emerging concept is that lifestyle choices can influence the composition and diversity of microbial species in the gut, which in turn can play a major role in modulating health and disease. Microbiota diversity appears to be increased by physical activity and consumption of diets rich in nondigestible carbohydrates (high in fibre content) such as fruits, vegetables, legumes, and whole-wheat grain products.[85,86] Dietary patterns associated with increased consumption of sterilized, processed foods rich in saturated fatty acids and simple sugars in place of fresh and seasonal produce could thus potentially affect gut microbial diversity and function in a detrimental fashion. For example, a high-fat, high-carbohydrate diet was shown to alter gut microbiota composition, namely the ratio of Firmicutes:Bacteroidetes, and was associated with altered glucose and lipid oxidative rates.[87] Interestingly, decreased microbiota diversity and an increased Firmicutes:Bacteroidetes ratio have been shown to be associated with overweight, obesity, and type II diabetes.[88,89] Decreased microbial diversity and low microbial gene richness were also linked to lower fruit and vegetable consumption and associated with low-grade inflammation and cardiometabolic abnormalities in overweight and obese individuals. A 6-week high-protein calorie-restricted diet restored microbial gene richness and diversity.[90] Differences in gut microbiota composition between patients with type II diabetes, obese individuals, and lean control subjects have also been associated with epigenetic modifications of toll-like receptor gene expression leading to increased intestinal gut permeability and systemic inflammation.[89] In mice, a high-fat diet was shown to increase microbial production of lipopolysaccharide, a potent mediator of endotoxemia, leading to inflammation, insulin resistance, and hepatic steatosis.[91] "Western" dietary habits could thus be associated with an altered and pro-inflammatory microbiota, which could in turn modulate the cardiometabolic effect of some controversial food items such as red meat and added free sugars.

Red Meat

Red meat consumption has long been thought to be associated with increased CV risk. However, controversy recently arose when 2 meta-analyses associated only processed red meat such as sausages and cold cuts with greater risk of CHD[92] and all-cause mortality.[93] Moreover, a recent Polish cohort study observed a 2.4-fold increased risk of incident HF among individuals who consumed $\geq$ 75 g/d of processed meat, and unprocessed meat had no effect on the risk of developing HF.[94] These findings suggest that an element other than fatty acid content in processed red meat might be responsible for its negative effect on CV health. In addition to sodium and nitrates that are added to processed meats, evidence points toward trimethylamine-N-oxide (TMAO). TMAO is a metabolite of gut microbial fermentation of L-carnitine and choline found in meat, and was shown to have proatherogenic properties.[95] For example, dietary L-carnitine supplementation in mice was associated with modification of gut flora leading to increased production of TMAO and the development of atherosclerosis. This was not observed in mice treated with antibiotics and reflects the obligatory role of the microbiota in TMAO production.[95] Similarly, in humans, higher plasma L-carnitine levels were predictive of prevalent CHD and incident major adverse cardiac events.[95] Increased level of TMAO was found to be independently associated with CV events at 3 years.[95,96]

Several unresolved issues and contradictions remain, however, including the fact that unprocessed meats and other food items associated with cardioprotective diets such as seafood, choline-rich foodstuffs, and nuts might lead to TMAO production.[95,97] Such inconsistencies could be explained by the idea that the global dietary pattern, in part through its influence on microbiota composition, might mediate the cardiometabolic effect of TMAO. For instance, dietary habits that positively affect gut microbiota composition such as vegetarianism were shown to attenuate TMAO production with L-carnitine supplementation.[95]

Fructose and Added Free Sugar Overconsumption

Gut microbiota composition and function could also be implicated in another current provocative aspect of nutrition, namely the controversy surrounding added free sugar overconsumption and its association with metabolic and CV health. The average Canadian now consumes approximately

110 grams (26 teaspoons or > 20% of total energy) of sugar daily, with >half of these calories coming from added free sugars, the major source being high-fructose corn syrup.[98,99] High-fructose corn syrup is produced through recent advances in food processing whereby fructose is isolated from its natural, fibre-rich, sugar/beet cane and fruit matrices. High-fructose corn syrup is added by the food industry to processed products such as sweets and sugar-sweetened beverages because of its relative low cost and high degree of sweetness.[100] Compared with glucose, fructose has several metabolic properties that make it particularly toxic. For one, fructose is known to be a potent stimulant of de novo lipogenesis, leading to ectopic fat deposition and insulin resistance.[101] Additionally, fructose does not stimulate insulin and subsequent leptin secretion thus failing to induce satiety signals.[102,103] Studies now show that excess sugar consumption is associated with obesity,[104] cardiometabolic risk,[105] and CV diseases.[106]

However, controversies remain as to whether the metabolic properties of fructose or the fact that it simply constitutes excess energy intake is responsible for its deleterious effects on CV health. Advocates of excess energy intake from sugar as being responsible for the current pandemic of obesity-related disorders often argue that isocaloric feeding of fructose shows no effect on weight gain.[107,108] Notwithstanding these authors' sometimes debatable affiliations and sources of funding, it can be argued that added free sugars rarely replace other calories equally and thus often constitute and promote excessive caloric intake in the real-life setting. In addition to the fact that fructose does not influence leptin signalling, added free sugars often come in liquid form, which are not as effective as solids in controlling appetite.[101,109] Furthermore, the detrimental effect of added free sugars on cardiometabolic markers has been shown to be independent of its effect on body weight.[105]

Finally, as with regular consumption of processed meats, sugar overconsumption could be associated with higher-risk demographic characteristics, and unhealthy lifestyle choices such as a lower nutrient-dense diet and physical inactivity. The gut flora of regular consumers of free sugar could thus be less diverse and altered in ways favouring proinflammatory response to sugars and processed meats, making these individuals even more susceptible to the detrimental effects of these ingredients.[110] An argument in favour of this idea is the fact that restoration of microbial diversity by probiotics suppressed high-fructose-induced metabolic alterations in mice.[111]

Pending Issues: What Can Be Done?

Issues regarding the role of microbiota in CV disease prevention still remain. For one, bacterial strains that constitute a "healthy" microbiota have not yet been characterized. Second, little is known about the influence of host genomics on microbiota function. Third, the causative link between microbiota diversity, response to dietary insults, and cardiometabolic health still needs to be explored. To foster Canadian research in these areas, we believe that the Canadian microbiome initiative sponsored by the Canadian Institutes of Health Research could play a major role. Unfortunately, this initiative has not received adequate funding on a regular, sustained basis.

From a population health and social perspective, federal bodies should actively educate and encourage healthy lifestyles and regulate the food industry. Currently, Health Canada has not set a daily limit regarding sugar consumption but recently proposed a daily recommended allowance of 100 grams (20% of energy) of sugar. Clearly this value is too high and is not consistent with other society recommendations or the current scientific literature. For example, the WHO, the US Department of Agriculture, and most recently, the Heart and Stroke Foundation of Canada have recommended that no more than 10% of daily calories be derived from sugar, and new WHO and Heart and Stroke Foundation draft guidelines could decrease that limit to 5%.[112,113] Industrial uses of added sugars should be regulated by federal guidelines that fall in line with other society recommendations and reflect scientific evidence, not food industry concerns. Food labelling in this country must also be simplified, and added sugars should be explicitly mentioned, as is done for trans fats, to allow Canadians to make informed decisions regarding their food consumption. Although still inadequate, we are glad that the federal government appears to be moving in this direction. Advertisement of processed and fast foods, especially to children, should also be limited. Finally, a frank open discussion must occur on the benefits of continued subsidies to corn producers and other stakeholders in the sugar industry, and to whether processed foods including sugar-sweetened beverages be taxed to subsidize the production of minimally processed, fresh produce.

Final Thoughts

It is our opinion that HIIT should be increasingly used as a training modality in the primary, secondary, and tertiary prevention of CV disease, because it is superior to MICET for improving VO_2 peak and is associated with superior effects on cardiometabolic and traditional risk factors, and is also safe and better tolerated. Finally, there is growing evidence linking unfavourable lifestyle habits to modulation of the intestinal microbiota composition and inflammatory and obesity-related disease risks. Future work will no doubt have to evaluate whether dietary interventions aimed at improving gut flora can reduce CV risk.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.09.014.

Table S1: HIIT protocols previously used in adults with a high cardiovascular risk (HCVR).

Studies and subjects	Modality	Interval duration		Interval intensity		HIIT duration/ Repetition	Training period
Primary prevention		**Work**	**Recovery**	**Work**	**Recovery**		
Coquart et al. 2008[1] Obese (T2DM or not) Women (n=20)	cycling	2 min	2 min	120% power at VT	80% power at VT	Total: 32 min 8 intervals 8 recoveries	12 weeks
Schjerve et al. 2008[2] Obese adults (n=14)	treadmill	4 min	3 min	85-95% HRmax	50-60% HRmax	Total: 28 min 4 intervals 4 recoveries	12 weeks
Tjonna et al. 2008[3] Metabolic syndrome (n=12)	treadmill	4 min	3 min	90% HRmax	70% HRmax	Total: 28 min 4 intervals 4 recoveries	16 weeks
Sartor et al. 2010[4] Obese adults (n=10)	cycling	4 min	2 min	90% HRmax	Passive	Total: 60 min 10 intervals 10 recoveries	2 weeks
Stensvold et al. 2010[5] Metabolic syndrome (n=21)	treadmill	4 min	3 min	90-95% HRmax	70% HRmax	Total: 28 min 4 intervals 4 recoveries	12 weeks
Little et al. 2011[6] Patients with T2DM (n=8)	cycling	1 min	1 min	60% PPO (>80% HRmax)	Passive	Total: 20 min 10 intervals 10 recoveries	2 weeks
Tjonna et al. 2011[7] Metabolic syndrome (n=11)	treadmill	4 min	3 min	90% HRmax	70% HRmax	Total: 28 min 4 intervals 4 recoveries	1 session
Molmen-Hansen et al. 2012[8] Hypertensive	treadmill	4 min	3 min	90-95% HRmax	60-70% HRmax	Total: 28 min 4 intervals	12 weeks

patients (n=31)						4 recoveries	
Gremeaux et al. 2012[9] Obese patients (n=62)	cycling	15-30 s	15-30 s	80% PPO RPE: 15	Passive	Total: 20 min Intervals: 10 min Recovery: 10 min	9 months
Gillen et al. 2012[10] Patients with T2DM (n=7)	cycling	1 min	1 min	60% PPO (>80% HRmax)	Passive	Total: 20 min Intervals 10 min recoveries: 10 min	1 session
Boyd et al. 2013[11] Obese men (n=10, n=9)	cycling	1 min	1 min	100% PPO (HI) 70% PPO (LO)	Active (Loadless)	Total: 16/20 min 8/10 intervals 8/10 recoveries	3 weeks
Drigny et al. 2013[12] Metabolic syndrome (n=35)	cycling	15-30 s	15-30 s	80% PPO RPE: 15	Passive	Total: 20 min Intervals:10 min Recovery: 10 min	9 months
Larsen et al. 2013[13]Metabolic syndrome (n=7)	treadmill	4 min	3 min	85-95% HRmax	70% HRmax	1:1 interval/recovery 4 intervals 4 recoveries	2 sessions
Mitranum et al. 2013[14]Patients with T2DM (n=14)	treadmill	1 min	4 min	80-85% VO_2peak	50-60% VO_2peak	Total: 20/30 min 4/6 intervals 4/6 recoveries	9 weeks
Dalzill et al. 2014[15] Obese patients (n=134)	cycling	15-30 s	15-30 s	80% PPO RPE: 15	Passive	Total: 20 min Intervals:10 min Recovery: 10 min	9 months
Lunt et al. 2014[16] Obese patients (n=16)	treadmill	4 min	3 min	85-95% HRmax	65-75% HRmax	Total: 28 min 4 intervals 4 recoveries	12 weeks

HRmax: Maximal heart rate

RPE: Relative perceived effort (Borg scale)
HRR: Heart rate reserve (HRR = maximal heart rate – resting heart rate)
MSEC: Maximum Short-Time Exercise Capacity (maximal power achieved in Watts during steep ramp test)
PPO: Peak power output (Watts)
VT: ventilatory threshold

Table S2: HIIT protocols previously used in patients with CHD.

Studies and subjects	Modality	Interval duration		Interval intensity		HIIT duration/ repetition	Training period
Patients with CHD		**Work**	**Recovery**	**Work**	**Recovery**		
Meyer et al. 1990[17] (n=9)	cycling	1 min	1 min	% of PPO Week 1: 104% Week 2: 125% Week 3: 145% Or 86% HRmax	20 W	Total 15 min 8 intervals 7 recoveries	3 weeks
Rognmo et al. 2004[18] (n=8)	treadmill	4 min	3 min	85-95% HRmax	65-75% HRmax	Total: 28 min 4 intervals 4 recoveries	10 weeks
Warburton et al. 2005[19] (n=7)	treadmill, stair climber, arm cycling, leg cycling	2 min	2 min	90% HRmax	40% HRmax	Total: 30 min 9 intervals 6 recoveries	16 weeks
Amundsen et al. 2008[20] (n=8)	treadmill	4 min	3 min	85-95% HRmax	50-60% HRmax	Total: 28 min 4 intervals 4 recoveries	10 weeks
Moholdt et al. 2009[21] (n=28)	treadmill	4 min	3 min	90% HRmax	70% HRmax	Total: 28 min 4 intervals 4 recoveries	6 months
Munk et al. 2009[22] (n=20)	cycling, treadmill	4 min	3 min	90% HRmax	70% HRmax	Total: 28 min 4 intervals 4 recoveries	6 months
Guiraud et al. 2010[23]	cycling	A: 15 s	A: 15 s	A: 100% PPO	A: passive	Time to	4 acute

(n=19)		B: 15 s C: 1 min D: 1 min	B: 15 s C: 1 min D: 1 min	B: 100% PPO C: 100% PPO D: 100% PPO	B: 50% PPO C: passive D: 50% PPO	exhaustion 28.7 min 12.2 min 25.4 min 13.9 min	sessions
Guiraud et al. 2011[24] (n=19)	cycling	15 s	15 s	100% PPO	passive	Total: 20 min Intervals: 10 min Recoveries: 10 min	1 session
Helgerud et al. 2010[25] (n=10)	treadmill	4 min	3 min	85-95% HRmax	60-70% HRmax	Total: 28 min 4 intervals 4 recoveries	8 weeks
Moholdt et al. 2011[26] (n=30)	treadmill	4 min	3 min	85-95% HRmax	70% HRmax	Total: 28 min 4 intervals 4 recoveries	12 weeks
Munk et al. 2011[27] (n=18)	cyclingtread mill	4 min	3 min	80-90% HRmax	60-70% HRmax	Total: 28 min 4 intervals 4 recoveries	6 months
Currie et al. 2012[28] (n=10)	cycling	1 min	1 min	80% of PPO	10% of PPO	Total: 20 min 10 intervals 10 recoveries	1 session
Morikawa et al. 2012[29] (n=26)	treadmill	3 min	3 min	75–85% HRmax	30-60% HRmax	Total: 24 min 4 intervals 3 recoveries	3 days
Aamot et al. 2013[30] (n=83)	Cycling, running, skiing, ergometers	4 min	3 min	85–95% HRmax	70% HRmax	Total: 24 min 4 intervals 3 recoveries	12 weeks
Currie et al. 2013[31] (n=11)	cycling	1 min	1 min	80-104% of PPO	10% of PPO	Total: 20 min 10 intervals 10 recoveries	12 weeks

Currie et al. 2013[32] (n=7)	cycling	1 min	1 min	80-89% of PPO	10% of PPO	Total: 20 min 10 intervals 10 recoveries	12 weeks
Moholdt et al. 2013[33] (n=112)	Cycling, running skiing, ergometers	4 min	3 min	<88% HRmax 88-92% HRmax >92% HRmax	70% HRmax	Total: 32 min 4 intervals 4 recoveries	12 weeks
Keteyian et al. 2014[34] (n=15)	treadmill	4 min	3 min	80–90% HRmax	60-70% HRmax	Total: 32 min 4 intervals4 recoveries	12 weeks

HRmax: Maximal heart rate
RPE: Relative perceived effort (Borg scale)
HRR: Heart rate reserve (HRR = maximal heart rate – resting heart rate)
MSEC: Maximum Short-Time Exercise Capacity (maximal power achieved in Watts during steep ramp test)
PPO: Peak power output (Watts)
VT: ventilatory threshold

Table S3: HIIT protocols previously used in patients with CHF and heart transplantation.

Studies and subjects	Modality	Interval duration		Interval intensity		HIIT duration/ repetition	Training period
Patients with CHF		**Work**	**Recovery**	**Work**	**Recovery**		
Meyer et al. 1996 [35] (n=18)	cycling, treadmill	30 s 1 min	60 s 1 min	50% MSEC 2.82-5.23 km/h	25 W 1.45 km/h	15 min 10 min	3 weeks
Meyer et al. 1996 [36] (n=16)	cycling	30 s 15 s 10 s	60 s 60 s 60 s	50% MSEC 70% MSEC 80% MSEC	15 W 15 W15 W	Total: 13 min 14 min: 45 s 16 min: 10 s	3 acute sessions
Meyer et al. 1997 [37] (n=18)	cycling, treadmill	30 s 1 min	60 s 1 min	50% MSEC 2.82-5.23 km/h	25 W 1.45 km/h	15 min 10 min	3 weeks
Meyer et al. 1998 [38] (n=11)	cycling	30 s	60 s	50% MSEC	25 W	15 min	3 weeks
Willenheimer et al. 1998 [39] (n=33)	cycling	90 s	30 s	80% VO_2peak	passive	15 min to 45 min	0-7 weeks7-16 weeks
Roditis et al. 2007[40] (n=11)	cycling	30 s	30 s	100% PPO	passive	40 min	12 weeks
Wisloff et al. 2007[41] (n=11)	treadmill	4 min	3 min	90-95% HRmax	50-70% HRmax	Total: 28 min 4 intervals 4 recoveries	12 weeks
Nilson et al. 2008[42] (n=40)	walking	5 -10 min	5 -10 min	90-95% HRmax	active	Total session: 3 intervals 3 recoveries	4 months
Bouchla et al. 2010[43] (n=10)	cycling	30 s	60 s	50% MSEC	25 W	15 min	12 weeks
Nilson et al. 2010[44]	walking	5 -10 min	5 -10 min	90-95% HRmax	active	Total session:	4 months

(n=39)						3 intervals 3 recoveries	
Tasoulis et al. 2010[45] (n=21)	cycling	30 s	60 s	50% MSEC	25 W	40 min	12 weeks
Tomczak et al. 2011[46] (n=12)	treadmill	4 min	3 min	90-95% HRmax	50-70% HRmax	Total: 28 min 4 intervals 4 recoveries	1 session
Anagnostakou et al. 2011[47] (n=28)	cycling	30 s	60 s	50% MSEC	25 W	20 min or 40 min	3 months
Freyssin et al. 2012[48] (n=12)	cycling	30 s	60 s	50 to 80% MSEC	25 W	71 min	8 weeks
Gayda et al. 2012[49] (n=13)	cycling	30 s	30 s	100% PPO	passive	16 min	1 session
Meyer et al. 2012[50] (n=20)	cycling	A: 30 s B: 30 s C: 90 s D: 90 s	A: 30 s B: 30 s C: 90 s D: 90 s	A: 100% PPOB: 100% PPOC: 100% PPOD: 100% PPO	A: passive B: 50% PPO C: passive D: 50% PPO	Time to exhaustion 27.5 min 16.4 min 26.2 min 16.0 min	4 acute sessions
Wang et al. 2013[51] (n=60)	cycling	3 min	3 min	80% HRR	40% HRR	Total: 27 min 4 intervals 3 recoveries	12 weeks
Iellamon et al. 2013[52] (n=8)	treadmill	4 min	3 min	75-80% HRR	45-50% HRR	50 to 100 min 4 intervals 4 recoveries	12 weeks
Gayda et al. 2013[53] (n=19)	cycling	30 s	30 s	100% PPO	passive	16 min	1 session
Guiraud et al. 2013[54] (n=19)	cycling	15 s	15 s	100% PPO	passive	16 min	1 session
Normandin et al. 2013[55] (n=20)	cycling	30 s	30 s	100% PPO	passive	16 min	1 session

Fu et al. 2013[56] (n=15)	cycling	3 min	3 min	80% HRR	40% HRR	Total: 27 min 4 intervals 3 recoveries	12 weeks
Isaksen et al. 2014[57] (n=26)	treadmill	4 min	3 min	85% HRmax	60-70% HRmax	28 min 4 intervals 4 recoveries	3 months
Heart transplant patients							
Nytroen et al. 2012[58] (n=24)	treadmill	4 min	3 min	85-95% HRmax	11-13 RPE	Total: 28 min 4 intervals 4 recoveries	8 weeks
Nytroen et al. 2013[59] (n=24)	treadmill	4 min	3 min	85-95% HRmax	11-13 RPE	Total 28 min 4 intervals 4 recoveries	8 weeks
Rustad et al. 2014[60] (n=24)	treadmill	4 min	3 min	85-95% HRmax	11-13 RPE	Total 28 min 4 intervals 4 recoveries	8 weeks

HRmax: Maximal heart rate
RPE: Relative perceived effort (Borg scale)
HRR: Heart rate reserve (HRR = maximal heart rate – resting heart rate)
MSEC: Maximum Short-Time Exercise Capacity (maximal power achieved in Watts during steep ramp test)
PPO: Peak power output (Watts)
VT: ventilatory threshold

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