National and Kapodistrian University of Athens
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High Intensity Interval Training in patients with Coronary Heart Disease

by

Serafeim Eleftheriou

Supervisors

Anastassios Philippou, Maria Maridaki, Michael Koutsilieris

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Abstract

Coronary Heart Disease (CHD) is the most common cause of death worldwide, as 1 out of 4 deaths in 2016 were linked with CHD, according to the World Health Organization (WHO). The pathophysiology of the disease involves atheromatous plaque formation inside the vessel and blood flow reduction to the heart muscle, that finally leads to myocardial ischemia. Cardiovascular risk factors such as blood pressure, smoking, high levels of blood glucose and cholesterol and chronic inflammation contribute to the manifestation of CHD. In addition, lack of exercise and poor diet have been shown to increase the risk of a cardiovascular event. On the contrary, aerobic exercise during cardiac rehabilitation, has been proven to offer various health benefits, by reducing cardiovascular risk factors and improving cardiovascular function after myocardial infarction. Despite the undisputed benefits of aerobic exercise, High Intensity Interval Training (HIIT) and its possible benefit for CHD patients has also drawn the scientific community's attention over the last years. In this review, the term HIIT and its application in cardiac rehabilitation as a complementary therapy for CHD are analyzed. Furthermore, it's effects on important variables such as peak aerobic capacity ($VO_{2\ peak}$), endothelial function, inflammation and cardiovascular risk factors are evaluated. According to the literature, HIIT is highly effective at improving cardiorespiraratory capacity, endothelial function and reducing inflammation. Conversely, research findings regarding the effect of HIIT on blood pressure, blood glucose and cholesterol levels are unclear, as some controlled trials reported a decrease in these markers, while others didn't find any statistically significant difference. Scientific data on the patients' safety and adherence to HIIT are also presented. Research has shown that HIIT is safe for stable and physically fit patients, as the risk of a cardiovascular event is low. Furthermore, patients seem to prefer HIIT over aerobic exercise, resulting in improved long-term adherence. Lastly, the basic principles of exercise prescription are elaborated through the presentation of different HIIT protocols, based on the patient's individual characteristics and needs. In conclusion, HIIT is an effective, safe exercise alternative for stable CHD patients. Thus, targeted implementation of HIIT is feasible. Nevertheless, additional research is required, with the participation of older, less physically fit patients in systematic controlled trials, before HIIT can be widely applied in cardiac rehabilitation settings.

Key words: High Intensity Interval Training; HIIT; Coronary Heart Disease; CHD; cardiac rehabilitation; $VO_{2\ peak}$; prescription

Περίληψη

Η Στεφανιαία Νόσος αποτελεί τη συχνότερη αιτία θανάτου παγκοσμίως, με 1 στους 4 θανάτους το 2016 να οφείλονται σε αυτήν, σύμφωνα με τον Παγκόσμιο Οργανισμό Υγείας. Η παθοφυσιολογία της νόσου χαρακτηρίζεται από τη δημιουργία αθηρωματικής πλάκας εντός των στεφανιαίων αγγείων, τη μείωση της αιματικής παροχής προς το μυοκάρδιο και τελικά την ισχαιμία του μυοκαρδίου. Παράγοντες καρδιαγγειακού κινδύνου, όπως η αρτηριακή πίεση, το κάπνισμα, τα υψηλά επίπεδα σακχάρου και χοληστερόλης στο αίμα, καθώς και η χρόνια φλεγμονή, συμβάλλουν στην εκδήλωση της νόσου, με την καθιστική ζωή και την πλούσια σε λιπαρά και ζάχαρη διατροφή να αυξάνουν περαιτέρω τον κίνδυνο για καρδιαγγειακό επεισόδιο. Στον αντίποδα, η άσκηση, ειδικότερα η αερόβια, παρουσιάζει αποδεδειγμένα οφέλη στην μείωση των προαναφερθέντων παραγόντων κινδύνου αλλά και στην βελτίωση της καρδιαγγειακής λειτουργίας μετά από καρδιαγγειακό σύμβαμα, κατά την διαδικασία της αποκατάστασης. Παρά τα αδιαμφισβήτητα οφέλη της αερόβιας άσκησης, το ενδιαφέρον της επιστημονικής κοινότητας τα τελευταία χρόνια έχει στραφεί στη μελέτη ειδικότερα της διαλειμματικής άσκησης υψηλής έντασης και της αποτελεσματικότητάς της σε ασθενείς με στεφανιαία νόσο. Στην παρούσα ανασκόπηση αναλύεται ο όρος διαλειμματική άσκηση/προπόνηση υψηλής έντασης και πώς εντάσσεται στην καρδιακή αποκατάσταση, ως συμπληρωματική θεραπεία στην στεφανιαία νόσο. Στην συνέχεια, αξιολογείται η επίδρασή της σε σημαντικούς βιοδείκτες, όπως η μέγιστη αερόβια ικανότητα, η ενδοθηλιακή λειτουργία, η φλεγμονή, αλλά και σε παράγοντες καρδιαγγειακού κινδύνου. Σύμφωνα με την υπάρχουσα βιβλιογραφία, η διαλειμματική προπόνησης υψηλής έντασης αποδεικνύεται ιδιαίτερα αποτελεσματική στην βελτίωση της καρδιοαναπνευστικής ικανότητας ($VO_{2\ peak}$), της ενδοθηλιακής λειτουργίας, αλλά και στην μείωση της φλεγμονής. Αντιθέτως, λιγότερο ξεκάθαρα είναι τα ευρήματα όσον αφορά την επίδραση της διαλειμματικής προπόνησης στην αρτηριακή πίεση, την δυσλιπιδαιμία και την υπεργλυκαιμία, καθώς κάποιες έρευνες καταγράφουν μείωση αυτών των δεικτών, ενώ άλλες δεν παρουσιάζουν στατιστικά σημαντική διαφοροποίηση. Επιπλέον, παρατίθενται βιβλιογραφικά στοιχεία σχετικά με την ασφάλεια εκτέλεσης διαλειμματικής προπόνησης σε καρδιαγγειακούς ασθενείς αλλά και την συμμόρφωσή τους σε αυτή την μορφή άσκησης. Τα αποτελέσματα των σχετικών ερευνών έδειξαν ότι η διαλειμματική προπόνηση είναι μια ασφαλής μορφή άσκησης σε καρδιοπαθείς με σταθερά συμπτώματα και καλή φυσική κατάσταση, καθώς ο κίνδυνος καρδιαγγειακού συμβάματος είναι αρκετά χαμηλός, ενώ οι ασθενείς φαίνεται να την προτιμούν σε σχέση με την αερόβια άσκηση, γεγονός που συμβάλλει στην μακροπρόθεσμη συμμόρφωσή τους. Τέλος, επεξηγούνται οι βασικές αρχές συνταγογράφησης διαλειμματικής άσκησης, μέσω της παρουσίασης διαφορετικών πρωτοκόλλων, βασισμένων στις εξατομικευμένες ανάγκες κάθε ασθενούς. Συμπερασματικά, η διαλειμματική προπόνηση υψηλής έντασης είναι μια αποτελεσματική, ασφαλής, εναλλακτική μορφή άσκησης σε σταθεροποιημένους ασθενείς με στεφανιαία νόσο. Η στοχευμένη εφαρμογή της στην καρδιακή αποκατάσταση είναι εφικτή. Ωστόσο, αναγκαία κρίνεται η διεξαγωγή περισσότερων μεγάλων, συστηματικών ερευνών, με την συμμετοχή ασθενών μεγαλύτερης ηλικίας, με βαρύτερο ιατρικό ιστορικό, για πιο γενικευμένη εφαρμογή της στον χώρο της καρδιακής αποκατάστασης.

Λέξεις κλειδιά: Διαλειμματική προπόνηση υψηλής έντασης, Στεφανιαία Νόσος, καρδιακή αποκατάσταση, μέγιστη πρόσληψη οξυγόνου, συνταγογράφηση άσκησης

Introduction

Coronary Heart Disease (CHD) is the number one cause of death worldwide, affecting millions of individuals every year. This dissertation is about epidemiologic and statistical data as well as the pathophysiology of CHD. In addition, the term High Intensity Interval Training (HIIT) is analyzed and different training protocols are presented.

The aim of the dissertation is the presentation and analysis of HIIT, as a secondary and complementary therapy for CHD patients. Additionally, conclusions will be drawn, and questions will be answered regarding the pros and cons and the safety of HIIT in the concurrent cardiac rehabilitation in patients with CHD. Finally, the ultimate goal is the broadening of scientific conversation, in regard to the best possible way of dealing with and preventing CHD.

Epidemiologic data

Coronary Artery Disease is the most common cause of death worldwide, as 17.5 million people died from CHD in 2016, according to a survey conducted by the World Health Organisation.[1] More precisely, 1 out of 4 deaths worldwide is attributed to Coronary Artery Disease, from 1 out of 5 twenty years ago.[2] In Europe, the number of deaths is estimated to 1.8 million people[3], with Russia having the highest mortality percentage (330 and 154/100,000 for men and women respectively from 1995 to 1998)[4], while in Greece the equivalent percentage was 175 and 49/100.000. In the United Kingdom, 2.3 million have been diagnosed with CHD, as 175.000 heart attacks are recorded every year.[5]

Furthermore, financial loss from CHD is enormous. It is estimated that 196 million euros are lost per year in Europe, with 54% of total costs coming from healthcare and 24% from low productivity and absence from work.[4]

In the United States, 15.4 million people over 20 years old have been diagnosed with ischemic heart disease, while 6.4% of them were diagnosed with CHD, according to a survey by the American Heart Association. The percentage and the effect of the disease is dramatically increased, in men over 65 years.[4]

Despite the alarming epidemiologic data above, a slight decrease in the number of CHD cases has been reported in the United States, (114 and 133/100.000 from 294 and 225/100.000 for men and women respectively) as well as in the developed European countries, with an exception been found in Eastern European countries.[4] This decrease is mostly attributed to advances in healthcare and early detection of the disease. Unfortunately, a major percentage of patients remains asymptomatic, resulting in underdiagnosis and reduced data recording of the disease.

Finally, an increase in CHD patients has been reported in the developing countries of Middle East, Latin America, India and China due to the adoption of the Western lifestyle (lack of exercise, poor diet and stress).[4] Based on the aforementioned data, Coronary Heart Disease is evolving rapidly into a global health problem, which creates an imperative need for improved treatment and prevention of the disease.

Pathophysiology

Coronary Heart Disease is a chronic, inflammatory disease, caused by atheromatosis, resulting in stenosis of one or more coronary arteries.[6] Atheromatosis involves the formation of atheromatous plaque in the inner layer of the wall of an artery, causing blood flow reduction to the heart muscle, that ultimately leads to myocardial ischemia.[7] Cardiovascular risk factors such as high blood pressure, smoking, hyperglycemia and hypercholesterolemia play a major role in the manifestation of CHD.[6]

The common denominator of the aforementioned risk factors is inflammation. According to the latest scientific research, inflammation plays a key role in every stage of atheromatous plaque formation, from inflammatory activation of endothelial cells on the early stages, inflammatory cytokine secretion from foam cells in a later stage, to plaque rupture and clot formation. C-Reactive Protein (CRP) is considered the main biomarker of inflammation. CRP levels provide vital information about diagnosis and treatment in CHD patients, because it can be detected in early and later stages of the disease, when its concentration is increased. Therefore, CRP is an important cardiovascular risk factor, whose reduction should be a priority for CHD patients.[8,9] Besides cardiovascular risk, high CRP levels can negatively affect parasympathetic function, which -under normal circumstances- can suspend the inflammatory response, by decreasing pro-inflammatory cytokine production.[10]

From the early stages of atheromatosis, when early endothelial damage is observed, high blood pressure, smoking, hyperglycemia, hypercholesterolemia and chronic inflammation have negative effects on endothelial homeostasis.[11] At a functional level, the endothelium is a vast body organ which is characterized by its selective permeability, contributing to the separation between vascular and other body compartments. It also regulates the transportation of macromolecules and fluids through communication between intracellular and transcellular vesicles. Furthermore, a healthy endothelium can accomplish various functions, such as lipoprotein metabolism, vasoactive molecule (NO) and prostaglandin (especially prostacyclin) synthesis, growth factor and cytokine processing, free radical elimination and recycling of the extracellular matrix (ECM). Endothelium homeostasis also involves low platelet aggregation and fibrinolysis.[12] Under abnormal circumstances, the endothelium is characterized by low NO production, increased accumulation and oxidation of lipoproteins, low (ECM) recycling and platelet adhesion-aggregation imbalance.[13]

Biochemically, endothelium homeostasis depends on the balance between vasodilation and thrombogenic factors. The former includes NO, prostacyclin, bradykinin and acetylcholine, which are part of an antithrombotic/anti-inflammatory phenotype. The latter include thromboxane A2, tissue factor, interleukin 8 and 6 and MCP-1 protein, which are part of a thrombotic/inflammatory phenotype. When the imbalance leans towards the second phenotype, then normal endothelium function is obscured.[12]

An important sign of endothelial dysfunction is low NO production. NO is produced by E-NOS synthase as a response to bradykinin, acetylcholine or mechanical stress. Also, scientific research on human and animal models showed that vessels characterized by continuous blood flow produce more E-NOS and subsequently NO. NO regulates vessel tone, causing vasodilation and blocks smooth muscle cell migration and proliferation in the intima as well as leukocyte and platelet aggregation. These constitute important steps of the pathway towards atherosclerosis.[11] Thus, normal E-NOS and NO production contribute to the anti-atherosclerotic phenotype, by protecting the endothelium.

The loss of the endothelium's eclectic permeability is another important factor of endothelial damage.[11] The endothelium ceases to be a natural barrier, allowing lipid (especially LDL) and leukocyte transport inside the vessel wall. Consequently, the lipoproteins are bound to proteoglycans, get oxidized and trapped in the intima. Oxidized lipoproteins (OxLDL) activate the endothelial cells to produce inflammatory mediators, cytokines like IL-6 and IL-8, extracellular adhesive molecules such as ICAM-1, VCAM-1 and selectins (E and P), that attract or bind to monocytes and T-lymphocytes, contributing to the inflammatory response[9]. Monocytes are differentiated into macrophages that incorporate OxLDL and transform into foam cells, through a process called esterification.[9] Foam cell accumulation contributes to the plaque's lipid core.[11]

T-lymphocytes also produce cytokines such as IL-1, cytotoxic molecules such as TNF-1 as well as growth factors and free radicals.[11] Those factors signal adjacent smooth muscle cells to proliferate, migrate to the intima of the vessel wall and produce ECM components and eventually form the fibrous capsule of the plaque.[12] The fibrous capsule consists mainly of collagen fibers, smooth muscle cells, macrophages and T-lymphocytes.[11] It lies on top of the lipid core, which is rich in lipids, cholesterol, oxidized lipoproteins, necrotic cell fragments and calcium, forming the atheromatous plaque.[12]

Inflammation plays a crucial role in all the stages of atheromatous plaque formation. It is particularly robust towards the shoulders of the plaque, where macrophages, T-cells and dendritic cells produce metalloproteinases, rendering it vulnerable for rupture.[9] Vulnerable (unstable) plaques are also characterized by a necrotic lipid core surrounded by a thin fibrous capsule, rich in inflammatory cells and newly formed capillaries and poor in smooth muscle cells. Those are prone to hemorrhage and rupture, which lead to thrombogenesis. In contrast to unstable plaques, stable plaques have a small lipid core, are poor in macrophages and small capillaries and they are surrounded by a thick fibrous capsule.[14]

Atheromatous plaque formation can lead to cardiac ischemia due to reduced blood flow to the myocardium. Symptoms of CHD appear when artery blockage surpasses 70% of the vessel's diameter. The most common manifestation of CHD is angina, which can be stable or unstable. Stable angina manifests during physical activity, due to the heart muscle's increased need for oxygen, that cannot be delivered due to the vessel's stenosis.[15] It is characterized by chest pain or pressure, that radiates to the neck, the jaw, the arms or epigastrium.[15] Those symptoms are relieved with rest or administration of nitroglycerin, while the severity and intensity of the pain is almost always the same during every episode. Unstable angina manifests during rest, while symptoms become more severe and intense during each episode.[16]

When an atheromatous plaque ruptures, its necrotic lipid core is exposed to thrombogenic factors and, as result, platelets aggregate, and a thrombus is formed inside the vessel[12]. The thrombus causes ischemia of the heart muscle and subsequent necrosis of cardiomyocytes or myocardial infarction (MI).

The symptoms of MI include chest pain for more than 10 minutes, that can spread to the left arm, neck or jaw, dyspnea, sweating, nausea and vomiting, stress, fatigue and weakness. More than 64% of patients that suffered MI report minimal or no symptoms at all (silent MI).[7] The most common diagnostic tools for MI is the electrocardiogram -which identifies the MI type and location- as well as troponin I and T and creatine kinase MB.

What is High Intensity Interval Training (HIIT)?

HIIT is a form of exercise which was initially described by German cardiologist Hans Reindell in the 50's.[17] Since then, it has been mostly utilized in athletic training. However, its benefits in the cardiorespiratory and musculoskeletal systems led scientists to examine the possibility of applying HIIT to patients with cardiovascular pathology.[18]

HIIT and its possible benefit for CHD patients has drawn the scientific community's attention, especially over the last 15 years. Specifically, the American Heart Association included HIIT in its exercise prescription recommendations in 2007.[19]

HIIT is now considered an alternative to aerobic exercise as well as a complementary form of secondary treatment in patients with CHD, offering similar, if not greater benefits.[20] The basic principle of HIIT is the alternation between short bursts of intense exercise (over 85% of $VO_{2\ peak}$) and low intensity recovery (or rest) periods (at 40-60% of $VO_{2\ peak}$).[18,21] This alternating form of exercise allows cardiovascular patients to train for longer periods of time at a higher intensity, compared to moderate intensity aerobic training.[19]

There are various HIIT exercise protocols in CHD patients, which are classified into 3 categories, depending on the duration of interval exercise[21]: Long-duration intervals: 3 to 15 minutes at 85–90 % of $VO_{2\ peak}$[22], moderate-duration intervals: 1 to 3 min at 95–100 % of $VO_{2\ peak}$ and short-duration intervals: 10 seconds to 1 min at 100–120 % of $VO_{2\ peak}$.[20]
An exercise protocol featuring long-duration intervals is the following: 10 minutes of warm-up at 50-70% $VO_{2\ peak}$, followed by four 3-4-minute intervals at 80-90% $VO_{2\ peak}$, with 3 minutes of active recovery at 50-60 $VO_{2\ peak}$[23,24,25,26.] Rate of Perceived Exertion (RPE), as measured by the Borg scale, ranges between 15 to 18 during the four-minute-high intensity interval, while the corresponding RPE range during active recovery is 11-13.[27] Lastly, cool down includes 3-5 minutes at 50-70% $VO_{2\ peak}$.[22,23,24]

A typical moderate-duration interval protocol, such as Currie's et al, includes a 10-15-minute warm-up, followed by ten 1-minute intervals at 89% of PPO (Peak Power Output) on a static bicycle, with 1 minute of active recovery at 10% of PPO. At the end of the session, participants performed static stretching and light aerobic work, as a cool down.[28] Cardozo's et al exercise protocol which consisted of eight 2-minute intervals at 90% of HR_{peak}, with 2 minutes of active recovery, is another example of moderate intervals.[29]

Finally, short-duration interval protocols typically include a higher number of intervals with shorter periods of active recovery. For instance, Garcia et al conducted a trial where participants exercised at 85-95% of $VO_{2\ peak}$ for ten 30-60 second intervals, with equal active recovery at 50-70% $VO_{2\ peak}$[22], while Jaureguizar et al tested a similar protocol, with 20-second intervals, followed by 40 seconds of active recovery.[30] All of the above exercise protocols can be performed on a treadmill, static bicycle or rowing machine. Alternatively, running outside, riding a bicycle, walking and swimming are great options.[19]

Another significant parameter for HIIT prescription is the estimation of exercise intensity. Intensity is usually described as a percentage of $VO_{2\ peak}$, Heart Rate Max (HR_{max}), Peak Power Output (PPO). Borg scale and Rate of Perceived Exertion (RPE) is also a tool to estimate exercise intensity.[20] In fact, PPO and Borg scale seem to be the most reliable estimation markers for long and moderate duration intervals, whereas $VO_{2\ peak}$ and HR_{max} are more accurate intensity markers for short duration intervals.[18]

Consequently, exercise induced physiological adaptations in patients with CHD are determined by exercise intensity, duration, type of recovery and its duration.[19]

Current data on cardiac rehabilitation and its importance for CHD patients

After the first stages of treatment that include revascularization and stabilization of CHD patients, exercise offers multiple benefits towards full recovery of cardiovascular function. Cardiac rehabilitation (CR) is a powerful tool for health care professionals, especially during the secondary prevention stage, as it helps patients resume their normal activities. Modern cardiac rehabilitation provides patients with educational content about health, exercise and nutrition. In addition, CR settings offer consulting, psychological support and most importantly, prescription of individualized, therapeutic exercise programs.[31]

More precisely, the main benefits of cardiac rehabilitation are increased aerobic capacity, improved endurance, musculoskeletal function, quality of life, decreased symptoms of depression, cognitive decline and inflammation.[20] Cardiac rehabilitation also plays a decisive role in the reduction of CHD risk factors such as dyslipidemia, hypertension and proper endothelial function. The latter is considered to be one of the most crucial factors for preventing a new cardiovascular event.[32]

Furthermore, numerous studies show a significant decrease in mortality rate, ranging from 15 to 31%, when patients entered a cardiac rehabilitation program. Participation in exercise programs has a profound effect on increasing $VO_{2\ peak}$, which is a major predictor of survival in Coronary Artery Disease.[30] An increase by 1 metabolic equivalent (1 MET = 3.5 ml/kg/min) in peak oxygen uptake resulted in decreased mortality rates ranging from 8 to 17%.[2] Consequently, cardiac rehabilitation is classified by researchers as a grade 1 recommendation for CHD patients.[33] As a result, exercise is now a huge part of the non-pharmacological treatment of CHD, integrated in most CR settings across Europe and North America.[19]

Moderate intensity continuous training (MICT) is the most common type of exercise, the cornerstone of cardiac rehabilitation programs for decades.[20] Aerobic exercise is recommended by guidelines in most countries of the world, while in some of them, such as Australia, New Zealand, Japan and the United Kingdom, it is preferred over other types of exercise.[2] MICT has been established as the primary form of exercise during cardiac rehabilitation for numerous reasons. First of all, aerobic exercise is safe, as it does not require a lot of effort from patients, can be performed either indoors or outdoors, without using any special equipment or supervision by a health professional. Aerobic exercise involves activities such as walking, running, stair climbing and hiking. Alternative types of aerobic exercise such as cycling, swimming and rowing are equally safe for CHD patients.[19] As safety is of paramount importance, it is easily understood why MICT has been the go-to choice in cardiac rehabilitation settings for so many years.

Secondly, but most importantly, aerobic exercise is highly effective at increasing peak oxygen uptake ($VO_{2\ peak}$), improving respiratory function and reducing, cholesterol levels, endothelial dysfunction symptoms of depression and mortality rates.[19]

Intensity of aerobic exercise remains moderate during cardiac rehabilitation, at 40-80% of $VO_{2\ peak}$ for 30-60 minutes.[34] Less physically fit patients, especially those at greater cardiovascular risk should exercise at 40-50% of $VO_{2\ peak}$ or at 11-12 RPE on the Borg scale, while patients at lower cardiovascular risk, with higher fitness levels, are advised to ramp up exercise intensity at 50-75% of $VO_{2\ peak}$ or at 12-15 RPE on the Borg scale.

As mentioned above, exercise intensity is usually based on percentages of Heart Rate Maximum (HR_{max}), Heart Rate Reserve (HRR) or Borg's 6-20 scale.[19]

Despite the undisputed health benefits of aerobic exercise, a lot of research has been carried out since 2007, when the American Heart Association's guidelines recommended HIIT for cardiovascular patients.[35]

Benefits of HIIT in CHD patients

In this section, the benefits of HIIT on peak oxygen uptake, endothelial function, inflammation, cardiovascular risk factors will be reviewed.
Furthermore, safety, adherence and the main principles of HIIT prescription for CHD patients will be analyzed.

$VO_{2\ peak}$

Physiological adaptations can vary depending on exercise duration, intensity and type of recovery (active or passive).

Probably the most recognized HIIT protocol in cardiac rehabilitation, also known as "The Scandinavian 4x4 Model" consists of four 4-minute intervals at 85-95% of HR_{max}, with 3 minutes of active recovery at 60-70% of HR_{max}.[36] This model was first tested by Norwegian researchers in 2004. Stable CHD patients were recruited and performed the 4x4 protocol 3 times a week, for 10 weeks. The results were impressive, as $VO_{2\ peak}$ increased by 17.9%, compared to a 7.9% increase in $VO_{2\ peak}$ for patients that exercised at 50-60% for 41 minutes. Total workload was equal between groups.[23]

Another Norwegian study that showed promising results, recruited 107 patients who sustained a myocardial infarction 2-12 weeks before the beginning of the study. Participants were categorized into 2 groups: the HIIT group that performed the 4x4 protocol and the aerobic exercise group that performed a 35-minute session consisting of walking, running, squats and lunges. Exercise frequency was 3 times a week for 12 weeks. According to the results, peak oxygen uptake increased by 14% and 7.5% in the HIIT and aerobic exercise group respectively.[24]

Moholdt et al. conducted an interesting 12-week study that included 112 stable CHD patients. The prescribed exercise protocol was the Scandinavian 4x4 model. Patients were then split into 3 subgroups, depending on interval intensity: the first group trained at an intensity lower than 88% of HR_{max}, the second group trained between 88 and 92% of HR_{max} and the third group at an intensity higher than 92% of HR_{max}. Warm up and cool down duration was 10 and 3 minutes respectively, at 60-70% of HR_{max}. On average, peak oxygen uptake increased by 3.9 ml/kg/min or 11.9% in 23.4 training sessions. More specifically, $VO_{2\ peak}$ increased by 3.1, 3.6 and 5.2 ml/kg/min respectively in each subgroup.[37]

Another study carried out by Keteyian et al, included patients aged 18-75 that were split into 2 training groups. The first group (13 participants) performed 30 minutes of moderate intensity aerobic exercise at 60-80% of Heart Rate Reserve (HRR). Warm up and cool down duration was 5 minutes. The second group (15 participants) performed HIIT, using the 4x4 model, with four 4-minute intervals at 80-90% of HRR, interspersed with 3 minutes of active recovery at 60-70% of HRR. These exercise protocols were applied during stage 2 of cardiac rehabilitation (improvement phase). Participants had previously undergone a 2-week, lower intensity, introductory program. The results showed an additional 8% increase in $VO_{2\ peak}$ in the HIIT group, compared to the aerobic exercise group. (3.6 mL/kg/min vs 1.7 mL/kg/min). Oxygen uptake at anaerobic threshold also increased more in the HIIT group (3.0 mL/kg/min vs 0.7 mL/kg/min).[38]

Apart from randomized controlled trials and studies, many systematic meta-analyses have examined HIIT and its effects on peak oxygen uptake in CHD patients.
One of the meta-analyses included 6 independent studies and 229 stable CHD patients in total, who had been following a rehabilitation program for at least 4 weeks. 99 of the participants were randomized to the HIIT group, while the remaining joined the aerobic exercise group. HIIT was defined as a training modality with short periods (1-4 minutes) of intense exercise (over 85% of HR_{max}), interspersed with periods of active recovery. Aerobic exercise was defined as a longer duration training modality (over 30 minutes) with an intensity lower than 80% of HR_{max}. Various forms of exercise were included, such as running, cycling,

walking and swimming. The results revealed a greater mean increase in $VO_{2\ peak}$ by 1.53 ml/kg/min in the HIIT group.[34]

Another meta-analysis included 10 studies with 472 CHD patients that participated in cardiac rehabilitation programs for at least 4 weeks. A number of 218 patients followed HIIT and 254 moderate intensity aerobic exercise. Mean $VO_{2\ peak}$ values were improved by 1.78ml/kg/min in the HIIT group compared to aerobic exercise.[39]

Similar increases in $VO_{2\ peak}$ were reported by Neto et al, whose systematic meta-analysis included 12 studies and 609 patients. Mean $VO_{2\ peak}$ values were increased by 1.3 ml/kg/min in comparison to aerobic exercise.[35]

A 2018 meta-analysis gathered 19 controlled studies, 9 of them were related to CHD (the remaining studies were related to heart failure). According to the results, mean peak oxygen uptake values were increased by 3.98 or 2.94-5.02 ml/kg/min in CHD patients.[22]

Finally, it is worth mentioning Hannan's et al large meta-analysis, which included 17 studies and 953 participants. 465 performed HIIT, 488 aerobic exercise. All 17 studies recruited patients that had been following cardiac rehabilitation programs for at least 4 weeks. In 16 out of 17 studies that were analyzed, HIIT was superior to aerobic exercise at increasing $VO_{2\ peak}$, by 0,34 ml/kg/min. A bigger effect on peak oxygen uptake was reported when cardiac rehabilitation lasted for 7-12 weeks, as $VO_{2\ peak}$ increased by 0,43 ml/kg/min. On the contrary, therapeutic interventions that lasted less than 6 weeks produced inferior results. Peak oxygen uptake increase was significantly lower (0.19 ml/kg/min). All VO_2 peak values were calculated using Standardized Mean Difference (SMD) method.[2]

Endothelial function

Another important parameter concerning patients with CHD is endothelial function. Endothelial dysfunction is a prerequisite of the formation of atheromatous plaque, raising the risk for myocardial infarction. Improved blood flow and slowing down or avoidance of plaque reformation can be a result of ameliorating endothelial function. According to the literature, HIIT improves blood flow and, as a result, endothelial function.

In one of the studies, 40 patients, who underwent PCI, were divided into two groups. The first group did six months of HIIT (4x4) and the second one was the control group.[40] After six months, parameters like re-stenosis of the vessel (measuring the loss of the vessels diameter, the maximum O_2 intake and the blood flow through reactive hyperemia Flow Mediated Dilation (FMD) were investigated. This method included induction of ischemia for 5 minutes using an inflating cuff and measurement of the increase of blood flow through the brachial artery after deflating the cuff.[26] Results showed a difference in vessel diameter loss amongst the patients of the first group compared to the control group (0.1mm and 0.39mm respectively), bigger increase on $VO_{2\ peak}$ (16.8% and 7.8% respectively). The measurement of blood flow via reactive hyperemia FMD showed an increase by 5.2% in the group that executed the HIIT protocol and a decrease by 0.1% in the control group.[40] The significant difference between the 2 groups can be explained by the fact that the first group followed a rehabilitation program, whereas the control group did not exercise at all. So, what would be the results if the 2 groups followed the same rehabilitation program?

A study in 2013 tried to answer this question by comparing the impact of moderate intensity aerobic exercise and HIIT on the brachial artery blood flow (FMD) and cardiorespiratory ability of 22 patients. These patients were randomized into 2 groups. The first group performed endurance training on a bike for 30-50 minutes at 58% of PPO. The second group performed HIIT that consisted of 10 1-minute intervals at 89% of PPO with intermediate active rehabilitation for 1 minute at 10% PPO. The study's duration was 12 weeks, with the supervised training sessions being carried out twice a week. Once a week, participants exercised their lower body without supervision, with similar intensity and duration to supervised sessions. FMD and $VO_{2\ peak}$ measurements were carried out before and after 12 weeks of training. Brachial artery blood flow increased in both groups, from 4.4% to 5.9% for the endurance group and from 4.6% to 6.1% for the HIIT group. $VO_{2\ peak}$ also increased from 18.7 mL/kg/min to 22.3 mL/kg/min for the endurance group and from 19.8 mL/kg/min to 24.5 mL/kg/min for the HIIT group. Although both exercise regimens resulted in similar modifications, the endurance group had twice the workload compared to the HIIT group.[28]

These findings are in keeping with those of previous studies, according to which the intensity of the exercise is of greater importance in patients with cardiovascular diseases.[41]

Ramos et al., performed a meta-analysis regarding the impact of HIIT and aerobic exercise on endothelial function. He included 7 randomized trials and 182 patients, who were mainly obese adults and post-menopausal women suffering from CHD, heart failure, hypertension and metabolic syndrome. The exercise protocol that was used in most of the studies was the Scandinavian model, that included 4x4 minutes at 85-95% HR_{max} with a 3-minute active rehabilitation at 60-70% 3 times a week for 12-16 weeks. In 6 of 7 studies endothelial function improved especially in patients following the HIIT 4x4 protocol, with the mean FMD increasing from 5.14 to 9.45% and from 5.12 to 7.27% for HIIT and aerobic exercise respectively. When HIIT regimens with shorter intervals but more cycles were performed (eg. 4-10x1 min at 80-85% of $VO_{2\ peak}$ with active rehabilitation at 50-60% for 4 minutes), FMD results were equal or superior to those of an isocaloric aerobic exercise protocol.[26]

Lastly, Guiraud et al., measured the endothelial microparticles, which are biomarkers of endothelial apoptosis and dysfunction during 2 isocaloric training HIIT session and aerobic training. No endothelial microparticle elevation was noted, even 72 hours after any training session took place. This proves that HIIT does not cause further damage to the endothelium.[18]

Inflammation

Besides endothelial function improvement, reducing inflammation levels is also crucial for CHD patients.

According to research, HIIT can contribute to the reduction of C-Reactive Protein (CRP). In one of the studies that confirmed that claim, 2 groups of 20 patients were formed. The first group exercised 3 times a week, following the 4x4 model for 6 months, while the control group did not exercise at all. After 6 months, CRP levels were decreased by 0.4mg/L (from 1.5 to

1.1mg/L) in the HIIT group and increased in the control group by 0.1 mg/L (from 1.1 to 1.2mg/L).[40]

In another study, Munk et al examined the effects of HIIT on other inflammation markers, such as Interleukin 8 (IL-8), Interleukin 6 (IL-6), TNF-a Factor, PTX3, VCAM, VCAM-1 adhesion molecules. Their study design had 2 groups, each of them consisted of 40 CHD patients who had undergone Percutaneous Coronary Intervention (PCI). The first group performed HIIT and the 4x4 model 3 times a week for 6 months, as the control group followed a lower intensity rehabilitation program at home. At 6 months, the results revealed a significant decrease in Interleukin 6 (IL-6) levels (from 1.0 to 0.39 pg/ml) and an increase in the anti-inflammatory cytokine Interleukin 10 (IL-10) levels (from 1.46 to 1.93 pg/ml) compared to baseline. In contrast, no statistically significant effects were reported in the control group, as Interleukin 6 (IL-6) was slightly decreased (from 1.15 to 1.13 pg/ml) and Interleukin 10 (IL-10) was slightly increased (from 1.52 to 1.62 pg/ml). TNF-a Factor and PTX3 didn't present any statistically significant difference in either groups. Interleukin 8 (IL-8) was decreased in the HIIT group (from 17.38 to 11.72 pg/ml) and increased in the control group (from 4.38 to 11.96 pg/ml). Chemokine CCL21 was significantly reduced, only in the HIIT group (from 277 to 217 pg/ml). E-selectin values were increased in both groups, while P-selectin recorded a slight increase in both groups as well. A moderate increase was reported in VCAM-1 values in the HIIT group. Lastly, RANTES, CXCL16, CCL19, MCP-1 and CD40L values remained stable in both groups after 6 months.[42]

Autonomic nervous system function plays a key role in regulating inflammation markers. At the same time, autonomic nervous system dysfunction has been correlated with sympathetic nervous system hyperstimulation, decreased heart rate variability and higher inflammation markers (CRP), leading to increased cardiovascular risk[43]. Exercise seems to offer positive adaptations in autonomous nervous system function by improving parasympathetic modulation.

This was the objective of a study conducted by Tamburus et al, to examine HIIT effects on CRP levels and heart rate variability in patients either with CHD or cardiovascular risk factors, such as obesity, hypertension, hypercholesterolemia, diabetes mellitus and smoking. 32 male participants with CHD and 32 with cardiovascular risk factors only, (mean age 57.88±6.20) were randomized into 2 training and 2 control groups, forming 4 groups in total (CHD-T, CHD-C and noCHD-T, no CHD-C respectively). It should be mentioned that both training groups received medication such as beta blockers and angiotensin converting enzyme inhibitors. Both training groups underwent a 16-week exercise program, at an intensity that corresponded to the respiratory anaerobic threshold. Respiratory anaerobic threshold was defined as the point of imbalance between oxygen consumption and exhaled carbon dioxide production. Control groups did not exercise at all. The exercise protocol included a 10-minute, low intensity warm-up consisting of walking and stretching. After that, participants performed a progressive ramp up training session, with 5 10-minute intervals at 80-110% of the workload recorded at anaerobic threshold. Active recovery was at 70% respectively. At cool down, patients did 10 minutes of stretching and breathing exercises. After 16 weeks, CRP levels were significantly decreased in both trained groups, from 1.2 to 0.7 mg/dL and from 0.18 to 0.04 mg/dL respectively, in contrast with the control groups where CRP levels recorded an increase, from 0.9 to 1.1 mg/dL and from 0.55 to 1.15 mg/dL respectively. Furthermore, parasympathetic modulation values were significantly increased in both training groups from 16.8 to 24.2 2UV% and from 12.5 to 19 2UV% respectively, while sympathetic modulation values were only decreased in the noCHD-T group, from 29.2 to 14.7 0V%.[44]

Cardiovascular risk factors

The majority of the studies mentioned also evaluate the effect of HIIT on glucose and lipid levels, body weight and blood pressure.

Moholdt et al. measured HDL and blood glucose levels of the two groups that participated in the study before and after 12 weeks. The first group performed HIIT 4x4 and the second 35 minutes of aerobic exercise. HDL increased only in the group that performed HIIT (from 1.28 to 1.32 mmol/L)(P=0.024), whereas blood glucose decreased slightly from 6 to 5.7 mmol/L). The respective values for the control group remained unchanged after 12 weeks.[24]

Furthermore, Mitranun et al. measured blood glucose, glycosylated hemoglobin and the lipoproteins HDL, LDL in the 3 groups of patients with type 2 Diabetes Mellitus, who participated in the study. One group followed a HIIT training regimen (4-6 1-minute intervals at 80-85% of $VO_{2\ peak}$ with a 4-minute active recovery at 60%, the second one performed aerobic exercise at 60-65% $VO_{2\ peak}$ and the third was the control group. The duration (30-40 minutes) of the 2 training protocols and overall calorie and O_2 consumption were the same in the 2 groups. Blood glucose levels decreased in both training groups, from 7.65 to 6.60 mmol/L in the HIIT group, from 7.65 to 6.66 in the group the performed aerobic exercise). HDL increased slightly more in the HIIT group compared to the aerobic group. There was also a slightly bigger decrease in LDL for the HIIT group compared to the aerobic group. Glycosylated hemoglobin showed a significant decrease (from 60 to 54 mmol/mol) in the HIIT group. The control group did not show any significant changes.[45]

As for the body weight, Munk et al. describe a significant difference between the 2 groups examined. The first group performed HIIT 4x4 and the control group followed a less intensive rehabilitation program at home. Patients in the first group lost weight (mean 1.7kg), whereas patients in the control group gained weight (mean 1.2kg).[42]

A drop in Body Mass Index (BMI) was described by a study in 2016, where 32 patients with CHD and 32 patients with cardiovascular risk factors were randomized into 4 groups: 2 groups that performed supervised HIIT 3 times a week for 16 weeks at 70-110% of aerobic respiratory threshold and 2 control groups that continued their everyday activity. Besides the significant increase of the peak oxygen uptake in the aerobic respiratory threshold in both training groups, researchers also described a decrease in body weight (-2.09 kg and -1.29 kg in the risk factor group and the CHD group respectively) and a decrease in BMI (-0.62 kg/m2 and -0.54 kg/m2 in the risk factor group and the CHD group respectively).[46]

Seven hundred and seventy two patients in North America followed a low intensity (60-80% $VO_{2\ peak}$) rehabilitation program 5 times a week for 26 weeks, while 772 more performed a progressive HIIT protocol, that consisted of alternating between running (12 min/mile) and walking (15 min/mile), for the same period of time. Results showed lower BMI (26.1kg/m_2 vs

28.5 kg/m_2), decrease in waist (90.9 vs 98.3 cm) and hip circumference (98.8 vs 103.9 cm) and triglycerides in the HIIT group (1.01 vs 1.27 mmol/L) a higher increase in $VO_{2\ peak}$ compared to the control group (3.84 ml/kg/min).[47]

Keech et al (further details on page 27) also reported a significant loss in body fat, as visceral fat was decreased by 8% and muscle mass was increased by 4%. Greater fat loss was recorded in the torso, legs and waist circumference.[36]

Keteyian et al. described a slight decrease in systolic and diastolic blood pressure, from 126 to 117 mmHg and from 78 to 71 mmHg respectively after the completion of HIIT. No alterations in BP were noted with aerobic exercise.[38] A decrease in systolic and diastolic blood pressure ranging from 5 to 10 mmHg was also reported by Tamburus et al. in patients that performed HIIT based on the respiratory aerobic threshold and also in the patients of the control group.[44] Simillar decreases in systolic and diastlic blood pressure (5-10 mmHg) were reported by Keech et al.[36]

HIIT and safety

HIIT has been associated with increased risk of cardiovascular adverse effects, as exercise-derived stimulus is greater than aerobic exercise (over 85% of HR_{max}).[48] Probably this is one of the reasons that HIIT is not widely applied in cardiac rehabilitation settings.

A large-scale Norwegian study examined the risk of cardiovascular adverse effects in 4846 patients with myocardial infarction (7%), angioplasty (40%), PCI (35%), valve replacement surgery (11%) and heart failure (7%). Patients were randomized into 2 groups, a moderate intensity aerobic group (lower than 70% of HR max for prolonged duration) and a HIIT group that performed the 4x4 model during their rehabilitation. 70% of patients were male, 30 % female and mean age was 57.8 years. Myocardial Infarction and Cardiac Arrest 1 hour after the end of training were defined as serious cardiovascular adverse effects. In a total of 175,820 training hours, 1 fatal cardiovascular event was reported (cardiac arrest) in the moderate intensity aerobic group after a total of 129,456 hours, whereas 2 non-fatal cardiovascular events occured in the HIIT group (in 46 364 training hours). No myocardial infarctions were recorded in either group. The ratio of serious adverse effects to training hours was 1/129.456 for the aerobic exercise group and 1/23.182 respectively for the HIIT group.[41] These results indicate that the risk of cardiovascular events is low in both training regimens.

A recent meta-analysis included 17 individual studies and 953 patients, aged from 52 to 76 years of age. 465 of them were classified as the HIIT group and the remaining 488 as the aerobic exercise group. Out of 953 patients, 633 had experienced a myocardial infarction, 477 had undergone percutaneous coronary intervention (PCI) and 361 patients had undergone coronary artery bypass graft surgery (CABG). All patients had been participating in cardiac rehabilitation programs for at least 4 weeks. No fatalities or serious cardiovascular events requiring hospitalization were reported in either groups. Only one study described 3 cardiovascular events related to the aerobic exercise group, 1 of them happened 1 hour after the end of the training session and the other 2 after the completion of cardiac rehabilitation. In total, 13 studies reported complications, 3 of them were related to HIIT groups and mostly included musculoskeletal injuries, such as ankle fractures, and hip or knee pain. Other complications involved gastroenteritis, pancreatitis and intermittent claudication. Additional adverse effects were mentioned in 5 studies in the HIIT intervention, including musculoskeletal injuries such as leg, knee or lower back pain, pericardial effusion, gastrointestinal bleed and bronchitis. In addition, 35% of the studies reported patients dropping out of cardiac rehabilitation. Of those, 39 participated in the HIIT group and 42 in the aerobic exercise group.[2]

A large meta-analysis by Wewege et al. offers valuable data on HIIT and safety issues concerning cardiac rehabilitation. This meta-analysis included 23 studies (13 were related to CHD patients, 9 to heart failure patients) and 1117 patients, whose mean age was 61±5 years. Of those, 668 were diagnosed with CHD, and 416 with heart failure. Of those patients, 547 followed a HIIT regiment while 570 an aerobic exercise regimen. The most common HIIT protocol was the 4x4 model, while other HIIT protocols included various intervals, ranging from 30 seconds to 3 minutes. Aerobic exercise lasted for 30-60 minutes at an intensity lower than 75% of HR_{max}. The aim of the meta-analysis was the recording of possible adverse effects during training sessions and up to 4 hours after their completion. There were 7 reported incidents of adverse effects, 5 related to HIIT and 2 to aerobic exercise. Of those 7 incidents, the 2 that were classified as cardiovascular, were related to heart failure patients following HIIT. The first incident was a serious, non-fatal cardiovascular event (ventricular arrhythmia leading to cardiac arrest during the first week of HIIT), while the second incident was considered to be minor (syncope during training), as the patient fully recovered and continued his program. The other 5 incidents were classified as non-cardiovascular, 2 of them were lower limb musculoskeletal pain. The first was about a CHD patient who had knee pain but continued his HIIT intervention, whereas the second incident also occurred in a CHD patient that followed aerobic exercise and had leg pain. Both patients participated in the same study. Based on scientific research and data, the total ratio of cardiovascular events to training sessions was 1/8541 in 5667 training hours, while the individual ratio for serious cardiovascular events was 1/17.083 in 11.333 training hours respectively.[48]

Patient compliance

Cardiac rehabilitation, and especially HIIT, has been proven extremely beneficial for patients with CHD. However, the percentage of patients who stick to an exercise regimen during cardiac rehabilitation remains low (20-50%).[48] HIIT constitutes a high intensity exercise regimen and is associated with low patient compliance.[49] Consequently, the success or failure of a rehabilitation program is based on the patient’s exercise preference.

Patients’ preference was studied in a review in 2012, where a different HIIT protocol was presented. This model included 15-second intervals of intense exercise at 100% of maximum aerobic power interspersed with 15 seconds of moderate passive rehabilitation (15s-15s). This exercise regimen was compared to an isocaloric program of continuous aerobic exercise at 70% of maximum aerobic strength. All patients preferred the 15-15 protocol, since the rating of perceived exertions was lower compared to continuous aerobic exercise (Borg scale: 14±2 and 16±2 respectively). Furthermore, patients reported lower levels of dyspnea, one of the main restrictive factors during exercise in patients with CHD. According to the study, lower perceived fatigue and dyspnea, despite the high intensity of the exercise (80-95% of $VO_{2\ peak}$), can raise long-term adherence to an exercise regimen.[18]

Another reason why many of the patients do not complete the rehabilitation program or do not continue training after the program ends is the distance between the hospital and their house. This phenomenon is more evident when patients work or have family obligations. For them, training at home could be a solution. A study by Aamot et al. compared the effect of 3 different types of HIIT (2 at a hospital, 1 at home) on the increase of $VO_{2\ peak}$ (further details below p. 28-29). VO_2 and maximum O_2 consumption were increased regardless of the place where the training program was performed.[50]

Moreover, a randomized trial, where all participants were adults who had previously completed a 12-week HIIT rehabilitation program, exhibited encouraging results regarding at home training. Patients could perform a HIIT regimen either at the hospital or at home. The training protocol was the same for all patients (Scandinavian model 4x4), with mean exercise intensity at 90% of HR_{peak}. After 12 weeks, patients were instructed to continue training, either performing HIIT or any other type of exercise, according to the international recommendations for physical activity (150 minutes/week). A year after that, scientists measured important markers such as $VO_{2\ peak}$, training and physical activity compliance and quality of life. Physical activity and quality of life were recorded by an accelerometer and questionnaires respectively. 76 of 90 participants completed all the tasks one year after the 12-week rehabilitation program. The mean difference in the VO_2 measurement pre to post-intervention was 3.5 mL/kg/min and the difference between baseline and follow-up (at 15 months) was 1.7 mL/kg/min. The difference between post-intervention and follow-up was 1.81 mL/kg/min. There were no statistically significant differences between the two training groups. All participants mentioned in the questionnaires that their physical activity had increased, and quality of life had significantly improved from pre-intervention period to follow-up after 15 months. The accelerometer recorded that the majority of the participants complied with the recommended 30 minutes of daily physical activity. Especially those who trained at home tended to exercise more on a daily basis than those that trained at the hospital. Furthermore, the group that trained at home presented a smaller loss in $VO_{2\ peak}$ values between post-intervention and follow up (from 37.4 to 36.7 ml/kg/min respectively), maintaining the adaptations of the 12-week program, whereas the 2 groups that exercised at hospital reported greater losses in $VO_{2\ peak}$. (from 40.1 to 37.4 ml/kg/min and from 36 to 34.1 ml/kg/min for treadmill and groups exercise groups respectively)[49]

A 2017 study also examined long term adherence and aerobic capacity maintenance. A total of 133 CHD patients entered the study (mean age was 57 years) and performed a modified Scandinavian training model during cardiac rehabilitation, which included music. Exercise intensity was adjusted based on the musical rhythm. The basic parameters analyzed were $VO_{2\ peak}$, exercise habits and quality of life. Data collection occurred in 3 different time periods: pre-intervention, post-intervention and follow up at 15 months. $VO_{2\ peak}$ values were measured with a cardiopulmonary stress test, as exercise habits and quality of life were evaluated by questionnaires. Participants trained 2 times a week and were encouraged to train one more time, either by taking part in a HIIT group program that included uphill running (uphill interval training, with 1 to 4-minute intervals) or by training alone on a treadmill or a static bicycle. At the end of the 12-week program, patients were advised to pursue an active lifestyle. Out of 133 patients, 86 completed the study by being present in all 3 measurements. VO_2 values were significantly increased from pre-intervention to post-intervention (from 31.9 ml/kg/min to 35.9 ml/kg/min respectively) and continued to increase up to follow up, at 15 months (36.8 ml/kg/min). Questionnaires revealed an equally significant improvement in all clinical parameters including physical activity, mental health and quality of life from pre-intervention period to follow up. Lastly, patients reported that they exercised 2.5±1 times a week on average for 30 minutes, at an intensity causing shortness of breath.[51]

Basic principles for HIIT prescription in CHD patients

After reviewing the main benefits of HIIT in CHD patients, the basic principles of HIIT prescription will be presented in this section, based on the patients' needs. As previously mentioned, there are 3 types of HIIT protocols, depending on the interval duration:[21] Long-duration intervals (3-15 minutes at 85-90% of $VO_{2\ peak}$), moderate-duration intervals (1-3 minutes at 95% of $VO_{2\ peak}$) and short-duration intervals (10-60 seconds at 100-120% of $VO_{2\ peak}$). Home based HIIT will also be mentioned.[20]

Guiraud et al. compared the responses between 4 short duration HIIT protocols. Interval duration and recovery type were different in each protocol. Specifically, protocols A and B included 15-second intervals at 100% of Maximal Aerobic Power (MAP), whereas the interval duration in protocols C and D was 60 seconds at the same intensity. Passive recovery of 15 and 60 seconds was used in protocols A and C respectively. In protocols B and D, active recovery was applied at 50% of MAP, while recovery time was equal to protocols A and B (15 and 60 seconds respectively).[17] The aim of the study was the examination of patients' tolerance of the aforementioned protocols. Out of the 20 stable CHD patients, 63% completed protocol A, as percentages for protocols B, C, D were 16%, 42 % and % respectively. To summarize, exercise protocols that included passive recovery were the most tolerable by patients, regardless of interval or recovery duration. These results were predictable, as passive recovery allows patients to perform more intervals and increases time to exhaustion.[18]

Additionally, Rate of Perceived Exertion (RPE) was lower, despite the fact that time spent near VO2peak was similar to the other protocols. The vast majority of the participants preferred protocol A (18/20), confirming that short interval HIIT (15-60 seconds) is well tolerated by patients, offering similar physiological adaptations to other exercise models. Short-duration HIIT is more suited for stages 2 (from 4 to 12 weeks) and 3 (after 12 weeks) of cardiac rehabilitation.[20]

A different short-duration HIIT protocol was presented by Jaureguizar et al. 72 patients (age 58±11 years) with CHD were separated into 2 groups. The program lasted 8 weeks. The first 4 weeks the HIIT group performed the following training program: 20 second intervals at 50% of workload (Watts) achieved during the exercise stress test, with a 40 second active recovery at 10%. The patients started at 15 intervals the first week and 5 more were added every week. In the last 4 weeks, the intensity was modified based on a new exercise test, whereas the number of intervals performed were constant at 30 intervals. For the aerobic group, the intensity of the exercise was based on zone 1 of respiratory threshold (45-65% of HR_{max}) for the first 4 weeks, with a gradual 5-minute increase in duration every week. The last four weeks were the same for the two groups. Duration of training was 40 minutes including warm-up and cool-down for both groups. After 8 weeks results showed a 24% and 12% increase in $VO_{2\ peak}$ for the HIIT group and aerobic group respectively (+4.5 mL/kg/min vs +2.5 mL/kg/min), while the submaximal oxygen consumption at intensity zone 1 and 2 of the respiratory threshold was bigger for the HIIT group.[30]

The application of a new short duration HIIT protocol was studied by Keech et al. The study included thirty patients (age range 42-67 years) with a history of myocardial infarction, PCI or coronary artery bypass graft. The participants performed a HIIT program of 15 30-second intervals at 85-90% of HR_{max} or 85-95% of maximum workload achieved during an exercise stress test, with active rehabilitation at 15% of the workload. Training sessions took place twice a week for 6 weeks. Results showed improvement of aerobic capacity by 12%, corresponding to 3.1 ml/kg/min or 1 MET. Patients were overall satisfied by the training protocol. Two minor adverse events were also described; one involving muscle trauma and another one a syncope.[36]

Moderate and high-duration protocols (1-4 minutes at 85%-95% of $VO_{2\ peak}$) with low intensity active rehabilitation and similar ratio of intense exercise/rehabilitation (eg. 4 minutes of exercise with 3 minutes of recovery) have been successfully applied in cardiovascular patients. The results were quite encouraging, as these protocols trigger greater physiological responses in less time.[38]

However, limitations must be placed on protocols regarding their appropriateness for CHD patients. According to recent studies, long-duration HIIT with active recovery are characterized by higher percentage of mean intensity ($VO_{2\ peak}$), higher numbers in Rate of Perceived Exertion (RPE), that lead to a lower percentage of training completion. Hence, scientists recommend that such training protocols should be carried out by stable and physically fit patients presenting with risk factors (diabetes, hypertension, obesity), during the later phases of cardiac rehabilitation (stage 3 or maintenance phase).[20] At the first two HIIT sessions, intensity is usually at 60% of PPO and it is increased to 80% or even 100% at later stages.[18]

On the contrary, for high risk patients, with low ejection fraction and comorbidities, that did not train, exercise initiation is gradual and includes lower intensity exercise for 2 weeks,[18] such as steady aerobic exercise at 50-70% of $VO_{2\ peak}$. Later on, based on the progression principle, exercise difficulty and intensity can be increased by incorporating low-duration HIIT with passive recovery.[19] In their study Keech et al. recommended a transient moderate intensity exercise protocol for 2 weeks at 11-13 RPE, before the initiation of the low-duration HIIT protocol.[36]

Therefore, the use of moderate and high-duration protocols are indicated during the third stage of cardiac rehabilitation (maintenance phase), with the frequency of training sessions per week ranging from 2 to 3, due to their high exercise-induced stimulus.[20] Garcia et al. also recommend the same training frequency and add that maximal physiological adaptations during cardiac rehabilitation were accomplished in at or less than 12 weeks. Programs that lasted more than 12 weeks did not show any additional benefit.[22]

It is worth mentioning home-based HIIT. One of a few studies that examined home-based HIIT, compared the effect of 3 different HIIT protocols. Aamot et al. recruited 83 patients and separated them into 3 categories: The first one exercised at the hospital, on a treadmill, the second performed an interval group training program consisting of running, cycling, squats and step-ups. Active recovery included strength exercises such as push-ups, sit-ups or walking. Patients in the third category exercised at home using a treadmill, static bicycle or cross trainer and recorded exercise intensity with heart rate monitors. Exercise protocols were performed 2 times a week for 12 weeks. $VO_{2\ peak}$ was significantly increased in all groups, from 34.7 to 39 ml/kg/min, from 32.7 to 36 ml/kg/min and from 34.4 to 37.2 ml/kg/min respectively. Therefore, home-based HIIT was proven to be as effective as hospital-based programs at improving aerobic capacity.[50]

In any case, cardiac rehabilitation programs must be individualized, based on the patient's medical history and characteristics such as age, fitness levels, severity of disease, symptoms, and comorbidities. Diagnostic tests such as the exercise stress test and electrocardiogram (ECG) are valuable tools that help health professionals better evaluate patient status, in order to minimize cardiovascular risk and maximize exercise benefit. For that reason, it is recommended they be carried out before the start of cardiac rehabilitation, as the extracted data will be used to determine training program variables such as exercise intensity (based on HR_{max} or $VO_{2\,peak}$ percentages) and duration. Furthermore, frequent recording and measurement of physiological responses such as heart rate, blood pressure, rate of perceived exertion based on the Borg scale, during or after a training session, is deemed necessary.[48]

Discussion

Based on the current literature, HIIT offers valuable health benefits to CHD patients.

HIIT seems to have a powerful effect on aerobic capacity improvement, by increasing $VO_{2\,peak}$ values. In point of fact, the vast majority of randomized controlled studies and meta-analyses have demonstrated bigger increases in peak oxygen uptake after implementing HIIT, compared to other forms of exercise, such as moderate intensity aerobic exercise.[2,22,23,24,34,35,37,38,39] Bearing in mind that an increase in $VO_{2\,peak}$ by 1 metabolic equivalent (1 MET=3.5ml/kg/min) corresponds to a 8-17% decrease in mortality risk, it is easily understood why $VO_{2\,peak}$ is so important in CHD patients.[2]

According to the literature, the largest physiological adaptations were accomplished in CR programs that lasted between 7 and 12 weeks, whereas training frequency should be at least 2 times a week.[2,22] Most studies utilized the highly effective 4x4 Scandinavian Model (4 minutes at 85-95%, 3 minutes at 60-70% of $VO_{2\,peak}$), which is classified as a long-duration

HIIT protocol. However, short-duration intervals (30-60 secs) were equally effective at improving peak oxygen uptake.[22]

These results indicate that exercise intensity is the primary mechanism behind further increases in $VO_{2\ peak}$, not exercise duration. Numerous studies have highlighted the importance of exercise intensity in improving cardiovascular adaptations such as stroke volume, contractility and filling of the left ventricle, ejection fraction, increased myocardial transverse section and synchronization of its motor units.[22,34,52]

On the contrary, there are studies supporting that HIIT triggers similar adaptations in $VO_{2\ peak}$ to aerobic exercise.[53] These findings are supported by a 3-study sub-analysis by Gomes-Neto et al, which concluded that HIIT's superiority over aerobic exercise was not the case, when 2 isocaloric protocols were compared, indicating that total energy expenditure is the most significant factor of increase in $VO_{2\ peak}$.[35] In the same meta-analysis by Gomes-Neto et al., 7 studies with non-isocaloric exercise protocols were included. The results in these studies showed a mean difference of +1.87ml/kg/min in favor of HIIT.[35] However, a conflict is observed between studies supporting that exercise intensity is the primary promoter of $VO_{2\ peak}$ improvement and studies that attribute these physiological adaptations to total energy expenditure during exercise. This notion would be valid assuming that energy consumption is higher during HIIT.[33]

According to a study by Pattyn et al. who recruited 18 male CHD patients, this hypothesis was disproven, as results showed that energy expenditure was lower in HIIT compared to aerobic exercise.[54] Moreover, the findings of this study are in agreement with previous meta-analyses in obese patients reporting that caloric expenditure was lower during HIIT.[55] The answer to this dilemma is possibly given by exercise physiology and the Excessive Post Oxygen Consumption (EPOC) principle. According to this principle, when exercise intensity is high, post-exercise energy consumption remains elevated for up to 24 hours until homeostasis is restored. This physiological process requires greater caloric expenditure. High intensity-shorter duration interval exercise is known to induce increased energy expenditure after exercise, due to high EPOC. On the other hand, moderate intensity-longer duration aerobic exercise produces a lower EPOC, as most calories are burned during exercise.[25,56]

It remains to be determined whether exercise intensity or total energy expenditure is the primary promoter of $VO_{2\ peak}$ improvement. More research on energy expenditure and its interaction with exercise variables (intensity, duration) is considered necessary in the future.[33]

Notable improvements in endothelial function were reported as well, based on Flow Mediated Dilation (FMD) measurements. Munk et al recorded a significant improvement of 5.3% in FMD for the HIIT group compared to the control group (they didn't exercise).[40]

A smaller but notable mean difference between HIIT and aerobic exercise was described by Ramos et al. In their meta-analysis, FMD values were further increased by 2.26% after following HIIT.[26] Post-exercise adaptations in FMD are attributed to an increase in blood flow which creates greater shear stress.[28] According to a study by Thijssen et al, blood flow and shear stress increases are analogous to exercise intensity.[57] In other words, when exercise intensity goes up, the shear stress applied to the endothelium is higher. High shear stress causes a higher concentration of potassium intracellularly, which promotes the activation of E-NOS synthase. NO production results in vasodilation, an essential process that plays a important role against atheroma formation.[26]

Besides blood flow and shear stress, another crucial factor for improving endothelial function is the reduction in inflammation markers. Previous studies have reported that CRP decreases NO production and increases Endothelin-1 production, a molecule causing vasoconstriction and related to endothelial dysfunction.[40]

Results from 2 separate studies conducted by Munk et al. report a decrease in CRP levels[40], cytokines IL-6, IL-8[42] after 6 months of HIIT, compared to the control group.
Furthermore, Mitranun et al noted a decrease in free radicals and an increase in glutathione peroxidase (an antioxidant substance), only after following HIIT.[45] Free radicals can cause E-NOS mutations, by converting its normal function, from a NO mediator to an enzyme generating superoxide anions, which impairs endothelial dysfunction.[26] Tamburus et al. presented a similar decrease in CRP levels.

Specifically, researchers attempted to correlate the reduction in CRP levels following HIIT, with improvements in autonomic nervous system function, such as increased parasympathetic modulation.

According to recent studies, excessive activation of the sympathetic nervous system leads to a higher concentration of catecholamines, promoting pro-inflammatory cytokine production and consequently the initiation of the inflammatory response. This process can be inhibited by improving parasympathetic nervous system function. Researchers claim that this can be achieved through the cholinergic anti-inflammatory pathway, where acetylcholine suppresses the release of pro-inflammatory cytokines from macrophages and other cells, resulting in decreased CRP levels. In addition, NO is not only a vasodilating compound, but it seems to increase parasympathetic modulation, as shear stress and E-NOS synthase upregulation facilitate the activation of the afferent baroreflex, which stimulates the vagus nerve and the consequent increase in parasympathetic (vagal) modulation.[44]

The above evidence indicates that there is a direct correlation between the reduction in inflammation levels and the improvement in endothelial function both in peripheral and central levels. HIIT could be the missing link between endothelium and inflammation, as some studies have reported increased NO bioavailability, only after performing HIIT.[45] On the contrary, though other studies found no statistically significant differences between HIIT and aerobic exercise.[24,53,58]

A possible explanation for these findings is the application of higher than normal intensity aerobic protocols. For example, Moholdt et al. don’t provide enough information on exercise variables such as intensity (based on HR_{max}%). In fact, the “usual care” protocol included challenging, high intensity exercises (squats, lunges, running) that probably increased patients’ heart rate beyond the predicted percentage. In addition, Conraads et al. report that the aerobic exercise group in their study performed a 37-minute session at 70-75% of HR_{max}.

Pedersen et al found non statistically significant differences in CRP and TNF-a levels after 12 weeks of HIIT, whereas at follow up (40 weeks) these levels were decreased, indicating that exercising beyond a 12-week cardiac rehabilitation program is crucial for long term decreases in inflammation.[59]

As for cardiovascular risk factors, the existing literature points out that HIIT has a strong effect on body weight, visceral fat and waist circumference reductions.[42,46,47] Visceral fat reduction is vital, as adipose tissue secretes numerous inflammatory factors such as adipokines, which are associated with diabetes mellitus and metabolic syndrome.[42]
Therefore, body fat loss promotes significant decreases in inflammation levels. HIIT’s effect on body composition can be augmented, if a calorie-restricted diet plan is applied.[59]

There are 2 physiological mechanisms/principles that make HIIT so effective in body weight/fat loss. The first is the increased oxygen consumption (EPOC), which can elevate caloric expenditure for up to 24 hours after a HIIT session.[56] The second is related to ghrelin, also known as the “hunger hormone”. HIIT seems to reduce ghrelin, especially in obese patients, resulting in decreased hunger levels.[60]

On the other hand, HIIT didn't have such a strong effect on HDL and LDL lipoproteins.
Despite some promising results in Moholdt’s et al. study, where HDL values were increased only after following HIIT,[24] the majority of randomized controlled trials and meta analyses did not record any statistically significant increases or decreases in HDL and LDL values respectively.[39] According to a meta-analysis carried out by Elliott et al, factors such as total CR program duration and weekly exercise duration may be of greater importance at improving lipid levels. Previous studies reported a significant increase in HDL in/for patients that exercised over 120 minutes per week for 2 years, but no statistically significant difference was observed after 1 year of exercise.[34] Dietary intervention may play a decisive role in lipid levels modulation, as Pedersen et al found that HDL was further increased when HIIT was combined with a calorie-restricted diet plan.[59] Studies related to patients with diabetes mellitus and metabolic syndrome are the exception to the rule, as HDL was significantly increased after HIIT.[45,61]

Similar findings were observed in studies regarding insulin sensitivity and glucose levels. While Moholdt et al. and Mitranun et al. reported a decrease in glucose levels and glycosylated hemoglobin respectively in all participating patients,[24,45] other studies observed insulin sensitivity improvement mostly on type 2 diabetes mellitus and metabolic syndrome patients.[45,61] Assuming that most CHD patients have comorbidities like type 2 diabetes mellitus and metabolic syndrome, HIIT may be beneficial in lowering blood glucose and improving the lipid profile.

As far as blood pressure is concerned, original studies' and meta-analyses results such as those of Keteyian et al.[38], Tamburus et al.[44] and Keech et al.[36] show high heterogeneity in systolic and diastolic blood pressure decrease, compared to either aerobic exercise group or the control group. Meta analyses by Elliott and Ribeiro concluded that systolic and diastolic blood pressure decrease after HIIT was similar or slightly larger compared to systolic and diastolic blood pressure decrease after aerobic exercise.[19,34] The mechanism involved in blood pressure decrease is the increased activity of the parasympathetic nervous system that results in decrease of the sympathetic tone of smooth muscle cells of the vessel wall and vasospasm. Furthermore, the possible increase in NO bioavailability and subsequent vasodilation lower vessel's peripheral resistance.[44] On the other hand, when patients' initial blood pressure was relatively low (130/80 mmHg) or was treated medically,[44] studies did not show significant decrease. Lastly, the method of blood pressure measurement was not uniform among the studies. Some studies mention that blood pressure was measured after a 5,10 or 15 minute rest in a quiet room with the patient seating,[61,63] while others measured blood pressure for 24 hours[62] or did not mention the method of measurement at all.[45] Further studies need to be carried out for definite answers on the matter.

As far as safety is concerned, literature shows that the risk of serious cardiovascular adverse events after HIIT is low. Musculoskeletal trauma and gastrointestinal disturbances are the most common side effects.[2] Rognmo et al. reported that the ratio of cardiovascular adverse events to hours of training was 1/129.456 for aerobic exercise and 1/23,182 for HIIT.[41] Similar results were described by Wewege et al. in their meta-analysis (1/11,333 for HIIT).[48] HIIT as a part of cardiac rehabilitation is safe regarding the absolute number of serious cardiovascular events. However, there are some reservations on the interpretation of the findings mentioned above. Firstly, systematic reviews included many small sampled studies, whereas large sample studies were very few. Furthermore, there's heterogeneity amongst patients' characteristics such as age, somatometrics and clinical history. In the studies of Aamot and al. and Wewege et al., patients' mean age was 57.8 and 61 years respectively,[48,50] while their clinical and physical condition was good. A few studies include patients older than 65 years old with severe comorbidities. Thirdly, some researchers do not analyze the main pillars of their studies, such as patient recruitment (volunteers or selected patients) and specific starting time of the study in regard to the patients' clinical condition (revascularization time and method).[48]

Patient compliance during or after the rehabilitation program is of equal importance. A determining factor of patient compliance is the patient's training preference. According to 2 studies by Aamot et al., home-based and hospital-based HIIT were equally effective,[50] as $VO_{2\ peak}$ adaptations in the home-based HIIT group were maintained at a larger degree after 12 months.[49] These findings indicate that patients who followed a home-based HIIT protocol had the same motivation and desire to train after the completion of a 12-week CR.[49] Nilsson et al. recorded similar results, as $VO_{2\ peak}$ was increased in patients who followed the modified HIIT protocol at 12 weeks, with further increases occurring at follow-up (after 12 months).[51]

Based on the above evidence, HIIT was preferred by most patients who kept exercising after the end of cardiac rehabilitation. The main reason that patients adhered to HIIT is the game-like character of HIIT that involves constant switches between high and moderate intensity exercise.[18] Additionally, group exercise and music can boost exercise adherence according to Nilsson et al, who reported that music created a sense of euphoria (well-being) in patients and increased their motivation to train harder.[51] Apart from the psychological factor, patients prefer HIIT because of its lower rate of perceived exertion, decreased dyspnea and shorter exercise duration, especially in short-duration HIIT protocols.[18] Therefore, HIIT significantly contributes to achieving long term exercise adherence and adopting a healthier lifestyle, which is the essence of cardiac rehabilitation.

However, there are some limitations in the literature that need to be addressed. First of all, according to Aamot et al. and Nilsson et al., the mean age of the participants was 57 and 59 years respectively.[49,51] Secondly, aerobic capacity in these patients is considered to be high (over 30ml/kg/min), indicating that they were stable, fit and highly motivated. Thirdly, a significant percentage of patients dropped out of cardiac rehabilitation without completing all the necessary measurements. For example, Nilsson et al reported that 35% of the participants withdrew from the program, with 23 out of 47 dropouts mentioning adverse effects such as musculoskeletal injuries, low back pain, chronic obstructive pulmonary disease and cardiac disease.[51] Lastly, it is worth mentioning the second study by Aamot et al. In this study, the group that followed home-based HIIT maintained most of the adaptations gained during CR after 1 year.[49] This happened because the home-based HIIT group initially gained fewer adaptations than the hospital-based groups during CR, so any losses observed were lower expected as it was. Future research that will include more female patients, as well as high-risk or fewer fit patients is expected with great interest.

Nevertheless, basic training variables such as exercise duration and recovery type can be modified depending on fitness levels and stage of cardiac rehabilitation.
Short-duration intervals (10-60 seconds at 100-120% of $VO_{2\ peak}$) with equal periods of passive recovery were as effective as higher duration intervals, as well as resulting in lower levels of dyspnea, rate of perceived exertion and time to exhaustion. These protocols are recommended for patients with lower aerobic capacity who participated in stage 2 (improvement phase) and stage 3 (maintenance phase) of cardiac rehabilitation.[20] For these patients, the transition to high intensity training must be progressive. Scientists suggest the application of moderate intensity aerobic exercise 50-70% of $VO_{2\ peak}$) for at least 2 weeks before introducing short-duration HIIT with passive recovery.[18,19]

Subsequently, based on the progressive overload principle, passive recovery can be progressed to active recovery and interval duration can be increased. Moderate and long-duration intervals (1-3 minutes at 95-100% of $VO_{2\ peak}$ and 3-15 minutes at 85-90% of $VO_{2\ peak}$ respectively) are more suitable for stable patients with higher aerobic capacity, fewer comorbidities such as reduced ejection fraction, diabetes mellitus, hypertension and obesity who join stage 3 (maintenance phase) of cardiac rehabilitation.[20] Regardless of exercise duration and recovery type, HIIT frequency must be at least 2 times a week for 7-12 weeks of cardiac rehabilitation.[2,22]

According to the above evidence, the one size fits all approach (using a specific protocol for all patients) is not a panacea. Exercise prescription must be individualized, based on the patient's medical history, age and fitness levels. For that reason, screening tests such as exercise stress tests and electrocardiograms are essential and must be carried out before patients start a cardiac rehabilitation program.

Conclusion

This review shows that HIIT is an effective alternative training method in patients with CHD, as it increases aerobic capacity, improves endothelial function and reduces inflammation and visceral fat. Various results were reported regarding blood pressure and lipoprotein HDL and LDL levels, with certain studies describing positive alterations and others similar ones compared to aerobic exercise. HIIT is safe for patients, who usually comply with the training regimen even after the completion of the rehabilitation program. However, the studies present with many limitations, such as heterogeneity in inclusion criteria, exercise protocols and patients’ characteristics. Most patients were stable and physically fit men with a mean age of 60 years. More studies that include older, less fit or female patients need to be carried out in order for safer conclusions to be drawn.

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