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Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

Ιατρική Σχολή

Πρόγραμμα Μεταπτυχιακών Σπουδών

<<ΚΛΙΝΙΚΗ ΕΡΓΟΣΠΙΡΟΜΕΤΡΙΑ, ΑΣΚΗΣΗ, ΠΡΟΗΓΜΕΝΗ ΤΕΧΝΟΛΟΓΙΑ ΚΑΙ ΑΠΟΚΑΤΑΣΤΑΣΗ>>

Impact of high intensity interval training on ejection fraction in stable coronary artery disease patients: A systematic review of randomized clinical trials

ΞΗΡΟΥΔΑΚΗΣ ΓΕΩΡΓΙΟΣ

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Αθήνα, 2019

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Ευχαριστίες

Η παρούσα εργασία αποτελεί διπλωματική εργασία στα πλαίσια του μεταπτυχιακού προγράμματος <<Κλινική εργοσπιρομετρία, άσκηση, προηγμένη τεχνολογία και αποκατάσταση>> της Ιατρικής Σχολής Αθηνών.

Πρώτα από όλα θα ήθελα να εκφράσω τις θερμές ευχαριστίες μου στον επιβλέπων καθηγητή κ. Φιλίππου Αναστάσιο τόσο για τη πολύτιμη βοήθεια και τις καθοριστικές παρεμβάσεις, όσο και για το άριστο κλίμα συνεργασίας που συνέβαλαν τα μέγιστα ώστε να ολοκληρωθεί με επιτυχία η εκπόνηση της διπλωματικής εργασίας.

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Περιεχόμενα

Κατάλογος Σχημάτων

Κατάλογος Πινάκων

Συντομογραφίες&Ακρωνύμια

ACS: Acute coronary syndrome

MI: Myocardial infarction

AHA: American Heart Association

HF: Heart Failure

MAP: maximal aerobic power

Bpm: beats per minute

ECG: Electrocardiogram

W: watt

MICE: medium intensity continuous exercise

NO: nitric oxide

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta- Analyses

VO2peak: Peak oxygen uptake

BMI: Body mass index

HRpeak: Peak heart rate

HR reserve: Heart rate reserve

PEDro scale:Physiotherapy Evidence Database

THR: target heart rate

CENTRAL:The Cochrane Central Register of Controlled Trials

CAD: coronary artery disease

CHD: coronary heart disease

HIIT: high intensity interval training

MICT: medium intensity continuous training

EF: ejection fraction

LVEF: left ventricular ejection fraction

HR target: target heart rate

EDV: end diastolic volume

ESV:end systolic volume

LVM:left ventricular mass

SV: stroke volume

CO: cardiac output

MET: metabolic equivalent

min: minute

LVID: Left Ventricular Internal Dimension

LV mass: Left ventricular mass

SR: strain rate

O2: oxygen

CI: Confidence Interval

RCT: randomized controlled trial

EMP: endothelial microparticles

Qol: Quality of life

AT: anaerobic threshold

Abstract

Coronary artery disease remains the leading cause of death globally, since the previous century. Specifically, cardiovascular disease is the leading global cause of death, accounting for more than 17.9 million deaths per year in 2015, a number that is expected to grow more than 23.6 million by 2030, according to American Heart Association (AHA). High-Intensity Interval Training (HIIT) has been presented mostly as an effective tool in cardiac rehabilitation, especially for patients with coronary artery disease. Indeed, medical literature about the utilization of HIITin coronary artery disease (CAD) patients has increased significantly in the last decade. The AHA has recently included this type of exercise in its recommendations for patients with heart disease, although without clearly indicating the prescription modalities for HIIT. Nevertheless, the short-term cardiovascular and bioenergetic responses to HIIT, incorporated invarious exercise protocols, have recently been studied in patients with heart disease. However, although Left ventricular ejection fraction is a powerful predictor of survival after acute myocardial infarction, there is not any systematic review or meta-analysis assessing the efficacy of HIIT in CAD patients, focusing particularly on ejection fraction. Therefore, the purpose of this study was to evaluate the effect of HIIT on ejection fraction in patients suffering from CAD. Three Databases MEDLINE via Pub-Med, PEDro and the Cochrane Central Register of Controlled Trials (CENTRAL) have systematically been searched up to May 2019 for published randomized trials that examined the variability of ejection fraction in CAD patients who underwent supervised implementation of HIIT as part of their cardiac rehabilitation. Specifically, the following PICOS criteria characterized this systematic review; Participants: coronary artery disease patients; Intervention: High-Intensity Interval Training (HIIT), Comparators: randomized controlled and non-cotrolled clinical trials; Outcomes: Ejection fraction. This study revealed that HIIT appears to be safe and appropriate for CAD patients and possibly superior to continuous aerobic exercise. However, it remains necessary to define the optimum time-point at which HIIT may be incorporated in the cardiac rehabilitation program after an acute coronary syndrome.

Περίληψη

Η στεφανιαία νόσος κατατάσσεται ως η πρώτη αιτία θανάτου παγκοσμίως. Συγκεκριμένα, οι καρδιαγγειακές νόσοι βρίσκονται στη κορυφή του καταλόγου θνησιμότητας παγκοσμίως, αριθμώντας περισσότερους από 17.9 εκατομύρια θανάτους κατά το έτος 2015, αριθμός που σύμφωνα με την Αμερικάνικη καρδιολογική εταιρεία (AHA), αναμένεται να αυξηθεί πάνω από 23.6 εκατομύρια θανάτους μέχρι το 2030. Η υψηλής έντασης διαλειμματική άσκηση (προπόνηση) (ΥΕΔΠ) φαίνεται να αποτελεί αποτελεσματικό μέσο στην καρδιοαγγειακή αποκατάσταση και την τελευταία δεκαετία έχει αυξηθεί σημαντικά η σχετική βιβλιογραφία που αφορά στην εφαρμογή προγραμμάτων ΥΕΔΠ σε ασθενείς με στεφανιαία νόσο. Η AHA πρόσφατα συμπεριέλαβε αυτό το είδος άσκησης στις συστάσεις που αφορούν στην αποκατάσταση καρδιολογικών ασθενών, χωρίς όμως σαφή συνταγογράφηση των χαρακτηριστικών της ΥΕΔΠ. Πρόσφατα έχουν μελετηθεί ποικίλα ερευνητικά πρωτόκολλα σχετικά με τα αποτελέσματα της ΥΕΔΠ σε καρδιολογικούς ασθενείς, τα οποία ανέδειξαν σημαντικά οφέλη για αυτούς τους ασθενείς. Από την άλλη, το κλάσμα εξώθησης της αριστερής κοιλίας αποτελεί ισχυρό δείκτη επιβίωσης μετά από έμφραγμα του μυοκαρδίου. Μέχρι τώρα δεν υπάρχει δημοσιευμένη συστηματική ανασκόπηση ή μετά-ανάλυση που να αξιολογεί την αποτελεσματικότητα της ΥΕΔΠ σε ασθενείς με στεφανιαία νόσο, εστιάζοντας συγκεκριμένα στο κλάσμα εξώθησης της αριστερής κοιλίας. Για αυτό, ο σκοπός αυτής της μελέτης ήταν να αξιολογήσει την αποτελεσματικότητα της ΥΕΔΠ, εστιάζοντας στο κλάσμα εξώθησης της καρδιάς, σε ασθενείς που πάσχουν από στεφανιαία νόσο. Τρεις διαδικτυακές βάσεις δεδομένων, οι MEDLINE via Pub- Med, PEDro, και Cochrane Central Register of Controlled Trials (CENTRAL) χρησιμοποιήθηκαν για την αναζήτηση δημοσιευμένων τυχαιποιημένων μελετών μέχρι το Μάιο του έτους 2019, που αξιολόγησαν τη μεταβλητότητα του κλάματος εξώθησης σε ασθενείς με στεφανιαία νόσο οι οποίοι είχαν υποβληθεί σε ΥΕΔΠ. Ειδικότερα, τα κριτήρια επιλεξιμότητας των μελετών που συμπεριελήφθησαν στην παρούσα συστηματική ανασκόπηση ήταν κατά σειρά: 1) Δείγμα πληθυσμού: ασθενείς με στεφανιαία νόσο, 2) Παρέμβαση: υψηλής έντασης διαλειμματική προπόνηση, 3) Μέσα σύγκρισης: τυχαιοποιημένες και μη τυχαιοποιημένες ελεγχόμενες μελέτες και 4) Έκβαση: κλάσμα εξώθησης αριστερής κοιλίας. Η παρούσα μελέτη ανέδειξε ότι η ΥΕΔΠ φαίνεται ότι είναι ασφαλής, κατάλληλη, πιθανώς και αποτελεσματικότερη από τη μέτριας έντασης συνεχή άσκηση για την αποκατάσταση ασθενών με στεφανιαία νόσο. Παρόλα αυτά, κρίνεται απαραίτητος ο σαφής προσδιορισμός των βέλτιστων χαρακτηριστικών της και του κατάλληλου χρόνου ενσωμάτωσής της στο πρόγραμμα καρδιολογικής αποκατάστασης, προκειμένου να επιτυγχάνεται η αποτελεσματική αποκατάσταση μετά από ένα επεισόδιο οξέος εμφράγματος του μυοκαρδίου.

Λέξεις κλειδιά:

Coronary artery disease, high-intensity interval training, ejection fraction

1 Epidemiology of coronary artery disease

Coronary artery disease (CAD), also known as ischemic heart disease or coronary heart disease, involves reduction of blood flow to heart muscle. It is caused by a disease of the blood vessels of the heart called atherosclerosis, which is the leading cause of death globally. CAD sometimes appears asymptomatic while, on the other hand, in the majority of cases acute coronary syndrome (ACS) usually presents with a symptom such as unstable angina, which is frequently associated with myocardial infarction (MI) regardless of the presence of CAD [1]. CAD is usually used to describe the pathologic process affecting the coronary arteries whilst coronary heart disease (CHD) includes the diagnoses of angina pectoris, MI and silent myocardial ischemia [2].

CHD is a major cause of death and disability in developed countries [3]. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years old [4, 5, and 6].

CHD is the leading cause of death in adults in the United States of America, accounting for one-third of all deaths in subjects over 35 years old [7]. The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) reported that overall death rate from CHD was 102.6 per 100,000 [8]. CHD is the leading cause (43.8%) of deaths attributable to cardiovascular disease in the United States of America, followed by Stroke (16.8%), Heart Failure (9.0%), High Blood Pressure (9.4%), diseases of the arteries (3.1%), and other cardiovascular diseases (17.9%) [8].

In general, cardiovascular disease is the leading global cause of death, accounting for more than 17.9 million deaths per year in 2015, a number that is expected to grow to more than 23.6 million by 2030, according to AHA. It is also important to be mentioned that the rehabilitation of cardiac disorder is significantly expensive. Cardiovascular diseases and strokes accounted for 14% of total health expenditures in 2013-2014. A number that is more than any major diagnostic group. Total direct medical costs of Cardiovascular diseases are projected to increase to $749 billion in 2035 [4].

Coronary heart disease accounts for 1 in 7 deaths in the United States of America, killing over 366,800 people a year. The overall prevalence for MI in the United States of America is about 7.9 million, or 3 percent. In 2015, heart attacks claimed 114,023 lives in the United States. The estimated annual incidence of heart attack in the United States of America is 720,000 new attacks and 335,000 recurrent attacks. There is a significant predominance in males over females. Average age at the first heart attack is 65.6 years for males and 72.0 years for females. Approximately every 40 seconds, an American will have a heart attack. From 2005 to 2015, the annual death rate attributable to coronary heart disease declined 34.4 percent but the burden and risk factors remain alarmingly high. However, the estimated direct and indirect cost of heart disease in 2013 to 2014 (average annual) was $204.8 billion. Heart attacks ($12.1 billion) and Coronary Heart Disease ($9.0 billion) were 2 of the 10 most expensive conditions treated in United States of America hospitals in 2013. Between 2013 and 2030, medical costs of Coronary Heart Disease are projected to increase by about 100 percent [5].

2 Introduction to High-Intensity Interval Training

2.1 Benefits of High- Intensity Interval Training over the years

High Intensity Interval Training (HIIT) is a modern form of exercise that seems to take a crucial advantage in cardiac rehabilitation. This particular training mode is consisted of two periods. The main characteristic is that intense anaerobic exercise is followed by recovery phase. Recovery period is might presented by short, long or passive intervals. According to Ribeiro et al, three different categories of HIIT have been described for CHD patients. Long intervals: 3 to 15 min at 85% to 90% of VO_2 peak, medium intervals: 1 to 3 min at 95% to 100% of VO_2 peak and short intervals: 10 sec to 1 min at 100% to 120% of VO_2 peak [9].

Mostly, HIIT is individualized by frequency, duration and intensity. HIIT certainly reflects the history of cardiac rehabilitation. Indeed, in the 1950s, it was considered unreasonable to expect patients with heart disease to perform exercise training [10]. It was not until the early 1970s that the benefits of HIIT were recognized by medical community. The benefits of physical exercise in patients with CAD and Heart Failure (HF) have since been proven and documented in many meta-analyses [11]. Elliott AD et al, conducted a meta-analysis of 229 stable coronary artery disease patients and concluded that high intensity interval training appears more effective than medium intensity continuous training on improvement of aerobic capacity [12]. In 2018 Hannan AL et al, published a meta-analysis of 953 participants suffer from cardiovascular disease which support HIIT is superior to MICT in improving cardio respiratory fitness in cardiac rehabilitation. Especially, HIIT program of 7-12 weeks seems to improve cardio respiratory fitness in coronary artery disease patients [13].

Thanks to a more systematic individualized approach in the management of cardiac rehabilitation, the benefits seem to be directly linked to the notion of training volume and intensity, although exercise prescription still needs to be clarified to enable the scientific community to develop even more precise recommendations [14].

2.2 HIIT appears efficient and cost effective for coronary artery disease patients

High-intensity interval training (HIIT) consists of alternating periods of intensive aerobic exercise with periods of passive or active moderate intensity recovery [15]. The principal interest lies in the fact that it offers the possibility to maintain high-intensity exercise for far longer periods than during continuous exercise. Therefore, HIIT Elicits a greater training stimulus which further improves maximal aerobic capacity [16]. In addition, HIIT appears to be of particular interest since high-intensity exercise (85–100% of peak oxygen uptake [VO_2peak]) is also more effective than moderate-intensity continuous exercise in improving cardiovascular risk factors [17]. VO_2peak seems to be a strong independent predictor of mortality in patients with coronary artery disease (CAD) [18]. Secondly control of risk factors such as diabetes, dyslipidaemia, being overweight and hypertension is a fundamental component of secondary prevention in these patients [19]. Given the above, interest in HIIT in the scientific literature continues to grow [20]. During the last decade, several studies have demonstrated the benefits of this type of exercise in patients who participate into cardiac rehabilitation programmes.

The American Heart Association [21] recently included this exercise technique in its recommendations for patients with heart disease, although without clearly indicating the prescription modalities. Prescription of HIIT is complex since there are an unlimited number of possible exercise/ recovery interval combinations, which should be adapted to a wide range of patients referred to cardiac rehabilitation [22]. In a paper of 5106 apparently healthy subjects has been shown that the relative intensity, and not the duration of cycling, is of more importance in relation to all-cause and coronary heart disease mortality. [23] This finding is in line with the previous study of Andersen et al. [24] showing that the time spent in leisure physical activity was inversely associated with all-cause mortality in both gender, men and women irrespective of age. The benefits were also found from moderate physical activity with further benefits from sports activity. The previous data suggest that HIIT is both efficient and particularly cost effective. The question of determining the most appropriate exercise intensity for cardiac patients is still a matter of debate given the heterogeneity of exercise protocols, patient types and timing of the implementation. The modification of a single parameter, such as the duration, the intensity or the type of recovery, significantly modifies the acute physiological response [25] and presumably long-term adaptations.

2.3 Physiological effects of High-Intensity Interval Training on patients with stable coronary artery disease

The short-term cardiovascular and bioenergetic responses to HIIT with different exercise protocols have recently been studied in patients with heart disease. These studies made it possible to characterize the optimal HIIT protocol on a cycle ergometer for patients with stable CAD according to their short-term response [26]. The method used aimed to identify the interval training protocol that resulted in the maximum amount of time spent at a high percentage of VO_2peak, as proposed for athletes by Dupont et al. [27] and Millet et al., [28] while taking into account Tim and the subjective patient comfort. Two variables were modified: duration of the exercise/recovery phases and the type of recovery (passive or active). Exercises phases were conducted at 100% of maximal aerobic power (MAP). The results showed that the Tlim of interval exercises incorporating passive recovery phases was significantly greater than during interval training sessions incorporating active recovery phases. When exercises were performed until exhaustion, the time spent at a high percentage of VO_2peak was independent of the recovery protocol, which is in accordance with the results of Dupont et al. [25] in healthy individuals.

HIIT could be an interesting training modality to improve long-term adherence in cardiac rehabilitation programmes. Another crucial issue is the alteration of program intensity. In addition, because of the rhythm change imposed by the exercise protocol, patients may treat it like a game which may help them forget the amount of exertion required [29]. Apart from the undeniable and enhanced physiological benefit of this type of exercise compared with continuous exercise, HIIT appears to a potential tool to improve adherence to exercise training. Two recent studies showed that, in patients with stable ischemic CAD, continuous exercise above the ischemic threshold is safe and well tolerated [30]. Scientific evidence suggests that HIIT may be a more attractive training modality in CAD than high-intensity continuous exercise for the simple reason that ischemia would be intermittent rather than continuous. Current guidelines state that in patients with stable angina, [31] MICT is recommended (target heart rate [HR] fixed at 10 beats per minute [bpm] below the ischemic threshold), because the risk-benefit ratio goes against higher intensities [32].

This opinion, however, is based on a single study in 21 patients with ischemic CAD [33]. These patients exercised for 10 minutes on a cycle ergometer at 75% of the maximal HR, twice a week, for 12 weeks. From Holter ECG (electrocardiogram) recordings, the authors identified ten episodes of ischemia associated with ventricular rhythm disturbances in five patients. However, the exercise protocol took patients to 75% of maximal HR within the first 2 minutes. This rapid start could have caused the rhythm disturbances, since the importance of a warm-up period in CAD patients with regard to the risk of ischemia [34] and arrhythmias is well known [35]. During coronary angioplasty, ST-segment elevation can be progressively reduced by repeated balloon inflation and intermittent arterial occlusion [36]. This could explain why successive phases of high-intensity exercise interspersed with periods of rest might induce adaptations that are beneficial for the ischemic myocardium. Although regular exercise training improves endothelial function in patients with CAD [37], a single high-intensity exercise session may also have acute beneficial effects on the endothelium. Guiraud et al. [38] recently measured endothelial microparticles (EMP), specific biological markers associated with the dysfunction and/or damage to endothelial cells [39] during single isocaloric sessions of optimized HIIT and MICT in patients with CAD [38]. No elevation in EMP levels was observed 20 minutes, 24 hours and 72 hours after either exercise session. These data suggest that repetitive short phases of high intensity aerobic exercise may not cause vascular shear stress that is sufficient to damage the underlying endothelium.

In summary, most studies on acute exercise showed that HIIT incorporating short exercise/ recovery intervals are safe, well tolerated and are associated with maintenance of a high percentage of VO_2max during exercise sessions, while generally enabling subjects to exercise longer relative to isocaloric MICT. Furthermore, the use of passive recovery phases is even more preferred by patients and may not come at the expense of significantly lower mean VO_2 response.

2.4 Long-term effects of High Intensity Interval Training in coronary artery disease patients

The first studies were conducted by Meyer et al., [40] who investigated the effects of HIIT during a cardiac rehabilitation programme following coronary bypass surgery (mean = 24 days post-operatively). Subjects performed 20 minutes of either interval training or continuous exercise every day for 3.5 weeks, initially at 86% of maximal HR. The workload was then increased by 20W/week. During the third week, the interval training group performed alternating 1-minute phases at 20W with 1-minute phases at 121 W, whereas the MICT group pedalled continuously at 83W. Although total energy expenditure was lower in the interval group, peak power improved more in the interval training group

(+0.63 vs +0.26W/kg for interval training and MICT groups, respectively; $p < 0.001$), while resting HR (-9 vs -4 bpm, respectively; $p < 0.04$), and HR at 75W (-12 vs -2 bpm, respectively; $p < 0.02$) were also reduced more in this group. The previous results demonstrate the effectiveness of interval training in improving physical performance without placing excessive demands on heart function (similar rate pressure product). Rognmo et al. [41] studied the impact of 10 weeks of either continuous (50–60% of VO_2peak) or isocaloric interval (ratio 4 : 3, MI 72%, amplitude 42%) exercise performed three times per week on functional capacity in a small sample of 21 stable CAD patients. There was a significant increase inVO_2peak in both groups (interval 17.9%; $p = 0.012$ and continuous 7.9%; $p= 0.038$), with a greater improvement in the HIIT group (interaction $p = 0.011$). This improvement in the HIIT group was all the more remarkable since initial VO_2peak was 32mL/min/kg, which is far higher than in most reported studies in patients with heart disease.

By dividing the increase in VO2peak by the number of exercise sessions, the authors noted a 0.6% improvement in VO_2peak per exercise session after interval training, compared with a 0.3% improvement after MICT training ($p = 0.006$). The results for this parameter must, however, be interpreted with caution, since the adaptation process to exercise training is not linear. These results are consistent with the results of Jensen at al. [42] who revealed the relationship between exercise intensity (50% and 85% of VO_2peak) and improvements in VO_2peak in a large cohort of CAD patients. Warburton et al. [43] studied the effects of 16 weeks of aerobic exercise in 14 patients with stable CAD, randomized to aerobic interval (ratio 1: 1, MI 65%, amplitude 77%) or MICT training. Subjects performed both a maximal cardiopulmonary stress test and a sustained submaximal exercise test (constant intensity = 90% of the reserve HR) continued to exhaustion, before and after exercise training. Surprisingly, VO_2peak improved to a similar degree in both groups. This could be explained by the fact that baseline VO_2peak in patients was already high (intensity >9 METs, equivalent to >42mL/min/kg of O_2). One significant restriction was the small sample size that limited statistical power in this study. Nonetheless, Tlim during the submaximal exercise test increased 5-fold in the interval training group and 2.5-fold in the MICE group ($p < 0.05$), which led the authors to suggest that interval training safely improved anaerobic tolerance [43]. However, these results must be interpreted with caution, as the contribution of anaerobic capacity during interval training is rather limited the intensity of interval training approximately corresponds to 85% of VO_2peak [44]. The improvement in Tlim most likely stems from the positive impact of interval training on aerobic endurance and energy costs at high intensity [45]. More recently, Amundsen et al. [46] compared the effects of two training protocols, interval (ratio 4: 3, MI 72%, amplitude 42%) and continuous on left ventricular diastolic function in CAD patients. After 10 weeks of training, the improvement in VO2peak was significantly greater in the HIIT group (17% vs 8% in HIIT and MICT groups, respectively; $p < 0.01$). Left ventricular filling speed and diastolic relaxation increased only in the HIIT group. HIIT thus improved left ventricular compliance and contributed to the increase in systolic ejection volume and cardiac output witnessed.

Munk et al. [47] compared the effect of interval training with usual care on in-stent restenosis after coronary angioplasty with stent implantation. After 6 months, restenosis, as measured by late loss in lumen diameter in the stented artery, was significantly lower (median value [range] = 0.10 [0.52] mm) in the exercise group relative to the control group, 0.39 (0.38) mm (interaction $p < 0.01$). Results were similar irrespective of the type of stent implanted (bare or medicated). Furthermore, HIIT resulted in a significant improvement in VO_2peak and endothelial function (flow-mediated dilatation [FMD] of the brachial artery) and a reduction in inflammation (hs- CRP). The preventive effects of exercise on restenosis can be explained in part by the fact that exercise improves endothelium-dependent vasodilation by activating synthesis of nitric oxide (NO), which increases levels of NO in coronary endothelial cells. Local release of NO seems to inhibit the neo-intimal proliferation, suggesting that exercise has a potential mechanical effect on late loss of lumen diameter [48].

In addition, these results were significantly correlated with the decrease in interleukin-6 and C-reactive protein levels, which may attenuate some inflammatory pathways that are potentially contributing to the beneficial effects of exercise training on restenosis [49]. In the HIIT group only, Munk et al. [50] also showed a significant improvement in regulation of the autonomous nervous system of the cardiac muscle. In a randomized study, Moholdt et al.[51] compared the effects of interval training (ratio 4 : 3, MI 72%, amplitude 42%) and MICT on functional capacity in patients after coronary bypass surgery during a stay in a rehabilitation unit (4 weeks) followed by 6 months of home-based training. Both exercise protocols generated a similar improvement in VO2peak in the short term (after 4 weeks: HIIT +12.2%, $p< 0.001$; MICT +8.8%, $p< 0.001$), but the long-term benefits on the maintenance or improvement were clearly greater following interval training (HIIT +5.9%; $p < 0.001$) with no change for MICT. In post myocardial infarction patients, this team also compared both types of supervised exercise training [52]. Both exercise protocols increased endothelial function, serum adiponectin quality of life (QoL), and reduced serum ferritin and resting HR. High density lipoprotein cholesterol (HDL-C) increased only after HIIT. The VO2peak increased more after HIIT than after usual care rehabilitation ($p < 0.005$). The difference between groups in terms Of VO2peak persisted after 30 months of homebased training ($p < 0.005$), which can be explained partly by a higher increase during the initial 12 weeks of supervised training and partly by a lower decline during follow-up [53].

In summary, HIIT appears to be well suited to CAD patients and its superiority to continuous type aerobic exercise is almost beyond doubt. However, it is still necessary to define when cardiac rehabilitation incorporating HIIT may commence after an acute coronary syndrome.

3 Ejection fraction as a tool in cardiac rehabilitation

Ejection fraction (EF) is the volumetric fraction of fluid ejected from a chamber with each heart contraction; it usually refers to the left ventricle of the heart. PH. It is also used as a strong prognostic indicator of the severity of heart failure [54]. Regular physical exercise may lead to changes in myocardial structure and function [55]. Furthermore, Morganroth J. et al supports that endurance training may cause eccentric Left Ventricular (LV) hypertrophy [56].

To the best of our knowledge, there is no systematic review with meta-analysis that evaluated the impact of HIIT in patients with coronary artery disease particularly focusing on ejection fraction. Considering the gap in this area of knowledge, we performed a comprehensive systematic review of the literature of randomized clinical trials with CAD patients to assess the efficacy of HIIT on EF in this complex syndrome.

Thus, the purpose of this study was to evaluate the effect of HIIT on ejection fraction in patients suffering from coronary artery disease.

4 Methods

This particular systematic review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [57].

4.1 Search strategy

Three electronic databases, MEDLINE via Pub Med, PEDro, and the Cochrane Central Register of Controlled Trials (CENTRAL) have systematically been searched for randomized trials, with or without control group, about the variability of ejection fraction in coronary artery disease patients. The sample of this study is consisted of patients suffering from coronary artery disease who also were able to exercise. Overall, eligible population should have undergone supervised implementation of HIIT within their cardiac rehabilitation program up to May 2019.

The particular search strategy was focused on four groups of keywords. Study design, population/ disease, intervention and primary outcome. The study design group of keywords included the terms randomized controlled trials, randomized clinical trial. The population/ disease group of keywords included the terms coronary artery disease, coronary heart disease, CAD, CHD. The intervention group of keywords included the terms of high-intensity interval training, high-intensity interval exercise, HIIT. Last but not least, the primary outcome group of search included ejection fraction, left ventricular ejection fraction, EF, LVEF.

4.2 Inclusion and Exclusion criteria

Eligible studies for this systematic review should meet the following inclusion criteria: 1) Randomized clinical trial design, 2) documented participants with coronary artery disease in stable cardiovascular situation, 3) implementation of high-intensity interval training within the cardiac rehabilitation program, with work load intervals at least one of the following:

>80% VO_2peak or

>85% HR peak or

>85% HR reserve or

>65% HR target according to Karvonen formula, 4) the primary outcome of interest was the cardiovascular parameter ejection fraction.

Studies were excluded from this systematic review if they have been conducted in patients with heart failure and/or other chronic cardiopulmonary disease and/or neurological limitations with contraindication to exercise.

4.3 Study selection

Figure 1 Illustrates the flow diagram of study selection according to PRISMA guidelines. At the beginning, 123 papers identified by searching through three electronic databases. 41 duplicates were removed from the initial list of total papers to last on 82 articles. 36 out of the 82 studies met at least one of the exclusion criteria to limited on 46. Then titles and abstracts of the remaining 46 articles were screened for appropriate content based on inclusion and exclusion criteria. 35 out of 46 studies which do not meet the inclusion characteristics from the searching list of this systematic review were removed. Finally, 11 full text articles checked by eligibility criteria for this systematic review to conclude in last four final studies because 7 full text articles excluded, of which 4 papers do not meet HIIT intervention characteristics of inclusion criteria on this systematic review and 3 papers had been composed of patients with coronary artery disease with unstable symptoms. Although, 4 studies included in qualitative synthesis of this systematic review of which Farheen H. et al., 2019 [58] both interventional and control group were eligible for this systematic review. As a result, there are independently both interventional and control group of previous study in table 1, table 2 and table 3.

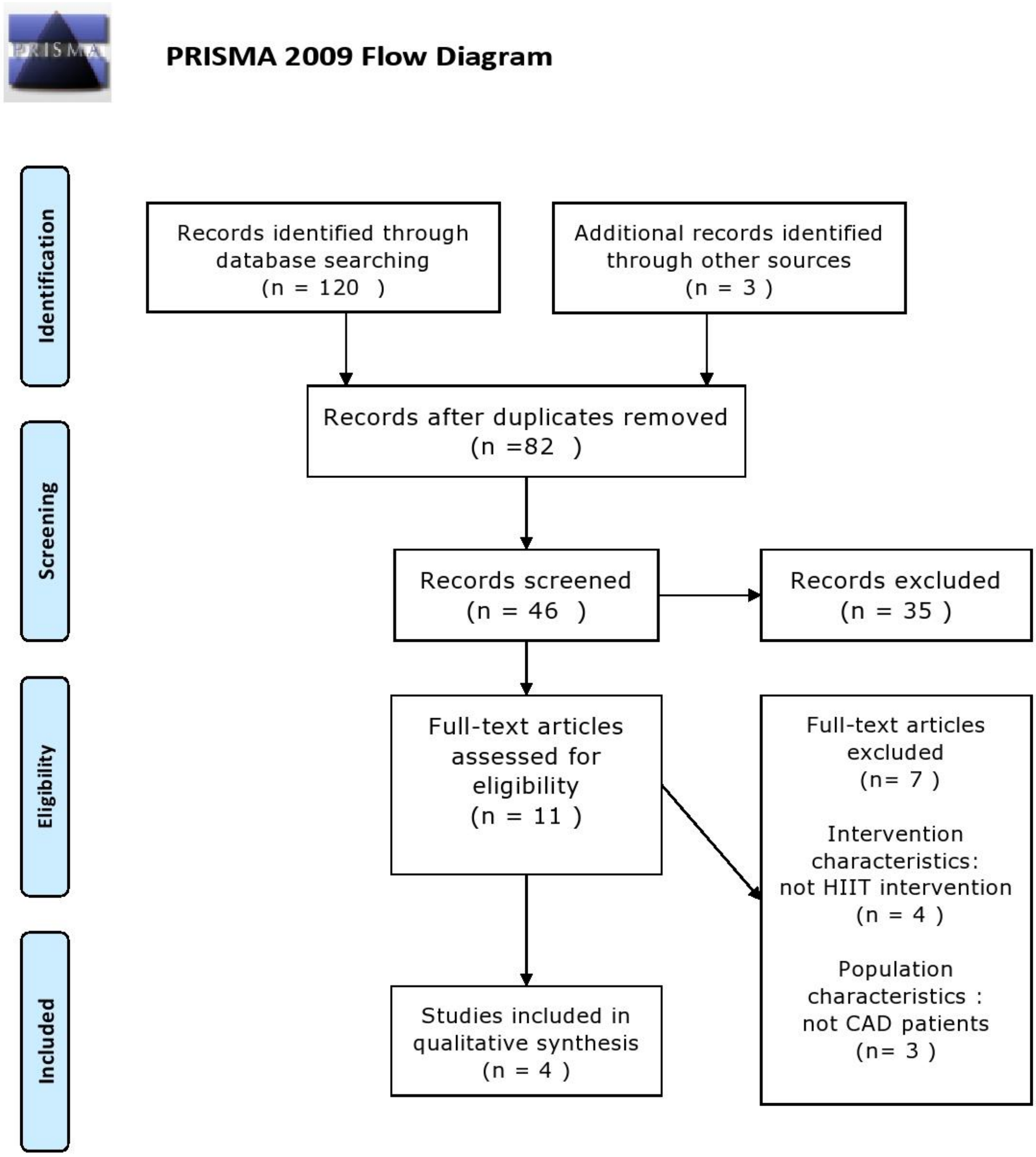

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection (PRISMA Flow diagram).

4.4 Data extraction and management

Table 1 presents collected data about demographic evidence of included studies, the most important of which are: first author's name, study location, total number of included participants after missing drop outs, drop outs, mean age, body mass index, VO_2peak, intervention and outcomes of each study. Body mass index and VO_2peak were not available from all included studies. Body mass index was not reported in 2 of 4 included studies. Moreover, VO_2peak was reported only in Helgerud J. et al., 2010 [59]. However, intervention's characteristics like frequency (days per week), total session duration (min), interval work (min), work intensity, interval recovery (min), recovery intensity, length duration (weeks) and number of sessions are appeared in Table 2. Primary outcome the variability of ejection fraction pre-post training and follow up (months) is presented in Table 3. The statistical significant P-value index refers to comparison between pre and post training of ejection fraction measurement. P value was reported only in two of included articles Caroline M.Van De Heyning et al., 2017 [60] and Helgerud J. et al., 2010 [59].

Table 1. Demographic data of included studies

Research studies	*Study location, Country*	*n_HIIT*	*Drop outs*	*Mean Age*	*BMI (kg/ m^2)*	*VO2peak (ml/kg *min)*	*Intervention*	*Outcome*
Caroline M.Van De Heyning et al., 2017	Antwerp, Belgium	81	19	57.0 +- 9.0	28.0 +- 4.4	Not reported	HIIT vs MICT	Cardiac function, Cardiac geometry
Helgerud J. et al., 2010	Trondheim, Norway	8	2	61.4 +- 3.7	26.1 +- 2.9	27.2 +- 4.5	HIIT vs RT	Cardiac function
Abdelhalem A.M. et al., 2018	Helwan and Ain Shams, Egypt	20	NO	54.65 +-7.63	Not reported	Not reported	HIIT vs MICT	Cardiac function, Quality of life
Hania Farheen et al,, 2019 (interv.)	Islamabad, Pakistan	13	2	57.23 +- 9.76	Not reported	Not reported	HIIT vs HIIT and RT	Cardiac function
Hania Farheen et al,, 2019 (control)	Islamabad, Pakistan	13	2	55.77 +- 10.46	Not reported	Not reported	HIIT vs HIIT and RT	Cardiac function

n_HIIT: Total number of included participants after missing drop outs; Drop outs: missing drop outs from the beginning of study; HIIT: High intensity interval training; MICT: Medium intensity continuous training; RT: Resistance training.

Table 2. Characteristics of HIIT programs in included studies

Research studies	frequency (days per week)	total session duration (min)	interval work (min)	work intensity	interval recovery (min)	recovery intensity	length duration (weeks)	number of sessions
Caroline M.Van De Heyning et al., 2017	3	38	4	85-95% HRpeak	3	50-70% HRpeak	12	36
Helgerud J. et al., 2010	5 (1st 4weeks) 3 (last 4weeks)	38	4	85-95% HRpeak	3	60-70% HRpeak	8	30
Abdelhalem A.M. Et al., 2018	2	40 -45	2 -5	85-95% HR reserve	Not reported	40-60% HR reserve	12	24
Hania Farheen et al. (interv), 2019	3	18	3	65-85% THR	3	Complete rest	6	18
Hania Farheen et al. (control), 2019	3	18	6	65-85% THR	3	Complete rest	6	18

HR peak: Heart rate peak; HR reserve: Heart rate reserve; THR: Target heart rate by Karvonen formula; Helgerud et al.: frequency of training was 5 days per week on first, second, third and fourth week. While it reduced for 3 days per week the fifth, sixth, seventh and eighth remaining week sessions.

Table 3. Summary of findings

Research studies	Pre-training Ejection Fraction (%)	Post-training Ejection Fraction (%)	Follow up (months)	p-value
Caroline M.Van De Heyning et al., 2017	56.7 +- 8.7	57.5 +- 8.0	3	p=0.008
Helgerud J. et al., 2010	62.3 +- 6.5	65.4 +- 7.2	2	p=0.06
Abdelhalem A.M. Et al., 2018	43.3 +- 5.3	48.3 +- 5.7	3	Not reported
Hania Farheen et al.,2019(interv)	45.0 +- 15.0	55.0 +- 10.0	1.5	Not reported
Hania Farheen et al., 2019(control)	45.0 +- 10.0	50.0 +- 5.0	1.5	Not reported

P-value index refers to comparison between pre-and post-training ejection fraction.

4.5 Risk of bias of included studies

The credibility of evidence syntheses may be compromised by reporting biases, which arise when dissemination of research findings is influenced by the nature of the results [61]. For instance, there may be bias due to selective publication, where a study is only published if the findings are considered interesting, also known as publication bias [62]. Moreover, bias due to selective non-reporting may occur, where findings; estimates of intervention efficacy or an association between exposure and outcome that are statistically non-significant are not reported or are partially reported in a paper. Most of the times stating only that P value>0.05 [63]. In addition, there may be bias in selection of the reported result, where authors perform multiple analyses for a particular outcome/association, yet only report the result which yielded the most favorable effect estimate [64]. Evidence from cohorts of clinical trials followed from inception suggest that biased dissemination is common. Specifically, on average, half of all trials are not published [61, 65], trials with statistically significant results are twice as likely to be published [65]. Only a third of trials have outcomes that are omitted, added or modified between protocol and publication [66].

Audits of systematic review conduct suggest that most systematic reviewers do not assess risk of reporting biases [67]. For example, in a cross-sectional study of 300 systematic reviews indexed in MEDLINE in February 2014 [67], the risk of bias due to selective publication was not considered in 56% of reviews. A common reason for not doing so was that small number of included studies, or inability to perform a meta-analysis, precluded the use of funnel plots. Only a low percentage at 19% of reviews included a search of a trial registry to identify completed but unpublished trials or prespecified and non-reported outcomes, finally only 7% included a search of another source of data disseminated outside of journal articles. The risk of bias due to selective non-reporting in the included studies was assessed in only 24% of reviews [67]. Another study of Page M.J. et al, showed that authors of Cochrane reviews routinely record whether any outcomes that were measured were not reported in the included trials, yet rarely consider if such non-reporting could have biased the results of a synthesis [68]. Researchers have summarized the characteristics of tools designed to assess various sources of bias in randomized trials, non-randomized studies of interventions, diagnostic test accuracy studies and systematic reviews [69]. Even though, others have summarized the performance of statistical methods developed to detect or adjust for reporting biases [70].

The risk of bias of included studies was scored using 11-item PEDro scale [71]. 11-item PEDro scale is based on the 9-item Delphi list developed by Verhagen and colleagues at the department of Epidemiology, university of Maastricht [72]. The first item on PEDro scale is related to the external validity and is generally not used to calculate the total score. So, range of PEDro scale is counted from 0 to 10 [73]. As a matter of fact every four of included studies has been assessed by PEDro scale in table 4.

Table 4. Assessment risk of bias of included studies.

	Caroline M.Van De Heyning et al., 2017	Helgerud J. et al., 2010	Abdelhalem A.M. Et al., 2018	Hania Farheen et al., 2019
(Eligibility criteria)	YES	YES	YES	YES
Random allocation	YES	YES	YES	YES
Concealed allocation	NO	NO	NO	NO
Baseline comparability	YES	YES	YES	YES
Blind subjects	NO	NO	NO	NO
Blind therapists	NO	NO	NO	NO
Blind assessors	NO	NO	NO	NO
Adequate follow up	NO	YES	YES	YES
Intention to treat analysis	NO	NO	NO	NO
Between group comparisons	YES	YES	YES	YES
Point estimates and variability	YES	YES	YES	YES
Total PEDro score	4/10	5/10	5/10	5/10

PEDro scale tool used to assess risk of bias and quality of methodology in included studies on this systematic review.

5 Results

5.1 Description of selected studies

A total number of 123 records were identified by the initial search of which 11 were considered eligible and assessed for full-text eligibility parameters. Four [58, 59, 60, 74] remaining articles were included for data extraction in this systematic review. Both control and interventional group met the inclusion criteria in Farheen H. et al., 2019 [58]. Seven papers were excluded for specific reasons. The most significant excluded reasons were study population and intervention characteristics. Figure 1. shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection (PRISMA Flow diagram) concluded in this review.

5.2 Study characteristics

The number of participants in all four included studies resulted in a total of 135 stable subjects with coronary heart disease. Caroline M.Van De Heyning et al., 2017 [60] included a powerful sample of 81 participants after missing drop outs. Helgerud J. et al., 2010 [59], Abdelhalem A.M. Et al., 2018 [74] and Farheen H. et al., 2019 [58] included lower sample of 8, 20 and 26 members each after calculated drop outs. The samples of the selected studies consisted of middle-aged patients whose mean age ranged from

54.65 +- 7.63 to 61.4 +- 3.7 years. All of four studies included of both gender, however there was a significant preponderance of male 85% in contrast to female 15%. Every study included diagnosed coronary artery disease patients with stable clinical condition who had not any contraindication to exercise. Mean value of Body Mass Index (kg/m^2) calculated in two out of four studies. Caroline M.Van De Heyning et al. [60] showed 28.0 +- 4.4 (kg/m^2) and Helgerud J. et al. [59] reported 26.1 +- 2.9 (kg/m^2). Mean value of VO2peak consumption (ml/kg*min) measured only in Helgerud J. et al. founded 27.2 +- 4.5 (ml/kg*min). Subjects of all studies were randomly allocated to intervention or control group. Furthermore, all studies were designed by a common exclusion criterion Heart failure patients about population. A comprehensive qualitative assessment of demographic data can be found in Table 1. i.e. Study location, sample size, drop outs, mean age (years), BMI ($kg/m^{2)}$, VO2peak (ml/kg*min), intervention and outcomes.

5.3 Characteristics of intervention programs

The length duration of the intervention programs ranged from 6 to 12 weeks. Intervention program was applied by Helgerud et al [59], lasted 8 weeks. On the other side, Caroline M.Van De Heyning et al., 2017 [60] and Abdelhalem A.M. Et al., 2018 [74] reported a 12 weeks protocol duration. Farheen H. et al., 2019 [58] conducted a 6 weeks duration intervention program. The frequency ranged from 2 to 5 days per week. There was a standard number of frequency in Caroline M.Van De Heyning et al., 2017 [60] and Farheen H. et al., 2019 [58] 3 days per week each respectively. Frequency in Abdelhalem A.M. et al., 2018 [74] reached 2 days per week. A more composite procedure about the frequency used by Helgerud J. et al., 2010 [59] in which subjects undertook 5 sessions of treadmill in first 4 weeks, followed by 3 weekly sessions the remaining 4 weeks to complete a total of 30 interval training sessions. Total session duration lasted 38 minutes in Caroline M.Van De Heyning et al., 2017 [60] and Helgerud J. et al., 2010 [59] with 4 intervals of 4 minutes followed by 3 minutes recovery each. In previous studies work intensity was the same 85-95% of peak HR. recovery intensity was 50-70% HRpeak in Caroline M.Van De Heyning et al., 2017 [60] and a little higher in Helgerud J. et al., 2010 [59] pointed 60-70% peak HR. In Abdelhalem A.M. Et al., 2018 [74] work and recovery intensity measured by heart rate reserve. Work intensity ranged from 85-95% of HR reserve and recovery intensity ranged from 40-60% of HR reserve. High intensity intervals lasted 2-5 minutes resulting in a total of 30 to 35 time training. Another, more popular method used by Farheen H. et al., 2019 [58] to estimate work intensity was Karvonen's formula [75]. Work intensity performed by Karvonen's formula calculated 65%-85% of target heart rate (THR) each patient throughout full 6 weeks intervention. Total session duration lasted 18 minutes with 3 minutes interval time in interventional group and 6 minutes in control group. Recovery time was 3 minutes of complete rest in both groups.

All included studies underlined clinical supervision on intervention group by specialist physiologist or physiotherapist. High intensity interval exercise characteristics of included studies are summarized in Table 2.

5.4 Risk of bias of selected studies

PEDro scale tool used to assess risk of bias and quality of methodology of the included studies in this systematic review. All of the eligible articles conducted by random allocation, also two of the included papers were organized by control group which followed supervised training with standard cardiac rehabilitation program. All studies reported statistical comparison between groups, before and after the intervention program. None of the included studies reported allocation concealment, blindness between therapists or assessors or patients and intention to treat analysis. Total PEDro score of each included study is presented in Table 4.

5.5 Ejection Fraction in selected studies

Transthoracic echocardiography was performed to measure 100 percentage of ejection fraction before and after training session in three out of four included papers Caroline M.Van De Heyning et al., 2017 [60], Abdelhalem A.M. Et al., 2018 [74] and Farheen H. et al., 2019 [58]. One study, Helgerud J. et al., 2010 [59] examined percentage of ejection fraction pre and post intervention by Cardiovascular magnetic resonance (CMR). There are plenty methods for Ejection fraction's measurement in existing literature. The most important of which are echocardiography, cardiac magnetic resonance imaging (MRI), cardiac computed tomography, ventriculography and nuclear medicine seems to be on top in diagnostic medicine [76]. The exercise training effect on cardiac function is commonly assessed by M-mode in echocardiography usually by two-dimensional speckle- tracking echocardiography, which only displays the size of ventricular cavity, myocardial thickness, the integrity of interventricular septum, and the motion of ventricular wall at rest [77]. Summary of ejection fraction's measurement is shown in Table 3.

6 Discussion

6.1 Ejection fraction

This study evaluated the efficacy of high intensity interval training on ejection fraction in patients with coronary artery disease. The results obtained from this study demonstrate that HIIT is a powerful tool on improvement of ejection fraction in CAD patients.

All the included studies showed an enhancement on ejection fraction after cardiac rehabilitation of HIIT program. Caroline M.Van De Heyning et al., 2017 [60] showed an improvement from 56.7 +- 8.7 to 57.5 +- 8.0 in 3 months follow up. Helgerud et al. [59] presented an increase from 62.3 +- 6.5 to 65.4 +- 7.2 in 2 months follow up. The most significant improvement reported by Abdeelhaleem et al. [74] from 43.30 +- 5.32 to 48.30 +- 5.72 in patients with mild left ventricular dysfunction. Probably this effect occurred because of the long duration on training intervention in 3 months. Farheen et al. [58] showed an increase in interventional group from 45.0 +- 15.0 to 55.0 +- 10.0 and in control group from 45.0 +- 10.0 to 50.0 +- 5.0 in 1.5 months.

Table 3 Shows summary of findings before and after the intervention with follow up of included studies. Two of four eligible studies, Van De Heyning et al, and Abdelhalem A. et al, [60, 74] have been conducted with control group which followed a standard cardiac rehabilitation program. Helgerud J. et al, included control group with strength training in which every single subject followed 24 sessions of maximal horizontal leg press [59]. The final study Farheen H. et al, [58] included two groups of which every single subject was eligible for this systematic review. The first group followed HIIT intervention and the second followed combined HIIT and strength training. Resistance training was at 30%- 50% of one maximum repetition.

Kokkinos P. and Myers J. reported Low increase in exercise capacity results in major health benefits. For instance, each increment of 1-MET in exercise capacity, probably leads to reductions of up to 25% in mortality [78]. Yadav Y. K. et al indicates that training period, exercise intensity and rest between sets play an important role in improving cardiac function on exercise training programs rehabilitation in patients with coronary artery disease [79]. There was a significant variation in some parameters of included studies about HIIT intervention. The length duration of intervention programs ranged from 6 to 12 weeks. The frequency ranged from 2 to 5 days per week. The total session duration ranged from 18 to 45 minutes each session. The interval phase ranged from 2 to 6 minutes. The work intensity had three different statuses 85-95% HRpeak, 85-95% HR reserve, 65-85% THR. The recovery intensity was various in every included study 50-70% HRpeak, 60-70% HRpeak, 40-60% HR reserve and also complete rest. Furthermore, interval recovery was 3 minutes duration in every eligible study. Although, interval recovery was not reported in Abdeelhaleem et al.

All these differences among included studies about HIIT protocols may underline the demand for global guidelines about recommendation of HIIT on patients with CAD or in general cardiac population.

6.2 Ejection fraction's measurement

There are many methods for Ejection fraction's measurement over cardiac rehabilitation program. The most important of which are echocardiography, although cardiac magnetic resonance imaging (MRI), cardiac computed tomography, ventriculography and nuclear medicine [80, 81]. The exercise training effect on cardiac function is commonly assessed by M-mode in echocardiography usually by two-dimensional speckle- tracking echocardiography, which only displays the size of ventricular cavity, myocardial thickness, the integrity of interventricular septum, and the motion of ventricular wall at rest [77].

Stress echocardiography has been reported to be a more reasonable and assessable approach to estimate the effects of cardiac training in global health community [82, 83]. Analyzing the strain rate (SR) of cardiac muscle through speckle-tracking echocardiography is a new noninvasive method for more sensitively detecting myocardial dysfunction than traditional echocardiographic indices (e.g., ejection fraction) [84]. Transthoracic echocardiography used by 3 of 4 authors of included studies Van De Heyning et al, [60] Abdelhalem A. et al**,** [74] and Farheen H. et al, [58] to calculate ejection fraction before and after the intervention. Cardiovascular magnetic resonance was applicated by Helgerud J. et al, 2010 to measure end diastolic volume (EDV), end systolic volume (ESV), left ventricular mass (LVM), stroke volume (SV), cardiac output (CO) and ejection fraction (EF) by semi automated segmentation of end-diastolic and end-systolic areas using dedicated software (Easy vision, Philips, Best, Netherlands) [59].

Although decreased left ventricular systolic function is a well-established independent predictor of mortality in CAD patients, little information is available regarding the effect of exercise training on LVEF [85]. The existing literature focuses more on heart failure patients and lacks methodological uniformity regarding the type of patients, time gap between post-discharge to begin with exercise training program in post-event patients or the intensity and type of exercise given to the patients. Koch, Duard and Broustet in 1992 upon a randomized clinical trial studied the effect of graded physical exercise on EF and found no significant effect. Nevertheless, their study was conducted on chronic heart failure population [86]. Adachi, Koiket and Obayshi (1996) reported improvement in cardiac function (such as stroke volume) both at rest and during exercise only with high-intensity exercise training [87].

A Randomized Controlled Trial by Mohammad H. Haddadzadeh et al. demonstrated two important findings. First, an early (within 1 month post-discharge) 12 weeks structured exercise-training program in post-event coronary artery disease patients could significantly improve the myocardial contractility in terms of LVEF. Second, a structured individually training program could be as effective as center-based programs and safely used not only in low-risk but also in moderate risk CAD patients. The writer reported that these programs could be started as early as 2 weeks post-discharge in uncomplicated patients.

Recent studies demonstrated that high-intensity interval training (HIIT) significantly improved O2 uptake efficiency by enhancing hemodynamic responses to exercise than traditional moderate-intensity continuous training (MICT) in heart failure patients and healthy sedentary men [88]. However, an effective training strategy that promotes cardiac inotropic and lusitropic effects by improving LV mechanics has not been established yet. The results of a randomized controlled trial [89] demonstrated that

HIIT is superior to MICT for remolding LV structure and improving LV mechanics by increasing both contractile and diastolic functions especially in radial direction. HIIT markedly increased LV mass and enlarged the diastolic LVID, which reflects a form of eccentric myocardial hypertrophy. In contrast, MICT only modestly increased LV mass and did not alter diastolic LVID. Furthermore, this present study demonstrated a positive effect on myocardial performance, indicated by decreased Tei index, in either HIIT or MICT.

6.3 Recent systematic reviews

There is a considerable variance on the duration of work intervals about HIIT protocols in cardiac rehabilitation. Both HIIT protocols with short and long intervals produce significant improvements in peak VO2 for patients with CAD [90, 91, 92].

This is because intensity may be the parameter that produces greater adaptations in the cardiovascular system such as an increase in muscle cross- sectional area, adaptations of energy reserves and increased synchronization of motor units [93, 94]. One previous review, Haykowsky M. J. et al., 2013 [95] examined whether interval is more effective than continuous training focus on VO2peak and LVEF in CHF patients. Haykowsky M. J. et al., 2013 [95] concluded HIIT is more effective than MICT for improving peak VO2 (MD 2.14 mL/kg/min, 95% CI 0.66 to 3.63 mL/kg/min) but further details about the LVEF had not been presented. However, this review focused only on CHF patients. Another recent meta-analysis including CAD patients by Pattyn et al., 2014 [96] reported higher increase in VO2 peak with HIIT (MD 1.6 mL/kg/min, 95% CI 0.8 to 3.02 mL/kg/min) but important indicators such as VE/VCO2 slope, LVEF, VO2 at AT, and body mass were not taken under consideration. Bin Xie et al., 2017 [97] concluded that authors of eight studies involving 170 patients presented increased LVEF following HIIT and MICT protocols for cardiac rehabilitation. HIIT intervention showed higher increased against MICT on LVEF. The included participants suffered from coronary artery disease and chronic heart failure.

The inclusion of “adapted” high intensity, relative to a subject’s current physical ability and endurance, in the exercise protocol is a key component for exercise to be more efficient as a “medicine.” Exercise protocols require a shorter exercise duration to obtain the same benefit as that provided by moderate-intensity exercises. However, maintaining a high intensity exercise workout for a longer duration could be preferred for moderate to high-risk patients, as high-intensity exercise can be realistically tolerated by people with sedentary lifestyle and cardiac disease only in the form of interval training. In this regard, HIIT consists of brief, intermittent bursts of vigorous activity less than VO2peak but usually involves < 100 percentage. For instance, 70%-90% of VO2peak or 85%-95% of the peak heart rate interspersed with active or passive rest periods [98]. There is a variety of HIIT protocols in existing literature about the duration of active and recovery period of training. The 4 × 4 minutes protocol is popularly used in patients with lifestyle-related plus cardiac disease, and was initially adapted for cardiac disease by Wisløff and Rognomo et al [99, 100]. In the first RCT on HIIT in a clinical setting, Rognmo et al [100] evaluated the effects of HIIT compared with those of MCT, with the same total training load, and found that HIIT produced a higher increase of VO2peak in patients with stable coronary artery disease than MCT. This trial adapted the 4 × 4 minutes method for patients with cardiac disease for the first time, using the same protocol as that used by the same group for young football players [101]. Leading researchers have reported the positive effects of HIIT on aerobic and metabolic capacity in single-center RCTs and meta-analyses. According to several RCTs, HIIT was superior in improving VO2peak in 60% (6/10) of patients with coronary artery disease and in 45.6% of those with CHF. The effect of HIIT depends on the workout duration/rest ratio. In contrast, the latest multicenter RCT Study of Myocardial Recovery After Exercise Training in Heart Failure showed a negative result using the 4 × 4 minutes method for patients with CHF with reduced left ventricular dysfunction [102] despite many other studies reporting positive results [99, 103, 104, 105]. Although the 4 × 4 minutes aerobic HIIT protocol has been used in many studies, it did not consistently yield good results. Some researchers do not recommend this protocol because they believe that the load is excessive and the workout duration is too long for patients with sedentary/cardiac diseases, suggesting that it is a clinically unrealistic training method.

The aerobic 10 × 1 minute HIIT protocol has also been developed by Gibala's group for broader targets including people with obesity and a sedentary lifestyle by decreasing the intensity from all-out performance to approximately VO2max and by increasing each workout duration from 30 seconds to 60 seconds [106, 107]. The number of repetitions was increased from 4-6 to 8-12 during the training course. This led to concomitant doubling of the total external energy expenditure. This protocol was utilized for patients with coronary artery disease by Currie et al. [108, 109] and in patients with CHF by Smart and Steele [110]. In a randomized contollled trial comparing the 10 × 1 minute HIIT and MCT, HIIT was not found to be superior in improving VO2peak. The intensity of exercise was similar to that of the 4 ×

4 minutes aerobic HIIT protocol. Each workout duration was as short as 1 minute, but the frequency was higher than that of the 4 × 4 minutes. There are fewer studies about the 10 × 1 minute HIIT protocol than those on the 4 × 4 minutes protocol. The duration of 1 minute at 89% (80%-104%) [109] might be rather short because the target heart rate cannot be attained within that time. RCTs that compare the superiority of multiple different HIIT protocols in improving aerobic and metabolic parameters are limited [111, 112]. Thus, researchers tend to select the protocol based on their experience, or they modify the exercise parameters of work and rest time. The effects of varying interval training intensities on the 40-km time-trial performance of trained cyclists were evaluated in a single study by Stepto et al [112], in which well-trained male cyclists were randomly assigned to 1 of 5 groups with different HIIT protocols (12 × 30 seconds at 175% PPO, 12 × 1 minute at 100% PPO, 12 × 2 minute at 90% PPO, 8 × 4 minute at 85% PPO, and 4 × 8 minute at 80% PPO). The cyclists completed 6 HIIT sessions over a 3-week period in addition to their habitual aerobic base training. The groups that followed the 12 × 30 seconds and 4 × 8 minutes protocols showed better improvement with respect to speed.

The aim of recent exercise trends is to obtain benefits with the lowest and shortest workload. Several groups have tried to establish shorter protocols in HIIT. These seem to be beneficial to the physical structure and fitness even in targets with lifestyle-related diseases, old age, or cardiac disorders. Matsuo et al [113]: The Japanese high-intensity interval aerobic training program: 3 sets of 2–3-minutes cycling at vigorous intensity (first and second sets: 3 minutes at 85%-90% VO2peak, third set: 3 minutes at 80%-85% VO2max) with 2-minutes active rest at

50%VO2peak between each set (healthy, sedentary young 20–30-year-old adults) [113]. This protocol was developed to control energy expenditure for astronauts participating in long-term space missions. Osuka et al [114]: The elderly Japanese male version of high-intensity interval aerobic training : 3 sets of 2–3 minutes cycling at 75%-85% VO2peak (first set: 3 minutes at 85% VO2peak, second set: 2 minutes at 80% VO2peak, and third set: 2 minutes at 75% VO2peak) with 1–2-minutes active rest at 50% VO2peak (first set: 2 minutes, second set: 1 minute) (60–69-year-old sedentary elderly men; mean age, 67.6 ± 1.8 years). A gradually decreasing load was planned for 2-3 weeks, aiming at the protocol described above. A significant aerobic and metabolic response was attained by the shorter protocol than the 4 × 4 minutes protocol with a completion rate of 100%. Alvarez et al. [115] During all training sessions, patients were instructed by exercise specialists to jog or run and walk at a steady pace, which should be controlled by maintaining a score of 15–17 (jogging/running) and < 9 (walking) in the 15-point rating of perceived exertion scale. The goal was to reach 90%-100% and 70% of their predicted reserve heart rate at the end of the jogging/running and walking intervals, respectively. The progressive HIIT protocol started with eight jogging/running intervals of approximately 30 seconds interspersed with approximately 120 seconds of low-intensity walking. To promote sufficient workloads for eliciting improvements throughout the 12-week follow-up, there was a 7%-10% increase in the high-intensity interval duration and a 4% decrease in the recovery interval duration every 2 weeks. There was also an increase of 2 exercise intervals every 4 weeks of follow-up. The total workout duration increased from 4 to 13.5 minutes (weeks 1–16). The total recovery duration ranged from 18 to 24 minutes (weeks 1–

16). The number of intervals ranged from 8 to 14 (weeks 1–16). The exercise duration ranged from 30 to 58 seconds. The target subjects were overweight/obese adult women aged 35–55 years with type 2 diabetes.

6.4 Study limitations

Limitations have been arisen by conducting this systematic review the most important of which are: The randomized clinical trials did not use the same methods to calculate the intensity of training session and ejection fraction variability. The protocols of intervention and the age of participants were widely heterogeneous. None of the included studies provided concealed allocation of participants. All of the included articles failed to describe blinding of subjects, therapists and assessors to treatment allocation. As a result, raises the possibility of performance bias. Although, there is an impression of publication bias because searching has only been conducted in three electronic databases. Moreover, only randomized clinical trials published in English have been searched for this systematic review. Consequently, the results may have been affected by publication bias because did not occur searching for unpublished trials.

Finally, most of the included studies involved a small sample without large-scale quality score, which likely influenced the objectivity and reliability of this systematic review.

6.5 Future studies

Left ventricular ejection fraction (LVEF) as a clinical index of myocardial contractility and its pumping action is a well-established predictor of mortality and long-term prognosis in acute myocardial infarction. However, exercise training is the core component of cardiac rehabilitation and secondary prevention of CAD and more cardiovascular diseases. There is a less body of evidence regarding the effectiveness of exercise training on LVEF in CAD patients. Previous published studies mainly studied this outcome in heart failure patients or they used a heterogeneous subject group with respect to the time gap between coronary event and start of exercise training or total duration of the program. The purpose of this study was to access the effect of structured high intensity interval exercise on LVEF in stable CAD patients. Future studies are likely to be designed to determine the appropriate intensity, duration and frequency of HIIT, which improves the quality of life on stable coronary artery disease patients.

7 Conclusion

To improve primary and secondary prevention methods in cardiovascular medicine, physical activity should be promoted as a first-line strategy despite new drug developments in the medical treatment field. Irrespective of disease severity, exercise leads to improvements in aerobic and metabolic capacity as well as cardiac function if performed with an optimal dose, frequency, and intensity. Despite the continuous recommendations by the American College of Sports Medicine and related professional societies worldwide, the effects of such recommendations on public awareness have been very limited. Many kinds of wearable heart rate monitors and accelerometers are commercially available. Although these state-of-the art products could motivate sedentary people and increase their frequency of exercise training or participation in sports events, more efficient and effective exercise training strategies are still required. Interestingly, high-intensity interval exercise protocols require shorter exercise duration to obtain the same benefit as that provided by moderate-intensity exercises. Furthermore, maintaining a high-intensity exercise workout for a longer duration could be preferred; high-intensity exercise can be realistically tolerated by people with sedentary lifestyle, obesity, old age, or cardiac disease only in the form of interval training. However, the risk of these protocols has also been a concern and more studies are warranted before these protocols are adopted for more common use. A supervised workout is mandatory to maintain high-intensity adherence until the participants become accustomed to the intensity and to heart rate measurements during physical activity by using a wearable heart rate monitoring portable device. High-intensity interval exercise as a part of cardiac rehabilitation aims to restore patients with coronary heart disease to health. However, left ventricular ejection fraction is clinically used as a predictor of long-term prognosis in coronary artery disease patients. There is a scarcity of data on the effectiveness of exercise-based cardiac rehabilitation on LVEF. The present findings provide a new insight into the superior effects of HIIT on EF in patients who suffer from CAD and may have important implications of exercise training in cardiac rehabilitation. Moreover, the development of global guidelines about the recommendation of HIIT in patients with cardiovascular disease should take priority in global health network. Based on the evidence revealed by this systematic review, it is concluded that recent literature worldwide has not, yet, carried through with the establishment of powerful recommendations and guidelines for HIIT in patients who suffer from cardiovascular disease. Finally, this review summarizes that HIIT seems to be safe and beneficial for CAD population, however not enough randomized clinical trials have been conducted yet to support these findings.

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Υπεύθυνη δήλωση Συγγραφέα

«Δηλώνω ρητά ότι, σύμφωνα με το άρθρο 8 του Ν.1599/1986, η παρούσα μεταπτυχιακή διπλωματική εργασία αποτελεί αποκλειστικά προϊόν προσωπικής μου εργασίας για διδακτικούς και ερευνητικούς σκοπούς στα πλαίσια του μεταπτυχιακού προγράμματος «Κλινική Εργοσπιρομετρία, Άσκηση, Προηγμένη Τεχνολογία και Αποκατάσταση» της Ιατρικής Σχολής του Εθνικού & Καποδιστριακού Πανεπιστημίου Αθηνών. Δεν προσβάλλει κάθε μορφής δικαιώματα πνευματικής ιδιοκτησίας και προσωπικά δεδομένα τρίτων με βάση την κείμενη νομοθεσία. Δεν είναι προϊόν μερικής ή ολικής αντιγραφής, αναπαραγωγής και αναδημοσίευσης. Τέλος, οι πηγές που χρησιμοποιήθηκαν περιορίζονται στις βιβλιογραφικές αναφορές πληρώντας όλους τους κανόνες της επιστημονικής συγγραφής, ηθικής και δεοντολογίας».