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REVIEW ARTICLE

Exercise Training: The Holistic Approach in Cardiovascular Prevention

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Abstract
Nowadays, there are robust clinical and pathophysiological evidence supporting the beneficial effects of physical activity on cardiovascular (CV) system. Thus, the physical activity is considered a key strategy for CV prevention. In fact, exercise training exerts favourable effects on all risk factors for CV diseases (i.e. essential hypertension, type 2 diabetes mellitus, hypercholesterolemia, obesity, metabolic syndrome, etc…). In addition, all training modalities such as the aerobic (continuous walking, jogging, cycling, etc.) or resistance exercise (weights), as well as the leisure-time physical activity (recreational walking, gardening, etc) prevent the development of the major CV risk factors, or delay the progression of target organ damage improving cardio-metabolic risk. Exercise training is also the core component of all cardiac rehabilitation programs that have demonstrated to improve the quality of life and to reduce morbidity in patients with CV diseases, mostly in patients with coronary artery diseases. Finally, it is still debated whether or not exercise training can influence the occurrence of atrial and ventricular arrhythmias. In this regard, there is some evidence that exercise training is protective predominantly for atrial arrhythmias, reducing the incidence of atrial fibrillation. In conclusion, the salutary effects evoked by physical acitvity are useful in primary and secondary CV prevention.

Keywords Type 2 diabetes · Insulin resistance · Sympathetic nervous system · Ischemic preconditioning · Physical activity · Leisure-time physical activity · Cardiac rehabilitation · Secondary prevention · Atrial fibrillation

1 Introduction

Cardiovascular (CV) prevention (primary and secondary) represent, nowadays, the principal objectives of the health care systems of the western countries. Usually, these goals are achieved through the control of the modifiable conventional CV risk factors, such as essential hypertension (EH), type 2 diabetes mellitus (T2D), hypercholesterolemia (H), obesity (OB), metabolic syndrome (MS), etc. In the last decades, it has become evident that beside to the pharmacological control of these risk factors, also the lifestyle changes play a key role in the CV prevention. In particular, the reduction of alcoholic intake, the smoking cessation, the caloric and salt restrictions, the regular physical exercise, the nutrient supplements (vitamins, micronutrients, natural antioxidants) etc. have been demonstrated to contribute to the reduction of CV events; and nowadays are highly recommended by the Scientific Societies as valid tools in CV prevention.

The regular physical activity and the exercise training, in the past, were poor considered for CV prevention; and were suggested by the physicians as a merely advice. On the other hand, these lifestyle interventions met a very low compliance from the patients. Nowadays, the scenario is completely changed. In fact, there are robust clinical and pathophysiological evidence supporting the beneficial effects of physical activity on CV system. Thus, the physical activity is considered as a key strategy in CV prevention [1–4].

The present review aims at (a) highlighting the main exercise-induced pathophysiological mechanisms underlying CV protection, (b) resuming the most significant clinical

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findings regarding the beneficial effects of exercise training in primary CV prevention, (c) highlighting the role of exercise training in cardiac rehabilitation programs, and (d) reporting the still controversial effects of physical activity on arrhythmogenic burden.

2 Pathophysiological Effects of Exercise on CV Homeostasis

In the Western Countries, the sedentary lifestyle is a very common attitude that accounts directly or, indirectly for the enhanced cardio-metabolic risk. Exercise exerts favourable effects on several pathophysiological mechanisms that are involved the pathogenesis of CV and metabolic diseases. In particular, the regular physical activity exerts different metabolic, neuro-hormonal, vasorelaxant, anti-inflammatory, and antioxidant effects, that act in concert to reduce the CV risk.

Insulin resistance (IR) is defined as the reduced biological response to the hormone, and usually is due to a defect of the insulin signal transduction machinery [5]. IR is the main pathogenic mechanism of T2D, MS, OB; moreover, it plays a key role also in the pathogenesis of EH, in the development and progression of target organ disease, and in the genesis of major CV events [6]. In general, IR can be considered as independent factor of CV risk. There are clear clinical and experimental evidence suggesting that exercise training interfere with the development of IR and improve insulin sensitivity [7]. This has several clinical implications, especially the prevention of T2D as well as its vascular complications. Low-grade chronic inflammation represents one of the principal mechanisms accounting for IR development; and, in general, for the increased CV risk [8]. Notably, the anti-inflammatory effects induced by exercise training could be responsible for the improvement of insuline sensitivity [9], mediated by the improvement of the redox balance. In fact, the exercise training evokes also the increase of gene expression and the synthesis of antioxidative molecules [10, 11]. Finally, this effect determines also the improvement of the rheologic properties of the blood, an antiplatelet action, and the increased fibrinolytic action. Altogether these actions contribute to ameliorate the CV risk profile.

Dysregulation of sympathetic nervous system, resulting in an adrenergic overdrive, and adrenergic receptors desensitization, represents a further mechanism that account for the increased CV risk [12, 13] and adverse CV prognosis [14]. There is clear evidence suggesting that exercise training reduces the burden of sympathetic dysfunction improving CV prognosis [15], not only through an improvement of sympatho-vagal balance, but also through the reduction of arrhythmogenic risk.

Although it is still debated, a further determinant of CV risk is the vitamin D deficiency [16, 17]. The principal sources of the vitamin D are the skin exposure to sun and diet. Thus, it is reasonable to hypothesize that the outdoor physical activities contribute to restore the levels of vitamin D. Noteworthly, it has been demonstrated that physical activity is associated with an increase of vitamin D levels, independently from sun exposure [18]. This indicates the pivotal role of the exercise in the vitamin D synthesis. In this regard, it has been proposed that exercise training stimulates the release of the vitamin from the adipose tissue storage [19].

Exercise training exerts cardioprotection also promoting more complex physiological processes such as the ischemic preconditioning (IP). This phenomenon consists in brief, repetitive, and sublethal ischemic stimuli. IP increases tolerance to a subsequent prolonged ischemic stress, and has a great pathophysiological relevance, since enhances the protection against the sustained ischemia-induced cell death to those organs that are composed of terminally differentiated cells, like brain and heart [20]. The remote preconditioning, is a feature of IP, and is defined as a protection from ischemia in one organ evoked by transient ischemia/reperfusion applied in a different (remote) organ [21]. Different molecules play a role of mediators of this phenomenon such as nitric oxide [22], opioids [23], adenosine [24], bradykinin [25]. There are experimental data that document the relevance of the remote ischemic precondition as mechanism that mediates the exercise-induced CV protection [26–28]. Interestingly, whereas IP and exercise training share many molecular pathways, the latter has been identified as a surrogate of IP [29].

In the Fig. 1 are summarized the principal mechanisms that account for the beneficial effects of the exercise training on CV system.

3 Exercise and Primary CV Prevention

The exercise exerts favourable effects on all determinants of CV risk. In particular, all forms of physical activities such as the aerobic (continuous walking, jogging, cycling, etc.) or resistance exercise (weights), as well as the leisure-time physical activity (LTPA) (recreational walking, gardening, etc.) have been demonstrated to prevent the development of the major CV risk factors, or to delay the progression of target organ damage, as well as to improve the cardio-metabolic risk.

3.1 Exercise and Type 2 Diabetes

The most convincing evidence regarding the beneficial effects of exercise in primary CV prevention come from studies that involved individuals at high risk to develop T2D or with overt diabetic disease. In particular the Diabetes Prevention Program Research Group demonstrated in a

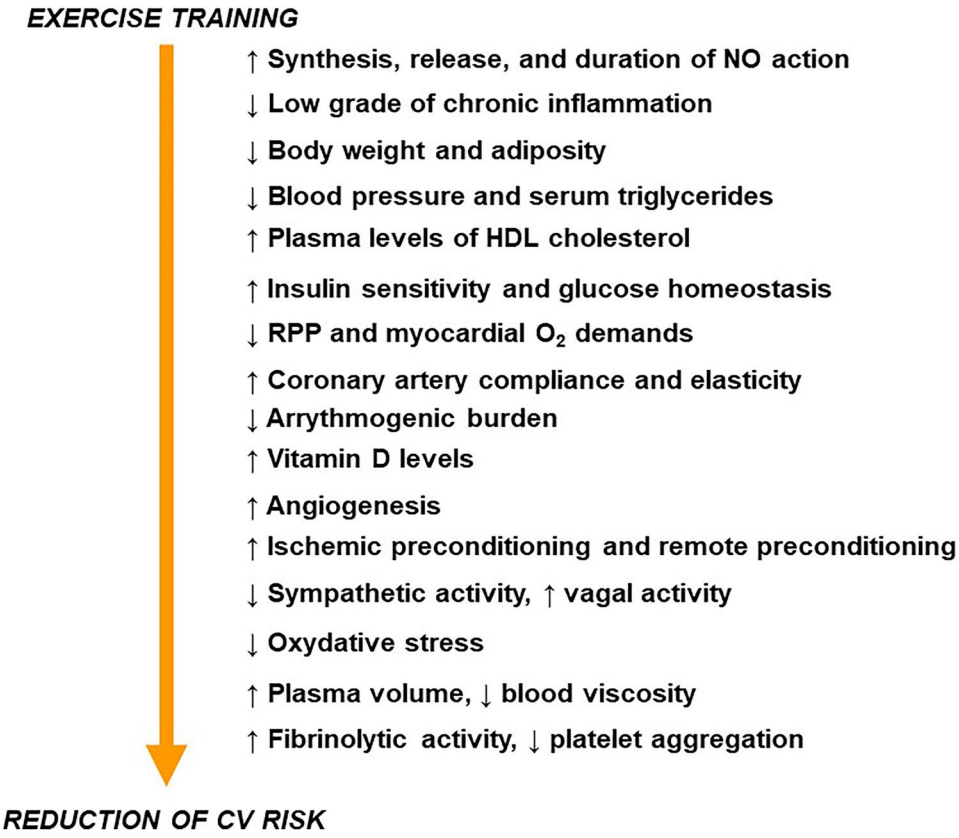

Fig. 1 Principal pathophysiological changes evoked by exercise training that account for the reduction of CV risk. *NO* nitric oxide, *HDL* high density lipoprotein, *RPP* rate pressure product, O_2 oxygen

longitudinal study, that recruited 3234 nondiabetic persons with elevated fasting and post-load plasma glucose, that were randomly assigned to 3 different treatments: placebo, metformin and lifestyle-modification program, (this latter included moderate intensity physical activity), showed, during a mean follow-up of 2.8 years, that the lifestyle-modification program was able to reduce the incidence of the T2D by 58% [30]. These results were confirmed by the Finnish Diabetes Prevention [31], and by other post hoc-analysis and by longitudinal studies [32, 33]. The beneficial effects of physical activity were summarized in different meta-analyses that clearly demonstrated also favourable effect of the LTPA the in the prevention of T2D. In particular, the analysis of 28 prospective studies, showed a reduction of risk to develop T2D by 26% in those subjects who performed at least 150 min/week of moderate physical activity, compared to sedentary subjects [34]. To note, that in T2D, several meta-analyses have demonstrated that regular physical activity is able also to improve the glycemic control [35, 36], the lipid and hemodynamic profiles [9, 37], and inflammatory pattern [38].

Unfortunately, exercise benefits in reduction of major CV events incidence in subjects with T2D are not demonstrated by clear evidence. However, indirect evidence seem to indicate that in T2D patients exist an inverse relationship between cardiorespiratory fitness and mortality [39, 40].

3.2 Exercise and Metabolic Syndrome

MS is a cluster of CV risk factors and is an independent determinant of CV risk. The MS is the result of the sedentary behaviour, and is considered the typical feature of IR. To note, that unlike the T2D that affects mainly adult subjects, MS has high prevalence in adolescents and young-adult individuals. This has an important clinical implication in terms of CV risk, emphasizing the role of lifestyle changes could have as the main tool for the CV prevention. It has been documented the beneficial effect of exercise training or LTPA in the prevention of MS. A meta-analysis, that evaluated 17 prospective studies that recruited 64,353 participants, showed that high intensity of LTPA was associated with a reduction of risk to develop MS by 20% [41]. These data were confirmed by a further meta-analysis that documented that, not only high intensity, but any amount of LTPA was associated with a reduction of incident MS. In particular, a reduction of 8% of risk to develop MS for each 10 increments of metabolic equivalent of task (MET) h/week of LTPA was estimated [42]. In addition, it has been documented that the exercise training exerts the favourable effects interfering also against the single components of MS. In fact, it has been reported, in a randomized controlled trial, hat analyzed 51 men and 53 women that exercise training reduced total and abdominal obesity, and increased lean

body mass, as well as ameliorated cholesterol-high density lipoproteins (HDL) and systolic blood pressure (SBP). At baseline, the criteria for the diagnosis of MS were present in 43.2% of the studied population, after 6 months of exercise training program, 17.7 and 15.1% in the exercise and in the control group, respectively, no longer had the criteria of MS [43]. Regarding the type of exercise, it has been reported that aerobic exercise, but not resistance exercise exerts a favorable effect on the all components of MS like waist circumference, fasting glucose, cholesterol-HDL, triglycerides and diastolic blood pressure (DBP) [44]. On the contrary, resistance exercise did not evoke any significant effect, However, it should be underlined that this notion could be due to limited data available.

3.3 Exercise and Obesity

OB is a key determinant of the CV risk. In fact, OB contributes to pathogenesis of all steps of continuum of CV disease, from development of cardiac hypertrophy [45] to the genesis of heart failure [46], from development of atherosclerosis [47], to the susceptibility of the atherosclerotic plaque [48] As for the T2D and MS, OB is an hallmark of the sedentary habits, and there is an inverse relationship between the physical activity and body mass index [49]. There are clear data that document in OB and overweight subjects the favorable effects of exercise training on weight reduction [50, 51]. However, in these subjects the exercise activity cannot be considered the unique strategy for weight loss, since its effect resulted to be modest (≈ 1.5 kg). Interestingly, in OB individuals the exercise training rather than on weight loss, seems to be more efficacious to reduce BP, ameliorate the metabolic asset and the quality of life [52]. On the contrary, the exercise activity seems to play a key role in the weight loss maintenance [53]. In this regard, it has been documented by a meta-analysis, that revised the results of 33 trials, that the treatment based on diet + exercise training, was more efficacious than diet alone in the keeping the weight loss [54]. These data were confirmed by the National Weight Control Registry that demonstrated that that long-term weight-loss maintenance requires the integration of LTPA, with hypocaloric diet [55]. Altogether these studies underlined the relevance of exercise training in weight-loss maintenance. In this regard, the American College of Sports Medicine that indicated "….after weight loss, weight maintenance is improved with physical activity > 250 min/weak" [56].

3.4 Exercise and Lipid Profile

Exercise training improves the lipid profile. High triglyceride (TG) levels are a feature of MS, and, as above mentioned, both exercise training and LTPA exert a favorable effect on the single components of the MS included the TG. The results of several studies are summarized in a recently published meta-analysis that analyzed the results of 48 studies, that included 2990 participants. The results of this analysis showed that the aerobic exercise training improved all lipid profile. Interestingly, the intensity of exercise was correlated with the reduction of TG, while the volume was associated with increase of HDL-cholesterol [57]. Non-alcoholic fatty liver disease (NAFLD) can be considered the hepatic manifestation of lipids disorder [58], and at the same time is an independent determinant of CV risk, To note that tit has been documented that the regular physical activity is also capable to improve the liver damage [59]. In particular, a recent meta-analysis that revised 15 controlled studies showed that aerobic exercise activity significantly improved the alanine aminotransferase (ALT) levels. This effect was associated with a reduction of intrahepatic TG and body mass index (BMI) [60], Low levels of cholesterol-HDL represent an independent risk factor for CV events. There are clear evidence that the exercise training is able to raise the levels of cholesterol-HDL. In particular, it has been demonstrated that the regular physical activity increases the plasma levels of HDL-cholesterol by 3–9% [61]. Consistently, a meta-analysis that revised 35 studies showed that physical activity was the most important determinant of cholesterol-HDL increase [62]. Beside these evidence, it has been also postulated the exercise training is also able to improve the function and metabolism of Cholesterol-HDL. However, this aspect needs to be deeper investigated. In summary, the beneficial effect of physical activity on the metabolic profile is an unquestionable clinical evidence.

3.5 Exercise and Hypertension

Exercise training exerts also favorable hemodynamic effects. In particular, it plays a role in the regulation of BP, in both normal subjects and in patients with EH. In particular, in a cross-sectional study it was documented that the physically active hypertensive patients had a lower 24-h and daytime DBP compared with the sedentary subjects [63]. The effects of exercise or the physical activity on office and ambulatory BP have been summarized in two meta-analyses. The first analysis that explored the effects of different types of exercise in 5223 individuals showed that all types of physical activities were able to reduce both office SBP and DBP. To note, that the magnitude of BP reduction, evoked training, was significantly higher in patients with EH (− 8.3/− 5.2 mmHg for SBP and DBP, respectively) in comparison with individuals with pre-hypertension (− 2.1/− 1.1 mmHg, for SBP and DBP) and normal subjects (− 0.75/− 1.1 mmHg for SBP and DBP) [64]. A further analysis that included 633 participants documented that aerobic exercise significantly reduced both day-time SBP and DBP (− 3.2 and – 2.7 mmHg, respectively), conversely, it

Table 1 Absolute changes of indexes of cardiovascular risk factors induced by exercise training

Parameter	
HbA1c (%)	− 0.5
Cholesterol-HDL (mg/dL)	+ 4
Waist circumference (cm)	− 3
Diastolic blood pressure (mmHg)	− 5
Systolic blood pressure (mmHg)	− 9
Body weight (Kg)	− 5

HbA1c glycated haemoglobin, *HDL* high density lipoprotein

did not affect the night-time BP [65]. The favorable effects of exercise training are not limited to the prevention and management of EH but also positively affect also prognosis, including the reduction of mortality. In general, there is the evidence that LTPS is inversely associated with all-cause mortality in both men and women [66].

In summary, it has been well documented the favourable effects of exercise training in primary CV prevention (Table 1). In this regard, the Scientific Societies, highly recommend practicing at least 150 min/week of moderate-intensity aerobic physical activity, or 75 min/week of high-intensity activity [67].

4 Exercise Training in Secondary CV Prevention

Cardiac rehabilitation is a multidisciplinary, multifactorial and comprehensive intervention used as secondary prevention of CV diseases [68]. The core component of cardiac rehabilitation is the assessment of patient' class of risk [69] together with dietary advice [70, 71], educational intervention [72, 73], psychological support [74], exercise training [75] and therapy management [69]. Nowadays great progresses have been made in drug therapy [76–80], devices [81–86], and diagnostic technologies [87–90], which allow for an even greater reduction of some risk factors. However, to further reduce risk of new CV events, it is important to act not only on optimization of therapy and its adherence, but also on other risk factors such as OB and lifestyle [91–93]. Among cardiac rehabilitation elements, exercise training showed to play a key role in improving quality of life and reducing morbidity in patients with CV diseases [94–97].

4.1 Pathophysiological Bases of Cardiac Rehabilitation

Mechanisms investigated work on the one hand on cardiac function and remodeling, on the other hand on inflammation and autonomic system [98]. After myocardial infarction, a sequence of events begins, divided into early remodelling and late remodelling [99], which result in alteration of cardiac structure and function. A 6-month exercise training program showed to improve statistically significantly systolic and diastolic left ventricular function and volumes and to reduce serum levels of NT-proBNP [100, 101], which, such as brain natriuretic peptide (BNP), is released from ventricular chambers when it occurs increase in filling pressure [102, 103]. The importance of this reduction is even more considerable because these markers are recognized morbidity and mortality predictors in coronary heart disease patients [104, 105]. Left atrium enlargement is a consequence of myocardial infarction, and it is predictive of atrial fibrillation onset, stroke and death [106, 107]. Exercise training proved to reduce, in addition to left ventricle, also left atrium remodelling and improve exercise capacity in patients with myocardial infarction [108].

About peripheral mechanism, adverse effects of adrenergic hyperactivation in cardiovascular diseases have been long investigated [109–111]. Several trials investigated exercise training capacity to reduce heart rate recovery (HRR) [112–114], i.e. heart rate fall in first minute after exercise, which is due to vagal tone increase and has been recognized as predictor of mortality in coronary heart disease patients [115, 116]. These effects on prognosis could be explained by recognized benefits of parasympathetic tone increase in patients with myocardial infarction: heart rate reduction at rest leads to decrease of cardiac work and myocardial oxygen demand [117], and in addition circulating acetylcholine could reduce norepinephrine release and catecholamines receptor affinity [118, 119], reducing myocardial exposure to cytotoxic effects of noradrenalin excess.

Moreover, exercise training showed to reduce plasma concentration of high-mobility group box-1 (HMGB-1) [120–124], a protein expressed in quiescent cells which acts as a chromatin protein but is also involved in inflammatory process after released from necrotic cells [125]. Increased HMGB-1 levels have been investigated for association with negative inotropic effects [126], genesis of microvascular thrombosis [127] and worsening in remodelling of left ventricle [128]. So, evidence that exercise training could reduce HMGB-1 levels helps to clarify one of the many mechanisms by which cardiac rehabilitation contribute to improve favourable cardiac remodelling. Furthermore, reduction in proinflammatory cytokines concentration in skeletal muscle and increase of antioxidative molecules production are observed in patients who performed exercise training [129–131].

An important characteristic of coronary artery disease is endothelial dysfunction, which caused pathological vasoconstriction [132, 133]: exercise training showed to improve endothelial function through upregulation of endothelial nitric oxide expression and resulting increasing

vasodilatation NO mediated [134, 135], also in patients with overt CV disease.

4.2 Cardiac Rehabilitation in CV Diseases

Favourable exercise training effects in coronary heart disease patients have been assessed also as regard to perfusion: patients enrolled in a 6-months exercise-based cardiac rehabilitation program early (about a week) after myocardial infarction showed a significant improvement in resting and stress wall motion and thickness at GATED-SPECT imaging [136, 137]. Different exercise training modalities have been investigated so far [138–147]. Before starting an exercise training program, a functional assessment (preferably using cardiopulmonary exercise testing) is indicated [148]. However, frail patients with CV diseases should be carefully evaluated by using specific tools [149–154]. Moderate continuous aerobic training is the oldest and most studied training modality [155, 156]; performed by using cycling or treadmill for about 20–30 min 2 or 3 times for week, maintaining a moderate intensity during effort (about 60–85% of peak heart rate or 11–14 on Borg scale) [148, 157]. Interval training is a kind of aerobic training which is generally performed using cycle ergometer, reaching high intensity (about 50–100% of peak VO_2 or maximum heart rate) for duration from 30 seconds to 4 minutes, followed by a recovery phase, lasting for few minutes [148, 158]. Conraads et al. compared interval training and moderate continuous training effects in two-hundred patients with coronary artery disease: investigators found similar improvements in endothelial function (measured as flow mediated dilation of right brachial artery) and exercise capacity (measured as peak VO_2 at CPET) in two groups [159].

Furthermore, interval training showed favourable ventricular remodelling, in addition to exercise capacity improvement, in patients with recent myocardial infarction [158]

A systematic review including 23 studies and 1117 patients (547 received high intensity interval training and 570 received moderate continuous training or usual care), investigated interval training safety in CV diseases patients [160]. In 11,333 training hours considered, only 1 major nonfatal CV adverse event (ventricular arrhythmia treating with electric cardioversion in a patient who refused cardioverter-defibrillator implantation before inclusion into the trial) occurred in interval training group, concluding that both interval and moderate continuous training appeared safe in patients with cardiovascular disease when performed in hospital setting. A different modality of training is resistance or strength training, which involves muscle contraction exercises against specific resistances, with aim of increase muscle mass and improve coordination [161].

Strength training alone showed to be effective and safe after myocardial infarction [162], but increasingly evidence suggest practicing in association to aerobic training to increase exercise capacity, muscle strength [163] and mobility in elderly patients with coronary artery disease [164].

Over the years, several meta-analyses have also been carried out to investigate effects of exercise training on mortality in patients with coronary artery disease.

The Cardiac Rehabilitation Outcome Study (CROS) in 2016 evaluated effectiveness of cardiac rehabilitation in patients with a recent cardiac event (were included studies about ACS, CABG or mixed population), treated with best actual therapies [165]: it demonstrated that cardiac rehabilitation was effective for reducing all-cause mortality, but not clear effects resulted for cardiovascular mortality and hospital readmissions, even if authors concluded that these last outcomes could be due to shift of potentially fatal re-infarctions to non-fatal events.

More recently, CROS-II meta-analyses, evaluating new evidences using the same inclusion criteria, confirmed the reduction in all-cause mortality in patients undergoing cardiac rehabilitation, showing in addition a favourable trend regarding cardiovascular mortality, but not clear trend were recognized about hospital readmission and cerebrovascular events [166]. However, a standardized protocol for cardiac rehabilitation should be defined in terms of training modality and duration. It could be reasonable that lifelong exercise training could attenuates left ventricular remodelling and other pathological consequences of myocardial infarction [167]. Notably, the effects of detraining evaluated in other cohorts of patients with increased cardiovascular risk showed that training suspension determine the loss of exercise-induced beneficial effects [168–175].

Therefore, studies providing long lasting and multifactorial cardiac rehabilitation programs were designed, aiming to reduce incidence of cardiovascular events following completion of rehabilitation and improve long term prognosis [176].

The multicenter randomized controlled GOSPEL trial showed reduction in cardiovascular mortality, nonfatal myocardial infarction and stroke in patients involved in a 3-years long intensive cardiac rehabilitation program after myocardial infarction, compared to usual care [177]. Patients undergoing to longer cardiac rehabilitation programs showed to maintain improvement in CPET parameters and cardiovascular risk profile, while impairment in the same parameters are observed in other group of patients at the end of usual exercise training [178].

Therefore, based on the above-mentioned evidence, exercise-based cardiac rehabilitation should be tailored according to the characteristics and needs of the patient, trying to include more training modalities to prevent cardiac remodelling, and to improve functional capacity and quality of life. Furthermore, it would be advisable for the duration to be longer as possible, to better reduce CV events onset and improve prognosis.

5 Exercise Training and Cardiac Arrhythmias

Physical activity has undeniable beneficial effects on the CV system and it also influences the cardiac electrical activity. Acutely, during exercise training, the release of catecholamines is responsible of the shortening of the action potential whereas in the long-term there is a parasympathetic tone enhancement and both conditions may enhance cardiac arrythmias [179].

Whether exercise training can influence the occurrence of atrial and ventricular arrhythmias has been a matter of debate. However, only for atrial arrhythmias there seems to be a protective effect whereas there are evidences supporting that physical activity can be a trigger for ventricular arrhythmias [180, 181].

5.1 Exercise Training and Atrial Fibrillation

As for the atrial arrhythmias, the relation of the exercise training with the atrial fibrillation (AF) has been the most investigated. The exercise training may include different activities and also different levels of intensity. In terms of cardiac excitability, there is a difference between endurance and strength exercise, indeed the former increases the oxygen uptake by increasing the heart rate and the cardiac output and decreasing the peripheral resistance, whereas the latter only modestly increases the cardiac output and greatly increases the peripheral resistance. These changes lead to a volume load for both ventricles in the endurance training and to a pressure load in the strength endurance [182].

Second, physical activity and AF are linked by a U-shaped relation, meaning that a moderate intensity of training can prevent AF whereas a more vigorous activity may promote this arrhythmia [183]. The study by Andersen et al. [184] is a large cohort study that investigated the incidence of AF and other arrhythmias over a 10 years follow-up period in 52,755 skiers who participated to the Vasaloppet, a 90 km cross-country skiing event. The investigators found higher incidence of AF and bradyarrhythmias in participants who completed more races and with faster finishing times, thus in more trained athletes, whereas no association with supra-ventricular tachycardia or ventricular tachycardia/ventricular fibrillation was found. These findings confirmed the results of previous case-control studies reporting that sport practice and in particular endurance sports represent a risk factor for the onset of lone AF [185–187]. The mechanisms leading to the onset of AF in the athlete's heart are several. First, endurance athletes have an enlargement of the left atrium diameter and of the left ventricular diameter related to an impaired diastolic function [188] as compared to controls. Second, the increased parasympathetic tone [189, 190] shortens the atrial refractory period and thereby facilitates re-entry and AF. Third, endurance athletes have greater atrial fibrosis [191] that at least in animal models is partially reversible after discontinuation of exercise training [192]. These changes that together account for the electrical and mechanical remodelling of the left atrium in athletes may be the substrate for the higher susceptibility to reentrant arrhythmias and in particular to AF. However, these changes can be observed only in highly trained individuals, whereas a moderate exercise has been proven to reduce the incidence of AF. The Cardiovascular Health Study [191] investigated the associations of leisure-time activity, exercise intensity, and walking habit with the incidence of AF in individuals $\geq$ 65 years over a follow-up period of 12 years. Of note, walking distance and pace were each associated with lower AF risk in a graded manner. Similar results were found in a cohort of younger individuals included in the Tromsø Study [193]. The investigators found that among a Norwegian cohort of 20,484 adults followed for a period of 20 years the moderately active individuals had a 19% lower risk of any AF and furthermore that a resting heart rate $<$ 50 b.p.m. was a risk factor for AF. Furthermore, it is noteworthy that physical activity is able to partially offset in men the risk of AF related to excess body weight as demonstrated in the Atherosclerosis Risk in Communities study [194]. Accordingly, the Ford Exercise Testing (FIT) Project demonstrated that in obese patients there is an inverse relationship between cardiorespiratory fitness and incident AF [195]. This was a large cohort study including more than 6400 individuals free from AF at baseline and underwent a treadmill test. Over a median follow-up of 5.4 years the investigators found a substantial dose–response relationship with a 7% lower risk of incident AF for every MET increase in cardio-respiratory fitness and the magnitude of the inverse association was greater among obese compared with nonobese individuals.

Lastly, exercise training may prevent the onset of AF by reducing BP, promoting weight loss, reducing glycaemic levels; indeed EH, OB and T2D represent risk factors for the onset of AF as they contribute to atrial electrical and mechanical remodelling, that represents the substrate for reentries [196, 197].

As for the effect of exercise training in patients who have already been diagnosed with AF, a plenty of studies have been demonstrating clear benefits. First, in patients with non-permanent AF the burden of arrhythmia is reduced by an aerobic exercise training. The study by Malmo et al. [198] was a randomized trial that measured via a loop recorder the burden before and after 12 weeks of aerobic interval training (four 4-min intervals at 85–95% of peak heart rate 3 times

a week) and demonstrated a marked reduction of the time in AF, that was accompanied by a reduction of symptoms severity and frequency and by an improvement in left atrial and ventricular ejection fraction, lipid values and quality of life compared to controls. The most recent ACTIVE-AF trial assessed the impact of a 6-month exercise programme combining supervised and home-based aerobic exercise on AF recurrence and symptom severity. The study included 120 patients with paroxysmal or persistent AF that were randomly assigned to the exercise intervention or to usual care. In the exercise group there was a lower rate of AF recurrence at 12 months and also a reduction of severity symptoms [in press]. Notably, exercise training in patient with AF is also associated with a reduction of hard outcomes such as all cause death as demonstrated by Proietti et al. [199]. In particular, among 2442 patients enrolled in the EURObservational Research Programme on AF (EORP-AF) Pilot Survey, lower rates of CV death, all-cause death, and composite outcomes were found in AF patients who reported regular and intense physical activity. Furthermore, the association between physical activity and the reduced risk of all- cause death was significant regardless of gender, older age ($\geq$ 75 years), presence of paroxysmal AF, and high thromboembolic risk (CHA2DS2-VASc score $\geq$ 2). A supposed mechanism is exercise capacity to improve VO_2 peak (a known prognostic factor) in patients with chronic AF suggesting that physical activity may be therapeutical in AF patients [200, 201].

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