Exercise effects on cardiovascular disease: from basic aspects to clinical evidence

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Abstract
Cardiovascular (CV) disease (CVD) remains the leading cause of major morbidity and CVD- and all-cause mortality in most of the world. It is now clear that regular physical activity (PA) and exercise training (ET) induces a wide range of direct and indirect physiologic adaptations and pleiotropic benefits for human general and CV health. Generally, higher levels of PA, ET, and cardiorespiratory fitness (CRF) are correlated with reduced risk of CVD, including myocardial infarction, CVD-related death, and all-cause mortality. Although exact details regarding the ideal doses of ET, including resistance and, especially, aerobic ET, as well as the potential adverse effects of extreme levels of ET, continue to be investigated, there is no question that most of the world’s population have insufficient levels of PA/ET, and many also have lower than ideal levels of CRF. Therefore, assessment and promotion of PA, ET, and efforts to improve levels of CRF should be integrated into all health professionals’ practices worldwide. In this state-of-the-art review, we discuss the exercise effects on many areas related to CVD, from basic aspects to clinical practice.

Keywords
Endurance exercise • Molecular mechanisms • Physiological adaptations • Mortality • Cardiovascular disease • Prevention

1. Introduction
Cardiovascular (CV) disease (CVD) appears, at least in part, to be due to inappropriate or poor dietary and other lifestyle habits, which can be summarized as maladaptive diet and lifestyle factors. A critical constituent element of lifestyle is physical activity (PA) and exercise training (ET). Discreet modifications in common CVD risk factors, mainly those related to inflammation, haemostasis, and blood pressure (BP), include countless significant benefits of PA on CVD, with important consequences on primary prevention of CVD.1 In effect, regular ET and a high level of physical fitness are correlated with decreased risks of myocardial infarction (MI) and stroke, CVD–related death, and all-cause mortality.2,3 Exercise is likely protective against coronary heart disease (CHD) events by reducing several physiological risk factors (i.e. elevated BP, obesity, hyperlipidaemia, and insulin resistance) and providing positive remodelling effects directly to the myocardium.3 Since it is recognized and well-known for centuries that being active is beneficial for the CV system in all populations, and in order to not reiterate the evident, we do not discuss here the history of ET in CV medicine, but provide a comprehensive review of the potential benefits of PA and/or ET by encompassing both basic molecular and clinical aspects. Isometric ET, i.e. muscle contractions with no change in the muscle length and no joint movement, scarcely affects volume load, stroke volume, or cardiac output, and minimally improve aerobic capacity or CV efficiency; therefore, the CV adaptations to isometric ET are different from those observed with dynamic ET (i.e. concentric and eccentric contractions in which the muscle shortens, generates force and the joints move). Although we are aware that practicing resistance training and maintaining an acceptable...
level of muscular strength is important to maintain a high cardiorespira-
tory fitness (CRF) and prevent CVD, we particularly focus on
one type of ET or PA, aerobic exercise, which is often referred to as
cardio training. Although there is a clear difference between the terms
PA (any movement requiring energy) and physical exercise or ET
(movement intended to maintain or increase physical health and/or
performance), in this manuscript, we will use interchangeably the terms
PA, physical exercise, aerobic ET, or simply ET since numerous studies
use these terms synonymously.

1.1 Conceptual framework of ET
In brief, a load of physical exercise or ET is essentially classified by
its type, frequency, duration, and intensity. ET can be performed
consistently (endurance), dynamically (e.g. cycling or running), or
statically. It can also be considered as exhaustive (aerobic or
anaerobic) or non-exhaustive. Depending on the athlete's fitness, ET
intensity and physiological demands will provoke certain physiological
stress levels and responses.

1.2 PA and ET: a treatment polypill and a
multisystemic-prevention CVD vaccine
The beneficial effects of regular PA/ET in promoting health and prevent-
ing CVD have been extensively documented. Physical exercise confers
salutary systemic effects in humans. Indeed, ET reduces the prevalence
of the most critical CVD-related risk factors, such as type 2 diabetes
mellitus (T2DM), hyperlipidaemia, obesity, and hypertension (HTN). In
effect, low levels of PA are associated with higher prevalence of all the
aforementioned CVD risk factors. A constellation of data supports the
routine prescription of exercise for all patients, and particularly for
patients with CVD, such as CHD and heart failure (HF). According to
up-to-date data, and from our point of view, physical exercise may rep-
resent a useful and practical prescription ‘drug,’ or even a ‘polypill,’ within
the armamentarium to treat CVD as well as a highly recommended ‘vag-
cine’ in CVD prevention, due to its cardioprotective effects (Figure 1)11
Finally, it should also be underlined that, while there is overwhelming
data on the association between exercise and lower CVD risk, there is
no large-scale randomized data to support actively prescribing high-
intensity endurance exercise (i.e. exercising at 70–85% of VO2max). Finally,
we must also keep in mind that high-intensity endurance exercise can be counterproductive to certain individuals.

2. Physiological CV adaptations in
response to physical exercise
2.1 Cardiac function and structure: the
athlete’s heart
The athlete’s heart, induced by the practice of long-term physical
exercise, is characterized by physiological adaptations, such as enlarged
left ventricle (LV) and increased LV muscle mass [LV hypertrophy
(LVH)], with normal or supranormal LV systolic/diastolic function.13-15
Greater ventricular diastolic chamber compliance and distensibility is
also commonly observed.16 This adaptations tend to disappear with ET
interruption. However, in pathological LVH, the septal wall thickness
decreases after only 3 months of detraining. The LV cavity dimension
returns to pre-training values after 1–13 years of ET cessation.
Although LV end-diastolic diameter can be persistently elevated for up
to 5 years of detraining, it is not accompanied by impaired LV function,
nor does it lead to adverse CVD events.19 Likewise, LV mass augmenta-
tion is usually associated with normal resting ejection fraction (EF),
whereas systolic volume is normal or augmented.20-23 In some individ-
uals, extreme endurance training and chronic participation in events,
such as marathons, ultra-marathons, long-distance bicycle races, and full
distance triathlons, has been associated with myocardial fibrosis, particu-
larly in the right ventricle and interventricular septum.24

2.2 CRF and CVD
CRF is closely linked to ET levels, and its relationship with CVD warrants
particular attention. CRF is a very useful prognostic tool, and indeed,
poor CRF is one of the most important CVD risk factors (Figure 2)26
High CRF itself is a robust indicator of low morbidity, low risk of death,
and good metabolic health.25 Cabanas-Sánchez et al.2 have recently
demonstrated that changes in the estimated CRF may predict the inci-
dence of biological CVD risk factors, particularly in patients with HTN
and T2DM. ET practiced regularly is the most effective strategy to im-
prove CRF, by increasing the mitochondrial content and desaturation of
myoglobin in skeletal muscle tissue, which ultimately improves skeletal
muscle oxidative capacity.28,29 An increase in CRF of only one metabolic
equivalent (MET) decreases the risk of CVD by 15%.30 CRF declines
with age, physical inactivity (PI), and sedentarism,30 while sitting time is
associated with CVD mortality.31 However, reaching moderate-to-high
CRF levels is associated with a reduced risk of CVD events.30

2.3 Modulation of autonomic function:
electrophysiological effects
Resting bradycardia is one of the most recognized adaptations to ET,32
resulting from a combination of (i) increased parasympathetic tone, (ii)
decreased response to adrenergic stimulation, and (iii) decreased intrin-
sic heart rate (HR).33 An increased parasympathetic tone also provokes
increased HR variability (HRV), then potentially lowering CVD morbidity
and mortality.32 HRV is a marker for the degree of activation of the effec-
tive vagal nerve to the heart.34 Regular ET augments cardiac parasympa-
thetic tone and improves HRV, including in patients with HF or T2DM,
restores normal β-adrenergic receptor equilibrium and protects against
ventricular fibrillation.35,36 ET also shortens cardiac action potentials by
activating adenosine triphosphate (ATP)-sensitive potassium channels,
which ultimately preserves myocardial energy.37 Low HRV has been as-
associated with impaired CV health and poor outcomes, such as increased
mortality in patients with MI or HF,38 or first CVD events in individuals
without apparent CVD.39 ET improves vagal tone by augmenting the
compliance of the blood vessels in barosensitive areas of the carotid
arteries, which makes them more distensible in response to BP incre-
ments,40 as well as increasing afferent signalling to the brainstem, activat-
ing the vagal nerve and inhibiting sympathetic activity to the heart.41
Finally, the autonomic nervous system, particularly increased vagal tone
induced by regular ET, is involved in protecting against life-threatening
arrhythmias, which will be further discussed below.

3. Molecular mechanisms involved
in CVD-ET benefits
As it has been shown above, a wide array of effects on CVD and its risk
factors can be attributed to different manifestations of long-term aerobic
physical exercise. The exact mechanisms through which these changes
take place at the molecular level are yet to be fully elucidated.42
However, an extensive body of research on this topic in recent years has led to the identification of different proteins, signalling molecules, and transcription factors involved in the exercise-induced CV function improvements.

### 3.1 Cardiac remodelling

Exercise has been found to stimulate the cardiac secretion of insulin-like growth factor 1 (IGF-1), which is closely related to ventricular hypertrophy.\(^\text{43,44}\) Rodents with elevated levels of IGF-1 presented with heavier hearts, with an increase in both the size and number of cardiomyocytes,\(^\text{45,46}\) whereas mice with a genetically induced deficiency of the IGF-1 receptor were unable to obtain these benefits following aerobic training.\(^\text{47}\)

IGF-1, along with neuregulin 1, which is also up-regulated by exercise,\(^\text{48}\) activates the phosphoinositide-3 kinase (PI3K)/serine-threonine kinase (AKT1) pathway. PI3K is a particularly interesting marker, since it plays a role in physiological cardiac hypertrophy, but is absent from pathological remodelling, thus differentiating both phenomena.\(^\text{49}\)

Downstream of this metabolic cascade is AKT1, which is also critical for cardiomyocyte growth.\(^\text{48}\) More specifically, AKT1 knockout mice did not experience adaptations when physically trained or treated with IGF-1.\(^\text{50}\)

Additionally, AKT1 down-regulates the expression in the nucleus of the transcriptional factor CCAAT-enhancer-binding protein β, which in turn stimulates cardiac myocyte hypertrophy and proliferation.\(^\text{51}\) This relation seems to be mediated by CBP/p300-interacting transactivator with ED-rich carboxy-terminal domain 4, a transcription factor that has recently been linked with inhibition of adverse cardiac remodelling.\(^\text{52}\)

### 3.2 Metabolic optimization

It has been extensively demonstrated in experimental models that ET has the potential to improve cardiac metabolic disturbances induced by T2DM and obesity.\(^\text{53,54}\)
As exercise demands an increase in the ATP requirements not only in the skeletal muscle but also in the myocardium, it becomes necessary to enhance the energy generation capability of the cardiomyocytes. The main mechanism to achieve this is mediated by the peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), a transcription factor that is also present in homeostatic thermoregulation.\textsuperscript{55,56} Its imbalance has been linked with different disorders, such as obesity, diabetes, and cardiomyopathy.\textsuperscript{57} Exercise increases the concentration of PGC-1α in the heart,\textsuperscript{58} where it promotes mitochondrial biogenesis and the expression of genes related to fatty acid oxidation, oxidative phosphorylation, and ATP synthesis,\textsuperscript{59} which is key in exercise-mediated cardioprotective effects. In addition, the transcriptional activity of PGC-1α can be directly increased by AMP-activated protein kinase (AMPK), a protein that is key for the equilibrium between anabolic and catabolic pathways regulating the energy availability in the cardiac tissue.\textsuperscript{60} Sirtuin protein that is key for the equilibrium between anabolic and catabolic pathways regulating the energy availability in the cardiac tissue.\textsuperscript{60} Sirtuin (Sirt) 1 and Sirt3, proteins linked to oxidative stress response and fibrosis resistance, also activate both AMPK PGC-1α.\textsuperscript{61}

At the mitochondrial level, proline dehydrogenase (PRODH) has recently been identified as an important regulator of normal mitochondrial function in hypoxic environments.\textsuperscript{62} In murine models, the deficiency of PRODH is present in HF and was linked to increased levels of CVD markers.\textsuperscript{63} Importantly, ET re-establishes its levels in an animal model of HF, representing a target of exercise in failing hearts.

### 3.3 Angiogenesis

The catecholamines epinephrine and norepinephrine that are released into the blood flow and into the heart directly after aerobic exercise, couple with the β3-adrenergic receptors of the cardiac tissue, resulting in the phosphorylation of the endothelial nitric oxide (NO) synthase (eNOS).\textsuperscript{64} The phosphorylated eNOS is active, and it liberates NO locally and back into the bloodstream, stimulating angiogenesis and reducing myocardial fibrosis.\textsuperscript{65} Likewise, vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α), both angiogenic factors induced by ET, play a central role in inducing endothelial cell mitosis and stimulating capillarization.

### 3.4 Protection against ischaemia-reperfusion injuries

Exercise-induced adaptations of the cardiac tissue have also been shown to act as a protective agent following acute ischaemic events, with a reduction in the infarcted area, cardiomyocyte apoptosis, and fibrosis. Exercise may mitigate cardiomyocyte death due to myocardial ischaemia-reperfusion (IR) and simulate the positive, cardioprotective effects of ischaemic preconditioning by reducing myocardial damage.\textsuperscript{2}

Some of the mechanisms previously described also play a part in the protection of the heart. In addition, the oxidative stress induced by exercise promotes the expression of heat shock protein 72, which shields the cardiac tissue from contractile dysfunction and infarction.\textsuperscript{66} Moreover, the HIF-1α is a transcription factor that is strongly activated after acute or chronic exercise that exerts an ischaemic/hypoxia preconditioning in the heart, by means of a complex mechanism involving the regulation of mitochondrial function, of reactive oxygen species (ROS) and vascular remodelling.\textsuperscript{67}

In mice after suffering a large MI, exercise attenuates global LV remodelling and dysfunction by normalizing MI-induced increase in myofilament Ca\textsuperscript{2+}-sensitivity and thus improving myofilament function. These effects were PKA-mediated and related to improvements in β1-adrenergic signalling. Exercise reduced diastolic Ca\textsuperscript{2+}-concentrations had no effect on Ca\textsuperscript{2+}-transient amplitude, which indicates that the improved LV and cardiomyocyte shortening were mainly due to myofilament function improvements.\textsuperscript{66} Moreover, these exercise-related effects on LV remodelling and dysfunction depend critically on endogenous eNOS expression.\textsuperscript{67} de Waard and Duncker\textsuperscript{68} also observed in an acute MI model that ET before MI decreases post-MI mortality. Likewise, the infarct area was thicker, whereas interstitial fibrosis and apoptosis in LV myocardium were blunted.

It is important to highlight that the processes described thus far do not take place independently, since these metabolic pathways are intertwined, resulting in an integrated response to exercise. For instance, P3K coordinates hypertrophic and metabolic adaptations,\textsuperscript{69} and both AMPK and AKT-1 are able to perform eNOS phosphorylation\textsuperscript{70,71} and the latter also presents cardioprotective functions, inhibiting cardiomyocyte apoptosis and preserving cardiac function.\textsuperscript{72,73} Additionally, the balance of NO plasma levels is crucial to ensure that the exercise-induced protective mechanisms against IR damage are operative.\textsuperscript{63} Likewise, the cardiac response to exercise in the context of IR injury is also affected by circulating levels of myokines (e.g. irisin and myonectin).\textsuperscript{74} This issue will be further discussed in a separate section.

### 3.5 Oxidative stress, antioxidant defence, and inflammation

The capacity of physical exercise to reduce ROS and inflammatory cytokines might be of particular relevance, given that different conditions associated with an increase in CVD risk, such as dyslipidaemia or insulin resistance, have a concomitant increase in oxidative stress and inflammation status.\textsuperscript{74}

It is well-known that mitochondrial dysfunction provokes increases in oxidative stress levels, which in turn cause systemic damage.\textsuperscript{25} As such, the increase in ROS that causes oxidative stress is associated with different manifestations of CVD\textsuperscript{75} and plays an important role in endothelial dysfunction.\textsuperscript{64,76} Although exercise acutely raises the mitochondrial ROS production, the exercise-related increase in the efficiency of antioxidant systems buffers this initial rise, resulting in a net loss of oxidative load.\textsuperscript{78} However, after about 50–60 min of continuous strenuous exercise, the ongoing generation of ROS outstrips the buffering capacity, resulting in systemic oxidative stress. Yet, when facing an episode of IR, which is characterized by an increase in the oxidative stress and inflammatory levels resulting from the absence of oxygen in the heart,\textsuperscript{79} the cardiomyocyte of a trained subject is more resistant to injury due to the improved mitochondrial antioxidant capability.\textsuperscript{80}

Inflammation is a controversial topic in cardioprotection. It is supposed that inflammation increases during IR and provokes cardiomyocyte damage, while PA decreases inflammation and protects the heart.\textsuperscript{81} For instance, both interleukin (IL)-6 and IL-10 increase with exercise and might be implicated in cardioprotection. Exercise-induced up-regulation of IL-6 and circulating levels of IL-6 receptors and the phosphorylated forms of p44/42 MAPK (Thr202/Tyr204) and p38 MAPK (Thr180/Tyr182) have been associated with an attenuation of IR-induced necrosis and arrhythmias, which suggest that these may also be mechanisms for cardioprotection.\textsuperscript{82} Administering IL-10 exogenously reduced myocardial infarct size and reduce neutrophil adhesion to vascular endothelium,\textsuperscript{83} while incrementing its circulating levels may prevent LV remodelling.\textsuperscript{84,85}
3.6 Calcium handling and cardiomyocyte contractility and relaxation

In animal models ET re-establishes both the abundance and activity of sarcoplasmic reticulum Ca²⁺ ATPase2a (SERCA2a) and its regulatory proteins (i.e., Ca²⁺/calmodulin-dependent protein kinase II) that control excitation–contraction coupling. Restoring SERCA2a levels improves myocardium contractility in older rats.⁸⁷ In aged rodents, ET also restores the levels and activity of SERCA2a, calcium handling, and cardiomyocyte contractility and relaxation.⁸⁸,⁸⁹

3.7 Emerging concepts and active areas of research in exercise science

3.7.1 microRNA

All the previous adaptations are based on a series of changes in the genetic regulation and transcription processes that initiate a cascade of genetic regulatory mechanisms. Additionally, small, non-coding fragments of RNA, denoted as microRNA (miR), have the potential to modulate the expression levels of up to 60% of all human genes.⁹⁰ miR can circulate in urine, blood, or plasma and, therefore, they are capable of fulfilling an endocrine function.⁹¹

The exact relationship between miR and different manifestations of exercise in humans is still unknown, but initial trials seem to point towards a potential dose–response relationship between these factors.⁹² Additionally, the efforts to catalogue the existence and function of all human miR are still ongoing. Stimulation of miR-17-3p by means of PA results in increments of hypertrophy in the cardiomyocytes and improves ischaemic protection, indirectly acting upon the PI3K-AKT1 cascade.⁹³ On the other hand, exercise decreases the levels of miR-233, which has been shown to inhibit cardiac hypertrophy, although, unlike PI3K or AKT, it does not allow the discrimination between physiological or pathological hypertrophy.⁹⁴

3.7.2 Myokines

Muscle was traditionally regarded as a merely mechanical organ. However, more than 600 signalling molecules secreted by myocytes during muscular contraction have been unveiled throughout the present century. These cytokines, known as myokines, are associated with muscular contraction and serve autocrine, paracrine, and endocrine purposes.⁹⁵ Three myokines have recently been associated with a cardiac response: irisin, myonectin, and follistatin-like 1 protein (Fst1). Irisin acts as a protective agent of cardiac tissue against IR injuries by means of a scavenging mechanism of the ROS,⁹⁶ although its excess can trigger an increase in oxidative stress and apoptosis.⁹⁷ Mice with an intact expression of myonectin showed a reduction in the infected area following an ischaemic procedure compared to their knockout counterparts.⁹⁸ Importantly, myonectin is up-regulated by ET, protecting the heart from IR injury.⁹⁹ Fst1 has been proposed as a potential mediator of exercise-induced cardioprotection.⁹⁹ This molecule is secreted by both the skeletal and cardiac muscle cells, so it can also be considered as a cardiomyokine.¹⁰⁰

Other myokines have also been suggested to be involved in exercise-induced cardioprotection, such as meteorin-like protein, an exercise-related myokine that improves glucose tolerance and stimulates thermogenesis.¹⁰¹ Fibroblast growth factor 21, a factor induced by the PI3K–AKT pathway that acts protecting muscle tissue against insulin resistance and increases brown fat thermogenesis,¹⁰² and musclin or osteocrin, a myokine that may improve CRF by activating mitochondrial biogenesis.¹⁰³ Exercise-induced benefits through sestrins (SESN) pathway are also relevant at the cardiac level,¹⁰⁴ especially in the elderly.¹⁰⁵ Loss of SESNs activity has been related to fat accumulation, mitochondrial dysfunction, and cardiac arrhythmias, which is why inactivity provokes accumulation of visceral fat, inflammation, insulin resistance, atherosclerosis, neurodegeneration, and tumour growth.¹⁰⁶ SESNs are involved in p53 and peroxiredoxins (PRX) signalling pathways.¹⁰⁷ In effect, the stress-inducible SESNs protein family is crucial in PRX regeneration. Exercise reduces age-related changes in p53 activity and raises its circulating levels, which ultimately induces protective effects in cardiac muscle. Likewise, exercise up-regulates PRX isoforms in cardiac muscle cells. Since the use of certain types of exercise is not a viable option for many patients with cardiac diseases, further research of molecules targeting cardiac SESNs is highly encouraged to reverse certain cardiac conditions.

3.7.3 Atrial and B-type/ventricular natriuretic peptides: exercise ‘Sacubitril-Like effect’

Important cardiokines involved in CV health are both the atrial and B-type/ventricular natriuretic peptides (ANP and BNP, respectively). Both cardiokines are released under atrial and ventricle stress, which activate downstream receptors leading to vasodilation, natriuresis, and diuresis. ANP and BNP are cleaved and inactivated by a ubiquitous membrane-bound endopeptidase, nephrinys. Inhibition of nephrinys leads to reduced breakdown and increased concentration of ANP and BNP. Interestingly, the drug sacubitril is a produg nephrinys inhibitor used in combination with valsartan to reduce the risk of CVD events in patients with chronic HF (NYHA Class II-IV) and reduced EF. Acute exercise increases cardiac output and ANP secretion.¹⁰⁸ It has been reported that ANP and BNP secretion increases during exercise.¹⁰⁹,¹¹⁰ Hamasaki et al.¹¹¹ also reported that circulating BNP levels were positively associated with PA levels. As a holistic view of the potential effects of exercise on the CV system further than the classic ones, these cardiokines should not be overlooked since they represent an important contributor in improving CV health. In effect, we can here suggest an exercise-induced ‘sacubitril-like effect’, which ultimately leads to reduced clearance of biologically active natriuretic peptides.

3.7.4 Cardiac regeneration capacity

Exercise can play an adjuvant role as regenerative medicine therapy by stimulating certain stem cells named circulating angiogenic cells (CAnCs), which are inversely associated with the risk of CVD.¹¹² Likewise, endurance ET increases telomerase activity and telomere length, which are directly involved in cellular senescence and regenerative capacity.¹¹³ From 17 to 90 years of age, we progressively lose ~30% of cardiomyocytes.¹¹⁴ The rate of cardiomyocyte turnover is very low (between 0.3% and 1% per year).¹¹⁵ Cardiomyocyte regeneration can be stimulated through different techniques.¹¹⁶ Exercise increased the formation of new cardiomyocytes in adult mice, which indicates that ET can activate the adult mammalian heart’s endogenous regeneration capacity.¹¹⁷ Although it remains controversial, ET stimulates the proliferation of CAnCs in subjects with CVD, with high-intensity ET being the most potent stimulus.¹¹⁸ From a mechanistic point of view, HIF-1α, VEGF, IL-6, and NO are among the factors mainly involved in CAnCs overstimulation.¹¹⁹

Finally, regular PA may overexpress ‘cardioregenerative’ myokines, such as Fst1, and that is why patients with CVD should be highly encouraged to stay fit and active.¹²⁰ Telomerase activation or NRG1-dependent activation of receptor tyrosine-protein kinase ERBB2 and
ERBB4 signalling are among other mechanisms implicated in exercise-induced myocardial repair after MI.121,122 Although this is still an evolving concept, it may represent a promising approach to prevent cardiac damage by means of ET-activated mechanisms.

4. Exercise effects on CVD risk factors

Aside from the effects on the molecular mechanisms directly involving CV structure and function, PA also attenuates different CVD risk factors, thus playing a crucial role in both primary and secondary prevention of CVD.

4.1 Plasma lipids and atherosclerosis

Higher plasma concentrations of atherogenic lipids expressed as total cholesterol, low-density lipoproteins (LDL), or the ratio of total cholesterol to high-density lipoproteins (HDL), are associated with increases in adverse CVD events.123 Moreover, a decrease in LDL levels results in a reduction of CVD risk, independently of the baseline level.124

The effects of PA on the lipid profile are not consistent since they appear to depend on the type, intensity, and duration of the ET, with diet as a potential confounding factor.125 Recent meta-analyses focused on different activity modalities have found disparate results, with benefits arising from aerobic training,126 particularly when performed at a high intensity,127 whereas no differences or minor improvement were noted in the lipid profile of either overweight or normal weight population following high-intensity resistance interval training.128 These effects, however, can be small even with high training volumes.129,129

Additionally, the inclusion of an exercise routine in dyslipidaemic subjects does not confer further LDL benefits than those achieved with statin administration.130

The degree to which the changes in the lipid profile contribute the ET-related reduction in CVD remains unclear.7 However, recent research suggests that the relationship between PA and atherogenic risk may not be merely limited to the modulation of plasma concentrations. HDL particle size affects cholesterol efflux capacity.131 In vitro cholesterol efflux capacity correlates with CVD prevalence, independently of HDL concentration.131 Therefore, the increase in HDL size observed after training can play a role in CVD prevention.132 Additionally, PA could also reduce atherosclerotic progression by altering the homeostasis of the arterial wall.7

The exact mechanism through which exercise affects the plasma lipids and the atherogenic risk is yet to be fully elucidated.133 Some proposed pathways involve the stimulation of lipoprotein lipase activity or an increase in the expression of ATP-binding cassette transporter A1 and liver X receptor-alpha.134,135

4.2 Insulin sensitivity

Insulin resistance is a strong mediator in the previously mentioned association between the lipid profile and CVD risk. An inadequate sensitivity to insulin of fat tissue causes it to release free fatty acids that trigger an increase of triglyceride and very-LDL production in the liver, resulting in a lipid imbalance which, in turn, provokes an increase in CVD risk.136 A reduction in HDL levels is an inherent component of insulin resistance and contributes to the formation and progression of atherosclerotic plaques.137 The compensatory hyperinsulinaemia, together with the increased sympathetic activity present in T2DM patients, can also elicit vascular smooth muscle proliferation and vasoconstriction of arterioles, contributing to the development of HTN and peripheral artery disease.138,139

Previous meta-analyses have shown that PA is able to improve glycemic control and insulin sensitivity.140,141 Aerobic exercise has shown to be more efficient than resistance exercise or a combined training for improving glycemic control.142

4.3 BP and vessels

Elevated BP or HTN is a highly-prevalent condition (with nearly a third of the population affected)131,144 that poses a significant risk for various CVD events, such as HF, MI, and stroke.133 ET reduces arterial stiffness, measured as pulse wave velocity, in adults with HTN.145 Higher intensity levels of ET provoke greater diminutions in resting BP than does lower intensity exercise.7

Acutely, PA elicits an increase in both HR and cardiac stroke volume, resulting in an augmented cardiac output which, in combination with the elevated peripheral vascular resistance produced by muscular contractions, causes an increase in mean BP.146 In contrast, the chronic adaptations to aerobic training include a decrease in resting and ambulatory BP of ~3 mmHg, as shown in previous meta-analyses.147,148 Even though this effect might seem clinically irrelevant, a recent multicentric study with over 15,000 participants showed that reductions in this parameter as small as 1 mmHg are associated with a significant decrease in the incidence of HF.149 In fact, this exercise-mediated reduction in BP has been proposed to be potentially higher than that of single antihypertensive drugs and similar to those of their most common treatment combinations.133

Different mechanisms contribute to the reduction of BP observed after long-term exercise, such as variations in artery diameter,150 prevention of arterial stiffness,151 inhibition of inflammatory status,152 reductions in sympathetic nervous activity,153 and restoration of the baroreflex sensitivity.154 However, the main factor associated with the anti-HTN properties of exercise seems to be a chronic reduction in peripheral resistance,155 resulting from an improved expression and activation of eNOS.156 The subsequent increase in NO generates a reduction in the tone of the vascular smooth muscle.157

5. Clinical evidence of ET-associated positive effects on CVD

5.1 Coronary artery disease (CAD)/CHD

Currently, it seems obvious that ET represents a key element of primary and secondary prevention in CHD. The connection between PI and CHD is well documented.158 The current burden of PI-related deaths caused by ischaemic heart disease is ~10% (5.46 out of 5.14 million deaths).159 ET increases coronary blood flow and myocardial oxygen delivery, reducing angina and MI. Coronary artery disease (CAD) patients who participated in exercise-based cardiac rehabilitation programmes have a 27% reduction in total mortality compared to those who received usual care.160 Moreover, ET improves the patient’s ability to conduct daily living activities and their quality of life (QoL).160 A meta-analysis from 48 studies with a total of 8940 patients who had MI, angina, CAD documented by angiography, or undergone percutaneous coronary intervention (PCI), showed a decrease of 20% in total mortality and of 26% in CVD mortality as a result of ET intervention.161 Similarly, Hambrecht et al.162 demonstrated that regular ET significantly increases
both peak oxygen uptake and event-free survival rate at 12 months follow-up in CAD patients who underwent PCI in comparison with those receiving medical therapy. In patients who enrolled in a PA programme after a PCI vs. those who remained inactive, the Exercise Training Intervention After Coronary Angioplasty trial reported increases in peak oxygen uptake of 26%, improvements in QoL of 27%, and reductions in CVD events of 20%, i.e. reductions in MI and hospital admissions.  

5.2 Stroke
Since ET has beneficial effects on many risk factors for stroke, such as HTN, dyslipidaemia, T2DM, obesity, excessive alcohol consumption, and tobacco use, physically active individuals have lower stroke risk than those with a low level of PA. A greater CRF is inversely associated with stroke mortality. Lee and Blair showed a 68% lower risk of stroke and death among individuals with higher CRF than those with lower CRF, remaining after adjusting for confounding variables, such as smoking, alcohol consumption, BMI, HTN, T2DM, and CAD history, while it was also demonstrated that the risk of stroke immediately after a coronary event is significantly higher among patients with lower CRF.  

5.3 Heart failure
The benefits of aerobic ET in HF have been extensively demonstrated, implicating both central and peripheral modifications. These benefits are clinically translated to increased exercise capacity, anti-remodelling effects, and reduced morbidity and mortality. ET has been proven to be safe and with no adverse effects on LV remodelling in HF patients. Although a Cochrane meta-analysis did not find significant differences in total mortality at 1-year follow-up in patients who underwent vs. those who did not exercise, the authors found a reduction in both overall and HF-related hospitalizations. The ExTraMATCH II meta-analysis also reported important benefits regarding CRF and QoL. The HF-ACTION trial concluded that ET was associated with an 11% lower adjusted risk for all-cause mortality or all-cause hospitalization and a 15% lower adjusted risk for CVD mortality or HF hospitalization in 2331 patients with HF with reduced EF. 

ET should be recommended to patients with HF regardless of their NYHA class. The beneficial effects of ET are also present in patients with impaired LV EF and are directly associated with patient compliance and ET intensity. Since the beneficial effects of ET are lost within few weeks after stopping ET, adherence is crucial. Finally, it is now well-known that certain HF patients do not respond to exercise. Accordingly, ET programmes should be specifically tailored to those individuals, possibly with higher intensity ET.  

5.4 Hypertension
HTN is the most prevalent, modifiable, and costly CVD risk factor. ET reduces both resting and ambulatory BP. For this reason, PA/ET is a cornerstone lifestyle and non-pharmacologic therapy for HTN. One bout of aerobic exercise consistently lowers both office and ambulatory BP of hypertensive adults for up to 2 h during the post-exercise period. However, this effect is variable in magnitude and duration, suggesting that individual and exercise characteristics might contribute to the variability of the aerobic post-exercise hypotension response. This wide range in the BP reduction magnitude associated with ET may in part be due to a paucity of studies on the effects of ET on HTN. Also, many studies performed on anti-HTN effects of ET are conducted in small samples and in individuals without HTN.  

Regarding regular aerobic ET practice, it has been found to significantly reduce both the office and ambulatory BP of hypertensive individuals. Thus, the final consensus is to practice 30 min/d or more of moderate-intensity aerobic exercise (i.e. exercising at 60–70% of VO2max) to a total of 150 min/wk or more for adults with pre- to established HTN.  

5.5 Cardiac arrhythmias
The risk of atrial fibrillation (AF) and ventricular arrhythmias is lower among physically active individuals. Exercising according to the guideline’s recommendations, i.e. >500 MET-min/wk, is associated with a reduced risk of AF probably due to increased risk factor control, preserved cardiac function, and lower exposure to the potential arrhythmogenic effects of inflammation and oxidative stress. 

The repeated exposure to extreme endurance exercise has potential arrhythmogenic effects, thereby increasing the risk of AF. Several studies indicated that long-term practice of very high doses of endurance exercise (i.e. those athletes who exercised a large part of their lives) is associated with a higher risk of AF. The association might be particularly strong in competitive athletes. Although more mechanistic studies are needed, potential factors by virtue of which long-term endurance exercise might trigger AF in previously ‘normal’ hearts include left-atrial enlargement, LVH or dilatation, and an increase in parasympathetic tone. The association of AF with strenuous exercise remains a topic of concern that should be clarified in future studies. An 11–22% risk reduction of ventricular arrhythmias among physically active individuals (range: 500–2500 MET-min/wk) has been reported, most likely as a consequence of the stabilization and regression of atherosclerosis and a more favourable autonomic balance. Interestingly, in an experimental model of dogs that were susceptible to ischaemia-induced ventricular fibrillation after suffering a MI, the animals showed a restoration of ryanodine receptor (RyR) channel activity mediated by the exercise-induced reduction in calcium/calmodulin-dependent protein kinase type II-mediated hyperphosphorylation of RyR at Ser2814, which Limited the spread of unstable cardiac electrical signals and thus preventing malignant arrhythmias. The association between PA and the incidence of bradyarrhythmias was also evaluated, concluding that bradyarrhythmias were not more common with higher volumes of total PA. They found that vigorous PA (500–2500 MET-min/wk) was associated with a 9–18% lower risk of bradyarrhythmias in women. Thus, higher PA may be associated with a preservation of sinus node function and AV nodal conduction.  

5.6 Gut microbiota-related CVD
Gut microbiota plays an important role in CVD, since it has been previously associated with certain microbial metabolites and gut microbiota. Recent studies implicate the gut microbiota in BP regulation, atherosclerosis and thrombosis development, HF, and cardiomyopathy. In effect, it has been recently demonstrated that gut microbiota changes are associated with the development of HF, which supports restoring gut microbiota to prevent HF. Increased production of the microbial metabolite trimethylamine N-oxide, endotoxaemia, and/or bacterial translocation may increase the risk of CVD. Habitual PA, aerobic ET, and high CRF can increase microbiota diversity and/or modulate the gut microbiota in effect, its composition may also influence ET adaptation and athletic performance. The alterations in the
composition and functional capacity of the gut microbiota induced by exercise are independent of diet. Future studies are needed to elucidate which metabolites produced by the gut microbiota are more affected by physical exercise and how exercise-induced modifications in the gut microbiota are connected to CVD risk.

5.7 PA and mortality

Exercise-based cardiac rehabilitation reduces exercise-associated total mortality. For instance, moderate-intensity PA frequently practiced (∼60–75 min per day) counteract the augmented risk of death associated with long periods of sitting time. Likewise, higher PA levels at whichever intensity plus less sedentary time reduce the risk for premature mortality. A recent meta-analysis concluded that achieving the recommended PA levels reduces the CVD events by 17%, CVD mortality by 23%, and the incidence of suffering T2DM by 26%. These results were also confirmed by Kivimäki et al., concluding that PA was associated with 24% higher risk of CHD, 16% enhanced risk of stroke, and 42% higher risk of T2DM.

6. Long-term potential deleterious effects of high-intensity ET

Sports-related sudden cardiac death (SCD) is a rare but alarming event. While some genetic disorders (cardiomyopathies/channelopathies) are the underlying disorder responsible for the fatal event in some young subjects (<35 years), unnoticed and asymptomatic coronary atherosclerosis—also referred to as subclinical CAD—is one of the most frequent causes of sudden cardiac arrest (SCA)/SCD in apparently healthy subjects aged ≥35 years. In effect, several SCA/SCD cases associated with subclinical CAD have been reported in competitive and recreational athletes.

Although PA is a large concern for the majority of the general population, little attention has been paid to the coronary atherosclerosis origination/progression in response to high-intensity ET over prolonged time periods and accompanied strenuous exercise events, such as endurance and/or ultra-endurance races (i.e. marathons, ultra-marathons, triathlons, or iron man). This fact is particularly relevant given the growing number of people taking part in these competitions; it is estimated that there are 50 million runners across Europe. In this regard, ET-induced inflammation has been connected with atherothrombotic disease.

In effect, the most active amateur endurance athletes (i.e. individuals who engage in ET on a regular basis and take part in competitions) have an increased risk for myocardial fibrosis and coronary calcification. Laddu et al. evaluated whether 25 years of practicing PA was associated with coronary artery calcification, concluding that the most active individuals has an increased probability of developing subclinical coronary atherosclerosis in older ages. Two other studies have reported that between 42% and 53% of veteran endurance athletes had calcific CAD. To be emphasized, the plaques in athletes were calcified rather than mixed, i.e. more benign and stable, less likely to rupture and cause an acute CHD event. Nevertheless, concerns about the safety of ET at the highest level for certain populations have emerged.

Notably, the European Association of Preventive Cardiology recommends that individuals with CAD must be discouraged from sports competitions only when there is a considerable risk of adverse CVD events or disease progression exists (i.e. asymptomatic patients with CAD and inducible ischaemia or arrhythmia on functional tests, among others).

Patients at low risk of CVD events may be individually advised to participate in sports competitions. However, to the best of our knowledge, the effect of an increase in the intensity of exercise (e.g. preparation for an endurance competition) on subclinical atherosclerosis (generation, progression, extent, and/or vulnerability) has not been longitudinally studied. Similarly, the impact of endurance training on myocardial phenotype, eventually predisposing to adverse CVD events (i.e. LV trabeculation) in this population, has been barely evaluated. Thus, the effects of high-intensity endurance ET might represent a stress for the CV system (vessel wall and myocardium) that may result in an adverse event where the subclinical atherosclerotic disease is involved. Importantly, vigorous physical exercise has been recently associated with a higher prevalence of CV magnetic resonance imaging-detected LV non-compaction phenotype in a recent community-based study, independently of LV volumes. Thus, vigorous exercise should be considered as a possible cause of LV hypertrabeculation in asymptomatic subjects.

7. ET, CV system, and viral infections, such as coronavirus disease 2019 (COVID-19): the importance of being fit to be protected against environmental threats

A higher COVID-19 severity is, at least in part, due to the presence of CVD risk factors, such as HTN, T2DM, obesity, or CAD, among others, which is associated with a less favourable prognosis and worse outcomes in COVID-19 patients. In effect, there is increased mortality in COVID-19 patients with CAD, which indicates that there is a connection between myocardial injury and COVID-19 severity, with a higher frequency of myocardial injury in critically ill patients and non-survivors. In addition, it has been recently reported that COVID-19 patients with ST-segment elevation MI (STEMI) show more HF on hospital arrival than non-COVID-19 patients (31.9% vs. 18.4%, P = 0.002). These authors also observed a substantial increase in in-hospital stent thrombosis and cardiogenic shock development after PCI in COVID-19 patients with STEMI. Importantly, it has been reported that maximal exercise capacity is independently and inversely correlated with the probability of hospitalization of COVID-19 patients, which supports the crucial connection between CRF and health outcomes.

Detrimental effects have also been described after acute PA interruption, which may occur in sudden quarantine. It has been associated with insulin resistance, muscle atrophy, decreases in venous return, and reductions in coronary perfusion. Positive metabolic and CV adaptations in response to ET can be lost in <2 weeks of PI, impairing CRF and/or increasing BP. The production of atherogenic lipoproteins may rise, which promotes the accumulation of circulating lipids and obesity, accelerating atherosclerosis. The resting HR also increases after the acute cessation of ET/PA, rapidly amplifying the risk of CVD events and mortality. During quarantines, staying physically active and regularly performing ET is essential to preserve CV health. Overall, it is important to be aware that exercise and increased CRF may protect against a wide range of environmental threats, including but not limited to viral (e.g. COVID-19) and bacterial infections.
8. Recommendations, future perspectives, and concluding remarks

It is now clear that regular ET/PA induces a wide range of direct and indirect physiological adaptations and pleiotropic benefits for human CV health. PA, exercise, and CRF evaluations and interventions should be incorporated into all health professionals’ practice. ET/PA is a mainstay to prevent and control the global problem of CVD. To this end, health care professionals must interact with individuals in our long-term efforts to reduce sedentarism and PA and increase ET/PA to reduce CVD. Although hypothetically, there is no universal exercise prescription, general guidelines can be developed for all levels of CRF. An individualized approach in terms of a patient’s CRF and health/disease status, on one side, and exercise type and dosage, on the other side, needs to be considered.

Despite the extensive history of research into exercise and cardioprotection, many questions remain unanswered. The duration and intensity of ET needed to optimize cardioprotection remain uncertain, and the underlying mechanisms are still unclear. Elucidating exercise-associated positive mechanisms may generate promising therapeutic targets for cardioprotection. In addition to improving traditional CVD risk factors (i.e. blood lipid and glucose levels, obesity, and HTN), exercise confers benefits through other mechanisms, such as myokines. Importantly, exercise is safe and with no adverse effects, and its benefits are, in some measure, dose-dependent. It is time to view exercise as medicine for the management of CVD.

Additionally, the molecular intermediaries involved in exercise effects may open new possibilities to enhance exercise’s effects using more effective or targeted strategies. The exercise-based concept for cardiac drug target discovery has great potential to positively affect society and public-health systems by alleviating CVD’s burden. Although this aim may appear futuristic, its positive benefits should be a robust motivation for further research in the field. Meanwhile, the evidence of benefits that are already obvious should be applied and adopted as critical priorities.

In the COVID-19 era, in which we are relying on an effective vaccine to protect the community against severe acute respiratory syndrome coronavirus 2, ET/PA represents a potent co-adjvant ‘vaccine’ or a non-pharmacological treatment that should be recommended and spread to prevent and/or treat one of the deadliest diseases in the world, CVD.

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