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Exercise Training and Cardiac Remodeling

*Dayanne Borges, Suzilene Ormond, Murilo Nogueira,
Keemilyn Silva and Jeaser Almeida*

Abstract

The exercise training promotes functional and structural changes on several systems, including cardiovascular, resulting in physiological modifications responsible for maintaining variables such as cardiac output, preservation of blood flow, and the metabolic demand required in different sports. Recently, cardiac remodeling has been studied in order to broaden knowledge about the effects of physical training on cardiovascular characteristics in different populations. However, the adaptive responses inherent in exercise on cardiac remodeling seem to be influenced by other variables relevant to training, regulatory systems, and population specificity. Thus, this chapter aimed to elucidate the adaptive hypertrophic changes caused by physical exercise.

Keywords: physiological hypertrophy, physical exercise, hypertension, cardiac adaptation, sports

1. Introduction

The leading causes of death are due to cardiovascular disease (CVD), contributing substantially to increased health expenditure in several countries [1]. Thus, physical inactivity, obesity, smoking, and diabetes mellitus increased the risk for CVD [1]. Currently, sedentarism has been recognized as a primary risk factor, and physical exercise is associated with a decreased mortality rate from coronary artery disease [2]. Thus, a sedentary lifestyle is characterized as any waking behavior whose energy expenditure is less than 1.5 METs (metabolic equivalent), sitting, reclining, or lying down. This behavior differs from physical inactivity, which the individual does not perform moderate-vigorous physical activities [3].

Among the cardiovascular benefits of exercise, it is possible to observe blood pressure reductions, resting bradycardia, and greater efficiency of the cardiovascular system [4]. Also, cardioprotective factors are observed with exercise training such as the reduction of the magnitude of myocardial infarction [5], through different mechanisms, such as reduction of the inflammatory process, molecular regulation, as well as control of the pathological cardiac hypertrophy [5]. However, not every exercise stimulus promotes the same responses. Thus, it is necessary to know how much and what type of exercise should be applied to generate cardioprotective effects. For the prescription of exercises, it is essential to emphasize the variables that make up the activity: the FITT (frequency, intensity, type, and time) [6].

Aerobic exercise is considered a strategy for the prevention/treatment of arterial hypertension in reducing the risk of cardiovascular disease. The intensity of these exercises ranges from 40 to 60% of $\text{VO}_{2\text{max}}$ or 11 to 14 of the perceived effort (Borg Scale). Current studies show that reductions in blood pressure by aerobic exercise are directly linked to intensity, so more vigorous activity may result in more significant reductions in blood pressure [6]. Frequency can range from 3 to 7 days a week [7, 8], and it is recommended to use large muscle groups, lasting 30–60 min [6]. Besides, several studies using resistance training (RT) as an intervention proposal are performed. Recent data indicate that RT has antihypertensive effects and can be used as a treatment strategy when combining with aerobic exercise [9, 10].

Consequently, exercise adaptations result in structural and physiological changes imposed on the heart. In this sense, cardiac remodeling occurs in different situations, which may be beneficial or harmful and widely studied in several aspects. Therefore, the purpose of this chapter is to review the aspects of cardiac remodeling associated with physical exercise.

2. Effects of exercise training in the arterial hypertension

For the past two decades, aerobic exercise (AE) has been used as a non-pharmacological therapy for cardiovascular disease control [11]. During an acute session of aerobic exercise, it is possible to verify the increase of specific cardiovascular parameters, such as cardiac output and blood pressure [12]. Interestingly, after the session, the values return to normal. However, blood pressure may fall below pre-exercise values; a phenomenon called post-exercise hypotension [13]. Additionally, aerobic training promotes significant changes in cardiovascular parameters. Long-term moderate-intense exercise promotes a reduction in arterial stiffness [14], a reduction in blood pressure [15], and an increase in cardiac efficiency [16]. Similarly, strength training is also helpful in lowering blood pressure as well as improving cardiovascular function [17].

Previous studies have shown that aerobic exercise causes structural and functional adaptations in the cardiovascular system [18, 19]. Thus, the heart has an essential morphological adaptation, characterized by an increase in the ventricular cavity, which is necessary for the more excellent supply of oxygen and nutrients [20]. The vascular system presents significant changes, such as increased vascular density due to the formation of new blood capillaries, associated with a higher vasodilator capacity [20]. RT has been well used to increase muscle strength, power, and endurance. However, it is essential to highlight how these effects are related to cardiovascular health in healthy individuals or those with CVD. Although RT is encouraged, the evidence is still controversial. However, evidence demonstrates a significant blood pressure reduction in unmedicated and medicated hypertensive patients [21].

Regarding the intensity of exercise, this may influence cardiovascular responses [22]. However, an optimal intensity for cardioprotection is not yet known [5]. In healthy individuals, cardiovascular changes seem to be more significant when subjected to the most intense effort [23]. Although high intensities have shown important outcomes for cardiovascular health, such as improved endothelial function, individuals with CVD need greater care in the assessment and prescription of intense exercise [5].

Arterial hypertension (AH) is considered as a major risk factor for diseases such as stroke and acute myocardial infarction [24]. SAH is diagnosed in individuals with sustained systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mm Hg [25]. The high prevalence of hypertension is related to

non-modifiable factors such as ethnicity, gender, genetic factors, as well as modifiable environmental factors such as eating habits, physical activity level, smoking, and alcohol use, among others [24]. However pharmacological strategies for the treatment of hypertension are effective in controlling the disease, side effects, and health-care expenses which are considered relevant problems. In this sense, physical exercise has been considered as one of the most important and efficient strategies for non-pharmacological control of hypertension [26, 27].

Among the potential effects of exercise on hypertensive patients, post-exercise hypotension is of clinical relevance because it indicates a reduction in the progression of cardiovascular disease, and low resting BP values are associated with reduced risk of death [28]. Interestingly, hypertensive individuals have more significant reductions in blood pressure when compared to non-hypertensive individuals, both acutely and chronically [29, 30]. Besides, it has recently been proposed that acute response may be able to predict the responsiveness of hypertensive individuals to chronic exercise [31].

Exercise recommendations for hypertension treatment and prevention are based on existing evidence and are continually updated [32]. Thus, aerobic, resistance, and combined exercise present as effective alternatives (90–150 min per week at moderate intensity) [33]. Besides, other alternative strategies such as tai chi chuan, yoga, and even Kaatsu training have shown promising results, but due to the low body of evidence, they were considered limited to include the new recommendations [34, 35]. A randomized controlled trial (RCT) of 207 hypertensive subjects showed that 120 minutes of walking at moderate intensity without dietary control twice a week was able to reduce cardiovascular disease [36]. Also, during controlled eating, moderate aerobic exercise reduced blood pressure, total cholesterol levels, medication use, and the risk of cardiovascular events [37].

However, high-intensity interval training (HIIT) in cardiovascular responses in hypertensive patients has been increasingly discussed [15]. Therefore, another RCT with 245 hypertensive men (45–70 years) showed that 8 weeks of interval training performed at intensities of 60–78% (heart rate reserve—HRR) 3 times a week was able to promote a decreasing effect in reducing blood pressure and promote an increase in high-density lipoprotein (HDL) levels, improving lipid profile [38]. Additionally, a protocol using higher intensities (85–90% of HRR) is equally effective in promoting hypotensive effect in elderly hypertensive individuals, besides promoting increased nitric oxide, and appeals to important hemodynamic modulators [39]. RT is part of the recommendation for treatment and prevention of hypertension. Recently, a systematic meta-analysis review showed that RT, performed 3 times a week, with loads of 40–80% of 1 maximal repetition (MR), can lower blood pressure in individuals with high blood pressure [40]. Thus, RT has been a valuable alternative or complementary treatment to reduce blood pressure levels.

3. Characteristics of cardiac remodeling: effects of exercise training

The myocardium is primarily composed of myocytes, vessels, and interstitial collagen matrix. Changes in the composition of these compartments reflect the process of cardiac remodeling that is closely associated with cardiac dysfunction [41]. Cardiac hypertrophy is more often related to these events, and according to the type of hypertrophy (physiological or pathological), different models of it are observed, with their signaling pathways.

Cardiac remodeling can be defined as the set of cardiac molecular, cellular, and interstitial modifications that will be clinically displayed by changes in cavity

diameter, mass (hypertrophy or atrophy), geometry (evidenced by wall thickness and heart shape), in response to a given stimulus, which may be aggression, such as areas with fibrosis and scarring observed in infarction [42] or even by adaptation, which is a physiological process, such as enlargement of the ventricular cavity of long-distance runners (eg marathon runners) [43–45]. The sequence of pathological events begins with aggressions to the cardiac tissue that maybe through reduction of myocyte changes in the energy system, pressure overload, and volume overload, among other factors. From one or a combination of these episodes, remodeling is a cascade of genetic, biochemical, molecular, cellular, and structural changes that most often culminate in ventricular dysfunction resulting in heart failure [46–48].

Myocytes perform the contractile function of the myocardium, and their preservation is fundamental since most of them are not capable of multiplication. Myocyte reduction can occur by three mechanisms: autophagy, apoptosis, and necrosis. New evidence indicates that for the latter, there is a confluence of mechanisms, and their close relationship is called necroptosis [49]. Autophagy, on the other hand, maybe adaptive or deleterious, depending on the context of protein balance. Fibrosis, observed in acute post-myocardial infarction situations, is a response to myocyte death since, after cardiac signaling for the removal of dead myocytes, cardiac fibroblasts secrete proteins such as collagen I to form a scar and prevent rupture of the myocardium cardiac wall. This condition, considered as remodeling, continues in response to ventricular wall stress, so we have another event called myocyte hypertrophy. This effect leads to increases in final systolic and diastolic volume and reduction in ejection fraction [50].

Energy metabolism and oxidative stress are factors potentially responsible for cardiac remodeling. The imbalance between oxygen supply and consumption, including decreased free fatty acids and increased glucose utilization, may contribute to lower energy availability for ATPase proteins, favoring the generation of reactive oxygen species (ROS), resulting in all the consequences of oxidative stress [51–53]. Lipid peroxidation, DNA damage, fibroblast proliferation, metalloproteinase activation, apoptosis stimulation, changes in proteins responsible for calcium transit, and activation of signaling pathways for hypertrophy are conditions involved in oxidative stress which is implied in the oxidative stress cardiac remodeling process due to cellular signaling and imbalances in homeostasis. In short, ROS directly influence contractile function from the modification of central proteins to the excitation-contraction. Continuous pressure overload promotes the addition of sarcomeres in parallel, that is, it promotes the increase in ventricular wall thickness, called concentric hypertrophy, which can be observed in advanced systemic arterial hypertension and aortic valve stenosis. On the other hand, volume overload (e.g., valve insufficiency) results in serial sarcomere increase, called eccentric hypertrophy [54], present in cases of acute myocardial infarction [55].

Regarding the pathological processes of concentric hypertrophy, muscle thickening hinders capillary filling in the deepest regions of the myocardium, specifically the subendocardium, which impairs the maintenance of blood flow. About eccentric hypertrophy, the increase in mass occurs with a predominance of increased intracavitary dimensions with less expression of myocardial thickening, causing cardiac fiber disarrangement and alteration in the angle between them, with loss of spiral architecture of the myocardial fibers, associated with a contractile deficit of the ventricle [55]. There is a blood damping in the cardiac chambers, decreasing the irrigation of peripheral tissues [56].

Regarding the process of physiological hypertrophy, both eccentric and concentric, the stimuli are similar to the process presented in serious pathologies (e.g., pressure and volume overload). However, what define the ventricular geometry

pattern presented during remodeling are the characteristics inherent to the stimulus received, in which, in physiological cases, there are no functional damages to the cardiovascular system. Even more, adaptations from exercise can be beneficial in improving heart function. Hence, the physiological adaptations occur from physical exercise, for example, depending on the type of exercise (e.g., running and strength training) of volume, intensity, and frequency. Regarding the benefits of regular aerobic exercise practice, there is a higher blood volume ejection due to increased ejection force or higher ventricular filling, thus reducing the resting heart rate.

Diverse molecular pathways are associated with exercise-induced cardiac remodeling. However, the gene pathway (IGF-1) is well characterized and evidenced in the literature [57], due to the increase in cardiomyocytes in response to aerobic exercise [58]. However, cardiac remodeling in response to aerobic training is dependent to PI3K pathway activation and AKT phosphorylation [59]. Interestingly, short-term, aerobic training (4 weeks) can reprogram cardiac remodeling through AKT activity [60]. Additionally, in both animal and human models, exercise can attenuate the deleterious effects of aging [61, 62].

The role of miRNAs is of fundamental importance in the cardiac remodeling process [55, 63] mainly associated with exercise training [64, 65], due to their participation in left ventricular hypertrophy in aerobic exercise. Also, HIIT protocols show miRNA expression in cardiac hypertrophy [55]. Thus, exercise is an essential factor in identifying miRNA signatures associated with cardiac remodeling. MiRNA-29 targets the collagen gene, which increases with the induction of physical exercise, reducing collagen I and III, resulting in better ventricular function [66]. Also, miRNA-29 reduces collagen fibrosis and attenuates the deleterious effects of cardiovascular disease [67]. Therefore, although miRNAs and genes are closely related to the cardiac remodeling process, other factors are also important, such as proteomics and metabolomics. So many pieces still need to be fitted into this cardiac puzzle.

4. Conclusions

Regardless of the type of stimulus imposed by exercise, the key point to ensuring positive myocardial adaptations is in the balance of training manipulation variables (frequency, intensity, and volume) as well as the nature of the modality chosen. Considering the intensity variable, which is widely investigated, it is clear that while low-intensity aerobic exercise improves cardiac remodeling in adult rats by reducing the size of the left atrium and the left ventricular (LV) posterior wall thickness, high-intensity aerobic exercise presents inverse responses, with increased left ventricular mass and LV posterior wall thickness. Dynamic exercise (running), which requires a continuous increase in cardiac function and contractility, differs from powerlifting which requires high blood pressure and a greater need for oxygen perfusion to skeletal muscles. This explains the ability of the circulatory system to differentiate exercise types according to different hematological stresses.

The responses related to the type of exercise are diverse, as they are interpreted from different experimental and clinical designs. Still, it is critical to search for research to assess the chronic effects of exercise, especially at the molecular level to find strategies for the prevention and treatment of cardiovascular disease. Perspectives point to the integration of studies involving immune response in the brain and heart in order to contribute to the understanding and longitudinal follow-up of several modalities, including the determination of the threshold of optimal internal and external stimulus loads to avoid cardiac toxicity, which leads to pathological cardiac remodeling, also considering the screening of individuals at risk.

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This chapter discloses the experiences of the group of teachers/researchers of the Faculty of Physical Education of Federal University of Mato Grosso do Sul which will be of great use to all students and health professionals interested in deepening their knowledge in the field of exercise cardiology.

Appendices and nomenclature

AKT	protein kinase B: is a threonine kinase that plays a critical role in cellular growth and survival
ATPase	an enzyme that catalyzes the breakdown of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and a free phosphate ion
IGF-1	insulin-like growth factor 1: peptide that acts on glucose and amino acid uptake into cells
HDL	high-density lipoprotein: is a strong inverse predictor of cardiovascular events
HIIT	high-intensity interval training: is an enhanced form of interval training involving brief, high-intensity, anaerobic exercise (ranging from 85–250% VO_{2max} for 6 s–4 min) separated by brief but slightly longer bouts of low-intensity aerobic rest (ranging from 20–40% VO_{2max} for 10 s–5 min)
HRR	heart rate reserve: it is the term used to describe the difference between the maximum HR (measured or calculated) and the basal (or resting) HR. It is used as an intensity control variable in aerobic exercises. The greater the difference between maximal HR and basal HR1, the higher the reserve HR, and the greater its potential to train at different intensities
MR	maximal repetition: used as a measure of muscle strength, whether in physical preparation, sports training, physical rehabilitation, or scientific research
METs	metabolic equivalent: Is equivalent to sufficient energy for an individual to remain at rest, represented in the literature by oxygen consumption (VO_2) of approximately 3.5 ml/kg/min. When expressing energy expenditure in METs, the number of times the resting metabolism was multiplied during an activity is expressed
MiRNAs	they are 19–25 molecules nonprotein-coding nucleotides that act as potent posttranscriptional regulators of gene expression in plants and animals
PI3K	phosphatidylinositol 3-kinase: constitutes a family of evolutionarily conserved lipid kinases that regulate a vast array of

	fundamental cellular responses, including proliferation, adhesion, cell size, and protection from apoptosis
RT	resistance training: resistance training is defined as an exercise that involves the participant exerting effort against their body weight or external resistance
ROS	reactive oxygen species: they are unstable and extremely reactive molecules capable of transforming other molecules with which they collide. The EROs are generated in large quantities during oxidative stress, a condition in which molecules such as proteins, carbohydrates, lipids, and nucleic acids are affected

Author details


Dayanne Borges¹, Suzilene Ormond¹, Murilo Nogueira¹, Keemilyn Silva¹ and Jeaser Almeida^{1,2*}

¹ Exercise and Nutrition Research in Health and Sports Performance–PENSARE, Health and Development in the Midwest Region, Federal University of Mato Grosso do Sul, Campo Grande, Brazil

² Graduate Program in Movement Sciences, Federal University of Mato Grosso do Sul, Campo Grande, Brazil

*Address all correspondence to: jeaser@gmail.com

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