Mini-Review

Exercise training on cardiovascular diseases: Role of animal models in the elucidation of the mechanisms

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Abstract — Cardiovascular diseases, which include hypertension, coronary artery disease/myocardial infarction and heart failure, are one of the major causes of disability and death worldwide On the other hand, physical exercise acts in the prevention and treatment of these conditions. In fact, several experiments performed in human beings have demonstrated the efficiency of physical exercise to alter clinical signals observed in these diseases, such as high blood pressure and exercise intolerance. However, even if human studies demonstrated the clinical efficiency of physical exercise, most extensive mechanisms responsible for this phenomenon still have to be elucidated. In this sense, studies using animal models seem to be a good option to demonstrate such mechanisms. Therefore, the aims of the present study are describing the main pathophysiological characteristics of the animal models used in the study of cardiovascular diseases, as well as the main mechanisms associated with the benefits of physical exercise.

Keywords: physical exercise; cardiovascular disease; experimental models.

Introduction

Cardiovascular disease (CVD) is the name of a larger construct, which involves diseases of the heart, brain vasculature and blood vessels[1]. Several data indicate that CVD is the major cause of disability and death worldwide[1,2]. To date, CVD seems to be responsible for 30% of the annual deaths in low and middle income countries[2]. Projections for the next years do not indicate a better scenario, since is expected that this number will increase exponentially[2].

Among the variety of CVD risk factors, physical inactivity is highlighted as a phenomenon strongly associated with CVD development, regardless of body mass index[2]. The effects of physical activity (PA) (e.g., walking, climbing stairs) on CVD risk factors are widely known, which explains its popularity with healthy individuals who want to avoid CVD[2]. In turn, physical exercise (PE), which concerns planned and structured body movement aimed to improve one or more physical capacities, has been widely suggested as a powerful non-pharmacological tool by different international associations, in order to prevent and counteract the deleterious effects of CVD in the organic system, due its capacity to offer larger effects in comparison with PA[2,3,4,5,6].

In fact, several studies, including systematic reviews and meta-analytic data, indicate that PE is capable of leading to changes in the pathophysiological course of different CVD, such as hypertension (HTN), coronary artery disease/myocardial infarction (MI) and heart failure (HF)[7,8,9,10]. Although the clinical effects of PE on the different CVD are already known, the mechanisms associated with such changes must still be elucidated.

It is widely acknowledged that experiments with humans have limited capacity to contribute to the investigation of the mechanisms associated with the effects of PE on CVD and, usually, inferences are limited to systemic analyses (i.e., plasma and/or serum).

In this sense, studies using animal models have emerged as an effective tool to explore the several mechanisms triggered by PE in different organs and tissues, as well as in the whole organic system. Regarding animal models in the CVD context, experiments have been performed with different types of animals, including species that spontaneously developed the disease due to genetic factors and animals that underwent surgical procedures.

In fact, HTN, for example, is commonly studied in Spontaneous Hypertensive Rats (SHR), since the pathogenesis of HTN in this species is multifactorial, as in humans. However, if necessary, researches can also study HTN triggered by specific alterations in the renal system (i.e., one kidney one clip [1K1C], two kidneys one clip [2K1C] and two kidneys two clip [2K2C]), using pharmacological approaches (i.e., L-NAME [N^{ω} – nitro-L-arginine methyl ester], DOCA [deoxycorticosterone acetate]) and associated with diseases, such as obesity, and physiological conditions, such as menopause (i.e., ovariectomized), for

example. Moreover, such possibilities are not exclusively related to HTN, and several possibilities are available in the context of MI (e.g., Left anterior descending coronary artery ligation [CAL], Ischemia-Reperfusion model [IRM] and MI-induced by isoproterenol) and HF (e.g., hyperadrenergic activity, CAL, doxorubicin, left coronary artery microembolization with polystyrene).

The mechanisms responsible for the beneficial effects of PE on CVD have been studied in some of the aforementioned models, and much has been discovered. To contribute with this Special Issue, denominated: *Animal Studies: Contributions to Exercise Physiology*, we aimed to provide a brief description of the mechanisms and clinical aspects observed in the animal models that are most used to study the effects of PE on CVD.

This knowledge is important not only for undergraduate students, but also for graduate and post-graduate students, as well as for researches that require an overview of the main animal models used in the context of PE and CVD.

Hypertension

HTN is one of the most prevalent diseases in adult life[11]. In older people, for example, the prevalence of HTN is elevated, reaching values above 60% in both sexes[11,12]. The main concern about this disease is its poor prognosis because patients with high blood pressure (BP) show increased risk for stroke (i.e., hemorrhagic and ischemic) and MI[11,12]. Moreover, a recent report from the World Health Organization (WHO) established HTN as the main risk factor for death worldwide[11,12].

SHR have been widely used in scientific experiments, mainly because it is considered analogous with essential HTN in human by several authors[13,14,15,16,17]. This animal model of HTN was created by mating Wistar rats that showed the highest BP levels. After 20 generations, the animals began to develop spontaneous HTN in early adulthood[13]. In these animals, BP increases exponentially with aging, which occur mainly due to elevated vascular peripheral resistance (VPR) rather than to modified cardiac output (CO)[15,18].

As in humans, the pathogenesis of HTN in SHR seems to be multifactorial, since these animals show morphological and functional alterations on the different physiological elements that compose BP control, such as heart, kidney, blood vessels and autonomic control. Interestingly, these alterations have dissimilar time-courses, and factors associated with elevated BP in SHR are observed from the first weeks of life.

Data are inconclusive about HTN condition in young SHR (ySHR) (~4 weeks old), once during this age the animals present a high oscillation in BP values (as demonstrated by data using direct and indirect measurements) with some evidence indicating HTN[19,20] — BP values next to 150 mmHg — and others not[21,22]. Therefore, during this time of life animals are generally denominated as pre-hypertensive. However, a significant number of evidence have been indicating that, even in the absence of alterations on BP measurements, morphological alterations on different vascular beds of the cardiovascular system and in the kidney, are observed in ySHR[21,22,23,24].

In the kidney, for example, increased cross-sectional area (CSA) of the intima and adventitia layer, concomitantly with increased wall lumen, are found in the renal arteries of ySHR in comparison with age-matched normotensive control[23]. Data are also observed in other vascular beds (i.e., aorta, mesenteric), and evidence indicate elevated intima (IT), media (MT) wall thickness (WT), media-lumen ratio (M/L), media cross-sectional area (MCSA) and hypertrophy of smooth muscle cells in ySHR[21,22,24,25]. Such alterations increase linearly and progressively with aging, and results of modified vascular structure in 8-week and 12-week old SHR (adult SHR [aSHR]) are larger than in ySHR and age-matched WKY control[22]. In this sense, results from analyses in the kidney of aSHR demonstrated increased indications of renal injury and abnormalities in comparison with normotensive animals[26].

Nevertheless, experiments in the thoracic aorta of aSHR identified elevated mRNA expression of α-actin (+9-fold), elastin (+6-fold) and collagen I and III (+11-fold) in comparison with normotensives27. Moreover, as observed in ySHR, the content of connective tissue, elastic fibers, and fibrils, as well as the CSA, were higher in the aorta of aSHR in comparison with age- matched control [27].

Regarding functional alterations, aSHR show an endothelium phenotypic profile close to what is generally observed in endothelial dysfunction, characterized by increased reactive oxygen species (ROS) synthesis, oxidative stress activity and decreased antioxidant activity, culminating in a substantial impairment on endothelium-dependent dilation[28,29,30]. In fact, endothelium-dependent dilation is decreased in the vessels of aSHR in comparison with WKY[28,29,30]. Participation of the endothelium in this phenomenon seems to be clear when pre-treatment with L-Nitro-Arginine Methyl Ester (L-NAME) — a nitric oxide (NO) inhibitor — abolishes differences between normotensive and hypertensive animals[30].

Noteworthy, NO is a molecule synthesized by the vascular endothelium is response to several stimuli (e.g., shear stress, acetylcholine [ACh]) and it is the main action that occurs in the smooth muscle cells, causing vasodilation by altering calcium kinetics, through activation of soluble guanylate cyclase (sGC)/ cyclic guanosine monophosphate (cGMP) (sGC/cGMP) pathway[31,32]. Moreover, this free radical seems to be important to mediate the effects of other vasodilatory molecules, such as angiotensin (ANG) (1-7)[33,34]. Interestingly, vasodilatory response to ANG (1-7) is decreased in the aorta of aSHR, and impairment on NO pathway activity is a possible hypothesis to explain this phenomenon[29].

As aforementioned, increased oxidative stress activity is generally observed during endothelial dysfunction. In aSHR, this phenomenon is not observed only in the heart, lung and kidney — organs associated with cardiovascular control — but also in the aorta and erythrocytes[35,36]. On the other hand, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) — antioxidant enzymes that contribute to the control of oxidative stress —, as well as the total antioxidant activity, are found decreased[35,36].

Oxidative stress decreases NO mainly due to anion superoxide (O2-) actions[37,38,39,40,41]. After superoxide anion (O2-) synthesis, by uncoupled endothelial NO synthase (eNOS), NAD(P)H oxidase and mitochondria, this molecule reacts quickly with NO, creating peroxynitrite (ONOO-)[37,38,39,40,41], which, in turn, reacts with cellular elements that act in NO synthesis, such as tetrahydrobiopterin (BH4), a precursor of NO[37,38,40]. Therefore,

it is possible to observe that decrease in NO bioavailability is a retro-pathway, which, if not stopped, can cause serious damages to the homeostasis of the organic system, mainly on endothelial function.

One interesting issue about SHR animals concerns the association between autonomic control and vascular function. In the mesenteric vessels, for example, ySHR show higher sensitivity to noradrenaline (NA), demonstrated by early vasoconstrictor response, than WKY rats, which is associated with higher influx of calcium and lower baroreflex sensitivity (gain) (BrS)[22,42,43].

This phenomenon is exacerbated by age, since aSHR demonstrate not only higher sensibility to NA infusion and electrical stimulus, but also decreased vasodilator response after ACh infusion in mesenteric and carotid vessels[22,23,43,44,45], as well as BrS in conscious and nonconscious rats[47,48,49]. Furthermore, evidence have been found that morphological and functional alterations on blood vessels, such as arterial stiffness, decreased endothelium-dependent dilation, and oxidative stress are associated with BrS impairment[35]. Thus, data indicate that vascular and morphological alterations in blood vessels are associated with cardiac autonomic control.

In this regard, aSHR showed increased cardiac and peripheral sympathetic activity[19,26,44,47,48] and blocked of α_1-receptor with prazosin inhibit in ~95% of the vasoconstrictor response to electrical stimulation, causing absence of differences in relation to the response of control animals[23]. Several evidence have showed that aSHR presents reduced heart rate variability (HRV) and increased systolic AP variability (SAP), followed by alterations in analyses of the frequency domain, indicating alteration in the sympathovagal balance[26]. Moreover, this phenomenon is not just an effect of increased sympathetic activity discharge from the central nervous system to the periphery, but an environmental complex proving vasoconstrictor response.

This idea seems to be clear in the experiment of Reja et al. (2002)[49], who observed elevated α_{1A}-receptor (α_{1A}-R), concomitantly with decreased α_{2A}-receptor (α_{2A}-R), gene expression levels on neural system — central (i.e., ventromedial hypothalamus [VHM] and rostral ventrolateral medulla oblongata [RVLM]) and peripheral (i.e., spinal cord) — and on peripheral organs associated with BP control, as myocardium and adrenal medulla tissue studying aSHR [50]. Furthermore, this overexpression of α_{1A}-R on the central and peripheral nervous system and on the peripheral organs are positively correlated with BP in SHR[49].

Yet, administration of phenoxybenzamine — a α-adrenergic receptor blocker — causes significant decrease on BP and HR in a dose-dependent manner in comparison with normotensive control rats[50]. High drug levels caused total absence of differences of the aforementioned parameters between aSHR and control groups[50]. Authors also tested the effects of β-adrenergic receptor blocker, propranolol, in cardiovascular parameters. Results indicate that inhibition of β-adrenergic receptor leads to significant decrease on HR in aSHR to levels similar to control group[50].

Additionally to the morphological and functional alterations in the vascular endothelium, in organs associated with BP control (e.g., heart, kidney), and in the autonomic control of the cardiovascular system, an upregulation of some molecular pathways in the brain areas responsible for BP control are found in SHR.

As in the peripheral tissues, brain renin-angiotensin system (RAS) acts regulating cardiovascular control[51,52]. Importantly, during HTN the blood-brain barrier (BBB) is markedly disrupted in areas associated with autonomic cardiac control — such as RVLM, nucleus tractus solitarius (NTS) and paraventricular nucleus (PVN) —, which allows for extravasation of peripheral ANGII to these areas, as demonstrated trough infusion of fluorescently labeled ANGII in SHR[117,118]. Therefore, it is possible that elevated ANGII in the brain is, partially, explained by the peripheral activity of RAS[117,118].

Regarding the pathway, in summary, after the cleavage of renin by the substrate angiotensinogen (Aogen), the decapeptide angiotensin I (ANG I) will be formed[51,52]. From the activity of the angiotensin-converting enzyme (ACE), ANG I is cleaved in an octapeptide, called angiotensin II (ANG II), which seems to be the neuropeptide responsible for RAS negative effects on cardiovascular control through its binding with AT_1R[51,52].

Seminal data demonstrated that inhibition of the activity of RAS components in the brain by direct ventricular infusion of saralasin — a ANGII antagonist —, or even by antisense treatment, with consequently impair AT_1R and Aogen, leads to decrease on BP values of aSHR in a dose-dependent manner[16,53]. Recent studies have confirmed these evidences, showing that the expression of RAS components, as ACE, AT_1R, Aogen, are increased in brain areas responsible for cardiovascular control (e.g., RVLM, NTS), which, in turn, is associated with BP values[34,54].

Interestingly, BP modulation by RAS does not seem to occur alone, but in conjunction with the activity of ROS and inflammatory elements, such as proinflammatory cytokines, adhesion molecules, and transcription factors (nuclear factor-κB [NFκB])[55]. In fact, blockade of NFκB in the PVN leads to lowering of mean BP, as well as decreased mRNA expression of proinflammatory cytokines, such as tumor necrosis factor-α (TNF – α), interleukin-1β (IL-1β) and IL-6 (IL-6), and ROS (e.g., O_2^-,$ONOO^-$)[56]. In addition, analysis of data from experiments on aSHR indicate that ROS and proinflammatory elements are elevated in similar brain areas, and times, supporting the idea of an integrated complex of cardiac control between these pathways in SHR[34,47,48,54].

After elevation of ROS by RAS, O_2^- and other ROS can lead to phosphorylation of the extracellular signal–regulated kinases ½ (ERK ½), — a signaling protein kinase — which promptly activates NFκB trough the inhibition of Iκβα, an inhibitory anchoring protein, allowing the translocation of NFκB to nucleus, increasing the synthesis of ROS and PICs[39,47,57]. In aSHR, mRNA expression of NAD(P)H oxidase and the activity of ROS are elevated in the PVN, followed by elevated phosphorylation of ERK ½ and IKKβ, in addition to NFκB binding to the DNA[33,58]. Moreover, data demonstrated that increased ROS, ERK ½ and NFκB activity is associated with increased levels of PICs, as well as decreased levels of anti-inflammatory cytokines (i.e., interleukin-10 [IL-10]) in aSHR[33]. Considered together, these data indicate that, in the brain of aSHR, a molecular complex formed by RAS, ROS and PICs acts on cardiovascular control.

Regarding the mechanisms responsible for increased BP observed in aSHR, downstream of ROS and proinflammatory cytokine activity lead to alteration in autonomic cardiac

control[59,60]. In the experiment of Takagishi et al.[60], for example, exogenous IL-6 administrated by microinjection in the NTS causes ~35% inhibition of baroreceptor bradycardia reflex gain in a dose-dependent manner[60].

Moreover — despite the exacerbation of activity of hypertensive elements in the brain areas of SHR — some pathways, such as ANG 1-7/Mas receptor and anti-inflammatory cytokines (i.e., IL-10), that could act as counter-regulatory agents, consequently decreasing BP values, show lower expression in the brain of aSHR in comparison with normotensive age-matched control[33,34]. ANG (1-7), for example, is formed by the cleavage of ANG II by ACE 2 and, in the brain areas of cardiovascular control, acts through Mas receptors in the tonic and reflex control of BP[52,61]. Yet, evidence indicates that ANG (1-7) control of BP can occur due to its influence on BrS[52,61].

The effects and mechanisms of PE on hypertension: evidences from SHR

PE is considered a beneficial non-pharmacological therapy to induce decrease on BP values in hypertensive patients, being considered one of the most important changes in lifestyle of these patients[3,62]. Several evidence indicate that aerobic PE is an effective stimulus to induce acute (hypotension post-exercise) and chronic decrease on BP values in humans[3,63,64,65]. Nevertheless, recent reviews (i.e., descriptive and meta-analyses) have described the potential of resistance training to contribute to this control[58,66].

Experiments have demonstrated lower BP values in trained aSHR in comparison with sedentary aSHR after treadmill, swimming and resistance exercise[26,33,34,47,48,54,67]. A recent meta-analysis, which analyzed 17 studies in SHR, confirmed these data and demonstrated that PE is capable of leading to significant decrease on BP values[17].

Morphological and functional alterations on organs associated with BP control (e.g., heart, kidney) and on blood vessels are one of the most evident alterations triggered by PE in aSHR. In the aorta, for example, low to moderate aerobic physical training performed 5 days per week, one hour per day, over three months caused decrease on smooth cells volume, elastic components and connective tissue in the aorta[27]. These effects are followed by significant decrease in the mRNA expression of α-actin, elastin, and collagen I and III[27]. Results were not different in the heart since collagen content and cardiac load were decreased, and myocardial performance index (MPI) and left ventricular chamber diameter were increased in aSHR submitted to moderate aerobic exercise during 10 weeks[68]. Yet, swimming exercise decreased the number of sclerosis glomerular index in the kidney of SHR[26].

Morphological alterations are generally followed by functional changes caused by oxidative stress and characterized by decreased endothelium-dependent dilation. PE seems to be an efficient stimulus to counter-regulate this phenotype. In fact, after PE, the total antioxidant activity was increased in the heart, kidney, aorta, and erythrocytes of aSHR[35,36]. Concomitantly, total oxidant activity was decreased in the lung, as well as lipid peroxidation (LPO) in the aorta[35,36]. Such alterations on pro and antioxidant molecules seem to be sensible, and after 10 weeks of detraining total oxidant activity is again increased in the kidney and in the liver[36].

Functionally, PE improves ACh-mediated vasodilation and flow-mediated dilation in aSHR, restoring endothelial function in hypertensive animals[28,30]. PE also increases the vasodilator response to ANG (1-7) and improves the expression of Mas receptor in the aorta[29]. Interestingly, this response seems to be endothelium-dependent, since in endothelium-denuded vessels from trained SHR the vasodilator effect induced by ANG (1- 7) was abolished. Moreover, NO and Mas receptor inhibition impairs the effects of PE[29].

Improvements on autonomic cardiac control have been extensively studied and suggested as one of the main benefits in response to PE in hypertensive patients. In turn, use of SHR models have contributed to a better understanding of this phenomenon and Krieger et al.[69] already indicated this change as one of the main physiological adaptations in response to PE.

As in humans, several evidence using different types of exercise (i.e., treadmill running, swimming) have indicated that PE is capable of improving HRV and SAPV, which is accompanied by improvement in sympathovagal balance in aSHR[26,47,48,68]. Furthermore, authors reported that the aforementioned changes are associated with total restore of BrS and vagal tonus, as well as sympathoinhibiton[26,47,48]. Regarding BrS, the effects of PE have been cited since the late 1990s[69]. In a seminal experiment, for example, Brum et al.[70] observed that after 13 weeks of low-intensity aerobic PE the AP range for triggering baroreceptor activation and the relation between the baroreflex discharge and changes on SAP of aSHR were increased in comparison with sedentary animals[70].

Interestingly, changes in cardiac and peripheral autonomic control after PE seem to occur through the afferent baroreceptor modulation68. In fact, experiments have indicated that aSHR submitted to sinoaortic denervation presented no alteration on BrS, HRV and SAP after PE protocol[68].

Results from experiments on aSHR have contributed to understanding the effects of PE on the expression and activity of hypertensive elements in the brain areas responsible for cardiovascular control. Nevertheless, evidence were not limited to this specific issue, also demonstrating a possible correlation with cardiovascular function.

In fact, data demonstrate that low to moderate and moderate PE can cause significant decrease on RAS in the brain areas responsible for cardiovascular control of SHR. Data indicate lower mRNA expression of Aogen, ACE and AT1R in the NTS and RVLM of trained aSHR in comparison with sedentary aSHR[34,54]. On the other hand, ANG (1-7) pathway components (i.e., ACE2 and Mas receptor) showed elevated expression in the RVLM after exercise[34]. Similarly, ROS generation, NAD(P)H subunits (i.e., $p47^{phox}$, $gp91^{phox}$) activity, phosphorylated ERK ½ and IKKβ, NFκB translocation and proinflammatory cytokines synthesis (i.e., IL-6 and TNF-α) were lower in the PVN, RVLM of aSHR[33,34,47,48]. Noteworthy, such alterations on gene expression and activity seem to be correlated with cardiovascular control since decrease on RAS components and proinflammatory cytokines are correlated with improved BrS and AP decrease[47,54].

In an interesting experiment, Masson et al.[47] described the time-course changes in the expression of the aforementioned pathways in the PVN of aSHR[47]. During 8 weeks, animals were submitted to low-to-moderate intensity PE, which occurred 5 days per week, 1 hour per day. To evaluate the time-course, evaluations occurred before the start and during the 1st, 2nd, 4th and 8th weeks of the PE program. Results showed that PE was capable of causing significant decrease on ROS, ERK1/2 phosphorylation, NFκB translocation and proinflammatory cytokines synthesis in the first two weeks of exercise[47]. These results remained during the next weeks of training and were accompanied by an increase on autonomic cardiac control[47].

In addition, experiments have demonstrated that PE can change the pattern of neurotransmitters release in PVN, as demonstrated by Jia et al.[33], who submitted aSHR to 16 weeks of moderate-intensity aerobic exercise (60% of maximal aerobic velocity, 5 days per week, 60 min per day). After exercise, authors observed lower levels of excitatory neurotransmitters — glutamate and NA — and high levels of inhibitory neurotransmitters — GABA — in the PVN of SHR[33].

Table 1 shows a summary of the pathophysiological elements present in SHR, as well as the effects of PE.

Table 1. Physiopathological characteristics observed in SHR and the effects of PE

Physiopathological characteristics	Effects of PE
Hemodynamic	
↑ Blood pressure	↓
Vascular	
↑ Adventitia CSA	↓
↑ Media CSA	↓
↑ Intima CSA	↓
Hypertrophy of smooth cells	↓
↑ mRNA expression of genes associated with vascular remodelling	↓
Endothelium	
↑ ROS	↓
↓ Antioxidant activity	↑
↓ endothelium-dependent dilation	↑
Cardiovascular autonomic control	
↑ Cardiac sympathetic activity	↓
↑ Perypheral sympathetic activity	↓
Central Nervous System	
↑ RAS activity	↓
↑ Oxidative stress	↓
↑ PICs	↓

CSA: Cross-sectional area; PE: Physical exercise; PICs: Proinflammatory cytokines; SHR: Spontaneuos hypertensive rats; RAS: Renin-angiotensin system; ROS: Reactive oxygen species.

Myocardial infarction

As aforementioned, CVDs are the leading cause of mortality worldwide[1]. Among them, coronary artery disease (CAD) stands out due to its high risk of death[11].

CAD has, as the main characteristic, the formation of atherosclerotic plaque in medium and large arteries. In summary, atherosclerotic plaque starts to build up due to endothelial dysfunction, which increases the permeability of the arterial intima layer to plasma lipoproteins — such as low-density lipoprotein (LDL), favoring the retention of such elements in the subendothelial space, when, later, in association with inflammatory markers (e.g., macrophages), the lipoproteins will undergo oxidation, forming the oxidized LDL (oxLDL)[71]. This phenomenon is followed by a myriad of inflammatory events, which have the formation of foam cells through phagocytosis of oxLDL by macrophages as the final event of the pathway[71]. It should be noted that the formation of oxLDL is associated with the quantum of available LDL in the plasma. Therefore, a higher number of LDL in the plasma will lead to increased formation of oxLDL and, consequently, of foam cells[71].

Once developed, atherosclerotic plaque is composed of a cholesterol-rich lipid and a collagen-rich fibrous cap. The lipid content of the atherosclerotic plaque is the element responsible for its integrity, since disruption of this structure leads to formation of thrombus, which, if in contact with coronary circulation, can impair myocardial blood flow, thus causing ischemia and, possibly, MI[71]. Therefore, MI is defined as myocardial cell death due to prolonged ischemia[72].

Studies using animal models are conducted to provide better understanding concerning the effects of PE pre and post MI. The most widely used protocol of MI in animals, mainly rodents, is occlusion of left anterior coronary artery. The MI surgery is conducted with the rat anesthetized with ketamine (80mg/kg) and xylazine (12mg/kg). After intubation, animals are positive-pressure ventilated with room air at 2.5mL, 65 strokes/minute with a pressure-cycled rodent ventilator. To induce MI, a 2-cm left lateral thoracotomy is performed in the third intercostal space, and the left anterior descending coronary artery is occluded with a nylon (6.0) suture at approximately 1 mm from its origin below the tip of the left atrium. It is important to mention that studies generally use a sham group, which is also submitted to the same procedures, except for myocardial ischemia, which was not induced in this case[73,74].

Following myocardial ischemia, it is possible to observe a substantial myocardial tissue loss, resulting in increased cardiac load that, in turn, induces ventricular remodeling of the infarcted border zone and the remote non-infarcted myocardium. Myocyte apoptosis, necrosis, and the resultant increased hemodynamic load activate multiple biochemical intracellular signaling that triggers left ventricular (LV) dilatation, hypertrophy, ventricular structure distortion, and collagen scar formations. Progression of MI observed in rats shows a similar pattern compared to that observed in human beings, since they have an altered survive rate and, after four weeks, present a phenotypic condition observed in HF[75].

The effects and mechanisms of PE on MI: evidence from the surgical MI model

PE is a non-pharmacological therapy widely recommended for CVD patients, which has been demonstrated to be effective in improving endothelial function[76], BrS, autonomic function[77], as well as reducing tissue and systemic inflammatory state[78].

Such improvements can be identified in human beings with tools already validated. Moreover, these evaluations are relatively easy and non-invasive if performed by an experienced evaluator, since, sometimes, just blood is necessary. However, in order to thoroughly evaluate the molecular, cellular and physiological mechanisms involved in these improvements, experimental models are necessary.

In fact, guidelines for rehabilitation programs in MI patients recommend that low-intensity PE starts approximately 1 month after MI[5]. However, animal studies have shown that if PE starts as soon as possible after MI this can further improve heart function, increasing maximum stroke volume, ejection fraction and attenuating the deterioration of LV contractility. These beneficial effects may be associated with PE-induced proliferation of cardiomyocytes, angiogenesis, attenuation of apoptosis in cardiomyocytes, due to improvement of myofilaments and management of intracellular calcium (Ca^{2+})[79].

It is known that — during and after MI — neurohumoral changes occur in order to minimize the consequences of reduced ventricular function and, consequently, cardiac output. On the other hand, chronically, autonomic imbalance is usually followed by abnormalities in cardiorespiratory reflex control, leading to impairment of BrS and function, and increased activation of ergoreflex and chemoreflex. In turn, evidence shows that PE allows for the improvement of autonomic function and subsequent reduction of mortality in humans[77].

In this sense, in order to identify the mechanisms associated with improvement in autonomic function after PE in MI, Jorge et al.[80] tested the effects of early aerobic exercise training on LV and autonomic function, hemodynamics, tissue blood flow, and mortality rate after MI in rats. Results from PE demonstrated that the intervention induced improvement of cardiac function (i.e., systolic and diastolic), followed by normalization of hemodynamic and regional blood flow, as well as improvement of autonomic control of peripheral circulation (i.e., BrS and increase on pulse interval [PI]) and cardiac function. Furthermore, the authors observed increased SERCA2 and VEGF mRNA expression in LV. However, these benefits resulted in significant reduction in mortality rate in trained animals. According to the authors, the fact that early training restored autonomic control of circulation – represented by BrS and HRV – suggests that training may not only increase reflex responses mediated by the parasympathetic nervous system, but also suppress the influence of the sympathetic nervous system on ischemic heart disease. Moreover, elevated SERCA2 and VEGF mRNA expression suggests that these improvements are associated with alterations in intracellular calcium handling and blood supply.

Nerve growth factor (NGF) inducing cardiac sympathetic nerve sprouting is another characteristic observed post-MI. This phenomenon causes substantial sustained increase in sympathetic activity, resulting in downregulation and desensitization of β1 and β2-adrenergic receptor (β1-AR and β2-AR, respectively), and in upregulation of β3-AR.

On the other hand, Chen et al.[79], assuming that several evidences indicate that PE decreases sympathetic activity after MI, investigated whether such phenomenon occurred by inhibition of sympathetic nerve sprouting and restoring of β3-AR/β1-AR ratio.

Results from the aforementioned study showed that PE inhibits cardiac sympathetic nerve sprouting and restores β3-AR/β1-AR balance after MI; which seems to occur due to increase in mRNA expression of β3-AR. Moreover, authors observed increased activation of NO synthase 1 (NOS1) and NOS2 in the heart of animals submitted to PE, indicating possible modulation of β3-AR through NO pathway. Therefore, considered together, these results indicate that the protective effect of PE in MI can be modulated by β3-AR/NO pathway[79].

In fact, it is known that after MI, β3-AR is upregulated and activated due to high availability of NA. Dissimilar from the other β-receptor subunits, β3 seems to play a protective role after MI, acting as a counterregulatory mechanism during sympathetic overstimulation. Activation of β3-AR induces NO production, which, in turn, is associated with NOS1 activity. NOS1 signaling leads to increased cardiac calcium cycling, followed by enhanced cardiac contraction and accelerated relaxation[79].

Thus, the authors suggested that the beneficial effects of β3-AR stimulation after PE are associated with the activation of NOS2 and NOS1, and the normalization of β-AR balance.

Regarding menopause, its main characteristic is the loss of the cardioprotective effects of estrogen, including on autonomic function. In this sense, Flores et al.[81] investigated the effects of PE in MI-rats with ovarian hormone deprivation. Results demonstrated PE-induced improvement in cardiopulmonary BrS, which was correlated with improvement in the autonomic control, represented by increased vagal tone in trained animals.

These data are confirmed by Rondon et al.[82], who observed that the improvement in BrS induced by exercise training in infarcted rats is due, in part, to increased aortic depressor nerve activity, concomitantly with improving cardiac vagal modulation.

Studies have not been exclusively developed in order to verify the effects of PE after MI, but also its cardioprotective effects. In the experiment of Bozi et al.[83] and Rodrigues et al.[74], for example, the authors conducted a study in which rats performed aerobic exercise training for 8 weeks prior to MI surgery. After MI event, trained rats showed a smaller infarct extension and sympathetic activity, as well as increased BrS, and parasympathetic modulation compared with sedentary infarcted animals. Additionally, Rodrigues et al.[74] observed that improvements in autonomic balance and in parasympathetic modulation were strongly correlated with structural, systolic, diastolic and global LV function.

A recent study aimed to explore the effects of prior PE on the inflammatory aspects associated with MI. In fact, Santos et al.[84] evaluated rats exercised prior MI and observed that exercise training modulated proinflammatory cytokines response triggered by MI. Furthermore, exercise group showed increased PPAR-α. This molecule is a ligand-activated transcription factor that modulates the activity of genes involved in energy metabolism

regulation and inflammatory processes, acting as a suppressor of the inflammatory state.

In the control group, negative correlation between TNF-α and NF-κB was observed. However, these results were not observed in the trained group, which seems to be mediated by PPAR-α activation. Therefore, these data demonstrated that previously exercised animals had lower levels of local inflammatory markers and less myocardial apoptosis, which seemed to be related to the presence of PPAR-α.

It is important to mention that due to significant functional loss in MI patients, mainly due to exacerbated muscle atrophy, resistance exercise was recommended as a complementary type of PE in relation to aerobic exercise. In this sense, Grans et al.[116] evaluated the effects of dynamic resistance training on cardiac and hemodynamic function, as well as cardiovascular autonomic control after MI in rats. Results demonstrated that resistance exercise did not improve cardiac function. On the other hand, PE improved exercise tolerance and prevented additional loss in cardiovascular autonomic modulation.

Interestingly, Barboza et al.[85] conducted one of the few studies that aimed to understand the effects of detraining on cardiac function, BrS, and mortality rate. To this end, MI rats were submitted to PE for 3 months with subsequent 1 month of detraining. The authors observed that PE reduced the infarcted area, concomitantly with improvement on systolic and diastolic functions, on BrS and reduction on mortality rate. Moreover, the detraining period was not enough to reverse the beneficial outcomes resulting from PE.

Table 2 presents a summary of the physiopathological elements present in MI rats, as well as the effects of PE.

Table 2. Physiopathological characteristics observed after MI in rats and the effects of PE

Physiopathological characteristics	Effects of PE
Heart morphology and function	
↑ Akinetic LV area	↓
↑ LV mass	↓
↓ EF shortening	↓
Cardiovascular autonomic control	
↓ BrS	↑
↓ Cardiac sympathetic activity	↓
↓ Cardiac parasympathetic activity	↑
Cardiac calcium handling and Inflammation	
↓SERCA2	↑
↑PICs	↓
Outcomes	
↓ Exercise tolerance	↑
↑ Mortality rate	↓

BrS: Baroreflex sensitivity; EF: Ejection fraction; LV: Left ventricular; PE: Physical exercise; SERCA2: sarcoplasmic reticulum Ca2+-ATPase; PICs: Proinflammatory cytokines.

Heart Failure

Heart failure (HF) is a complex clinical condition that occurs in response to ventricular dysfunction due to structural and functional alterations in the heart, which lead to decreased capacity of the heart to pump blood to itself and to the periphery[5,6,86]. To counteract such alterations, in an attempt to regulate CO, neurohumoral compensatory mechanisms (e.g., the sympathetic nervous system [SNS]) are increased during HF[87]. Although, initially, this phenomenon seems advantageous, chronic activation of the SNS has a toxic effect on the organic system of HF patients[87].

In this sense, in order to study the relation between hyperadrenergic activity and HF, α_{2A}/α_{2C} adrenergic receptor (AR) knockout (KO) mice was developed by mating two heterozygous C57B16 mice: a α_{2A}-ARKO and a α_{2c}-ARKO[88]. During the first months of life (1st to 4th month), these animals present no evident signals of HF, although muscular and cardiac abnormalities may be observed in this period[88].

In fact, exercise intolerance, pulmonary edema associated with ventricular dysfunction (e.g., lower fractional shortening), and cardiac remodeling (e.g., cardiac hypertrophy) are significantly highlighted from the 5th month of life[89,90,91]. The development of HF reaches the peak during the 7th month when it is proposed that these animals developed a severe HF phenotype[91,92,93]. In addition to the high mortality rate found in α_{2A}/α_{2Ca}ARKO mice, the animals present rest tachycardia and increased plasma NA levels due to increased adrenergic activity[92,93,94,95.]

Cardinal manifestations in HF patients involve limited muscular and cardiac functioning, leading the patient to poor prognosis[6]. Regarding muscular functioning, skeletal myopathy consists of intrinsic alterations in skeletal muscle observed during HF, which are indicated to be responsible for exercise intolerance and early fatigue[96,97]. This condition is one of the main features present in cardiac cachexia syndrome and is strongly associated with poor outcomes[96]. In addition to the alterations in skeletal muscle structure and function, skeletal myopathy is associated with a shift toward fast twitch fibers, oxidative stress, local and systemic inflammatory state (i.e., elevated TNF-α), and muscle metabolic dysfunction (i.e., mitochondrial respiration, energy transfer system and pH regulation) in response to stress[93,96,98,99,100,101].

This phenotype is not well established in 3-month old α_{2A}/α_{2Ca}ARKO mice[90,92,102]. However, from the 5th month of life, these animals present suggestible muscle profile of skeletal myopathy due to decreased motor performance (i.e., Rotard test), increased oxidative stress (i.e., lipid hydroperoxidation and protein carbonylation), gastrocnemius capillary rarefaction, muscle atrophy of type I and type II fibers and, due to all these factors, exercise intolerance[89,91,93,95,101,102].

Catabolic (i.e., ubiquitin-proteasome system [UPS]) and anabolic muscle pathways (i.e., insulin growth factor-1 [IGF- 1]) are not exclusively associate with muscle mass homeostasis during aging and stroke[57], to name a few, but also seem to be present in skeletal myopathy of HF[93,101]. Observations in α_{2A}/α_{2Ca}ARKO mice with established congestive HF (i.e., 7 months of age) showed that these animals present decreased IGF-1 protein content, and phosphorylated AKT^{Ser473}, $4E\text{-}BP1^{Thr37/46}$, $p70S6K^{Thr389}$ and $GSK3\beta^{Ser9}$ protein content, as well as increased 26S proteasome activity, in

soleus muscle[93]. Moreover, evidences allow to infer that catabolic pathways are activate by oxidative stress and inflammatory state[99,101]. Besides muscular functioning disorders, several levels of alterations — functional and structural — are observed in the heart of HF patients. In relation to cardiac function, is knowledge that HF associated with hyperadrenergic activity is followed by calcium (Ca^{2+}) cardiac kinetics impairment.

It is important to mention that Ca^{2+} has a crucial role in cardiac excitation-contraction coupling (ECC), since this molecule regulates muscle contraction acting as a critical intermediary between the electrical stimulus and the coupling of actin. Here, it is described an overview of this phenomenon, while more detailed and extensive reviews were performed by several authors[103,104,105].

Initially, to generate cardiac systole, the action potential propagates trough the membrane of the cardiomyocyte leading to its depolarization (from ~ – 90mV to ~+20mV) and, consequently, opening of the voltage-gated sodium (Na^+) channels, mainly $Na_y1.5$, allowing Na^+ influx[103,105]. The crescent increase on ion Na^+ concentration alters the membrane voltage, until reaching the threshold to the opening of the L-type voltage-gated Ca^{2+} channels — in this case, $Ca_v1.2$[105]. Subsequent to the increase in cytosolic Ca^{2+} bioavailability (~10-fold), the ryanodine receptors 2 (RyR2) — the predominant subtype of RyR in the cardiac sarcoplasmic reticulum (SR) — are activated by a Ca^{2+}-dependent mechanism, leading to Ca^{2+} release in the junctional zone — a space between cardiac sarcollema and SR —, which, subsequently, migrates to the cytosol, binding in its site on the troponin C, allowing for muscle contraction through actin-myosin interaction[103,104,105]. During cardiac diastole, a decrease in Ca^{2+} bioavailability is necessary to cause cardiac muscle relaxation[104,105]. This process is dependent on proteins involved in transsarcolemmal flux and sarcoplasmic reuptake of Ca^{2+}[103,105]. Regarding transsarcolemmal flux, $Na^+/Ca2^+$ exchanger (NCX) is one of the main cellular mechanisms responsible for the clearance of Ca^{2+} in the cardiomyocyte[103]. NCX is located in the cardiac cell membrane and — through the electrochemical gradient — exchanges one $Ca2^+$ ion to the extracellular milieu at the same time that uptakes three Na^+ ions[103,105]. The sarco/endoplasmic reticulum Ca^{2+}-ATPase protein 2a, henceforth denominated as SERCA2a, is another important cardiac structure with key role in calcium handling[103]. During cardiac systole, SERCA2a remains inhibited by dephosphorylated phospholamban (PLN)[103,105]. However, after its phosphorylation by PKA and Ca^{2+}/calmodulin-dependent protein kinase (CaMKII), PLN allows SERCA to sequester $Ca2^+$ from cytosol, contributing to cardiac relaxation[103,104,105]. It is important to mention that other structures, such as plasma membrane Ca^{2+} ATPase (PMCA) and the mitochondrial uniporter seem to contribute, in a lower magnitude, to Ca^{2+} clearance during cardiac diastole[103].

The failing heart is characterized by marked contractile (i.e., systolic and diastolic) dysfunction and high prevalence of arrhythmias, which has been considered, at least in part, as a result of decreased SR Ca^{2+} handling[104,105,106]. In fact, *in vitro* experiments with human HF cardiac cells demonstrated smaller amplitude of Ca^{2+} transient, followed by lower SR Ca^{2+} content and load, as well as slow decline of Ca^{2+} during action potential depolarizing in comparison with healthy hearts[107].

Moreover, detailed analysis adds data to the aforementioned and mentions several other alterations on cardiac Ca^{2+} transient, such as decreased Ca^{2+} sequestration during cardiac diastole, decreased SR Ca^{2+} stores during cardiac systole, elevated Ca^{2+} availability during cardiac diastole and elevated SR Ca^{2+} leak — which is the inappropriate Ca^{2+} release during diastole[104,105]. Interestingly, authors have suggested the key role of SERCA2a and RyR2 in this phenotype[104,105].

Regarding cardiac SERCA2a, experiments have demonstrated a decrease of 57% on its activity in HF hearts[107]. This phenomenon seems to be strongly associated with decreased cardiac Ca^{2+} uptake during diastole, concomitantly with increased inhibition on PLN[104]. In turn, in the experiment of AI et al.[106], the authors observed decreased RyR2 mRNA and protein expression in the LV of HF rabbits[106]. However, during chronic hyperadrenergic state, which is present in HF, activation of cardiac β-receptors leads to decrease on calstabin 2 and increase on PKA phosphorylation at Ser 2808 causing "leaky" of RyR2 and, consequently, diastolic SR Ca^{2+} leak[104].

SERCA2a, NCX and SERCA2a/NCX are decreased by 26% and 34%, respectively, in the heart of α_{2A}/α_{2Ca}ARKO mice[92,94]. Concomitantly, it is possible to observe increase on NCX[94]. In relation to RyR2, its expression is not changed in α_{2A}/α_{2Ca}ARKO mice[92].

Due to several compensatory stimuli, including hyperadrenergic activity, HF patients may present cardiac remodeling, which involves the combination of several mechanisms. Cardiac hypertrophy is the major pathophysiological response to stress in HF. Initially, the hypertrophic response is beneficial, since it minimizes parietal stress and maintains contractile performance. However, over time, this response becomes harmful, aggravating HF. Nevertheless, such response is usually related to detrimental changes in the components of extracellular matrix, reduced myocardial vascularization, and fibrosis[87,108,109].

Cardiac fibrosis is caused by excessive accumulation of collagen in the heart during pathological remodeling. As a result of fibrosis, electrical conduction is impaired and the risk of arrhythmias is increased[110,111]. The development of fibrosis alters the normal operation of the extracellular matrix and may lead to systolic and diastolic dysfunctions. The fibrotic tissue also contains myofibroblasts with contractile properties, participating in the collagen regulation. In response to paracrine and autocrine components, such as circulating hormones, mechanic stress, and proinflammatory cytokines, and segregation of fibrillar collagen precursors, as well as signaling molecules responsible for the interaction between parenchymal cells and extracellular matrix[111].

Another mechanism involved in cardiac remodeling is oxidative stress, which may impair the contractile function — through changes in the proteins that participate in the excitation-contraction coupling — and activate signaling kinases hypertrophy, activate matrix metalloproteinases, and trigger apoptosis[112]. In this sense, cardiomyocyte apoptosis mechanism has been considered fundamental in the progress of HF. The apoptotic rate occurring in HF is small; however, this phenomenon has a larger influence on myocardial structure and function. Apoptosis begins by activation of caspases (cysteinyl-aspartate-directed proteases), which cleave vital substrates causing cell death.

Caspase substrates in the heart comprise, for example, troponin, tropomyosin, α-actin, and myosin chains[113].

Apoptosis may occur by the extrinsic or intrinsic pathways. Briefly, in the extrinsic pathway, a death binder (such as FasL or TNF-α) activates a death receptor, triggering the death-inducing signaling complex, activating caspase-8, which, in turn, activates caspase-3, causing apoptosis. In the intrinsic pathway, mitochondria are essential to mediate the apoptotic process. The mitochondria release cytochrome c into the cytosol, causing the formation of an activation complex — the apoptosome — containing apoptotic protein activating factor-1 and caspase-9, leading to activation of other caspases, such as caspase-3[114].

In 5–7-month old α_{2A}/α_{2Ca}ARKO mice, it is possible to observe increased heart height, LV mass, cardiomyocyte width and CSA, as well as cardiac fibrosis and collagen volume, suggesting a phenotype generally observed in remodeled hearths[89,91,94,95,102]. In the study of Pereira et al.[90], quantitative morphometric analyses indicated that cardiomyocyte width and cardiac collagen were, respectively, 28% and 55% increased in α_{2A}/α_{2Ca}ARKO mice in comparison with age-matched control[90].

Nevertheless, the failing heart of α_{2A}/α_{2Ca}ARKO mice show, associated with structural alterations, decreased fractional shortening (FS) and increased LV dilation linked to increased left ventricular end-systolic dimension (LVSED) and left ventricular end-diastolic dimension (LVEDD), characterizing LV dysfunction phenotype[89,94,95,102].

The effects and mechanisms of PE on HF: evidence from α_{2A}/α_{2C}ARKO

Physical inactivity contributes to the progression of HF, whereas PE has been widely recommended as a non-pharmacological therapy capable of counteracting the deleterious effects of HF on the organic system[4,97,109].

Evidence have demonstrate the effectiveness of moderate intensity PE (i.e., 60% of the maximal workload, 1 hour per day, 5 days per week, for 8 weeks) to increase exercise tolerance in α_{2A}/α_{2Ca}ARKO mice to levels similar to those observed in age-matched WT[90,93,94,95,96,97,101]. Of interest, PE does not seem to act just by reversing the deleterious effects of HF in muscle functioning in the established pathology, but evidence has indicated its action in preventing the development of such effects[92,102].

In fact, in the experiments of Medeiros et al.[92,115], low-to-moderate swimming trained 3-month old α_{2A}/α_{2Ca}ARKO mice (5 days per week, 60 minutes per day, during 8 weeks) presented preserved exercise tolerance during the development of HF, in comparison with age-matched control[92,111]. Moreover, it is important to mention that inhibition of the development of exercise intolerance seems to be an adaptation exclusively in response to PE since data have demonstrated that treatment with β-blocker — carvedilol — did not alter exercise tolerance in α_{2A}/α_{2Ca}ARKO mice[102].

Such improvements in exercise tolerance after PE are probably associated with changes in the catabolic profile present in α_{2A}/α_{2Ca}ARKO, such as capillary rarefaction[93,102] . Recently, in the experiment of Bacurau et al.[93], HF mice submitted to low-to-moderate aerobic exercise presented elevated exercise tolerance and motor performance, as well as attenuated soleus muscle mass atrophy in comparison with age-matched control[93]. Authors also demonstrated that attenuated muscular atrophy could be associated with changes on regulating muscle mass pathways, since PE elevated the protein content of the anabolic arm (i.e., IGF-1, PI3K, phosphorylated AKT^{Ser473}, $4E\text{-}BP1^{Thr37/46}$, $p70S6K^{Thr389}$) and decreased the catabolic arm (i.e., proteasome activity)[93].

Functional and structural parameters in α_{2A}/α_{2C}ARKO also seem to be responsive to PE[109]. In fact, experiments have demonstrated the effectiveness of PE to lead to decreased Ca2+ decay, concomitantly with the peak of Ca2+ transient increase in the cardiomyocytes of α_{2A}/α_{2Ca}ARKO[95]. PE increases the balance between Ca^{2+} reuptake by SERCA2a and Ca^{2+} clearance by NCX[92]. These alterations on Ca^{2+} after PE are associated with improvement on cardiac function[91,95].

Regarding molecular mechanisms, PE increases SERCA2a and SERCA2A/NCX ratio toward control group levels[92,94]. This phenomenon is an isolated product of increase on SERCA2a since NCX levels are found decreased in the heart of α_{2A}/α_{2Ca}ARKO mice[92,94]. Furthermore, it is possible to observe an increase in the phosphorylation of PLN at Ser16 and Thr17 after PE[92,94,95].

Therefore, considered together, these data indicate that PE leads to significant phosphorylation of PLN at Ser16 and Trh17 removing its inhibitory effect on SERCA2a, thus contributing to enhanced Ca^{2+} transient observed in trained animals[95].

In turn, morphological alterations generally observed in remodeled hearts are impaired in trained α_{2A}/α_{2C}ARKO, since heart weight, cardiomyocyte width, LV mass, collagen content and cardiomyocyte CSA are decreased in these animals in comparison with sedentary age-matched control[89,95]. Considering these data it is possible to indicate that PE has an anti-remodeling effect on the heart of α_{2A}/α_{2C}ARKO mice[89].

Moreover, some studies have aimed to describe the mechanisms associated with the anti-remodeling effect of PE. Experiments demonstrated that PE is capable of triggering significant decrease on the translocation to the nucleus of elements strongly associated with cardiac remodeling, such as calcineurin and its downstream targets — NFATe3 and GATA-4 — in the heart of α_{2A}/α_{2C}ARKO[89]. It is important mention that, in the heart of sedentary mice, both results were increased and associated with elevated β-MHC expression, suggesting a key role of this pathway in cardiac hypertrophy[89]. However, other factors indirectly associated with cardiac remodeling (i.e., RAS system) also demonstrated responsiveness to PE, since ANGII and ACE activity were decreased, while ACE2 expression was increased, after PE[90].

Such post-PE improvements on cardiac Ca^{2+} handling, remodeling, and skeletal myopathy occur in conjunction with improving FS in α_{2A}/α_{2C}ARKO to levels similar to those observed in control non-KO mice[89,91,95,102]. As in skeletal myopathy, data indicate that PE can also act as a preventive tool, since 3-month old animals — without evident signals of HR — submitted to swimming exercise demonstrated preserved FS in comparison with sedentary mice[92].

Table 3 shows a summary of the physiopathological elements present in α2A/α 2CaARKO, as well as the effects of PE.

Table 3. Physiopathological characteristics observed in α2A/α 2CaARKO mice and the effects of PE

Physiopathological characteristics	Effects of PE
Musculosqueletal functioning-Outcomes	
↑ Muscle atropy	↓
↓ Exercise tolerance	↑
Cardiac calcium handling	
↓ SERCA2a	↑
↑ NCX	↓
↓ SERCA2A/NCX ratio	↑
↓ Phosphorylation of PLN	↑
Heart morphology and function	
↑ Heart weight	↓
↑ LV mass	↓
↑ Cardiomyocyte CSA	↓
↑ Calcineurin	↓
↑ NFATe3	↓
↑ GATA-4	↓
↑ β-MHC expression	↓
↑ RAS	↓
↓ FS	↑

CSA: Cross-sectional area; PE: Physical exercise; RAS: Renin-angiotensin system; EF: Ejection fraction; LV: Left ventricular; PE: Physical exercise; SERCA2: sarcoplasmic reticulum Ca2+-ATPase; NCX: Na+/Ca2+ exchanger; PLN: Phospholamban; MHC: myosin heavy chain; FS: Fractional shortening

Conclusions

In conclusion, when the ethical principles of animal experimentation are considered, the use of animals in Physical Education as a field of knowledge has gained great prominence, particularly in understanding the pathophysiological mechanisms of CVD and the effects of PE on parameters that are unquantifiable in humans. Moreover, considering the data observed in this review, it is possible to infer that animal models of CVD seem to be an efficient and reliable tool to study the mechanisms responsible for the effects of PE on CVD.

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