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REVIEW ARTICLE

Estrogen Deprivation and Myocardial Infarction: Role of Aerobic Exercise Training, Inflammation and Metabolomics

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Abstract: In general, postmenopausal women present higher mortality, and worse prognosis after myocardial infarction (MI) compared to men, due to estrogen deficiency. After MI, cardiovascular alterations occur such as the autonomic imbalance and the pro-inflammatory cytokines increase. In this sense, therapies that aim to minimize deleterious effects caused by myocardial ischemia are important. Aerobic training has been proposed as a promising intervention in the prevention of cardiovascular diseases. On the other hand, some studies have attempted to identify potential biomarkers for cardiovascular diseases or specifically for MI. For this purpose, metabolomics has been used as a tool in the discovery of cardiovascular biomarkers. Therefore, the objective of this work is to discuss the changes involved in ovariectomy, myocardial infarction, and aerobic training, with emphasis on inflammation and metabolism.

Keywords: Ovariectomy, estrogen, aerobic training, myocardial infarction, inflammation, metabolomics.

1. INTRODUCTION

Despite technological advances, cardiovascular diseases (CVDs) continue to be the leading cause of death in the world, surpassing even the number of cancer deaths and respiratory conditions [1, 2].

Generally in women, CVDs tend to appear later when compared to men due to the protective effect of ovarian hormones, such as estrogen [3]. Menopause is characterized by the drastic reduction of estrogen levels, culminating in changes in body composition, increased oxidative stress, central accumulation of fat and compromised vasodilation. These effects may increase the risk of CVDs, such as hypertension and atherosclerosis, which may result in myocardial infarction (MI) [4].

The prevention of CVDs is possible, in order to control the risk factors for these diseases [2]. The improvement of physical capacity and cardiorespiratory fitness has been pointed out as possible prevention [5].

In this sense, studies have already shown the efficacy of aerobic training (AT) in cardiovascular protection. However, the mechanisms involved have not yet been elucidated [6-8].

In this sense, the aim of this work is to discuss the changes involved in estrogen deprivation, MI, and AT, with emphasis on inflammation and metabolism.

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2. MENOPAUSE AND CARDIOVASCULAR RISK

In recent decades, CVDs remain among the leading causes of death worldwide. Recent research has shown an increase in CVD incidence and mortality in women <55 years, as well as in postmenopausal women [1].

Menopause is an impairment that includes loss of ovaries reproductive function and menstruation absence (amenorrhea), either occurring spontaneously with advancing age or secondary to other conditions, such as medication or surgery. In this sense, a significant number of women enter menopause early (<45 years) or prematurely (<40 years), due to hysterectomy with or without ovariectomy, chemotherapy, radiotherapy or surgeries [9, 10].

Hormonal changes that begin during the menopausal transition affect many biological systems [11]. Studies have provided evidence that early menopause can negatively impact neurological health. For example, the Mayo Clinic Cohort Study of Aging Oophorectomy revealed that early surgical induction of menopause increased the risk of ischemic stroke, Parkinson's disease, doubled the risk of dementia, increased risk of depression and anxiety as well as the risk of mortality due to neurological disorders increased fivefold [9, 12-19]. Interestingly, these damaging effects increase when the age at the onset of menopause decreases. Similarly, The Nurses Health Study found that premenopausal oophorectomy was associated with significantly increased risks for cognitive impairment, dementia, depression, anxiety, stroke, Parkinson's disease, CVDs - such as coronary artery disease (CAD) - fractures and mortality [20-22].

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In the past, estrogen was thought of as just a sex hormone; however, over time it has been shown that this hormone plays an important role in the regulation of behavioral and physiological events beyond the reproductive system. Estrogen has shown, for example, neuroprotective and neurogenesis effects *in vivo* and *in vitro* after ischemic stroke in animals [23]. Also, a drop in ovarian estrogen production can often cause debilitating physical symptoms, including heat waves and sweating, changes in sleep, urogenital atrophy, sexual dysfunction, changes in the central nervous system (CNS), mood changes and metabolic changes that predispose CVDs and diabetes [3, 11]. In particular, it has been shown that moderate to severe heatwaves and sleep problems are related to increased sympathetic nerve activity, based on the increase in LF / HF (low frequency / high frequency bands of heart rate variability) [24]. Also, estrogens are potent vasoactive hormones that promote vascular remodeling and elasticity, as well as regulate vasodilation and local inflammatory activity [3].

The reduction of circulating concentrations of estradiol in the climacteric period (transition from reproductive to non-reproductive life) promotes changes in the adipose tissue metabolism resulting in central accumulation of fat [25]. Postmenopausal estrogen deficiency leads to the activation of the renin-angiotensin system, supra-regulation of endothelin (a potent vasoconstrictor that increases sodium reabsorption in the kidney) and nitric oxide (NO)-mediated vasodilation impairment, thus increasing blood pressure (BP). Oxidative stress, increased by endothelins and angiotensin II, also results in increased BP and may contribute even more to an atherosclerotic process (Fig. **1**) [26].

Some studies have shown that estrogen may have an antioxidant and antiatherogenic effect [27], affect cholesterol metabolism and disposition, increase plasma levels of high-density lipoprotein [28] and protect coronary arteries against myointimal proliferation in premenopausal women [29]. Other studies have demonstrated the beneficial influence of ovarian hormones on cardiovascular autonomic control; es-

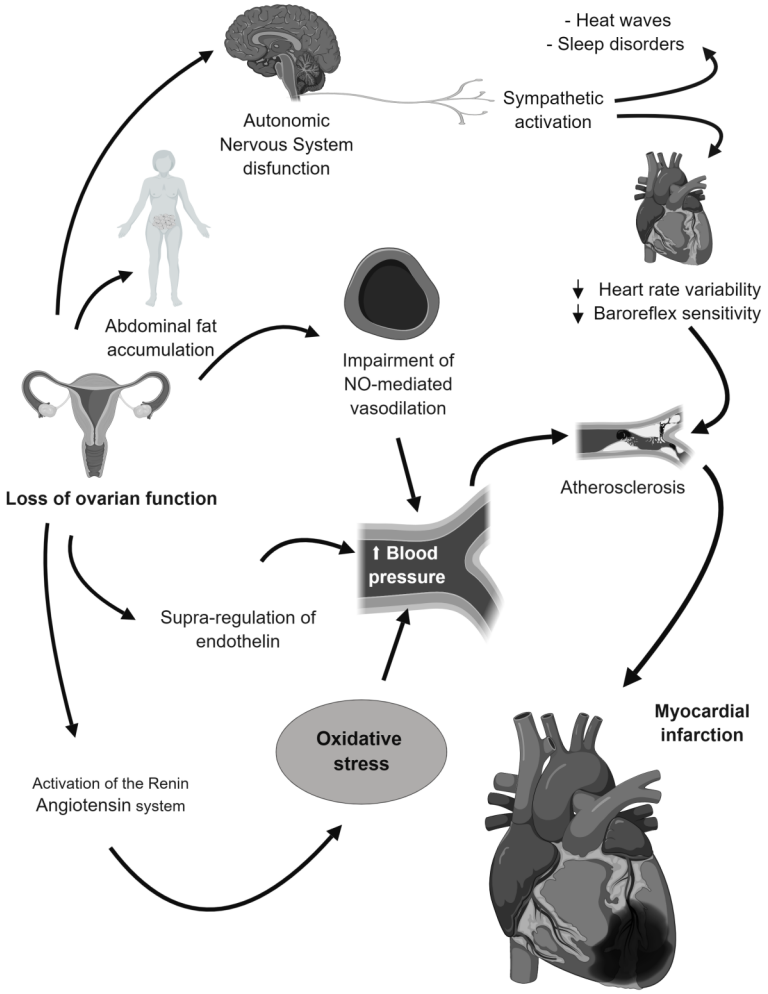

Fig. (1). Alterations triggered by the loss of ovarian function and myocardial infarction. Loss of ovarian function may lead to changes in the central nervous system. Increased sympathetic control triggers debilitating physical symptoms such as heatwaves and sleep disturbances, decreases heart rate variability and baroreflex sensibility. Menopause is also related to changes in adipose tissue metabolism, culminating in abdominal fat accumulation. Estrogen promotes vascular remodeling, elasticity, and regulates vasodilation and local inflammatory activity. Thus, postmenopausal estrogen deficiency culminates in vascular changes, activation of the renin-angiotensin system, supra-regulation of endothelin, and impairment of nitric oxide-mediated vasodilation that may increase blood pressure. In addition, oxidative stress, increased by endothelin and angiotensin II, also results in increased blood pressure and may contribute even more to an atherosclerotic process. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

trogen seems to be able to increase vagal influence in heart and to reduce cardiovascular sympathetic discharge [30-33].

As a result, studies on hormone deficiency in postmenopausal women have revealed additional autonomic damage, such as reductions in heart rate variability and baroreflex sensitivity [30, 34-36]. These changes appear to be directly related to the increase in cardiac sympathetic activity combined with the reduction in vagal influence [24, 37]. In addition, it has been shown that ovarian hormones also appear to influence the cardiac contractile response, suggesting a possible direct suppressive effect of ovarian hormones on the expression of cardiac β-adrenergic receptors in young rats submitted to ovariectomy [38,39], as well as in postmenopausal women [40]. In the latter case, the responses were altered with hormone replacement therapy. Changes resulting from estrogen deficiency may be responsible for elevated BP at rest and exaggerated pressure responses to exercise and mental stress in postmenopausal women [37]. Finally, ovarian hormone deprivation decreases the expression of oxytocin in oxytocinergic neurons of the paraventricular nucleus of the hypothalamus, culminating in baroreflex dysfunction and autonomic dysregulation [41].

Shortly after menopause, in addition to increased BP, women also have subclinical vascular disease, which can be observed by the increase in the carotid and femoral artery intima-media thickness, elevation of coronary calcium score and decline in endothelial function with increase in oxidative stress, arterial stiffness, as well as impairment of flow-mediated vasodilation [42-44]. The risk of stroke doubles during the first decade after menopause and exceeds that of men at higher ages [45]. These vascular events, however, tend to have a more severe prognosis in women, since within five years after the first MI, 18% of women and 8% of men aged 45-64 develop HF [46].

The gold standard in the preclinical field to evaluate the effects of ovarian hormones in animal models is the ovariectomy, or surgical removal of the ovaries, often abbreviated as OVX. A disadvantage for the OVX model in the context of translational research is that most women retain all of their reproductive tracts during the menopause transition. However, removal of the ovaries prior to the onset of reproductive senescence allows researchers to control the impact of particular hormones and the main elements of reproduction processes without aging as a confounding factor, making it possible to mimic the condition of menopause and to explore new avenues of intervention associated with already known health risks [47].

Studies have used a model of ovarian hormone deprivation in the investigations of cardiovascular, autonomic and inflammatory alterations in rodents, in the presence or not of associated comorbidities (such as hypertension, diabetes, and metabolic syndrome) [48-52] as well as the influence of physical training on these parameters. Thus, findings show that OVX may have an impact on body weight, triglyceride concentration, insulin sensitivity, aerobic exercise capacity, baroreflex dysfunction, and inflammation. AT in animal models has shown to be effective in mitigating these effects, reducing oxidative stress, lipoperoxidation and mortality, increasing NO bioavailability and antioxidant defenses in cardiac and renal tissues, improving the hemodynamic state at rest, reflex control of the circulation and the anti-inflammatory response with the increase of the interleukin-10 (IL-10) in the cardiac tissue [48-51].

Estrogen replacement therapy failed to decrease cardiovascular events in randomized clinical trials, such as the Heart and Estrogen/progestin Replacement Study (HERS) [53], the Estrogen Replacement and Atherosclerosis [54], the Women's Angiographic Vitamin and Estrogen (WAVE) [55] the Papworth HRT Atherosclerosis (PHASE) study [56] and the Women's Health Initiative (WHI) study [57] that provided the initiation of estrogen replacement therapy in elderly women after menopause and already established CAD. Thus, interventions to detect, prevent and mitigate the clinical and pathological consequences of ovarian hormone deprivation have been seen as new and important strategies in the prevention of CVDs in this population. Again, AT seems to be an important factor, since physically active women demonstrate higher levels of heart rate variability and baroreflex sensitivity compared to their sedentary pairs and better inflammatory profile [34, 58].

3. MYOCARDIAL INFARCTION

The clinical consequences of CVDs usually occur later in women than in men, so CAD usually manifests ten years later and MI with sudden death 20 years later [46]. The reason for the relative protection of women against the development of atherosclerosis before menopause is poorly understood. This protective effect may be related to natural estrogen levels before menopause [59]. The protection conferred by sex hormones may be important, since women with hormone disorders develop atherosclerosis and MI earlier compared to healthy women. Polycystic ovary syndrome, for example, maybe associated with early onset of multiple risk factors, such as abdominal obesity, dyslipidemia, and diabetes mellitus [60, 61]. Ovarian hormones have been also associated with a less atherogenic lipid profile and a healthier fat distribution. However, these differences are attenuated after menopause and may increase the risk of MI [61].

The role of estrogen and its receptor (ER) in cardioprotection is corroborated by the fact that even men with ERα (ESR1) mutation have early CAD and, in animal models of cardiac ischemia, ERα activation reduces myocardial infarction size, cardiomyocyte apoptosis, inflammation and oxidative stress, induces vasodilation and increases neovascularization [62, 63].

MI is defined as myocardial cell death as a consequence of prolonged ischemia [64]. It usually results from the conversion of an atherosclerotic plaque into an atherothrombotic lesion in the coronary arteries. The alteration of this plaque may lead to the formation of overlapping thrombi resulting from exposure to subepithelial collagen, platelet aggregation, and fibrin deposition, resulting in coronary tree obstruction and consequently in MI [65]. Therefore, MI is a dynamic process that does not occur instantly but progressively and evolves over a few hours. Complete necrosis of myocardial cells takes 2 to 4 hours, or more [64].

After coronary occlusion, there is a complex and interrelated sequence of events called: post-infarction left ventricular remodeling (LVR). This remodeling describes the com-

pensatory responses of the cardiovascular system when confronted with contractile function acute loss of the myocytes supplied by this artery [66]. In this sense, the myocytes may present areas of dyssynchrony, dyskinesia, hypokinesia, and akinesia. On the other hand, the non-infarcted myocardium presents hyperkinesia as a result of acute compensatory mechanisms, such as activation of the sympathetic nervous system, renin-angiotensin-aldosterone system and Frank-Starling mechanism [64, 67-69]. Ventricular remodeling process is characterized by the left ventricle (LV) dilation, ventricular wall structure rearrangement, and increase of the remaining muscle mass [66]. LVR may continue for weeks or months until the tensile forces are counterbalanced by the tensile strength of the collagen scar [67]. At the biochemical level, there is a fast decrease in aerobic metabolism, leading to the production of high energy phosphates and degradation products, such as H^+ ions and lactic acid. In addition, when ischemia is severe, loss of myocardial contractility occurs in 60 seconds, leading to early HF. Even so, damage caused by MI (necrosis) is irreversible only when ischemia is intense and prolonged for at least 20 minutes [65].

These compensatory mechanisms have a finite capacity to sustain cardiac function and are initially beneficial, maintaining cardiac output and perfusion to vital organs. However, when they are perpetuated, they become deleterious, when the remaining contractile tissue fails to maintain hemodynamics under normal conditions, the individual has a dilated and malfunctioning ventricle that eventually progresses to HF [76-72]. Neurohormonal activation increased sympathetic activity, and decreased parasympathetic activity, as well as the alteration in their respective receptors, which are characteristic of HF, may impair cardiac structure and function, promote changes in cardiorespiratory reflex control and baroreflex dysfunction and reduce the total heart rate variation [71, 73-78].

It is possible to evaluate myocardial lesion with necrosis through markers such as the MB (cardiac muscle) fraction of creatine kinase (CKMB), which is increased. Cardiac troponins I and T are contractile apparatus components of myocardial cells expressed usually in the heart, so the elevation of these biomarkers in the blood reflects a possibility of myocardial necrosis. In addition, normal turnover of myocardial cells, apoptosis, cellular release of troponin degradation products, increased cell wall permeability, and the formation of membranous blisters are possible structural protein release factors [64]. Necrosis completes around 6 hours, or 12 hours when there is an arterial collateral system stimulated [65].

For reasons that are still unknown, acute mortality in the first days after MI is higher in younger women than in men of the same age [79]. A cardiac rupture in acute MI has been reported more often in women than in men in studies in the United States, Europe, and Japan. These studies suggest that women die less frequently from arrhythmia, but more often from cardiac rupture [80-84]. In some, but not all studies, a higher in-hospital mortality rate after MI was observed in females, calculated based on age differences and associated comorbidities [85]. Thus, studies aimed at elucidating mechanisms associated with higher mortality and worse prognosis in women after a cardiac event are important, as well as the use of therapies that can prevent the most exacerbated consequences of MI in females associated with ovarian hormone deprivation.

In order to understand the effects of MI on the cardiovascular system and the autonomic nervous system in experimental models, occlusion of coronary artery branches has been used, showing both damages caused exclusively by MI and damage related to other risk factors such as hypertension, hyperglycemia, and diabetes [73, 86-96].

In this sense, these studies evaluated different therapeutic approaches in the management of MI deleterious effects and in the mortality index, such as mesenchymal and bone marrow stem cell therapy [88, 96] the inhibition of acetylcholinesterase by pyridostigmine bromide [77, 97] and AT, suggesting that it may attenuate dysfunctions related to baroreflex sensitivity and pulse interval variability, as well as the mortality induced by an ischemic event [75, 76, 77, 95, 98-100]. In addition, AT was shown to be important for the improvement of autonomic control, resting hemodynamic status and circulation reflex control, as well as the reduction of proinflammatory cytokines in animals submitted to IM [73, 99].

4. OVARIECYOMY, MYOCARDIAL INFARCTION AND METABOLOMICS

The heart needs to maintain adequate cardiac output to meet the needs of the body both in rest and effort [101]. Therefore, it is an organ that has a high energy demand and must produce a great quantity of ATP in order to keep it functioning [102]. Approximately 60-70% of the ATP hydrolysis increases the contractile shortening, and the remaining 30 to 40% is mainly used for the Ca^{2+} -ATPase pump and other ion pumps [103]. Most of these ATPs come from mitochondrial oxidative phosphorylation and the other part of glycolysis. In this way, the heart can use different substrates to produce energy, among them, fatty acids, carbohydrates, ketones, and amino acids. These substrates produce Acetyl-CoA that will participate in the tricarboxylic acid cycle (or Krebs cycle). In this cycle, reduced equivalents will be produced that will later enter the electron transport chain and together with the oxygen will produce ATP [102].

The healthy heart has some metabolic flexibility so that it can alternate between the fatty acids and carbohydrates oxidation depending on the workload and the supply of energy substrates. In this sense, the heart can produce the amount of energy required to sustain cardiac contractility against a variety of conditions [102].

For metabolites analysis (small endogenous molecules that are present in a single biological sample) on a large scale, the metabolomics is used [104]. This methodology has been widely applied as a new diagnostic tool in clinical and biomedical studies. The metabolic analysis has been used to understand the pathophysiological processes involved in the progression of the disease, as well as the search for new diagnostic or prognostic biomarkers of many comorbidities [105].

The non-target metabolomics is the unbiased analysis of all the metabolites presents within a biological system, under a given set of conditions. This process includes a selection of biological samples, pretreatment of the sample, the

configuration of the analytical conditions, data acquisition, data analysis by chemometrics, database search and biological interpretation. Thus, this method provides a holistic approach in the field of biomedical research, in order to improve the diagnosis of the disease and to understand the mechanisms involved in the pathology [106].

In this sense, several studies have attempted to identify, through metabolomic analysis, potential biomarkers for CVDs [107, 108]. In particular, clinical studies of metabolic changes in the plasma of infarcted individuals suggest potential biomarkers of MI, such as phytosphingosine, sphinganine, acetylcarnitine, adenine, and inosine [109-112]. However, circulating biomarkers can be easily influenced by many tissues, affecting their specificity. A study evaluated the metabolic profile of cardiac tissue - left ventricle - in the infarcted and non-infarcted area of rats [113]. The authors demonstrated that most of the fatty acids and intermediate metabolites of the tricarboxylic acid cycle are significantly decreased, the lactate and phosphate are elevated in the ischemic myocardium, which implies the greater decomposition and less synthesis of ATP and mitochondrial dysfunction after MI.

Also, plasma levels of each lipid class (phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, lysophosphatidylcholine, lysophosphatidylcholine, sphingomyelin, ceramide, triacylglycerol, diacylglycerol, and cholesterol ester, except for free fatty acids) in animals with a greater ischemic event were significantly elevated when compared to normal animals [114].

A study that compared the metabolic profile of ovariectomized rats and sham rats showed OVX-specific variables, including arachidonic acid, eicosapentaenoic acid, ergocalciferol, and cholecalciferol [117]. In addition, ovarian hormone deprivation induces increased levels of cholesterol, glycerol, glucose, arachidonic acid, glutamic acid, glycine, and cystine. These effects suggest that OVX implies changes in the glucose metabolism, energy metabolism, lipid metabolism, and amino acid metabolism [118]. In this sense, another study showed that early estrogen replacement after OVX may prevent oxidative stress and metabolic alterations [119]. However, studies that determine the metabolic profile of cardiac tissue of rats submitted to ovarian hormone deprivation and myocardial ischemia are scarce and deserve attention, since future biomarkers can be determined by such conditions.

5. CHOLINERGIC ANTI-INFLAMMATORY REFLEX

The immune system's main function is to defend the body against invading agents, thus triggering an involuntary inflammatory response in order to prevent pathogenic action. However, when the inflammatory response is insufficient, the individual may become immunodeficient and may develop infection or diseases such as cancer. On the other hand, an excessive inflammatory response can lead to morbidity and mortality in diseases such as rheumatoid arthritis, atherosclerosis, cerebral ischemia, and myocardial ischemia. In this way, the inflammatory response may cause more damage than the initial stimulus. However, homeostasis is restored when inflammation is limited by anti-inflammatory response [118]. Chronic systemic inflammation is one of the causes of metabolic syndrome in menopause [119]. In ovariectomized rats, AT inhibits visceral macrophage infiltration and attenuates inflammatory cytokines production [120].

Some studies show that there is a neural pathway that, through a reflex, modulates the inflammatory response [118]. It can be said that the immune system and nervous system are not independent so that both produce cytokines and neurotransmitters that bind to receptors involved in physiological functions [121]. In this sense, immunity is mediated by interactions between immune cells and immunocompetent cell products [122]. Although many studies have demonstrated the action of the sympathetic nervous system, recent studies have shown the anti-inflammatory potential of the parasympathetic nervous system through the vagus nerve [123-125]. Therefore, different studies have shown that the electrical and pharmacological stimulation of the vagus nerve restricts the release of cytokines, using the cholinergic receptor to mediate the anti-inflammatory action of acetylcholine in immune cells [113, 124, 125].

Anti-inflammatory reflex is composed of afferent and efferent signals transmitted by the vagus nerve in response to agents derived from infections (cytokines, PAMPs, DAMPs) [122]. The action of pathogens culminates in the cytokines production that signals the bulb through the vagal afferent pathway [126]. Signs of the efferent vagus nerve are then transmitted through the celiac ganglia, where the vagus nerve ends. Soon after, the signals are sent to the spleen *via* the splenic nerve [125]. Activation of adrenergic neurons occurs in the spleen, resulting in the release of norepinephrine in T cells that can release acetylcholine. Acetylcholine crosses the marginal zone and enters the red pulp where interaction occurs with the nicotinic subunit of the alpha 7 receptor (α7 nAChR) present in macrophages. The α7 nAChR transduction signal suppresses the synthesis and release of inflammatory agents (TNF, IL-1, IL-18, HMGB1, and other cytokines). In this way, the inhibition of the inflammatory reflex can also be done through the pharmacological activation of the splenic neurons with the use of cholinergic agonists [122, 127-129]. α7 nAChR is negatively controlled by the gene expression of CHRNA7 which mediates the ability of the vagus nerve to regulate the inflammatory response to lesions and infections and positively by CHRFAM7A which is elevated in human leukocytes and increases the inflammatory response [130].

Another mechanism of action α7 nAChR occurs through ligand-receptor interaction in cells expressing cytokines, so that, after binding to acetylcholine, α7 nAChR transmits cholinergic anti-inflammatory signals into the cytoplasm, activating Janus kinase 2 (JAK2) [126, 131, 132]. Phosphorylation of JAK2 subsequently triggers the phosphorylation of signal transducer and activator of transcription 3 (STAT3), promoting its dimerization. The phosphorylated STAT3 is translocated from the cytoplasm to the nucleus and competes with the nuclear factor kB (NF-kB). These alterations decrease the production of tumor necrosis factor alpha (TNF-α) and other proinflammatory cytokines, such as high mobility group 1 (HMGB1) proteins, macrophages inflammatory protein 2 (MIP-2) and interleukin 6 (IL-6). Also, the anti-inflammatory action of α7nAChR agonists or vagus nerve stimulation is associated with down-regulation of CD14 ex-

pression and toll-4 receptor (TLR4) in immune system cells [133]. Thus, increasing the bioavailability of acetylcholine in order to prevent the translocation of NF-κB as well as the expression of CD14 and TLR4 in response to endotoxins, injury, ischemia, and other stimuli may be essential for the reduction of pro-inflammatory cytokines [131, 132].

It is known that vagus nerve may play a key role in controlling inflammation through the cholinergic anti-inflammatory pathway, which is mediated by α7 nAChR in macrophages. However, intracellular mechanisms are not yet fully elucidated. In this way, other studies have sought to understand such mechanisms [124, 134, 135]. In their study, Sun (2013) has shown that micro-RNA 124, for example, modulates LPS-induced cytokine production (through STAT3) by decreasing IL-6 production and TNF-α release, an important mediator of cholinergic anti-inflammatory action [135]. Another study showed that vagal nerve stimulation regulated the expression of PPARγ (peroxisome proliferator-activated receptor gamma) that plays an important role in the anti-inflammatory response in the Central Nervous System, reducing the extent of ischemic infarction, suppressing both the expression of cytokines pro-inflammatory effects on immune cell activation. In this way, PPARγ may be involved in the process by which the vagal stimulation modulates the neuroinflammatory response in ischemia [136]. Finally, although many studies show the participation of the Autonomic Nervous System in the anti-inflammatory response, further studies are needed to understand the molecular mechanisms behind this reflex.

6. OVARIECTOMY, MYOCARDIAL INFARCTION AND ANTI-INFLAMMATORY REFLEX DAMAGE

It is already established that ovariectomy induces negative changes in autonomic control and inflammation, thus contributing to cardiovascular risk and MI [49, 50]. Several molecular and cellular processes appear to be particularly important for pathologic ventricular remodeling after MI. The communication between fibroblasts, myocytes, and endothelial cells, as well as the extracellular matrix, is critical for alterations in the composition and function of the heart during normal development and pathological condition. Thus, the production of inflammatory cytokines such as IL-6 and TNF-α by activated fibroblasts, monocytes/macrophages and cardiomyocytes after an ischemic event has been demonstrated as an important link in the direct and indirect interaction between these cell types, culminating in a robust pathological cardiac remodeling [137, 138].

In cardiac hypertrophy, both the excessive increase of cardiac myocytes (CMs) and progressive fibrosis occur simultaneously. Thus, communication between different cell types through inflammatory mediators in the interstitium of the heart leads to the formation of an important immunoregulatory network that can lead to disordered hypertrophy, cardiac fibrosis and, consequently, HF [138]. Therefore, interventions that aim to reduce proinflammatory cytokine production by different heart cellular components may lead to cardiac remodeling closer to a physiological one, attenuating the loss of cardiac function after MI [139].

The maintenance of inflammatory status after MI has many lines of investigation, and there is no consensus. The chronic autonomic imbalance that favors the increase of the activity of the sympathetic nervous system and, especially, the reduction of the parasympathetic has been pointed out as a potentially involved mechanism [140-144]. Thus, it is possible to suggest that the reduction of the parasympathetic regulation after the ischemic event could negatively affect the anti-inflammatory reflex, reducing the action of the cholinergic pathway [144]. However, although some suggestions in the literature corroborate this information [145-147], there is still no robust evidence supporting a cause-and-effect relationship. Thus, it is possible that preventing and attenuating the autonomic dysfunction triggered by MI (mainly the reduction of cardiac vagal activity), it could lead to a less intense inflammatory response, to the point of reducing structural and functional impairment cardiac.

7. AEROBIC TRAINING

Several studies have shown the benefits of a healthy lifestyle, such as improvements in the cardiovascular system, metabolic profile, autonomic control, inflammation, as well as functional benefits, thus suggesting BP as important non-pharmacological conduct in the prevention and treatment of CVD risk factors [148-153]. Also, AT is effective in reducing body weight, increasing insulin sensitivity and glycemic control, preventing obesity and diabetes mellitus, as well as alleviating anxiety and stress [154].

There is a large literature that reports the effects of physical activity and BP on the reduction of CVDs mortality, especially about their action on traditional risk factors [155-157]. Thus, studies show that regular AT improves cardiovascular health, reduces the risk of heart disease, cerebrovascular diseases and various chronic conditions such as hypertension, accelerated biological aging, sarcopenia, liver disease, osteoporosis, some type of cancer (such as colon and breast cancer) and rheumatoid arthritis, in addition to preventing motor disorders and oxidative imbalance arising from cerebral ischemia [154, 158, 159].

In addition, AT has been used as an important approach in the prevention of cardiovascular comorbidities associated with ovarian hormone deprivation [160]. Benefits include inhibition of oxidative stress in the myocardium, avoidance of hypertension, glucose intolerance, dyslipidemia, and heart disease [160, 161]. In ovariectomized rats, AT also increases hippocampal estrogen levels [162] and improves autonomic control [49, 50].

Trained menopausal women have decreased arterial stiffness. This effect can be explained by the increase of nitric oxide synthase and increased NO release [119]. Exercise can also alleviate menopausal symptoms [158], and improve quality of life [159]. Moreover, AT can increase anti-inflammatory response after menopause reducing the risk of CVD [119]. Vieira-Potter *et al.* (2015) suggest that improvement of mitochondrial function and reduction of inflammation due to exercise may improve immuno-metabolism of adipose tissue [163].

For healthy adults (18-65 years), the American Heart Association recommends AT of moderate intensity, with a minimum of 30 minutes per day and five days per week, or AT of vigorous intensity, for a minimum of 20 minutes per

day and three days per week for prevention and maintenance of health [164]. Mora *et al.* (2007) evaluated several factors such as lipids, inflammatory biomarkers, level of physical activity, weight, blood pressure and glycemia of 27,055 healthy women, showing that the risk of CVD decreased linearly with higher levels of activity [165]. Of these women, those who had reported levels of physical activity with energy expenditure greater than 1,500 calories per week, had a 40-60% reduction in the relative risk of coronary artery disease.

AT is also important in improving vascular alterations, including endothelial dysfunction, remodeling and arterial stiffness, present in type 2 diabetes, obesity, hypertension and metabolic syndrome (Fig. **2**) [166]. Another study has shown that AT concomitant with high fructose intake prevented metabolic, hemodynamic and diastolic dysfunction from developing metabolic syndrome [167].

In this sense, AT seems to have a preventive effect against these types of attacks, so that researchers have sought to identify the possible cardioprotective mechanisms of exercise to ischemia and reperfusion. Among these mechanisms, we can mention the alteration of coronary endothelial and vascular smooth muscle cell phenotype, the increase in the myogenic activity of the coronary arteries, the increase of angiogenesis and the decrease of arterial thickness [168, 169]. Another study suggested that elevation of heat shock proteins such as HSP-72 may increase cardioprotection against and ischemia and apoptosis [170]. The increased activity of myocardial cyclooxygenase (COX-2) seems to be related to late-phase ischemic preconditioning, thus having a protective effect. However, AT does not induce the increase of its expression [170]. A recent study showed that the combination of 17β-estradiol and AT had a positive protective effect on ovariectomy-induced cardiac apoptosis. This result suggests an important therapeutic ap-

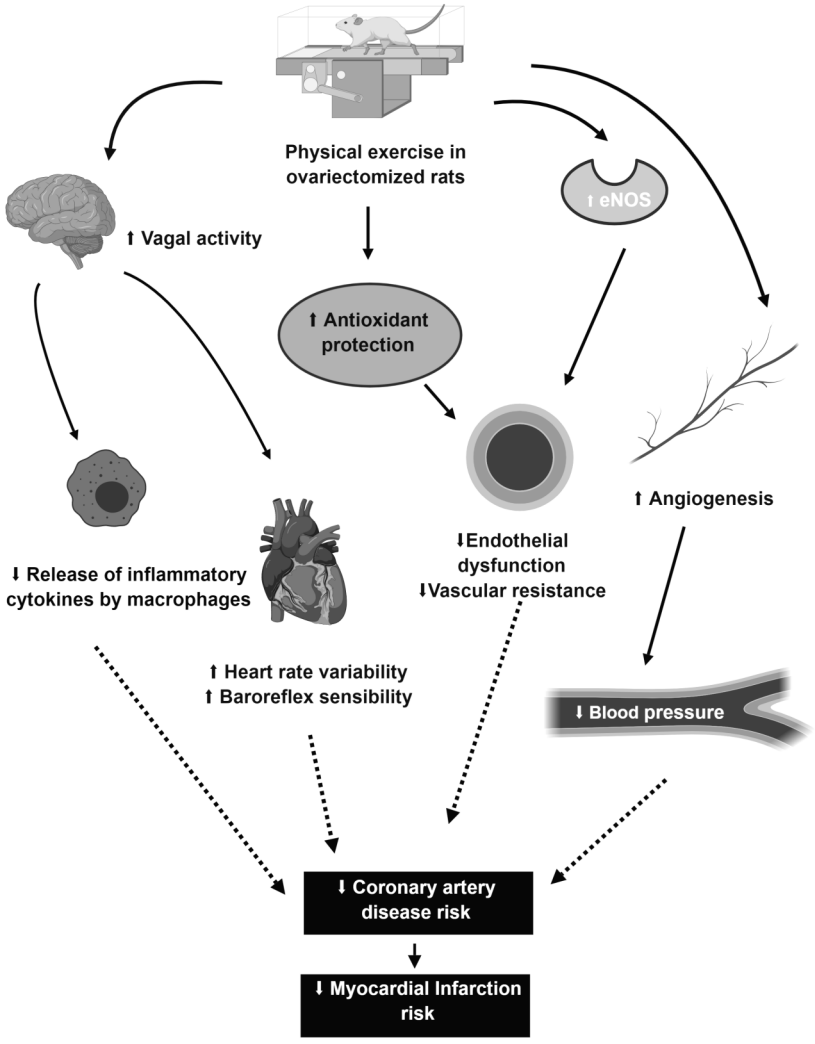

Fig. (2). Effects of aerobic training previously myocardial infarction. Physical exercise has a cardioprotective effect in increasing vagal activity. This change in the central nervous system culminates in increased heart rate variability and baroreflex sensitivity and decreased the release of pro-inflammatory cytokines through the cholinergic anti-inflammatory reflex. In addition, aerobic training culminates in angiogenesis, increased concentration of endothelial nitric oxide synthase (eNOs) and antioxidant protection. These factors decrease endothelial dysfunction and vascular resistance, culminating in lower blood pressure. These benefits are related to lower risk of coronary artery disease and consequently lower incidence of myocardial infarction. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

proach in cardiac protection in bilaterally oophorectomized or menopausal women [171].

Antioxidant protection is also important in preventing risk factors. Elevation of exercise-induced manganese superoxide dismutase (MnSOD) activity decreases the risk of arrhythmias [172]. Also, physical exercise plays an anti-inflammatory role, triggering protection against cardiovascular diseases and type 2 diabetes, decreasing TNF-α [173, 174].

Regarding the prevention of comorbidities associated with MI, some studies have used the physical exercise model performed before the ischemic event. However, the number of studies is still scarce, and the results are contradictory [99, 100, 175-179]. Dayan *et al.* (2005) showed that 3 weeks of swimming before the induction of acute myocardial infarction significantly decreased ventricular remodeling and improved LV function in Sprague Dawley rats [175]. The first swimming session lasted from 20 to 30 minutes and was gradually increased by 30 minutes each session to 90 minutes on the 4th day, and was maintained until the end of the training period (5 days/week). Freimann *et al*. (2005) showed that 8 weeks of swimming increased arterial density and manifested the adaptation of genes related to stress and energy metabolism that may contribute to improving cardiac function during cardiac remodeling in Sprague Dawley rats submitted to ischemia surgery followed by 4 weeks of detraining [179]. The rats were subjected to a daily swimming session six days a week for seven weeks. The first session was held in 15 minutes and the duration increased by 15 minutes each session, reaching 90 min on the sixth day and maintained until the end of the training. However, Veiga *et al.* (2011 and 2012) pointed out that 8 weeks of swimming do not attenuate changes in systolic and diastolic functions following myocardial infarction induced by left coronary artery occlusion, suggesting that cardioprotection cannot be provided by physical training in this experimental model with female rats [176, 178]. Training initially consisted of a 10-minute swimming session, increasing the time by 10 minutes per day until 60 minutes on the sixth day. The training was maintained for a total period of eight weeks, five days a week, 60 min/day.

Already in an experimental treadmill model, Bozi *et al.* (2013) showed that 8 weeks of AT attenuated cardiac dysfunction and structural deterioration promoted by myocardial infarction in Wistar rats so that such benefits were associated with morphological and contractile properties of preserved cardiomyocytes [177]. The running velocity, treadmill inclination, and session duration were progressively increased throughout the protocol, and up to the 6th week, the rats were continuously running for 60 min at 18 m / min with a slope of 10 °, these measures were maintained until the end of the protocol. Rodrigues *et al.* (2014) showed that the AT before an ischemic event is effective in altering the aerobic capacity, morphology and left the ventricular function in rats submitted to MI [99]. In addition, these cardioprotective effects were associated with attenuated cardiac autonomic dysfunction seen in trained rats. The AT was performed on a treadmill, in low to moderate intensity (maximum running speed of 50% -70%) for 1 hour a day, 5 days a week for 8 weeks, with a gradual increase of speed from 0.3 to 1, 2 km/h. Finally, a recent study with Wistar rats showed that before MI, AT prevented additional losses in aerobic capacity, left the ventricular function, baroreflex sensitivity and cardiovascular autonomic control (attenuating sympathetic tone increase and reduction of parasympathetic tone) after ischemia. The AT was performed on a treadmill in low to moderate intensity (50 to 70% of maximum running speed) for one hour a day, five days a week, for eight weeks. Based on maximum treadmill exercise tests, training velocities ranged from 0.3 to 1.5 km / h during the eight weeks of training [100].

There is already a great deal of evidence about AT as a tool in the treatment of patients with established CAD. Thus, a meta-analysis based on 48 randomized controlled trials (8940 patients) showed that, compared to usual care, cardiac rehabilitation programs based on aerobic exercise were associated with a reduction in all causes of mortality, total cholesterol and triglyceride levels, and systolic blood pressure. There were no significant differences in infarct rates and nonfatal myocardial revascularization, in high and low-density lipoprotein cholesterol levels and diastolic pressure. Health-related quality of life improved to similar levels both with cardiac rehabilitation and with usual care [180]. Another meta-analysis, based on 34 studies, pointed out that exercise, even for a short period (1 to 3 months), reduces reinfarction rates and all causes of CVDs mortality. In addition, it had favorable effects on cardiovascular risk factors, including smoking, blood pressure, body weight, and lipid profile. It is worth remembering that the overall benefits observed by the practice persisted beyond the period of active intervention after MI [181].

Thus, exercise is a physiological stressor that can have multiple beneficial effects on the cardiovascular system. Therefore, a better understanding of the molecular mechanisms related to such benefits is predictable. The evidence collected suggests that TA, if adequately prescribed and supervised, is a very important tool in the prevention of CVDs, especially CAD and HF [182, 183]. However, cardiac rehabilitation is still underutilized; only one-third of patients with CAD receive any form of intervention [182]. Also, inadequate levels of physical activity are said to be a major health risk in the 21st century [183].

A study of rats submitted to the deprivation of ovarian and infarcted hormones showed that eight weeks of AT were able to improve hemodynamic state at rest and reflex control of the circulation, probably due to an increase in the vagal component. This suggests a homeostatic role for AT in reducing the autonomic impairment of myocardial infarction in postmenopausal women [73]. In another study, Almeida *et al.* (2015) found improvement in the cardiac function associated, among other factors, to the attenuation of the cardiac remodeling, the decrease in the expression of reactive oxygen species and the increase in antioxidant defenses [184]. Trained infarcted rats showed a reduction in expression of both type 1 angiotensin II receptor and Gp91phox (a subunit of NADPH oxidase generating superoxide anions) when compared to untrained infarcted rats. Also, these rats presented increased catalase antioxidant enzyme, which contributes to the reduction of oxidative stress. There was also a decrease in the production of collagen, an important fact in

cardiac function since its increase impairs the force of ventricular contraction.

Thus, AT seems to be an important therapeutic target in the prevention and treatment of MI, especially with regard to the reduction of the chronic inflammatory response and autonomic remodeling and the improve of vagal activity to the heart, thus reducing cardiac work, the risk of fatal arrhythmias and the risk of HF, as well as increasing the survival of the affected individuals [73, 184]. However, there are still gaps in the knowledge of the cardioprotective mechanisms to MI, associated with AT in rats submitted to ovarian hormone deprivation.

CONCLUSION

Menopause induces various cardiometabolic and inflammatory changes in women, such as increased blood pressure, autonomic imbalance, change in adipose tissue metabolism, increase of pro-inflammatory cytokines and oxidative stress, which can culminate in CAD. However, several studies have shown that AT has a cardioprotective effect and is able to minimize these deleterious effects.

LIST OF ABBREVIATIONS

AT	=	Aerobic Training
BP	=	Blood Pressure
CNS	=	Central Nervous System
CVDs	=	Cardiovascular Deseases
eNOS	=	Endothelial Nitric Oxide Synthase
HF	=	High Frequency
LF	=	Low Frequency
MI	=	Miocardial Infarction

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Benjamin EJ, Muntner P, Alonso A, *et al.* Heart disease and stroke statistics-2019 update: A report from the American Heart Association. Circulation 2019; 139(10): e56-e528. http://dx.doi.org/10.1161/CIR.0000000000000659 PMID: 30700139

[2] Reamy BV, Williams PM, Kuckel DP. Prevention of cardiovascular disease. Prim Care 2018; 45(1): 25-44. http://dx.doi.org/10.1016/j.pop.2017.11.003 PMID: 29406943

[3] Hage FG, Oparil S. Ovarian hormones and vascular disease. Curr Opin Cardiol 2013; 28(4): 411-6. PMID: 23736815

[4] Casanova G, Pritzer PM. Aspectos Fisiopatológicos: Estrogênios, menopausa e terapia hormonal. Revista da Sociedade Brasileira de Hipertensão 2007; 10: 131-4.

[5] Al-Mallah MH, Sakr S, Al-Qunaibet A. Cardiorespiratory fitness and cardiovascular disease prevention: An update. Curr Atheroscler Rep 2018; 20(1): 1. http://dx.doi.org/10.1007/s11883-018-0711-4 PMID: 29340805

[6] Giada F, Biffi A, Agostoni P, *et al.* Exercise prescription for the prevention and treatment of cardiovascular diseases: Part I. J Cardiovasc Med (Hagerstown) 2008; 9(5): 529-44. http://dx.doi.org/10.2459/JCM.0b013e3282f7ca77 PMID: 18404008

[7] Hivert MF, Arena R, Forman DE, *et al.* Medical training to achieve competency in lifestyle counseling: An essential foundation for prevention and treatment of cardiovascular diseases and other chronic medical conditions: A scientific statement From the American Heart Association. Circulation 2016; 134(15): e308-27. http://dx.doi.org/10.1161/CIR.0000000000000442 PMID: 27601568

[8] Lanier JB, Bury DC, Richardson SW. Diet and physical activity for cardiovascular disease prevention. Am Fam Physician 2016; 93(11): 919-24. PMID: 27281836

[9] Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: Long-term health consequences. Maturitas 2010; 65(2): 161-6. http://dx.doi.org/10.1016/j.maturitas.2009.08.003 PMID: 19733988

[10] Jin M, Yu Y, Huang H. An update on primary ovarian insufficiency. Sci China Life Sci 2012; 55(8): 677-86. http://dx.doi.org/10.1007/s11427-012-4355-2 PMID: 22932883

[11] Monteleone P, Mascagni G, Giannini A, Genazzani AR, Simoncini T. Symptoms of menopause - global prevalence, physiology and implications. Nat Rev Endocrinol 2018; 14(4): 199-215. http://dx.doi.org/10.1038/nrendo.2017.180 PMID: 29393299

[12] Rivera CM, Grossardt BR, Rhodes DJ, Rocca WA. Increased mortality for neurological and mental diseases following early bilateral oophorectomy. Neuroepidemiology 2009; 33(1): 32-40. http://dx.doi.org/10.1159/000211951 PMID: 19365140

[13] Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ III. Survival patterns after oophorectomy in premenopausal women: A population-based cohort study. Lancet Oncol 2006; 7(10): 821-8. http://dx.doi.org/10.1016/S1470-2045(06)70869-5 PMID: 17012044

[14] Rocca WA, Bower JH, Maraganore DM, *et al.* Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 2007; 69(11): 1074-83. http://dx.doi.org/10.1212/01.wnl.0000276984.19542.e6 PMID: 17761551

[15] Rocca WA, Shuster LT, Grossardt BR, *et al.* Long-term effects of bilateral oophorectomy on brain aging: Unanswered questions from the Mayo Clinic Cohort Study of oophorectomy and aging. Womens Health (Lond) 2009; 5(1): 39-48. http://dx.doi.org/10.2217/17455057.5.1.39 PMID: 19102639

[16] Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen, and cognitive aging: The timing hypothesis. Neurodegener Dis 2010; 7(1-3): 163-6. http://dx.doi.org/10.1159/000289229 PMID: 20197698

[17] Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen treatment, and cognitive aging: Clinical evidence for a window of opportunity. Brain Res 2011; 1379: 188-98. http://dx.doi.org/10.1016/j.brainres.2010.10.031 PMID: 20965156

[18] Rocca WA, Grossardt BR, Miller VM, Shuster LT, Brown RD Jr. Premature menopause or early menopause and risk of ischemic stroke. Menopause 2012; 19(3): 272-7. http://dx.doi.org/10.1097/gme.0b013e31822a9937 PMID: 21993082

[19] Shuster LT, Gostout BS, Grossardt BR, Rocca WA. Prophylactic oophorectomy in premenopausal women and long-term health. Menopause Int 2008; 14(3): 111-6. http://dx.doi.org/10.1258/mi.2008.008016 PMID: 18714076

[20] Parker WH. Bilateral oophorectomy *vs.* ovarian conservation: Effects on long-term women's health. J Minim Invasive Gynecol 2010; 17(2): 161-6. http://dx.doi.org/10.1016/j.jmig.2009.12.016 PMID: 20226402

[21] Parker WH, Broder MS, Chang E, *et al.* Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol 2009; 113(5): 1027-37. http://dx.doi.org/10.1097/AOG.0b013e3181a11c64 PMID: 19384117

[22] Parker WH, Feskanich D, Broder MS, *et al.* Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. Obstet Gynecol 2013; 121(4): 709-16. http://dx.doi.org/10.1097/AOG.0b013e3182864350 PMID: 23635669

[23] Shao B, Cheng Y, Jin K. Estrogen, neuroprotection and neurogenesis after ischemic stroke. Curr Drug Targets 2012; 13(2): 188-98. http://dx.doi.org/10.2174/138945012799201702 PMID: 22204318

[24] Lee JO, Kang SG, Kim SH, Park SJ, Song SW. The relationship between menopausal symptoms and heart rate variability in middle aged women. Korean J Fam Med 2011; 32(5): 299-305. http://dx.doi.org/10.4082/kjfm.2011.32.5.299 PMID: 22745867

[25] SPRITZER PM. Aspectos fisiopatológicos: Estrogênios, menopausa e terapia hormonal. Revista da Sociedade Brasileira de Hieprtensão 2007; 10(4): 131-4.

[26] Abramson BL, Melvin RG. Cardiovascular risk in women: focus on hypertension. Can J Cardiol 2014; 30(5): 553-9. http://dx.doi.org/10.1016/j.cjca.2014.02.014 PMID: 24786446

[27] Sack MN, Rader DJ, Cannon RO III. Oestrogen and inhibition of oxidation of low-density lipoproteins in postmenopausal women. Lancet 1994; 343(8892): 269-70. http://dx.doi.org/10.1016/S0140-6736(94)91117-7 PMID: 7905101

[28] Ross RK, Paganini-Hill A, Mack TM, Henderson BE. Cardiovascular benefits of estrogen replacement therapy. Am J Obstet Gynecol 1989; 160(5 Pt 2): 1301-6. http://dx.doi.org/10.1016/S0002-9378(89)80017-1 PMID: 2655453

[29] Vargas R, Wroblewska B, Rego A, Hatch J, Ramwell PW. Oestradiol inhibits smooth muscle cell proliferation of pig coronary artery. Br J Pharmacol 1993; 109(3): 612-7. http://dx.doi.org/10.1111/j.1476-5381.1993.tb13616.x PMID: 8358561

[30] Huikuri HV, Pikkujämsä SM, Airaksinen KE, *et al.* Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation 1996; 94(2): 122-5. http://dx.doi.org/10.1161/01.CIR.94.2.122 PMID: 8674168

[31] Saleh TM, Connell BJ. Centrally mediated effect of 17beta-estradiol on parasympathetic tone in male rats. Am J Physiol 1999; 276(2): R474-81. PMID: 9950927

[32] Saleh MC, Connell BJ, Saleh TM. Autonomic and cardiovascular reflex responses to central estrogen injection in ovariectomized female rats. Brain Res 2000; 879(1-2): 105-14. http://dx.doi.org/10.1016/S0006-8993(00)02757-8 PMID: 11011011

[33] Dart AM, Du XJ, Kingwell BA. Gender, sex hormones and autonomic nervous control of the cardiovascular system. Cardiovasc Res 2002; 53(3): 678-87. http://dx.doi.org/10.1016/S0008-6363(01)00508-9 PMID: 11861039

[34] Davy KP, DeSouza CA, Jones PP, Seals DR. Elevated heart rate variability in physically active young and older adult women. Clin Sci (Lond) 1998; 94(6): 579-84. http://dx.doi.org/10.1042/cs0940579 PMID: 9854454

[35] Ribeiro TF, Azevedo GD, Crescêncio JC, *et al.* Heart rate variability under resting conditions in postmenopausal and young women. Braz J Med Biol Res 2001; 34(7): 871-7. http://dx.doi.org/10.1590/S0100-879X2001000700006 PMID: 11449305

[36] Neves VF, Silva de Sá MF, Gallo L Jr, *et al.* Autonomic modulation of heart rate of young and postmenopausal women undergoing estrogen therapy. Braz J Med Biol Res 2007; 40(4): 491-9. http://dx.doi.org/10.1590/S0100-879X2007000400007 PMID: 17401492

[37] Vongpatanasin W. Autonomic regulation of blood pressure in menopause. Semin Reprod Med 2009; 27(4): 338-45. http://dx.doi.org/10.1055/s-0029-1225262 PMID: 19530068

[38] Thawornkaiwong A, Preawnim S, Wattanapermpool J. Upregulation of beta 1-adrenergic receptors in ovariectomized rat hearts. Life Sci 2003; 72(16): 1813-24. http://dx.doi.org/10.1016/S0024-3205(02)02473-6 PMID: 12586219

[39] Kam KW, Qi JS, Chen M, Wong TM. Estrogen reduces cardiac injury and expression of beta1-adrenoceptor upon ischemic insult in the rat heart. J Pharmacol Exp Ther 2004; 309(1): 8-15. http://dx.doi.org/10.1124/jpet.103.058339 PMID: 14718598

[40] Sherwood A, Park SB, Hughes JW, *et al.* Cardiovascular hemodynamics during stress in premenopausal *vs.* postmenopausal women. Menopause 2010; 17(2): 403-9. http://dx.doi.org/10.1097/gme.0b013e3181b9b061 PMID: 19770780

[41] De Melo VU, Saldanha RR, Dos Santos CR, *et al.* Ovarian hormone deprivation reduces oxytocin expression in paraventricular nucleus preautonomic neurons and correlates with baroreflex impairment in rats. Front Physiol 2016; 7: 461. http://dx.doi.org/10.3389/fphys.2016.00461 PMID: 27790154

[42] Moreau KL, Hildreth KL, Meditz AL, Deane KD, Kohrt WM. Endothelial function is impaired across the stages of the menopause transition in healthy women. J Clin Endocrinol Metab 2012; 97(12): 4692-700. http://dx.doi.org/10.1210/jc.2012-2244 PMID: 22969140

[43] Stamatelopoulos KS, Armeni E, Georgiopoulos G, *et al.* Recently postmenopausal women have the same prevalence of subclinical carotid atherosclerosis as age and traditional risk factor matched men. Atherosclerosis 2012; 221(2): 508-13. http://dx.doi.org/10.1016/j.atherosclerosis.2011.12.006 PMID: 22196935

[44] Hildreth KL, Kohrt WM, Moreau KL. Oxidative stress contributes to large elastic arterial stiffening across the stages of the menopausal transition. Menopause 2014; 21(6): 624-32. http://dx.doi.org/10.1097/GME.0000000000000116 PMID: 24149926

[45] Lisabeth L, Bushnell C. Stroke risk in women: The role of menopause and hormone therapy. Lancet Neurol 2012; 11(1): 82-91. http://dx.doi.org/10.1016/S1474-4422(11)70269-1 PMID: 22172623

[46] Lobo RA, Davis SR, De Villiers TJ, *et al.* Prevention of diseases after menopause. Climacteric 2014; 17(5): 540-56. http://dx.doi.org/10.3109/13697137.2014.933411 PMID: 24969415

[47] Koebele SV, Bimonte-Nelson HA. Modeling menopause: The utility of rodents in translational behavioral endocrinology research. Maturitas 2016; 87: 5-17. http://dx.doi.org/10.1016/j.maturitas.2016.01.015 PMID: 27013283

[48] Irigoyen MC, Paulini J, Flores LJ, *et al.* Exercise training improves baroreflex sensitivity associated with oxidative stress reduction in ovariectomized rats. Hypertension 2005; 46(4): 998-1003. http://dx.doi.org/10.1161/01.HYP.0000176238.90688.6b PMID: 16157791

[49] Conti FF, Brito JdeO, Bernardes N, *et al.* Positive effect of combined exercise training in a model of metabolic syndrome and menopause: autonomic, inflammatory, and oxidative stress evaluations. Am J Physiol Regul Integr Comp Physiol 2015; 309(12): R1532-9. http://dx.doi.org/10.1152/ajpregu.00076.2015 PMID: 26423710

[50] Sanches IC, Conti FF, Bernardes N, *et al.* Impact of combined exercise training on cardiovascular autonomic control and mortality in diabetic ovariectomized rats. J. Appl. Physiol 2015; 119(6): 656-2. http://dx.doi.org/10.1152/japplphysiol.00883.2014

[51] da Palma RK, Moraes-Silva IC, da Silva Dias D, *et al.* Resistance or aerobic training decreases blood pressure and improves cardiovascular autonomic control and oxidative stress in hypertensive menopausal rats. J. Appl. Physiol 2016; 121(4): 1032-8. http://dx.doi.org/10.1152/japplphysiol.00130.2016

[52] Machi JF, Dias DdaS, Freitas SC, *et al.* Impact of aging on cardiac function in a female rat model of menopause: Role of autonomic control, inflammation, and oxidative stress. Clin Interv Aging 2016; 11: 341-50. http://dx.doi.org/10.2147/CIA.S88441 PMID: 27042032

[53] Hulley S, Grady D, Bush T, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280(7): 605-13. http://dx.doi.org/10.1001/jama.280.7.605 PMID: 9718051

[54] Herrington DM, Reboussin DM, Brosnihan KB, *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med 2000; 343(8): 522-9. http://dx.doi.org/10.1056/NEJM200008243430801 PMID: 10954759

[55] Waters DD, Alderman EL, Hsia J, *et al.* Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: A randomized controlled trial. JAMA 2002; 288(19): 2432-40. http://dx.doi.org/10.1001/jama.288.19.2432 PMID: 12435256

[56] Clarke SC, Kelleher J, Lloyd-Jones H, Slack M, Schofiel PM. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: The Papworth HRT atherosclerosis study. BJOG 2002; 109(9): 1056-62. http://dx.doi.org/10.1111/j.1471-0528.2002.01544.x PMID: 12269682

[57] Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; 288(3): 321-33. http://dx.doi.org/10.1001/jama.288.3.321 PMID: 12117397

[58] Izzicupo P, D'Amico MA, Di Blasio A, *et al.* Aerobic training improves angiogenic potential independently of vascular endothelial growth factor modifications in postmenopausal women. Front Endocrinol (Lausanne) 2017; 8: 363. http://dx.doi.org/10.3389/fendo.2017.00363 PMID: 29312152

[59] Pedersen LR, Frestad D, Michelsen MM, *et al.* Risk factors for myocardial infarction in women and men: A review of the current literature. Curr Pharm Des 2016; 22(25): 3835-52. http://dx.doi.org/10.2174/1381612822666160309115318 PMID: 26956230

[60] Legro RS. Polycystic ovary syndrome and cardiovascular disease: A premature association? Endocr Rev 2003; 24(3): 302-12. http://dx.doi.org/10.1210/er.2003-0004 PMID: 12788801

[61] Vryonidou A, Papatheodorou A, Tavridou A, *et al.* Association of hyperandrogenemic and metabolic phenotype with carotid intima-media thickness in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005; 90(5): 2740-6. http://dx.doi.org/10.1210/jc.2004-2363 PMID: 15741256

[62] Sudhir K, Chou TM, Chatterjee K, *et al.* Premature coronary artery disease associated with a disruptive mutation in the estrogen receptor gene in a man. Circulation 1997; 96(10): 3774-7. http://dx.doi.org/10.1161/01.CIR.96.10.3774 PMID: 9396482

[63] Puzianowska-Kuźnicka M. ESR1 in myocardial infarction. Clin Chim Acta 2012; 413(1-2): 81-7. http://dx.doi.org/10.1016/j.cca.2011.10.028 PMID: 22061094

[64] Thygesen K, Alpert JS, Jaffe AS, *et al.* Third universal definition of myocardial infarction. J Am Coll Cardiol 2012; 60(16): 1581-98. http://dx.doi.org/10.1016/j.jacc.2012.08.001 PMID: 22958960

[65] Siervuli MTF. Silva AdS, Silva ACd, Muzzi RAL, Santos GAB. Infarto do miocárdio: Alterações morfológicas e breve abordagem da influência do exercício físico. Rev Bras Cardiol 2014; 27: 349-55.

[66] Yousef ZR, Redwood SR, Marber MS. Postinfarction left ventricular remodelling: Where are the theories and trials leading us? Heart 2000; 83(1): 76-80. http://dx.doi.org/10.1136/heart.83.1.76 PMID: 10618340

[67] Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: Pathophysiology and therapy. Circulation 2000; 101(25): 2981-8. http://dx.doi.org/10.1161/01.CIR.101.25.2981 PMID: 10869273

[68] Francis J, Weiss RM, Wei SG, Johnson AK, Felder RB. Progression of heart failure after myocardial infarction in the rat. Am J Physiol Regul Integr Comp Physiol 2001; 281(5): R1734-45. http://dx.doi.org/10.1152/ajpregu.2001.281.5.R1734 PMID: 11641147

[69] Shih H, Lee B, Lee RJ, Boyle AJ. The aging heart and post-infarction left ventricular remodeling. J Am Coll Cardiol 2011; 57(1): 9-17. http://dx.doi.org/10.1016/j.jacc.2010.08.623 PMID: 21185495

[70] Barretto AC, Ramires JA. Heart failure. Arq Bras Cardiol 1998; 71(4): 635-42. http://dx.doi.org/10.1590/S0066-782X1998001000014 PMID: 10347943

[71] La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 1998; 351(9101): 478-84. http://dx.doi.org/10.1016/S0140-6736(97)11144-8 PMID: 9482439

[72] Negrao CE, Middlekauff HR. Adaptations in autonomic function during exercise training in heart failure. Heart Fail Rev 2008; 13(1): 51-60. http://dx.doi.org/10.1007/s10741-007-9057-7 PMID: 17932745

[73] Flores LJ, Figueroa D, Sanches IC, *et al.* Effects of exercise training on autonomic dysfunction management in an experimental model of menopause and myocardial infarction. Menopause 2010; 17(4): 712-7. PMID: 20577132

[74] Ponikowski P, Chua TP, Anker SD, *et al.* Peripheral chemoreceptor hypersensitivity: An ominous sign in patients with chronic heart failure. Circulation 2001; 104(5): 544-9. http://dx.doi.org/10.1161/hc3101.093699 PMID: 11479251

[75] Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. Circulation 2001; 104(19): 2324-30. http://dx.doi.org/10.1161/hc4401.098491 PMID: 11696473

[76] Jorge L, Rodrigues B, Rosa KT, *et al.* Cardiac and peripheral adjustments induced by early exercise training intervention were associated with autonomic improvement in infarcted rats: role in functional capacity and mortality. Eur Heart J 2011; 32(7): 904-12. http://dx.doi.org/10.1093/eurheartj/ehq244 PMID: 20675661

[77] Feriani DJ, Souza GIH, Carrozzi NM, *et al.* Impact of exercise training associated to pyridostigmine treatment on autonomic function and inflammatory profile after myocardial infarction in rats. Int J Cardiol 2017; 227: 757-65. http://dx.doi.org/10.1016/j.ijcard.2016.10.061 PMID: 27823896

[78] Feriani DJ, Coelho-Júnior HJ, de Oliveira JCMF, *et al.* Pyridostigmine improves the effects of resistance exercise training after myocardial infarction in rats. Front Physiol 2018; 9: 53. http://dx.doi.org/10.3389/fphys.2018.00053 PMID: 29483876

[79] Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med 1999; 341(4): 217-25. http://dx.doi.org/10.1056/NEJM199907223410401 PMID: 10413733

[80] Chandra NC, Ziegelstein RC, Rogers WJ, *et al.* Observations of the treatment of women in the United States with myocardial infarction: A report from the National Registry of Myocardial Infarction-I. Arch Intern Med 1998; 158(9): 981-8. http://dx.doi.org/10.1001/archinte.158.9.981 PMID: 9588431

[81] Wong SC, Sleeper LA, Monrad ES, *et al.* Absence of gender differences in clinical outcomes in patients with cardiogenic shock complicating acute myocardial infarction. A report from the SHOCK Trial Registry. J Am Coll Cardiol 2001; 38(5): 1395-401. http://dx.doi.org/10.1016/S0735-1097(01)01581-9 PMID: 11691514

[82] Mirić L, Mirić D, Duplancić D, *et al.* Specific and gender differences between hospitalized and out of hospital mortality due to myocardial infarction. Coll Antropol 2008; 32(2): 361-7. PMID: 18756882

[83] Honda S, Asaumi Y, Yamane T, *et al.* Trends in the clinical and pathological characteristics of cardiac rupture in patients with acute myocardial infarction over 35 years. J Am Heart Assoc 2014; 3(5)e000984 http://dx.doi.org/10.1161/JAHA.114.000984 PMID: 25332178

[84] Lam CS, McEntegart M, Claggett B, *et al.* Sex differences in clinical characteristics and outcomes after myocardial infarction: Insights from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Eur J Heart Fail 2015; 17(3): 301-12. http://dx.doi.org/10.1002/ejhf.238 PMID: 25655011

[85] Kytö V, Sipilä J, Rautava P. Gender and in-hospital mortality of ST-segment elevation myocardial infarction (from a multihospital nationwide registry study of 31,689 patients). Am J Cardiol 2015; 115(3): 303-6. http://dx.doi.org/10.1016/j.amjcard.2014.11.001 PMID: 25488357

[86] Pfeffer MA, Pfeffer JM, Fishbein MC, *et al.* Myocardial infarct size and ventricular function in rats. Circ Res 1979; 44(4): 503-12. http://dx.doi.org/10.1161/01.RES.44.4.503 PMID: 428047

[87] Palojoki E, Saraste A, Eriksson A, *et al.* Cardiomyocyte apoptosis and ventricular remodeling after myocardial infarction in rats. Am J Physiol Heart Circ Physiol 2001; 280(6): H2726-31. http://dx.doi.org/10.1152/ajpheart.2001.280.6.H2726 PMID: 11356629

[88] Braga LM, Rosa K, Rodrigues B, *et al.* Systemic delivery of adult stem cells improves cardiac function in spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 2008; 35(2): 113-9. PMID: 17973933

[89] Malfitano C, Barboza CA, Mostarda C, *et al.* Diabetic hyperglycemia attenuates sympathetic dysfunction and oxidative stress after myocardial infarction in rats. Cardiovasc Diabetol 2014; 13: 131. http://dx.doi.org/10.1186/s12933-014-0131-x PMID: 25301475

[90] Malfitano C, Alba Loureiro TC, Rodrigues B, *et al.* Hyperglycaemia protects the heart after myocardial infarction: Aspects of programmed cell survival and cell death. Eur J Heart Fail 2010; 12(7): 659-67. http://dx.doi.org/10.1093/eurjhf/hfq053 PMID: 20406798

[91] Rodrigues B, Rosa KT, Medeiros A, *et al.* Hyperglycemia can delay left ventricular dysfunction but not autonomic damage after myocardial infarction in rodents. Cardiovasc Diabetol 2011; 10: 26. http://dx.doi.org/10.1186/1475-2840-10-26 PMID: 21470409

[92] Tucci PJ. Pathophysiological characteristics of the post-myocardial infarction heart failure model in rats. Arq Bras Cardiol 2011; 96(5): 420-4. http://dx.doi.org/10.1590/S0066-782X2011005000049 PMID: 21503387

[93] Mill JG, Stefanon I, dos Santos L, Baldo MP. Remodeling in the ischemic heart: The stepwise progression for heart failure. Braz J Med Biol Res 2011; 44(9): 890-8. http://dx.doi.org/10.1590/S0100-879X2011007500096 PMID: 21829898

[94] Rodrigues B, Mostarda CT, Jorge L, *et al.* Impact of myocardial infarction on cardiac autonomic function in diabetic rats. J Diabetes Complications 2013; 27(1): 16-22. http://dx.doi.org/10.1016/j.jdiacomp.2012.08.002 PMID: 23044051

[95] Rodrigues B, Jorge L, Mostarda CT, *et al.* Aerobic exercise training delays cardiac dysfunction and improves autonomic control of circulation in diabetic rats undergoing myocardial infarction. J Card Fail 2012; 18(9): 734-44. http://dx.doi.org/10.1016/j.cardfail.2012.07.006 PMID: 22939043

[96] de Macedo Braga LM, Lacchini S, Schaan BD, *et al.* In situ delivery of bone marrow cells and mesenchymal stem cells improves cardiovascular function in hypertensive rats submitted to myocardial infarction. J Biomed Sci 2008; 15(3): 365-74. http://dx.doi.org/10.1007/s11373-008-9237-z PMID: 18256904

[97] de La Fuente RN, Rodrigues B, Moraes-Silva IC, *et al.* Cholinergic stimulation with pyridostigmine improves autonomic function in infarcted rats. Clin Exp Pharmacol Physiol 2013; 40(9): 610-6. http://dx.doi.org/10.1111/1440-1681.12121 PMID: 23701019

[98] Barboza CA, Rocha LY, Mostarda CT, *et al.* Ventricular and autonomic benefits of exercise training persist after detraining in infarcted rats. Eur J Appl Physiol 2013; 113(5): 1137-46. http://dx.doi.org/10.1007/s00421-012-2533-3 PMID: 23108584

[99] Rodrigues F, Feriani DJ, Barboza CA, *et al.* Cardioprotection afforded by exercise training prior to myocardial infarction is associated with autonomic function improvement. BMC Cardiovasc Disord 2014; 14: 84. http://dx.doi.org/10.1186/1471-2261-14-84 PMID: 25022361

[100] Barboza CA, Souza GI, Oliveira JC, *et al.* Cardioprotective properties of aerobic and resistance training against myocardial infarction. Int J Sports Med 2016; 37(6): 421-30. http://dx.doi.org/10.1055/s-0035-1565136 PMID: 26928914

[101] Gupta A, Houston B. A comprehensive review of the bioenergetics of fatty acid and glucose metabolism in the healthy and failing heart in nondiabetic condition. Heart Fail Rev 2017; 22(6): 825-42. http://dx.doi.org/10.1007/s10741-017-9623-6 PMID: 28536966

[102] Lopaschuk GD. Metabolic modulators in heart disease: Past, present, and future. Can J Cardiol 2017; 33(7): 838-49. http://dx.doi.org/10.1016/j.cjca.2016.12.013 PMID: 28279520

[103] Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiol Rev 2005; 85(3): 1093-129. http://dx.doi.org/10.1152/physrev.00006.2004 PMID: 15987803

[104] Eckerle M, Ambroggio L, Puskarich MA, *et al.* Metabolomics as a driver in advancing precision medicine in sepsis. Pharmacotherapy 2017; 37(9): 1023-32. http://dx.doi.org/10.1002/phar.1974 PMID: 28632924

[105] Bujak R, Struck-Lewicka W, Markuszewski MJ, Kaliszan R. Metabolomics for laboratory diagnostics. J Pharm Biomed Anal 2015; 113: 108-20. http://dx.doi.org/10.1016/j.jpba.2014.12.017 PMID: 25577715

[106] Naz S, Moreira dos Santos DC, García A, Barbas C. Analytical protocols based on LC-MS, GC-MS and CE-MS for nontargeted metabolomics of biological tissues. Bioanalysis 2014; 6(12): 1657-77. http://dx.doi.org/10.4155/bio.14.119 PMID: 25077626

[107] Cheng S, Shah SH, Corwin EJ, *et al.* Potential impact and study considerations of metabolomics in cardiovascular health and disease: A scientific statement from the American Heart Association. Circ Cardiovasc Genet 2017; 10(2)e000032 http://dx.doi.org/10.1161/HCG.0000000000000032 PMID: 28360086

[108] Ruiz-Canela M, Hruby A, Clish CB, Liang L, Martínez-González MA, Hu FB. Comprehensive metabolomic profiling and incident cardiovascular disease: A systematic review. J Am Heart Assoc 2017; 6(10):e005705. http://dx.doi.org/10.1161/JAHA.117.005705 PMID: 28963102

[109] Lewis GD, Wei R, Liu E, *et al.* Metabolite profiling of blood from individuals undergoing planned myocardial infarction reveals early markers of myocardial injury. J Clin Invest 2008; 118(10): 3503-12. http://dx.doi.org/10.1172/JCI35111 PMID: 18769631

[110] Bodi V, Marrachelli VG, Husser O, Chorro FJ, Viña JR, Monleon D. Metabolomics in the diagnosis of acute myocardial ischemia. J Cardiovasc Transl Res 2013; 6(5): 808-15. http://dx.doi.org/10.1007/s12265-013-9505-9 PMID: 23990264

[111] Ganna A, Salihovic S, Sundström J, *et al.* Large-scale metabolomic profiling identifies novel biomarkers for incident coronary heart disease. PLoS Genet 2014; 10(12)e1004801 http://dx.doi.org/10.1371/journal.pgen.1004801 PMID: 25502724

[112] Laborde CM, Mourino-Alvarez L, Posada-Ayala M, *et al.* Plasma metabolomics reveals a potential panel of biomarkers for early diagnosis in acute coronary syndrome Metabolomics 2014; 10(3): 414-24. http://dx.doi.org/10.1007/s11306-013-0595-9

[113] Wang X, Wang D, Wu J, *et al.* Metabolic characterization of myocardial infarction using GC-MS-based tissue metabolomics. Int Heart J 2017; 58(3): 441-6. http://dx.doi.org/10.1536/ihj.16-432 PMID: 28484125

[114] Takeda H, Koike T, Izumi Y, *et al.* Lipidomic analysis of plasma lipoprotein fractions in myocardial infarction-prone rabbits. J Biosci Bioeng 2015; 120(4): 476-82. http://dx.doi.org/10.1016/j.jbiosc.2015.02.015 PMID: 26162515

[115] Zhu X, Liu X, He P, *et al.* Metabolomics in serum of ovariectomised rats and those exposed to 17β-oestradiol and genistein. Gynecol Endocrinol 2010; 26(10): 760-7. http://dx.doi.org/10.3109/09513590.2010.487615 PMID: 20500111

[116] Ma B, Zhang Q, Wang GJ, *et al.* GC-TOF/MS-based metabolomic profiling of estrogen deficiency-induced obesity in ovariectomized rats. Acta Pharmacol Sin 2011; 32(2): 270-8. http://dx.doi.org/10.1038/aps.2010.196 PMID: 21293480

[117] López-Grueso R, Gambini J, Abdelaziz KM, *et al.* Early, but not late onset estrogen replacement therapy prevents oxidative stress and metabolic alterations caused by ovariectomy. Antioxid Redox Signal 2014; 20(2): 236-46. http://dx.doi.org/10.1089/ars.2012.5112 PMID: 23725100

[118] Tracey KJ. The inflammatory reflex. Nature 2002; 420(6917): 853-9. http://dx.doi.org/10.1038/nature01321 PMID: 12490958

[119] Mendoza N, De Teresa C, Cano A, *et al.* Benefits of physical exercise in postmenopausal women. Maturitas 2016; 93: 83-8. http://dx.doi.org/10.1016/j.maturitas.2016.04.017 PMID: 27137981

[120] Jun JK, Lee WL, Park HG, Lee SK, Jeong SH, Lee YR. Moderate intensity exercise inhibits macrophage infiltration and attenuates adipocyte inflammation in ovariectomized rats. J Exerc Nutrition Biochem 2014; 18(1): 119-27. http://dx.doi.org/10.5717/jenb.2014.18.1.119 PMID: 25566447

[121] Pereira MR, Leite PE. The involvement of parasympathetic and sympathetic nerve in the inflammatory reflex. J Cell Physiol 2016; 231(9): 1862-9. http://dx.doi.org/10.1002/jcp.25307 PMID: 26754950

[122] Andersson U, Tracey KJ. Neural reflexes in inflammation and immunity. J Exp Med 2012; 209(6): 1057-68. http://dx.doi.org/10.1084/jem.20120571 PMID: 22665702

[123] Ulloa L. The anti-inflammatory potential of selective cholinergic agonists. Shock. 36. United States 2011; pp. 97-8. http://dx.doi.org/10.1097/SHK.0b013e31821820d2

[124] Ulloa L. The vagus nerve and the nicotinic anti-inflammatory pathway. Nat Rev Drug Discov 2005; 4(8): 673-84. http://dx.doi.org/10.1038/nrd1797 PMID: 16056392

[125] Tracey KJ. Understanding immunity requires more than immunology. Nat Immunol 2010; 11(7): 561-4. http://dx.doi.org/10.1038/ni0710-561 PMID: 20562838

[126] Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 2007; 117(2): 289-96. http://dx.doi.org/10.1172/JCI30555 PMID: 17273548

[127] Watkins LR, Goehler LE, Relton JK, *et al.* Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: Evidence for vagal mediation of immune-brain communication. Neurosci Lett 1995; 183(1-2): 27-31. http://dx.doi.org/10.1016/0304-3940(94)11105-R PMID: 7746479

[128] Goehler LE, Relton JK, Dripps D, *et al.* Vagal paraganglia bind biotinylated interleukin-1 receptor antagonist: A possible mechanism for immune-to-brain communication. Brain Res Bull 1997; 43(3): 357-64. http://dx.doi.org/10.1016/S0361-9230(97)00020-8 PMID: 9227848

[129] Rosas-Ballina M, Olofsson PS, Ochani M, *et al.* Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science 2011; 334(6052): 98-101. http://dx.doi.org/10.1126/science.1209985 PMID: 21921156

[130] Costantini TW, Dang X, Yurchyshyna MV, Coimbra R, Eliceiri BP, Baird AA. Human-Specific α7-nicotinic acetylcholine receptor gene in human leukocytes: Identification, regulation and the consequences of CHRFAM7A expression. Mol Med 2015; 21: 323-36. http://dx.doi.org/10.2119/molmed.2015.00018

[131] Gallowitsch-Puerta M, Pavlov VA. Neuro-immune interactions *via* the cholinergic anti-inflammatory pathway. Life Sci 2007; 80(24-25): 2325-9. http://dx.doi.org/10.1016/j.lfs.2007.01.002 PMID: 17289087

[132] de Jonge WJ, Ulloa L. The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation. Br J Pharmacol 2007; 151(7): 915-29. http://dx.doi.org/10.1038/sj.bjp.0707264 PMID: 17502850

[133] Hamano R, Takahashi HK, Iwagaki H, Yoshino T, Nishibori M, Tanaka N. Stimulation of alpha7 nicotinic acetylcholine receptor inhibits CD14 and the toll-like receptor 4 expression in human monocytes. Shock 2006; 26(4): 358-64. http://dx.doi.org/10.1097/01.shk.0000228168.86845.60 PMID: 16980882

[134] Borovikova LV, Ivanova S, Zhang M, *et al.* Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000; 405(6785): 458-62. http://dx.doi.org/10.1038/35013070 PMID: 10839541

[135] Sun J, Zhao Y, Hu J. Curcumin inhibits imiquimod-induced psoriasis-like inflammation by inhibiting IL-1beta and IL-6 production in mice. PLoS One 2013; 8(6)e67078 http://dx.doi.org/10.1371/journal.pone.0067078 PMID: 23825622

[136] Jiang Y, Li L, Liu B, Zhang Y, Chen Q, Li C. PPARγ upregulation induced by vagus nerve stimulation exerts anti-inflammatory effect in cerebral ischemia/reperfusion rats. Med Sci Monit 2015; 21: 268-75. http://dx.doi.org/10.12659/MSM.891407 PMID: 25619160

[137] Fredj S, Bescond J, Louault C, Potreau D. Interactions between cardiac cells enhance cardiomyocyte hypertrophy and increase fibroblast proliferation. J Cell Physiol 2005; 202(3): 891-9. http://dx.doi.org/10.1002/jcp.20197 PMID: 15389635

[138] Bowers SL, Borg TK, Baudino TA. The dynamics of fibroblast-myocyte-capillary interactions in the heart. Ann N Y Acad Sci 2010; 1188: 143-52. http://dx.doi.org/10.1111/j.1749-6632.2009.05094.x PMID: 20201897

[139] Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000; 35(3): 569-82. http://dx.doi.org/10.1016/S0735-1097(99)00630-0 PMID: 10716457

[140] Aronson D, Mittleman MA, Burger AJ. Interleukin-6 levels are inversely correlated with heart rate variability in patients with decompensated heart failure. J Cardiovasc Electrophysiol 2001; 12(3): 294-300. http://dx.doi.org/10.1046/j.1540-8167.2001.00294.x PMID: 11291801

[141] Lanza GA, Sgueglia GA, Cianflone D, *et al.* Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. Am J Cardiol 2006; 97(12): 1702-6. http://dx.doi.org/10.1016/j.amjcard.2006.01.029 PMID: 16765117

[142] Shishehbor MH, Alves C, Rajagopal V. Inflammation: Implications for understanding the heart-brain connection. Cleve Clin J Med 2007; 74(Suppl. 1): S37-41. http://dx.doi.org/10.3949/ccjm.74.Suppl_1.S37 PMID: 17455542

[143] Huston JM, Tracey KJ. The pulse of inflammation: heart rate variability, the cholinergic anti-inflammatory pathway and implications for therapy. J Intern Med 2011; 269(1): 45-53. http://dx.doi.org/10.1111/j.1365-2796.2010.02321.x PMID: 21158977

[144] Rodrigues B, Santana AA, Santamarina AB, *et al.* Role of training and detraining on inflammatory and metabolic profile in infarcted rats: influences of cardiovascular autonomic nervous system. Mediators Inflamm 2014; 2014207131 http://dx.doi.org/10.1155/2014/207131 PMID: 25045207

[145] Vybiral T, Glaeser DH, Morris G, *et al.* Effects of low dose transdermal scopolamine on heart rate variability in acute myocardial infarction. J Am Coll Cardiol 1993; 22(5): 1320-6. http://dx.doi.org/10.1016/0735-1097(93)90537-B PMID: 8227787

[146] Casadei B, Pipilis A, Sessa F, Conway J, Sleight P. Low doses of scopolamine increase cardiac vagal tone in the acute phase of myocardial infarction. Circulation 1993; 88(2): 353-7. http://dx.doi.org/10.1161/01.CIR.88.2.353 PMID: 8339398

[147] Androne AS, Hryniewicz K, Goldsmith R, Arwady A, Katz SD. Acetylcholinesterase inhibition with pyridostigmine improves heart rate recovery after maximal exercise in patients with chronic heart failure. Heart 2003; 89(8): 854-8. http://dx.doi.org/10.1136/heart.89.8.854 PMID: 12860856

[148] La Rovere MT, Bersano C, Gnemmi M, Specchia G, Schwartz PJ. Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. Circulation 2002; 106(8): 945-9. http://dx.doi.org/10.1161/01.CIR.0000027565.12764.E1 PMID: 12186798

[149] Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports 2006; 16(Suppl. 1): 3-63. http://dx.doi.org/10.1111/j.1600-0838.2006.00520.x PMID: 16451303

[150] Lakka TA, Laaksonen DE. Physical activity in prevention and treatment of the metabolic syndrome. Appl Physiol Nutr Metab 2007; 32(1): 76-88. http://dx.doi.org/10.1139/h06-113 PMID: 17332786

[151] Mann N, Rosenzweig A. Can exercise teach us how to treat heart disease? Circulation 2012; 126(22): 2625-35. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.060376 PMID: 23184282

[152] Ertek S, Cicero A. Impact of physical activity on inflammation: Effects on cardiovascular disease risk and other inflammatory conditions. Arch Med Sci 2012; 8(5): 794-804. http://dx.doi.org/10.5114/aoms.2012.31614 PMID: 23185187

[153] Xing Y, Yang SD, Dong F, Wang MM, Feng YS, Zhang F. The beneficial role of early exercise training following stroke and possible mechanisms. Life Sci 2018; 198: 32-7. http://dx.doi.org/10.1016/j.lfs.2018.02.018 PMID: 29452165

[154] Siddiqui NI, Nessa A, Hossain MA. Regular physical exercise: Way to healthy life. Mymensingh Med J 2010; 19(1): 154-8. PMID: 20046192

[155] Booth FW, Gordon SE, Carlson CJ, Hamilton MT. Waging war on modern chronic diseases: Primary prevention through exercise biology J Appl Physiol 2000; 88(2): 774-87.

[156] Joyner MJ, Green DJ. Exercise protects the cardiovascular system: Effects beyond traditional risk factors. J Physiol 2009; 587(Pt 23): 5551-8. http://dx.doi.org/10.1113/jphysiol.2009.179432 PMID: 19736305

[157] Blair SN, Morris JN. Healthy hearts--and the universal benefits of being physically active: Physical activity and health. Ann Epidemiol 2009; 19(4): 253-6. http://dx.doi.org/10.1016/j.annepidem.2009.01.019 PMID: 19344864

[158] Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol 2012; 2(2): 1143-211. http://dx.doi.org/10.1002/cphy.c110025 PMID: 23798298

[159] Sosa PM, Schimidt HL, Altermann C, *et al.* Physical exercise prevents motor disorders and striatal oxidative imbalance after cerebral ischemia-reperfusion. Braz J Med Biol Res 2015; 48(9): 798-804. http://dx.doi.org/10.1590/1414-431x20154429 PMID: 26222650

[160] Tang Z, Wang Y, Zhu X, Ni X, Lu J. Exercise increases cystathionine-γ-lyase expression and decreases the status of oxidative stress in myocardium of ovariectomized Rats. Int Heart J 2016; 57(1): 96-103. http://dx.doi.org/10.1536/ihj.15-099 PMID: 26673437

[161] Grindler NM, Santoro NF. Menopause and exercise. Menopause 2015; 22(12): 1351-8. http://dx.doi.org/10.1097/GME.0000000000000536 PMID: 26382311

[162] Kaidah S, Soejono SK, Partadiredja G. Exercise improves hippocampal estrogen and spatial memory of ovariectomized rats. Bratisl Lek Listy 2016; 117(2): 94-9. http://dx.doi.org/10.4149/BLL_2016_019 PMID: 26830040

[163] Vieira-Potter VJ, Zidon TM, Padilla J. Exercise and estrogen make fat cells "Fit". Exerc Sport Sci Rev 2015; 43(3): 172-8. http://dx.doi.org/10.1249/JES.0000000000000046 PMID: 25906425

[164] Haskell WL, Lee IM, Pate RR, *et al.* Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007; 39(8): 1423-34. http://dx.doi.org/10.1249/mss.0b013e3180616b27 PMID: 17762377

[165] Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: Potential mediating mechanisms. Circulation 2007; 116(19): 2110-8. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.729939 PMID: 17967770

[166] Roque FR, Hernanz R, Salaices M, Briones AM. Exercise training and cardiometabolic diseases: Focus on the vascular system. Curr Hypertens Rep 2013; 15(3): 204-14. http://dx.doi.org/10.1007/s11906-013-0336-5 PMID: 23519745

[167] Mostarda C, Moraes-Silva IC, Salemi VM, *et al.* Exercise training prevents diastolic dysfunction induced by metabolic syndrome in rats. Clinics 2012; 67(7): 815-20. http://dx.doi.org/10.6061/clinics/2012(07)18 PMID: 22892928

[168] Laughlin MH, Oltman CL, Bowles DK. Exercise training-induced adaptations in the coronary circulation. Med Sci Sports Exerc 1998; 30(3): 352-60. http://dx.doi.org/10.1097/00005768-199803000-00004 PMID: 9526880

[169] Xi Y, Ma WH, Tian ZJ. Research advance on angiogenesis in ischemic heart induced by aerobic exercise and stem cell mobilization. Sheng Li Ke Xue Jin Zhan 2014; 45(5): 343-8. PMID: 25764793

[170] Quindry JC, Hamilton KL, French JP, *et al.* Exercise-induced HSP-72 elevation and cardioprotection against infarct and apoptosis. J Appl Physiol 2007; 103(3): 1056-62.

[171] Lin YY, Chen JS, Wu XB, *et al.* Combined effects of 17β-estradiol and exercise training on cardiac apoptosis in ovariectomized rats. PLoS One 2018; 13(12):e0208633. http://dx.doi.org/10.1371/journal.pone.0208633 PMID: 30571718

[172] Hamilton KL, Quindry JC, French JP, *et al.* MnSOD antisense treatment and exercise-induced protection against arrhythmias. Free Radic Biol Med 2004; 37(9): 1360-8. http://dx.doi.org/10.1016/j.freeradbiomed.2004.07.025 PMID: 15454275

[173] Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol 2005; 98(4): 1154-62. http://dx.doi.org/10.1152/japplphysiol.00164.2004

[174] Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 2011; 11(9): 607-15. http://dx.doi.org/10.1038/nri3041 PMID: 21818123

[175] Dayan A, Feinberg MS, Holbova R, Deshet N, Scheinowitz M. Swimming exercise training prior to acute myocardial infarction attenuates left ventricular remodeling and improves left ventricular function in rats. Ann Clin Lab Sci 2005; 35(1): 73-8. PMID: 15830712

[176] Veiga EC, Antonio EL, Bocalini DS, *et al.* Prior exercise training does not prevent acute cardiac alterations after myocardial infarction in female rats. Clinics 2011; 66(5): 889-93. http://dx.doi.org/10.1590/S1807-59322011000500028 PMID: 21789396

[177] Bozi LH, Maldonado IR, Baldo MP, *et al.* Exercise training prior to myocardial infarction attenuates cardiac deterioration and cardiomyocyte dysfunction in rats. Clinics 2013; 68(4): 549-56. http://dx.doi.org/10.6061/clinics/2013(04)18 PMID: 23778353

[178] Veiga EC, Portes LA, Bocalini DS, *et al.* Cardiac implications after myocardial infarction in rats previously undergoing physical exercise. Arq Bras Cardiol 2013; 100(1): 37-43. http://dx.doi.org/10.1590/S0066-782X2012005000117 PMID: 23224349

[179] Freimann S, Scheinowitz M, Yekutieli D, Feinberg MS, Eldar M, Kessler-Icekson G. Prior exercise training improves the outcome of acute myocardial infarction in the rat. Heart structure, function, and gene expression. J Am Coll Cardiol 2005; 45(6): 931-8. http://dx.doi.org/10.1016/j.jacc.2004.11.052 PMID: 15766831

[180] Taylor RS, Brown A, Ebrahim S, *et al.* Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and meta-analysis of randomized controlled trials. Am J Med 2004; 116(10): 682-92. http://dx.doi.org/10.1016/j.amjmed.2004.01.009 PMID: 15121495

[181] Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. Am Heart J 2011; 162(4): 571-584.e2. http://dx.doi.org/10.1016/j.ahj.2011.07.017 PMID: 21982647

[182] Villella M, Villella A. Exercise and cardiovascular diseases. Kidney Blood Press Res 2014; 39(2-3): 147-53. http://dx.doi.org/10.1159/000355790 PMID: 25117881

[183] Lavie CJ, Arena R, Swift DL, *et al.* Exercise and the cardiovascular system: Clinical science and cardiovascular outcomes. Circ Res 2015; 117(2): 207-19. http://dx.doi.org/10.1161/CIRCRESAHA.117.305205 PMID: 26139859

[184] Almeida SA, Claudio ER, Mengal V, *et al.* Exercise training reduces cardiac dysfunction and remodeling in ovariectomized rats submitted to myocardial infarction. PLoS One 2014; 9(12):e115970. http://dx.doi.org/10.1371/journal.pone.0115970 PMID: 25551214