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Review Article

Autonomic Cardiovascular Damage during Post-menopause: the Role of Physical Training

Hugo C. D. Souza*, Geisa C. S. V. Tezini

Exercise Physiology Laboratory of the Department of Biomechanics, Medicine and Rehabilitation, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

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ABSTRACT: Menopause is part of the aging process and is characterized by the natural cessation of menstruation; during this time, the production of ovarian hormones, especially estrogen, is sharply reduced. This reduction can cause symptoms and disorders that affect most women and can interfere with their quality of life. Women are also more susceptible to cardiovascular diseases during this period, considering that these ovarian hormones would be associated with a protective effect on the cardiovascular system, by acting at various levels, contributing to the body homeostasis. Among several effects on the cardiovascular system, the ovarian hormones seem to play an important role in the autonomic control of heart rate and blood pressure. A reduction in ovarian hormones causes an autonomic imbalance and increases the risk of cardiovascular diseases. In fact, this increased risk is justified by the key role the autonomic nervous system plays in all cardiac regulatory mechanisms, exerting a tonic and reflexive influence on the main variables of the cardiovascular system. The autonomic system controls various cardiovascular parameters, such as the modulation of heart rate and blood pressure, myocardial contractility and venous capacitance, directly participating in the regulation of cardiac output. Over the years, the standard treatment for menopause symptoms and disorders has been hormone replacement therapy (HRT). However, many studies have indicated the risks of HRT, which justify the need for new non-pharmacological therapies. To this end, physical training, mainly aerobic, has been applied with excellent results on the cardiovascular autonomic nervous system, as it reduces the risk of cardiac diseases and improves the survival rate with direct beneficial effects on the quality of life of these women during the aging process.

Key words: Menopause, Aging, Physical Training, Cardiovascular Autonomic Control.

The World Health Organization defines menopause (mensis= month; pausis= pause) as the permanent cessation of menstruation due to the loss of ovarian follicular activity. This event occurs following changes in the levels of female sex hormones, decreases in the circulating levels of estrogen and progesterone, and concomitant increases in the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The diagnosis is mainly clinical and retrospective, confirmed after twelve months of amenorrhea [1].

The median age of menopause in developed countries is 51 years**,** but it may sometimes occur earlier (before the age of 40) for surgical, autoimmune, genetic, iatrogenic and idiopathic reasons [2,3]. This condition is defined as early menopause [1,4].

The features of this period have received particular attention in recent decades, considering that the average life expectancy for women in developed countries is estimated at 80 but the average age of natural menopause has remained virtually unchanged, i.e., around the age of

***Correspondence should be addressed to:** Hugo C.D. Souza, Ph.D., Department of Biomechanics, Medicine and Rehabilitation, School of Medicine of Ribeirão Preto, Ribeirão Preto, SP, Brazil. Email: hugocds@fmrp.usp.br

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51 [1]. Therefore, women live approximately one-third of their lives in the post-menopausal period, which explains the great interest in the management of this population, both in terms of epidemiological and public health and in terms of scientific research. Consequently, the introduction of preventive strategies during menopause can serve as a determinant in the survival and quality of life of these women during the aging process.

Menopause and Cardiovascular Risk

Cardiovascular diseases (CVDs) are among the greatest public health problems of the modern world [5–7], being responsible for the highest mortality and morbidity rates among various pathologies in both men and women.

Although women and men share the stronger risk factors for CVDs (family history, diet, obesity, tobacco smoking, lack of physical activity, high blood pressure, dyslipidemias, diabetes mellitus, among others), a number of epidemiological studies have shown a sexual dimorphism with respect to CVDs, as the prevalence of these diseases in 30- to 45-year-old individuals is higher in men than in women of the same age [8,9]. This difference decreases with age, and after menopause, the cardiovascular risk increases exponentially [10,11].

Considering this feature, recent studies have shown that after menopause, women experience a higher risk of coronary insufficiency, with heart disease being the leading cause of death [12,13]. Epidemiological evidence suggests that the hormonal changes during this period, particularly the decline in estrogen, are primary factors contributing to the increased risk of CVDs [14–18].

Additionally, many studies have shown that early menopause has been associated with an increased risk of myocardial infarction, stroke and mortality, either by natural or surgical causes [14,19–21]. Some authors have suggested that this condition, compared to physiological menopause, carries an even greater cardiovascular risk [22–25].

Based on this information, the ovarian hormones have been shown to protect the cardiovascular system [26], especially with respect to the homeostasis of the autonomic neural mechanisms of cardiovascular control.

Ovarian Hormones and Autonomic Cardiovascular Control

The autonomic nervous system plays a key role in all cardiac regulatory mechanisms, as it tonically and reflexively affects the main parameters of the cardiovascular system. It is mainly responsible for the control of various cardiovascular parameters, including the modulation of heart rate (HR) and arterial pressure (AP), the myocardial contractility and the venous capacitance, each of which directly participate in regulating cardiac output. Autonomic cardiovascular control can be evaluated using the following tools: pharmacological autonomic blockers, baroreflex sensitivity analysis, heart rate variability analysis, recording the electrical activity of the autonomic efferent and afferent nerves, *plasma catecholamines*, and the expression and activation of cardiac autonomic receptors. These methods have been widely used to evaluate the cardiac sympathovagal balance and to predict cardiovascular risks [25,27–31].

In other words, many studies have demonstrated the beneficial influence of ovarian hormones on the cardiovascular autonomic control; estrogen appears to be able to increase the vagal influence on the heart and reduce the cardiovascular sympathetic drive [32–35]. As a result, studies on hormonal deficiency in women after menopause revealed additional autonomic damages, such as reductions of the heart rate variability and baroreflex sensitivity [32,36–39]. These changes seem to be directly related to an increase in the cardiac sympathetic activity combined with a reduction in the vagal influence [40,41]. In addition, it was shown that the female hormones also appear to influence the cardiac contractile response; this effect was observed in a study of young rats that were subjected to ovariectomy [42,43] and in a study of post-menopausal women [44]. In this case, the experimental studies revealed a reduced β-adrenergic responsiveness and an increased β_1-adrenergic expression after ovariectomy, which were reversed with hormone replacement therapy.

Hormone Replacement Therapy

Initially, hormone replacement therapy (HRT) with exogenous supplementation of female sex hormones (estrogen and/or progestin) was the primary choice to attenuate the risks of CVDs and help control menopausal symptoms. However, over the last two decades, HRT has incited doubts and uncertainties following the results of several studies of its use. Therefore, the advantages and disadvantages of this treatment should be carefully analyzed while considering that contradictory studies sometimes arise regarding replacement therapy of ovarian hormones.

The benefits of the HRT after menopause and some of the possible autonomic cardiovascular drawbacks have been widely discussed. Observational studies showed that HRT has been associated with a reduction of up to 50% in the incidence of CVD. [45–48]. Additionally, several studies have also shown the positive effects of hormone therapy on cardiovascular autonomic control, reporting improvements in the heart rate variability and baroreflex

sensitivity, in the cardiac autonomic tone, in addition to an improvement in the regulation of AP [32,36,49,50].

However, these cardiovascular and autonomic effects favoring HRT have been contested [51,52] and also rebutted by several clinical trials. A randomized, placebo-controlled study from the Heart and Estrogen-Progestin Replacement Study (HERS) was published in 1998 to determine the efficacy of conjugated estrogen (0.625 mg) combined with medroxyprogesterone (2.5 mg) for the prevention of new events in patients with previous coronary disease. The results showed an increase in venous thromboembolism and coronary events during the first year of follow-up after acute myocardial infarction [53].

In 2002, the WHI (Women's Health Initiative) was published, a prospective trial of primary prevention of CVD in which the average age of the participants was 63.3 years, and they received the same hormonal treatment as that of the HERS study. The results indicated that HRT significantly increased the risk of CVDs in this group of women compared to the placebo group [54].

It is important to note that these studies were criticized for at least two aspects: the selection of patients, which included women whose average age was a decade higher than that of other studies and to whom the hormone therapy is commonly recommended and the use, in both studies, of the same hormone replacement therapy for all women, including the same administration route and fixed doses [55].

These findings certainly have a strong impact on hormonal therapy prescriptions, indicating that their use should be reconsidered and that new forms of therapy should be sought [56–58]

Change of Lifestyle – Physical Training

To mitigate the risks and comorbidities associated with menopause, recommendations have been made to change one's lifestyle through regular physical exercise. This non-pharmacological behavior, which is important in the treatment of various diseases, results from observations of the cardiovascular, autonomic and metabolic benefits after acute and chronic physical exercises. In fact, epidemiological, clinical and experimental data confirm that regular physical exercises improves the quality of life and reduces the progression of CVDs and, consequently, cardiovascular morbidity and mortality [59–61].

In general, physical training, mainly aerobic fitness, promotes important autonomic cardiovascular adaptations, characterized by reduced sympathetic autonomic drive and increased vagal autonomic drive [62–65]. These changes lead to an improvement of the baroreflex sensitivity and heart rate variability, both in experimental models [66–69] and in human samples [57,70,71]. In addition, several studies have also shown increased cardiac β-adrenergic responsiveness after physical training [72–76], without any alterations [73,77] or reductions in the density of cardiac β-adrenergic receptors [72,78–80].

Although the benefits of aerobic physical training have been well demonstrated in various populations, only a few studies have examined the autonomic cardiovascular effects on post-menopause.

Effects of Physical Training during Post-menopause

A few studies have shown that physical training can positively alter the cardiac autonomic control in women after menopause; these effects frequently involved increases in the heart rate variability and baroreflex sensitivity [37,81–83]. A review article [84] showed other beneficial effects of physical activity on bodyweight control; composition and bone strength; muscle strength and endurance; flexibility, balance and coordination; oxygen consumption; blood pressure; and metabolic control in post-menopause women. Furthermore, an experimental study that compared the autonomic adaptations in response to physical training in female rats during physiological and early menopause showed that contrary to what happened in physiological menopause (≅ 72 weeks of life), physical training was not able to mitigate the negative effects on the autonomic cardiovascular control in animals subjected to early menopause (10 weeks) [25]. These results suggest that the ovarian hormone deprivation associated with the aging process causes autonomic cardiac damages that are not fully attenuated by physical training, or at least physical training of the type, intensity and duration used in the mentioned study.

In fact, menopause is closely associated with the aging process, which may result in autonomic and even hemodynamic changes. Clinical and experimental studies have shown that both aging and menopause are marked by important autonomic cardiovascular and hemodynamic changes, such as an increased AP and reductions in the heart rate variability and baroreflex sensitivity [85–90].

Physical Training during Post-menopause and Hemodynamic Changes

A high AP during this phase of life can be attributed to other effects associated with the aging process, such as a reduced arterial compliance and an increased arterial wall thickness [91–93]. However, ovarian hormone deprivation can also contribute to hypertension, as experimental studies with young ovariectomized rats have demonstrated higher levels of AP [68,94–96]. Possible mechanisms that can cause high AP due to a reduction in

estrogen include the following: an increase in the sympathetic drive and in the activity of the renin-angiotensin-aldosterone system, endothelial dysfunction, and an increase in oxidative stress and in the plasma levels of endothelin and testosterone [97–102]. However, as described above, it is difficult to account for the effects of aging on ovarian hormones deprivation in this case.

In contrast, physical training reduces the AP in this population, regardless of its origin. The cause of this reduction also seems to involve several factors that require a better understanding, such as an attenuation of sympathetic neural activity, a reduction in cardiac output, decreased serum levels of vasoconstrictive factors and increased levels of endothelium-derived vasodilator factors, resulting in decreased peripheral vascular resistance [59,103–105]. In this case, it worth mentioning that a reduction in the AP level is considered to represent an important target for reducing the risk of morbidity and mortality in patients with associated cardiovascular diseases [106].

Physical Training during Post-menopause and Cardiovascular Autonomic Adaptations

With respect to cardiovascular autonomic control, important changes resulting from the aging process have already been observed. Common examples of these changes include reductions in the heart rate variability and baroreflex sensitivity and an increase in the AP variability [85–90]. In turn, similar results were obtained during the postmenopausal period, emphasizing the difficulty of separating the effects of aging and those of a reduced ovarian function.

In this context, a recent experimental study of rats [25] showed a reduction in the low (LF) and high frequency (HF) oscillations of the heart rate variability in sedentary animals that had reached menopause during physiological aging and animals submitted to early menopause by ovariectomy. Both conditions lead to a reduction in the cardiac vagal modulation [107], as this autonomic component is responsible for the HF oscillations and part of the LF oscillations of the heart rate variability [29,108,109]. However, the reduction in the LF oscillations of the heart rate variability also suggests a decrease in cardiac sympathetic modulation, although some studies indicate that aging is marked by increases in plasma catecholamine levels [110,111] and in peripheral sympathetic nerve activity [112,113]. These studies have also revealed that baroreflex sensitivity would also be impaired in this model and concluded that a deficit in the cardiac autonomic modulation could be attributed to a loss of baroreflex sensitivity.

It is common to observe an increase in the AP variability after menopause; however, this effect could be partly due to the aging process. This finding is relevant because clinical and experimental studies on aging have demonstrated that an increase in the AP and a subsequent increase in the AP variability could be associated with higher target-damage organs and cardiovascular events [114,115].

The cause of the increase in AP variability remains controversial, but a few studies have indicated that vascular sympathetic hyperactivity is an underlying mechanism of this phenomenon [114,116]. In turn, other studies have also attributed the reduction of baroreflex sensitivity to be a determinant factor for the AP variability. It has also been claimed that a lower inhibition of the vasomotor centers, resulting from the adaptation of the baroreceptors, could be responsible for the increased sympathetic activity and perpetuation of hypertension [117]. Additionally, other causes associated with aging can be mentioned, such as a decreased arterial compliance and/or an increased arterial stiffness associated with the endothelial dysfunction, as mentioned above [91,92,105].

In contrast, other studies have suggested that menopause can also influence the cardiovascular autonomic control through interactions in the central nervous system (CNS). This conclusion is based on studies that have showed that estrogen deficiency promotes adjustments in the autonomic nervous system, including in the CNS areas related to cardiovascular control. This effect is based on the identification of estrogen receptors (ER) in CNS nuclei that are involved in cardiac autonomic control [118,119]. However, blockage or activation of these receptors in specific areas seems to produce a range of cardiovascular responses. Therefore, a study showed that the administration of estrogen to the parabrachial nucleus of rats caused hypotension, bradycardia, a reduction in renal sympathetic nerve activity and an increase in the cervical vagal nerve activity [120]. These responses were inhibited when estrogenic receptor antagonists, $GABA_A$ and NMDA, were administered. In contrast, another study involved infusing estrogen into the insular cortex; there was an increase in the renal sympathetic drive without affecting the AP and HR, possibly via the activation of $GABA_A$ receptors [121]. When the baroreceptor reflex was analyzed under conditions of estrogen deficiency, there was an observed reduction in the baroreflex sensitivity that was restored by hormone replacement [90,96,122].

Therefore, the results on the HR and AP variability suggested that the damage in cardiovascular autonomic modulation could result from baroreflex dysfunction, which may be influenced by both menopause and aging, as previously discussed. However, the results found after physical training in the study carried out by TEZINI et al. (2013) suggest that the lack of the ovaries for a long

period of time is critical for autonomic adaptations. This conclusion is based on the fact that physical training did not have the same effects on both the physiological and early menopause groups. The former group showed significant improvements in most of the parameters evaluated, characterized by a vagal predominance in the determination of HR to the double pharmacological blockade, improvement in the baroreflex sensitivity and a reduction in the LF oscillations, in both the heart rate and AP variability. In contrast, the early menopause group exhibited an improvement in the baroreflex sensitivity and a minor reduction of the sympathetic predominance to pharmacological blockade. This discrepancy between the two groups is unexpected, as physical training seems to promote cardiovascular, autonomic and metabolic adaptations, which are considered beneficial in many pathophysiological situations, suggesting that physical exercise should be indicated as a non-pharmacological treatment in the prevention and treatment of various diseases [123].

The mechanisms responsible for the beneficial exercise-induced autonomic adjustments, including the modulation of heart rate and AP variability, have not yet been completely determined. However, it was observed that in central areas, such as the paraventricular nucleus of the hypothalamus (PVH), the nucleus of the solitary tract (NST) and the rostral ventrolateral medulla (RVLM), physical training promotes adjustments that can decrease both the sympathetic autonomic modulation and drive, even implicating the participation of endothelial factors, such as nitric oxide [124–128].

Conversely, the reason for the reduced effect of physical training on cardiovascular autonomic adaptations observed in animals submitted to early menopause is unclear. Moreover, this finding cannot be attributed to the removal of the ovaries, as other studies have shown that physical training promotes beneficial autonomic changes in young ovariectomized rats, promoting improvements in the baroreflex sensitivity and cardiovascular autonomic modulation [31,68,129]. However, these studies were performed exclusively in young rats; therefore, neglecting to make an association with the aging process.

Therefore, although the autonomic damage was observed to be similar among sedentary animals undergoing menopause, it is possible that the early ovarian hormone deprivation promotes further deterioration and cardiovascular dysfunction relative to physiological menopause, such as hypertrophy and cardiac fibrosis, contractility dysfunction and vascular damage associated with endothelial dysfunction, affected, at least in part, by a lower adaptation to physical training. These observations emphasize the role of the ovaries in several cardiovascular autonomic adaptive processes, which need further investigation.

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