Review article

Effects of estrogen deprivation and physical exercises on the arterial wall: a literature review

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Abstract

Over the past few decades, there has been a surge of interest in the study of the effect of estrogen on the female organism and the benefits of physical activities on different species of animals. The literature review provides a review of the existing literature on the morphological and/or physiological effects of the estrogen deprivation and/or the role of physical exercises on the arteries of different species of animals and humans. This review includes last decade publications found in the PubMed database. One of the most relevant findings concerning estrogen deprivation was the arterial complacency reduction due to the reduction of elastin, whereas physical exercises have been widely indicated for the treatment of several cardiovascular disorders and for the hardening of central arteries.

Keywords: artery, morphology, physiology, estrogen, aerobic physical exercise.

1 Introduction

The effects of estrogen (MALINOW, 1960) and the benefits of physical exercises to the arterial system of living organisms (HICKAM and CARGILL, 1948) have been investigated for over four decades.

It is well known that reducing the estrogen levels can cause important morphofunctional changes increasing the risk of diseases and contributing to life quality and independence loss, besides being costly for the public health system (EAKER, CHESEBRO and SACKS, 1993; CASTILLO, ARIZNAVARRETA, LAHERA et al., 2005); not to mention the increase in the incidence of atherosclerosis (WENGER, O'ROURKE and MARCUS, 1988). These morphofunctional changes are closely related to menopause since the reduction of estrogen levels is inherent in the menopausal phase (IDICULLA and GOLDBERG, 1987; MISZKO and CRESS, 2000).

Projections for the world population have indicated an increase in the number of women in menopause from 467 million, in the 1990s, to 1.2 billion in 2030 (WORLD HEALTH ORGANIZATION, 1996). Data from the Brazilian Institute of Geography and Statistics (IBGE), 2008, revealed that in 2007 the female population aged over 45 years old was almost 27 million in Brazil (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2008). Demographic indicators of the Ministry of Health show that the Brazilian female population aged over 45 years old has been growing in the recent years. In the beginning of the 1990s, there were over 13 million, and in 2006 it reached over 23 million (DATA SUS, 2008).

The increase in life expectancy of women in developed countries, which increased from over 50 years of age in the beginning of the 20th century to 80 years of age in the beginning of the 21st century, has contributed to the increase raise in the amount of research of cases in which there is reduction of estrogen levels in the female organism since in such cases women spend approximately one third of their life in the post-menopausal period (PAOLETTI and WENGER, 2003; NORTH AMERICAN MENOPAUSE SOCIETY, 2007). According to data on the world and Brazilian population, the morphofunctional changes in the cardiovascular system are those that cause more diseases in women during the climacteric period (DATA SUS, 2008).

Consequently, several different resources have been indicated for the prevention and treatment of cardiovascular and metabolic disorders of the post-menopausal period including hormone therapy, diet, and physical exercises (TCHERNOF, CALLES-ESCANDON, SITES et al., 1998; SIMON, 2006). Actually, the last ones have been indicated for the non-pharmacological treatment of many disorders, and their use has been recommended in public health services (PATE, PRATT and BLAIR, 1995). Practiced regularly and moderately, physical exercises, associated to lifestyle changes, can have beneficial effects on the cardiovascular system of individuals, including elderly, obese and sedentary people, and women in the post-menopausal period (BEITZ and DÖREN, 2004; CARELS, DARBY, CACCIAPAGLIA et al., 2004; RACKLEY, 2004).

Physical exercise can also have hormonal effects resulting in protein and receptor changes (PATE, PRATT and BLAIR, 1995; COPELAND, CHU and TREMBLAY, 2004). It can be a modulator in the event of arterial complacency reduction and other physiological and physiopathological consequences (SEALS, 2003). In addition, epidemiological studies have supported the hypothesis that a sedentary lifestyle is related to the development of more cardiovascular diseases for over 40 years (KANNEL, 1967; PAFFENBARGER, WING and HYDE, 1978).

As with the national and international literature, it is still difficult to find reviews that gather previous studies on estrogen deprivation and the practice of physical exercises based on morphofunctional aspects of the artery wall. The purpose of this study was to gather relevant literature and offer a tool to researchers interested in this field.

2 Material and methods

The PubMed (www.pubmed.nl) and MEDLINE databases were used to conduct the literature search using keywords without time restrictions. In this systematization, papers were searched using the following keywords: artery, arterial wall, vessels, morphology, physiology, estrogen, aerobic physical exercise.

3 Results

Estrogens are ovarian sex hormones responsible for cell proliferation and the growth of the tissues of the sex organs and other organs related to reproduction. They promote the development of most female secondary sexual characteristics. Beta-estradiol is the most important estrogen. Estrogens are mainly synthetized from blood cholesterol, but also, to a lesser extent, from acetyl-coenzyme A. They are excreted mostly by the ovaries although a minimum amount is excreted by the suprarenal glands (GUYTON and HALL, 1996).

The estrogen deprivation can be due to pathological aspects that attack the ovaries such as tumors which can result in ovariectomy before the fourth decade of a woman's life (BOZAS, DIMOPOULOS, KASTRITIS et al., 2006), in adolescents before 15 years of age (ZUCKER, 1982), in children (HOREJSÍ and ROB, 2003), and even during menopause, a consequence of the natural process of maturation and aging of the female organism. It is diagnosed after 12 months of amenorrhea resulting from the definitive cessation of ovary function that in general begins in the fourth decade of a woman's life and ends at menopause at about 51 years of age (GREENDALE, LEE and ARRIOLA, 1999).

The climacteric, which culminates with menopause, besides being a period of a substantial fall in the production and release of estrogen, has been associated to the process of aging favoring morpho-physiological changes and leads to the development of disorders such as systemic arterial hypertension (SAH), Hypercholesterolemia, diabetes mellitus, obesity, and atherosclerosis (GIAMPAOLI, PANICO, MELI et al., 2000; BITTNER, 2002, 2006; RACKLEY, 2004). During menopause, there is a greater decline in the estrogen levels than that observed in the androgens (testosterone, for example).i.e., the ratio androgens/estrogens is increased. This could cause cardiovascular diseases (CVDs) since high levels of male and female sex hormones are associated to dyslipidemia, diabetes mellitus, and SAH (HAFFNER, NEWCOMB and MARCUS, 1995; PHILLIPS, JING and LARAGH, 1997; OH, BARRETT-CONNOR, WEDICK et al., 2002).

With regard to aging changes of the arterial wall, it is known that there are extracellular matrix changes (ROBERT, 1996). Two factors are related to it: the progressive deposition of lipids and calcium in the elastic fibers (JACOB, 2003) and the age-dependent factor that increases the elastase activity (LABAT-ROBERT and ROBERT, 1988). Concomitantly, both factors deprive the elastic tissue of its flexibility and increase susceptibility to elastolytic enzymes (LABAT-ROBERT and ROBERT, 1988). This explains the predominance of collagen in the aged aorta, the increased collagen/elastin ratio, and the progressive rigidity of the vessels (ROBERT, 1996).

Such alterations can also dilate the artery walls and become an aneurysm, for example, which can rupture causing death (MORIGUCHI, Y. and MORIGUCHI, EH., 1988). Any anatomical disturbance that compromises the blood supply to tissues due to obstruction of blood flow or hemorrhage caused by aneurysm rupture can result in the necrosis of the adjacent tissue (JUNQUEIRA and CARNEIRO, 2008).

With regard to CVDs, in 2005, the death rate due to diseases in this group in women over 50 years of age was 722.58 (per 100,000 inhabitants); for women between 30 and 49 years old, this rate declined to 41.36 (DATA SUS, 2008).

That besides being a consequence of aging, SAH can also be caused by the decline in estrogen levels during post-menopause period is still debated (RAPPELLI, 2002). Some studies show that the high prevalence of SAH is greater in women in the climacteric period than those in the prior period (STAESSEN, CELIS and FAGARD, 1998).

Menopause also contributes to atherosclerosis since among its causes are the hormonal disturbances and cholesterol metabolic changes that are common during the post-menopause period (SILVA, BRUM, NEGRÃO et al., 1997). Atherosclerosis is characterized by the focal intima thickening, by the proliferation of smooth muscular cells and cellular and extracellular elements of the connective tissue, and by the accumulation of cholesterol in smooth muscular cells. It is believed that the uniform intimal thickening is a phenomenon of normal aging.

An intima balance alteration (endothelium lesion, for example) can lead to calcium and lipids deposit. It has already been shown that a significant reduction in the estrogen levels, especially the 17-beta-estradiol, causes important changes of the lipid profile since it increases the low-density lipoprotein (LDL), or aterogenic, and decreases the high-density lipoprotein (HDL), called protection against atherosclerosis. Smooth muscular cells that migrate from the media to the intima also take part in this process. Despite the intima thickening, the media thickening remains almost unaltered (TAKANO and MINEO, 1990; PINOTTI, HALBE and HEGG, 1995).

Although the exact mechanism by which estrogens provide protection to the cardiovascular system is not yet known, some studies suggest that they might have an effect on apolipoproteins besides decreasing the total cholesterol and LDL levels (SULLIVAN, 1996).

During the reproductive age, women show lower incidence of coronary diseases than do men at the same age rate (WONG, S. and WONG, J., 1999). Estrogen affect the receptors and arterial wall enzymes reducing the blood pressure and improving blood flow, stimulate the prostanoides (prostaciclins) that act as vasodilators and antiplatelet agents, stimulate the vasodilator pepitide that reduces stress, and is beneficial to the lipid metabolism and phibrinolitic proteins (PINOTTI, HALBE and HEGG, 1995; MENDELSOHN and KARAS, 1999). The association of estrogens with progesterones can provide an antiatherogenic benefit to the aorta besides the effects exerted by steroids on preventing calcium accumulation in the arterial wall (ALDRIGHI,1996).

Nevertheless, the experimental data on the effect of estrogens on cardiovascular disorders are controversial and have not been fully understood since the hormonal reposition therapy, TRH, during the climacteric period has been questioned in terms of risks and benefits; the latter are inconsistent and inconclusive (CAULEY, CUMMINGS and BLACK, 1990; STAMPFER and GOLDITZ, 1991; MATTHEWS, KULLER, WING et al., 1996; McKECHNIE, RUBENFIRE and MOSCA, 2001; TATCHUM-TALON, MARTEL and MARETTE, 2002; BUPHA-INTR and WATTANAPERMPOOL, 2003; GROSS, RITZ, KORSCH et al., 2005; MAAS, SHOUW, GROBBEE et al., 2004; STICE, EISERICH and KNOWLTON, 2009).

Researchers have been investigating non-pharmacological treatments to prevent CVDs in women in menopause. Among them, is regular physical exercises practice (NAGPAL, WALIA, LATA et al., 2007; PINES and BERRY, 2007).

The cardiovascular and metabolic risk in women during the post-menopause period increases due to aging or estrogen deprivation, but it is also a consequence of the reduction of physical exercises and diet changes, which cause total fat increase, atherogenic dyslipidemia, reduction in glucose tolerance, insulin resistance, and an increase in the procoagulant factors (BUPHA-INTR and WATTANAPERMPOOL, 2003). Physical exercises combined with an appropriate diet contributes to increase the body mass index and energy consumption, decreases the total body fat and visceral fat indexes, improves insulin sensitivity, reduces hyperfibrinogenemia, and optimizes the hemodynamic parameters (GASPARD, BUICU and CREUTZ, 2001).

The effects of physical exercises on the human organism are quite far-reaching. Some benefits are facilitating learning new activities, improving cognitive functions, reducing the likeability of diseases, and from the 20th century onward it has increased women's life expectancy to around 25 years (IDICULLA and GOLDBERG, 1987). They provide improvement in the health-related quality of life and physical fitness, ameliorate some physiological changes associated to aging, prevent chronic diseases, reduce bone loss, typical of the post-menopause period, and promote functional independence (MISZKO and CRESS, 2000).

Physical exercises practice has been widely reported in the literature due to its benefits to the cardiovascular system. According to a 20-year study on middle-aged women by Owens, Matthews, Raïkkönen et al. (2003), it is never late to reduce the cardiovascular risk by increasing the level of physical activities. Usual physical activities (exercises during regular activities such as transportation, work, home, and recreation), contribute to low risk of CVDs in women (SILVA, COSTA-PAIVA, PINTO NETO et al., 2006), prevent coronary artery diseases in women (MANSON, 1999; DUVERNOY, MARTIN, BRIESMIESTER et al., 2006), and are associated to low death rates in middle-aged women (DAM, LI, SPIEGELMAN et al., 2008).

In 2002, the Women's Health Initiative Observational Study investigated 74,000 women in menopause, aged between 50 and 79 years old. The study demonstrated that high levels of physical activity showed reverse reaction, either gradual or intense, with risk of coronary and cardiovascular diseases (MANSON, 2002).

Aerobic physical exercises in elderly men have a favorable role if practiced regularly over decades resulting in minimum loss of oxygen without the increase of blood pressure at rest or body composition (KASCH, BOYER, SCHMIDT et al., 1999). In sedentary young men, alternate day low intensity physical exercises practiced for 60 minutes in fitness bicycles, at 70% of maximum oxygen consumption, can improve aortic distensibility, but the effects can be lost without the exercises (KAKIYAMA, SUGAWARA, MURAKAMI et al., 2005).

The benefits of aerobic physical exercises to the healthy cardiovascular system have been widely discussed and can be characterized as acute or chronic. During physical exercises, the muscles need increased blood flow to provide them with oxygen. Part of this oxygen is supplied by local vasodilatation of muscle vasculature, which is produced by the increase in the metabolism of muscular cells. On the other hand, the bulb activation and the sympathetic nervous system response increase the cardiac debt and increase the arterial pressure. During vigorous exercises this increase can reach 30 to 40%, which increases the blood pressure two times or more and stretches the vessels. Initially, the vessel is subject to a higher pressure, but complacency enables the muscular fibers to stretch, and the vessel resistance decreases (SILVERTHORN, 2003; BRUM, FORJAZ, TINUCCI et al., 2004).

The systolic volume increases, and consequently, the amount of blood to be accommodated in the arterial tree with each heartbeat will be larger. The increase in the arterial pressure results in the reticular activation of the cerebral trunk including increased stimulation of the vasoconstrictor and cardio-accelerator areas of the vasomotor center (SILVERTHORN, 2003).

Skeletal muscle contractions during physical exercises compress the blood vessels all over the body transferring high amounts of blood from the peripheral vessels to the heart and lungs resulting in a five to six times increase in the cardiac debt. The cardiac debt, in turn, increases the systolic arterial pressure and is responsible for the maintenance or reduction of the diastolic arterial pressure (FORJAZ, MATSUDAIRA, RODRIGUES et al., 1998), which increases the strength that tends to push the blood across the vascular bed stretching the vessels. Consequently, the peripheral vascular resistance decreases, and the increase in the cardiac debt maintains the arterial pressure high. This suggests that the normal baroreceptor that controls arterial pressure does not work during physical exercises, but it fits to avoid a decrease in the arterial pressure keeping an adequate blood flow to remove the muscle metabolites or to maintain the muscle under aerobic metabolism (SILVERTHORN, 2003).

Nonetheless, according to (BRUM, SILVA, MOREIRA et al., 2000), physical exercises increase the baroreceptor sensitivity in normotensive individuals, which can lead to a more efficient result in the arterial pressure by the baroreflex, or baroreceptor reflex.

In order to avoid excessive filling of the vessels, which is potentially dangerous due to the excessive stretching of the muscle fibers, the sympathetic nervous system maintains the cardiac frequency and the heart contraction force increased, in order for the heart to eject more blood per heartbeat (SILVERTHORN, 2003). Immediately after physical exercises, there is a decrease in the arterial pressure during the recovery period, and thus the pressure values are smaller than those observed before the exercises, and they last for 24 hours after the end of the exercises.

The effect of the aerobic physical exercises in the long run involves the well-known hypotension action both in animals and in humans (BRUM, SILVA, MOREIRA et al., 2000; KOKKINOS, NARAYAN and PAPADEMETRIOU, 2001). However, the mechanisms that explain such event are considered controversial. Aerobic exercises stimulates the hypothalamic-pituitary axis that controls the release of several neuroendocrine hormones (LEAL-CERRO, GIPPINI, AMAYA et al., 2003) and acetylcholine (DÖRNYEI, MONOS, KALEY et al., 2000) reducing the level of adrenergic hormones and causing the unbalance between the adrenergic and parasympathetic systems predominating the vagal action (KENNEY, 1985). As a response, there is a rest Bradycardia and lesser tachycardic response during the exercises (BRUM, FORJAZ, TINUCCI et al., 2004).

Physical exercises increase the blood flow in the coronary arteries by inducing their vasodilatation. Such vascular response is greatly dependent on the integrity of the endothelium since the endothelium modulation effect is controlled by the release of endothelium-derived relaxing factors (EDRFs) (SESSA, 1994). Physical exercises increase the bio-availability of the Nitric oxide (NO), an EDRF, which improves the endothelial function in patients with cardiovascular disorders (GRAHAM and RUSH, 2004; SUVORAVA, LAUER and KOJDA, 2004) since physical exercises regulate and induce the genetic expression of the synthesis of NO (YEN, CHEN and WU, 1995) with a consequent reduction in the peripheral resistance (SHEN, ZHANG, ZHAO et al., 1995). Once formed, the NO migrates quickly to the adjacent smooth muscle cells, and, after several biochemical reactions, the vascular smooth muscle relaxes due to the desphosphorylation of myosin light chains. These events reduce the influx of the calcium ion through the sarcolemma and the release of its intracellular deposits. This results in a decrease in the concentration of cytosolic free calcium ion. The NO can also open potassium channels promoting hyperpolarization in the smooth muscle cell thus helping to reestablish the cell's resting potential with a consequent vascular relaxation (OHESEN, CLAPHAM and DAVIES, 1988; MARTINEZ, 2005).

Therefore, physical exercises reduce the risk of CVDs through the same mechanisms used by the estrogens: change in the concentrations of lipoproteins in the blood plasma and the reduction in the blood pressure and increase in the endothelium-dependent vasodilatation due to an increase in the synthesis and EDRFs release (WONG, S. and WONG, J., 1999). The several different molecular changes, particularly NO endothelium changes, can contribute, at least in part, to the benefits provided by physical exercises to maintain the aortic elasticity (MAEDA, IEMITSU, MIYAUCHI et al., 2005).

On the other hand, physical inactivity causes endothelial dysfunction in young and healthy rats, but it is completely reversible by moderate physical exercises in a short period of time (SUVORAVA, LAUER and KOJDA, 2004).

Central arteries such as aortic and carotid arteries have good distensibilty absorbing impacts during pressure variations (NICHOLS and O'ROURKE[1], 1998 apud HAYASHI, SUGAWARA, KOMINE et al., 2005). Moderate physical exercises can reduce the rigidity of these vessels of healthy, sedentary individuals (TANAKA, DE SOUZA and SEALS, 1998; TANAKA, DINENNO, MONAHAN et al., 2000). Through aortic pulse wave velocity measurements, it was possible to evaluate the arterial complacency and the diameter of the lumen of central vessels during diastole.

After the practice of regular moderate aerobic physical exercises, there was reduction in the resistance of those vessels in healthy middle-aged men although the physiological mechanism that explains the relationship between aerobic physical exercises and the reduction in the arterial resistance is not clear (HAYASHI, SUGAWARA, KOMINE et al., 2005). An increase in the diameter of the lumen of central and peripheral arteries was observed after three months of aerobic physical exercises practice, which can be related to the structural remodeling tor to the reduction in the vascular tonus of the smooth muscular cells contributing to the reduction of peripheral arterial resistance (DINENNO, TANAKA, MONAHAN et al., 2001). In addition, it can suggest that cyclic physical exercises can, even acutely, reduce the central and peripheral arterial resistance (KINGWELL, BERRY, CAMERON et al., 1997).

Through a simultaneous evaluation by ultrasound and applanation tonometry of the common and femoral carotid arteries of oarsmen and control individuals of both sexes and aged between 41 and 59, it was observed grater arterial complacency in the oarsmen than in the control individuals. The femoral artery, on the other hand, did not present differences in the level of rigidity. The increase in the carotid complacency in the oarsmen is associated to higher cardiovagal baroreflex sensitivity as it occurs in the Valsalva maneuver. It can be said that in middle-aged oarsmen the regular practice of resistant activity is associated to effects that favor the elastic properties of central arteries, which can null the rigidity that the strength exercise can cause to the arteries (COOK, DEVAN, SCHLEIFER et al., 2006). Using the same evaluation methods, Sugawara, Otsuki, Tanabe et al. (2006) selected 103 women aged between 47 and 82 years old, who were subject to light, moderate, and vigorous aerobic exercises. The results show that the rigidity index of the carotid artery decreased after the exercises.

Nevertheless, it is known that resistance training is associated to the reduction of elastic properties of central arteries. It is not known, however, whether this resistance occurs as a consequence of the resistance resulting from physical exercises, or it is an adaptation to the increasing

[1] NICHOLS, W. and O'ROURKE, M. *McDonald's Blood Flow in Arteries:* Theoretical, Experimental and Clinical Principles, Aenord, London: [s.n.] 1998.

resistance training. In a study consisting of two groups individuals of both sexes and aged 27 years old, in which one group was trained and the other was the control, no differences were found in terms of hemodynamic changes, but the complacency of the carotid, evaluated simultaneously by ultra-sound and applanation tonometry, decreased after the resistance training for a period of 30 minutes and recovered to the basal levels after 60 minutes. However, this study was not clear in terms of what happens to the arterial complacency after this period of time (ALLISON, ANTON, COOK et al., 2005).

Changes in lifestyle, particularly in terms of aerobic exercises and diet with sodium restriction, seem to be clinically efficient interventions to prevent and treat arterial rigidity (TANAKA and SAFAR, 2005). Some studies demonstrate that individuals with high level of physical exercises practice present reduction in the arterial rigidity if compared to those who are sedentary (FERREIRA, TWISK, MECHELEN et al., 2002; BOREHAM, FERREIRA, TWISK et al., 2004). Nonetheless, in cases with isolated SAH, the arterial rigidity can be reversible, and in those cases, the practice of physical exercises will not be efficient (TANAKA; SAFAR, 2005).

Hence, physical activities should start earlier as prevention and not as a treatment (FERREIRA, BOREHAM and STEHOUWERB, 2006). Sugawara, Otsuki, Tanabe et al. (2006) highlight the benefits of physical exercises to improve arterial rigidity in women in post-menopause associating this exercise practice to a 12-week aerobic exercise program. The authors concluded that both moderate and vigorous exercises can reduce arterial hardening.

It is known that the physical exercises practice improve some factors such as body fat rate, resistance to insulin, and arterial pressure, which are related to the increase in arterial rigidity (STEHOUWER and FERREIRA, 2006). In addition, it is also known that physical exercises have a profound impact on the endothelium function, inflammation, and sympathetic activities. It has also been demonstrated that these factors are associated to arterial rigidity (TANAKA and SAFAR, 2005). However, the mechanisms by which the exercises affect the properties of the vessels in humans, have not been widely studied (STEHOUWER and FERREIRA, 2006).

Our research group investigated the morfoquantitative characteristics of the extracellular matrix of the tunica media of the ascending aorta of female *Rattus norvegicus* of Wistar strain subject to aerobic physical exercises and to ovariectomy. The morfoquantitative analysis indicated that this kind of exercises, even if the practice starts during the adult age, can be a way to minimize the loss of arterial elasticity in cases of estrogen deprivation (MARIOTTI, 2009).

4 Conclusion

From the data described earlier, it can be said that the reduction in the estrogen levels results in arterial hardening due to the marked reduction of elastin in the vessel walls. On the other hand, the vasodilatation produced by the nitric oxide during aerobic physical exercises favors the arterial distensibility contributing to the reduction of arterial rigidity.

References

ALDRIGHI, JM. *Repercussões dos estrogênios e progesterônios sobre as lesões ateroscleróticas da aorta e das artérias coronárias em coelhas ovariectomizadas submetidas à dieta hipercolesterolémica*. São Paulo: Faculdade de Saúde Pública, Universidade de São Paulo, 1996. 101 p. [Tese de Livre Docência].

ALLISON, E. de van, ANTON, MM., COOK, JN., NEIDRE, DB., CORTEZ-COOPER, MY. and TANAKA, H. Acute effects of resistance exercise on arterial compliance. *Journal of Applied Physiology*, 2005, vol. 98, no. 6, p. 2287-2291.

BEITZ, R. and DÖREN, M. Physical activity and postmenopausal health. *Journal of the British Menopause Society*, 2004, vol. 10, no. 2, p. 70-74.

BITTNER, V. Menopause and cardiovascular risk cause or consequence? *Journal of the American College of Cardiology*, 2006, vol. 47, no. 10, p. 1984-1986.

BITTNER, V. Women and coronary heart disease risk factors. *Journal of Cardiovascular Risk*, 2002, vol. 9, no. 6, p. 315-322.

BOREHAM, CA., FERREIRA, I., TWISK, JW., GALLAGHER, AM., SAVAGE, MJ. and MURRAY, LJ. Cardiorespiratory fitness, physical activity and arterial stiffness: The Northern Ireland Young Hearts Project. *Hypertension*, 2004, vol. 44, p. 721-726.

BOZAS, G., DIMOPOULOS, MA., KASTRITIS, E., EFSTATHIOU, E., KOUTSOUKOU, V., RODOLAKIS, A., VLAHOS, G., VOULGARIS, Z., PAPAGEORGIOU, T., GIKA, D., PAPADIMITRIOU, C. and BAMIAS, A. Young age is associated with favorable characteristics but is not an independent prognostic factor in patients with epithelial ovarian cancer: a single institution experience. *Oncology*, 2006, vol. 70, no. 4, p. 265-272.

BRUM, PC., FORJAZ, CLM., TINUCCI, T. and NEGRÃO, CE. Adaptações agudas e crônicas do exercício físico no sistema cardiovascular. *Revista Paulista de Educação Física*, 2004, vol. 18, p. 21-31.

BRUM, PC., SILVA, GJ., MOREIRA, ED., IDA, F., NEGRÃO, CE. and KRIEGER, EM. Exercise training increases barorecepator gain-sensitivity in normal and hypertensive rats. *Hypertension*, 2000, vol. 36, p. 1018-1022.

BUPHA-INTR, T. and WATTANAPERMPOOL, J. Cardioprotective effects of exercise training on myofilament calcium activation in ovariectomized rats. *Journal of Applied Physiology*, 2004, vol. 96, p. 1755-1760.

CARELS, RA., DARBY, LA., CACCIAPAGLIA, HM. and DOUGLASS, OM. Reducing cardiovascular risk factors in postmenopausal women through a lifestyle change intervention. *Journal of Women's Health*, 2004, vol. 13, no. 4, p. 412-426.

CASTILLO, C., ARIZNAVARRETA, MC., LAHERA,V., CACHOFEIRO,V., GIL-LOYZAGA, P. and TRESGUERRES, JA. Effects of ovariectomy and growth hormone administration on body composition and vascular function and structure in old female rats. *Biogerontology*, 2005, vol. 6, no. 1, p. 49-60.

CAULEY, JA., CUMMINGS, SR. and BLACK, DM. Prevalence and determinants of estrogen replacement therapy in elderly women. *American Journal of Obstetrics and Gynecology*, 1990, vol. 163, p. 1438-1444.

COOK, JN., DEVAN, AE., SCHLEIFER, JL., ANTON, MM., CORTEZ-COOPER, MY. and TANAKA, H. Arterial compliance of rowers: implications for combined aerobic and strength training on arterial elasticity. *American Journal of Physiology Heart and Circulatory Physiology*, 2006, vol. 290, no. 4, p. H1596-H1600.

COPELAND, JL., CHU, SY. and TREMBLAY, MS. Aging, physical activity, and hormones in women--a review. *Journal of aging and physical activity*, 2004, vol. 12, no. 1, p. 101-116.

DAM, RM. van, LI, T., SPIEGELMAN, D., FRANCO, OH. and HU, FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *British Medical Journal*, 2008, vol. 16, no. 337, p. 1-8.

Data Sus. *Indicadores Demográficos do Ministério da Saúde*. [on-line]. [2007-09-08]. Available from: <http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2007/a02.def>.

DINENNO, FA., TANAKA, H., MONAHAN, KD., CLEVENGER, CM., ESKURZA, I., DE SOUZA, CA. and SEALS, DR. Regular endurance exercise induces expansive arterial remodeling in the trained limbs of healthy men. *The Journal of Physiology*, 2001, vol. 534, p. 287-295.

DÖRNYEI, G., MONOS, E., KALEY, G. and KOLLER, A. Regular exercise enhances blood pressure lowering effect of acetylcholine by increased contribution of nitric oxide. *Acta Physiologica Hungarica*, 2000, vol. 87, no. 2, p. 127-138.

DUVERNOY, CS., MARTIN, JW., BRIESMIESTER, K., MUZIK, O. and MOSCA, L. Self-reported physical activity and myocardial flow reserve in postmenopausal women at risk for cardiovascular disease. *Journal of Women's Health (Larchmt)*, 2006, vol. 15, no. 1, p. 45-50.

EAKER, ED., CHESEBRO, JH. and SACKS, FM. Cardiovascular disease in woman. *Circulation*, 1993, vol. 88, p. 1999-2009.

FERREIRA, I., BOREHAM, CA. and STEHOUWERB, CDA. The Benefits of Exercise for Arterial Stiffness. *American Journal of Hypertension*, 2006, vol. 19, no. 10, p. 1037-1038.

FERREIRA, I., TWISK, JW., MECHELEN, W. van, KEMPER, HC. and STEHOUWER, CD. Current and adolescent levels of cardiopulmonary fitness are related to large artery properties at age 36. The Amsterdam Growth and Health Longitudinal Study. *European Journal of Clinical Investigation*, 2002, vol. 32, p. 723-731.

FORJAZ, CL., MATSUDAIRA, Y., RODRIGUES, FB., NUNES, N. and NEGRÃO, CE. Post-exercise changes in blood pressure, heart rate and rate pressure product at different exercise intensities in normotensive humans. *Brazilian Journal Medicine Biological Research*, 1998, vol. 31, no. 10, p. 1247-1255.

GASPARD, U., BUICU, C. and CREUTZ, V. Multiple benefits of physical exercise in menopausal women. *Revue Médicale de Liège*, 2001, vol. 56, no. 4, p. 219-222.

GIAMPAOLI, S., PANICO, S., MELI, P., CONTI, S., LO NOCE, C., PILOTTO, L. and VANUZZO, D. Gruppo di ricerca dell'osservatorio epidemiologico cardiovascolare. Cardiovascular risk factors in women in menopause. *Italian Heart Journal. Supplement: Official Journal of the Italian Federation of Cardiology*, 2000, vol. 1, no. 9, p. 1180-1187.

GRAHAM, DA. and RUSH, JW. Exercise training improves aortic endothelium-dependent vasorelaxation and determinants of nitric oxide bioavailability in spontaneously hypertensive rats. *Journal of Applied Physiology*, 2004, vol. 96, no. 6, p. 2088-2096.

GREENDALE, GA., LEE, NP. and ARRIOLA, ER. The menopause. *Lancet*, 1999, vol. 353, p. 571-80.

GROSS, ML., RITZ, E., KORSCH, M., ADAMCZAK, M., WECKBACH, M., MALL, G., BERGER, I., HANSEN, A. and AMANN, K. Effects of strogens on cardiovascular structure in uninephrectomized SHRsp rats. *Kidney International*, 2005, vol. 67, p. 849-857.

GUYTON, AC. and HALL, JE. *Tratado de fisiologia médica*. 9ª ed. Rio de Janeiro: Guanabara-Koogan, 1996. 1014 p.

HAFFNER, SM., NEWCOMB, PA. and MARCUS, PM. Relation of sex hormones and dehydroepiandrosterone sulfate (DHEA-SO4) to cardiovascular risk factors in postmenopausal women. *American Journal of Epidemiology*, 1995, vol. 142, p. 925-934.

HAYASHI, K., SUGAWARA, J., KOMINE, H., MAEDA, S. and YOKOI, T. Effects of aerobic exercise training on the stiffness of central and peripheral arteries in middle-aged sedentary men. *Japanese Journal of Physiology*, 2005, vol. 55, no. 4, p. 235-239.

HICKAM, JB. and CARGILL, WH. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *The Journal of Clinical Investigation*, 1948, vol. 7, no. 1, p. 10-23.

HOREJSÍ, J. and ROB, L. Malignant tumors of the female genitalia in childhood--yesterday, today and tomorrow. *Cas Lek Cesk*, 2003, vol. 142, no. 2, p. 84-87.

IDICULLA, AA.; GOLDBERG, G. Physical fitness for the mature woman. *The Medical Clinics of North America*, 1987, vol. 71, no. 1, p. 135-148.

Instituto Brasileiro de Geografia e Estatística. *Fonte de dados estatísticos da população brasileira 2007*. [on-line] [2008-09-08]. Available from: <http://www.ibge.gov.br/home/estatistica/populacao/contagem2007/defaulttab.shtm>.

JACOB, MP. Extracellular matrix remodeling and matrix metalloproteinases in the vascular wall during aging and in pathological conditions. *Biomedicine & Pharmacotherapy*, 2003, vol. 57, no. 5-6, p. 195-202.

JUNQUEIRA, LCU. and CARNEIRO, J. *Histologia básica*. 11ª ed. Rio de Janeiro: Guanabara-Koogan, 2008. 524 p.

KAKIYAMA, T., SUGAWARA, J., MURAKAMI, H., MAEDA, S., KUNO, S. and MATSUDA, M. Effects of short-term endurance training on aortic distensibility in young males. *Medicine and Science in Sports and Exercise*, 2005, vol. 37, no. 2, p. 267-271.

KANNEL, WB. Habitual level of physical activity and risk of coronary disesase: The Framingham study. *Canadian Medical Association Journal*, 1967, vol. 96, p. 811-812.

KASCH, FW., BOYER, JL., SCHMIDT, PK., WELLS, RH., WALLACE, JP., VERITY, LS., GUY, H. and SCHNEIDER, D. Ageing of the cardiovascular system during 33 years of aerobic exercise. *Age and Ageing*, 1999, vol. 28, p. 531-536.

KENNEY, WL. Parasympathetic control of resting heart rate: relationship to aerobic power. *Medicine and Science in Sports and Exercise*, 1985, vol. 17, p. 451-455.

KINGWELL, BA., BERRY, KL., CAMERON, JD., JENNINGS, GL. and DART, AM. Arterial compliance increases after moderate-intensity cycling. *The American Journal of Physiology*, 1997, vol. 273, p. H2186-H2191.

KOKKINOS, PF., NARAYAN, P. and PAPADEMETRIOU, V. Exercise as hypertension therapy. *Cardiology Clinics*, 2001, vol. 19, no. 3, p. 507-516. Review.

LABAT-ROBERT, J. and ROBERT, L. Aging of the extracellular matrix and its pathology. *Experimental Gerontology*, 1988, vol. 23, no. 1, p. 5-18. Review.

LEAL-CERRO, A., GIPPINI, A., AMAYA, MJ., LAGE, M., MATO, JA., DIEGUEZ, C. and CASANUEVA, FF. Mechanisms underlying the neuroendocrine response to physical exercise. *Journal of Endocrinological Investigation*, 2003, vol. 26, no. 9, p. 879-885. Review.

MAAS, AHEM., SHOUW, YT., GROBBEE, DE. and GRAAF, Y. Rise and fall of hormone therapy in postmenopausal women with cardiovascular disease. *Menopause*, 2004, vol. 11, no. 2, p. 228-235.

MAEDA, S., IEMITSU, M., MIYAUCHI, T., KUNO, S., MATSUDA, M. and TANAKA, H. Aortic stiffness and aerobic exercise: mechanistic insight from microarray analyses. *Medicine and Science in Sports and Exercise*, 2005, vol. 37, no. 10, p. 1710-1716.

MALINOW M.R. In vitro effects of estradiol on the aorta of chickens. *Circulation Research*, 1960, vol. 8, p. 506-508.

MANSON, JE. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in

women. *The New England Journal of Medicine*, 1999, vol. 341, no. 9, p. 650-658.

MANSON, JE. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *The New England Journal of Medicine*, 2002, vol. 347, no. 10, p. 716-725.

MARIOTTI, VB. *Análise morfoquantitativa da matriz extra-celular da túnica média da aorta de ratas ovariectomizadas submetidas a exercício físico aeróbio*. São Paulo: Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, 2009. 109 p. [Dissertação de Mestrado].

MARTINEZ, RPZ. *Alterações cardiovasculares causadas pelo tratamento prolongado com dose baixa de nitro-largina metil éster (l-name) em ratos: efeito do enalapril e losartan*. Campinas: Faculdade de Ciências Médicas, Universidade Estadual de Campinas, 2005. 79 p. [Dissertação de Mestrado].

MATTHEWS, KA., KULLER, LH., WING, RR. and MEILAHN, EN. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *American Journal of Epidemiology*, 1996, vol. 143, no. 10, p. 971-978.

McKECHNIE, R., RUBENFIRE, M. and MOSCA, L. Association between self-reported physical activity and vascular reactivity in postmenopausal women. *Atherosclerosis*, 2001, vol. 159, no. 2, p. 483-490.

MENDELSOHN, ME. and KARAS, RH. The protective effects of estrogen on the cardiovascular system. *The New England Journal of Medicine*, 1999, vol. 340, p. 1801-1811.

MISZKO, TA. and CRESS, ME. A lifetime of fitness. Exercise in the perimenopausal and postmenopausal woman. *Clinics in Sports Medicine*, 2000, vol. 19, no. 2, p. 215-32.

MORIGUCHI, Y. and MORIGUCHI, EH. *Biologia geriátrica ilustrada*. São Paulo: Fundo Editorial BYK, 1988. 239 p.

NAGPAL, S., WALIA, L., LATA, H., SOOD, N. and AHUJA, GK. Effect of exercise on rate pressure product in premenopausal and postmenopausal women with coronary artery disease. *Indian Journal of Physiology And Pharmacology*, 2007, vol. 51, no. 3, p. 279-283.

North American Menopause Society. *Menopause practice: a clinician's guide*. [on-line] [2007-04-10]. Available from: <http://www.menopause.org>.

OH, JY., BARRETT-CONNOR, E., WEDICK, NM., WINGARD, DL. and RANCHO, BS. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. *Diabetes Care*, 2002, vol. 25, p. 55-60.

OHESEN, SP., CLAPHAM, DE. and DAVIES, P. Haemodynamic shear stress activates a K+ current vascular endothelial cells. *Nature*, 1988, vol. 331, p.168-170.

OWENS, JF., MATTHEWS, KA., RÄIKKÖNEN, K. and KULLER, LH. It is never too late: change in physical activity fosters change in cardiovascular risk factors in middle-aged women. *Preventive Cardiology*, 2003, vol. 6, no. 1, p. 22-28.

PAFFENBARGER, RS., WING, AL. and HYDE, RT. Physical activity as an index of heart attack risk in college alumni. *American Journal of Epidemiology*, 1978, vol. 108, no. 3, p. 161-175.

PAOLETTI, R. and WENGER, NK. Review of the international position paper on women's health and menopause: a comprehensive approach. *Circulation*, 2003, vol. 107, no. 9, p. 1336-1339.

PATE, RR., PRATT, M. and BLAIR, SN. Physical activity and public health. A recommendation from de Centers for Disease Control and Prevention and the American College of Sports Med. *The Journal of the American Medical Association*, 1995, vol. 273, p. 402-407.

PHILLIPS, GB., JING, TY. and LARAGH, JH. Serum sex hormone levels in postmenopausal women with hypertension. *Journal of Human Hypertension*, 1997, vol. 11, p. 523-526.

PINES, A. and BERRY, EM. Exercise in the menopause - an update. *Climacteric*, 2007, vol. 10, supl. 2, p. 42-46.

PINOTTI, JA., HALBE, HW. and HEGG, R. *Menopausa*. São Paulo: Roca, 1995. 355 p.

RACKLEY, CE. Hormones and coronary atherosclerosis in women. *Endocrine*, 2004, vol. 24, no. 3, p. 245-250.

RAPPELLI, A. Hypertension and obesity after the menopause. *Journal of Hypertension Supplement*, 2002, vol. 20, no. 2, p. S26-S28.

ROBERT, L. Aging of the vascular wall and atherogenesis: role of the elastin-laminin receptor. *Atherosclerosis*, 1996, vol. 126, no. 1-2, p. 169-179.

SEALS, DR. Habitual exercise and the age-associated decline in large artery compliance. *Exercise and Sport Sciences Reviews*, 2003, vol. 31, no. 2, p. 68-72.

SESSA, WC. The nitric oxide synthase family of proteins. *Journal of Vascular Research*, 1994, vol. 31, no. 3, p. 131-43. Review.

SHEN, W., ZHANG, X., ZHAO, G., WOLIN, MS., SESSA, W. and HINTZE, TH. Nitric oxide production and NO synthase gene expression contribute to vascular regulation during exercise. *Medicine and science in sports and exercise*, 1995, vol. 27, no. 8, p. 1125-1134. Review.

SILVA, GJJ., BRUM, PC., NEGRÃO, CE. and KRIEGER, EM. Acute and chronic effects of exercise on baroreflexes in spontaneously hypertensives. *Hypertension*, 1997, vol. 30, no. 3, p. 714-719.

SILVA, RB., COSTA-PAIVA, L., PINTO NETO, AM., BRAGA ADE, A. and MORAIS, SS. Habitual physical activity and cardiovascular risk in post menopause. *Revista da Associação Médica Brasileira*, 2006, vol. 52, no. 4, p. 242-246.

SILVERTHORN, DU. *Fisiologia humana*: uma abordagem integrada. 2ª ed. São Paulo: Manole, 2003. 816 p.

SIMON, T. Why is cardiovascular health important in menopausal women? *Climacteric*, 2006, vol. 9, no. S1, p. 13-18.

STAESSEN, JA., CELIS, H. and FAGARD, R. The epidemiology of the association between hypertension and menopause. *Journal of Human Hypertension*, 1998, vol. 12, no. 9, p. 587-592.

STAMPFER, MJ. and COLDITZ, GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiological evidence. *Preventive Medicine*, 1991, vol. 20, p. 47-63.

STEHOUWER, CD. and FERREIRA, I. Diabetes, lipids and other cardiovascular risk factors. In SAFAR, ME. and O'ROURKE, MF. (Eds.). *Arterial stiffness in hypertension* – handbook of hypertension. Amsterdam: Elsevier, 2006. p. 427-456.

STICE, JP., EISERICH, JP. and KNOWLTON, AA. Role of Aging vs. the Loss of Estrogens in the Reduction in Vascular Function in Female Rats. *Endocrinology*, 2009, vol. 150, no. 1, p. 212-219.

SUGAWARA, J., OTSUKI, T., TANABE, T., HAYASHI, K., MAEDA, S. and MATSUDA, M. Physical activity duration, intensity, and arterial stiffening in postmenopausal women. *American Journal of Hypertension*, 2006, vol. 19, no. 10, p. 1037-1038.

SULLIVAN, JM. Estrogen replacement therapy. *American Journal of Medicine*, 1996, vol. 101, no. 4A, p. 56S-60S.

SUVORAVA, T., LAUER, N. and KOJDA, G. Physical inactivity causes endothelial dysfunction in healthy young mice. *Journal of the American College of Cardiology*, 2004, vol. 44, no. 6, p. 1320-1327.

TAKANO, T. and MINEO, C. Atherosclerosis and molecular pathology: mechanisms of cholesteryl ester accumulation in foam cells and extracellular space of atherosclerotic lesions. *Journal of Pharmacobio-Dynamics*, 1990, vol. 13, no. 7, p. 385-413.

TANAKA, H. and SAFAR, ME. Influence of lifestyle modification on arterial stiffness and wave reflections. *American Journal of Hypertension*, 2005, vol. 18, p. 137-144.

TANAKA, H., DE SOUZA, CA. and SEALS, DR. Absence of age-related increase in central arterial stiffness in physically active

women. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 1998, vol. 18, p. 127-132.

TANAKA, H., DINENNO, FA., MONAHAN, KD., CLEVENGER, CM., DE SOUZA, CA. and SEALS, DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation*, 2000, vol. 102, p. 1270-1275.

TATCHUM-TALOM, R., MARTEL, C. and MARETTE, A. Influence of estrogen on aortic stiffness and endothelial function in female rats. *American journal of physiology. Heart and Circulatory Physiology*, 2002, vol. 282, p. H491-H498.

TCHERNOF, A., CALLES-ESCANDON, J., SITES, CK. and POEHLMAN, ET. Menopause, central body fatness, and insulin resistance: effects of hormone-replacement therapy. *Coronary artery disease*, 1998, vol. 9, p. 503-511.

WENGER, NK., O'ROURKE, RA. and MARCUS, FI. The care of elderly patients with cardiovascular diseases. *Annals of Internal Medicine*, 1988, vol. 109, no. 5, p. 425-428.

WONG, S. and WONG, J. Is physical activity as effective in reducing risk of cardiovascular disease as estrogen replacement therapy in postmenopausal women? *International Journal of Nursing Studies*, 1999, vol. 36, no. 5, p. 405-414.

World Health Organization. *Technical report series*: report of a WHO Scientific Group. Research on menopause in the 1990s. [on-line]. [2007-07-27]. Available from: <http://whqlibdoc.who.int/trs/WHO_TRS_866.pdf>.

YEN, MH., CHEN, SJ. and WU, CC. Comparison of responses to aminoguanidine and N omega-nitro-L-arginine methyl ester in the rat aorta. *Clinical and Experimental Pharmacology and Physiololgy*, 1995, vol. 22, no. 9, p. 641-645.

ZUCKER, JM. Malignant ovarian tumors in childhood. *Bulletin du Cancer*, 1982, vol. 69, no. 3, p. 304-13.

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