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REVIEWS

Physical exercise and arterial stiffness in elderly

Efortul fizic şi rigiditatea arterială la vârstnici

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Abstract
Increased arterial stiffness is an important feature of vascular aging. Pathogenic mechanisms of arterial stiffness are complex and incompletely elucidated. Very many clinical and experimental data support the involvement of oxidative stress, systemic inflammation and neuro-hormonal mechanisms in arterial wall alteration. Structural modifications which accompany arterial stiffness involve both cellular and extracellular matrix of the vascular wall, including fragmentation of elastin fibers with increase in collagen, irreversible cross-linking between matrix fibers through advanced glycation end-products, vascular fibrosis and calcification. It has been shown that aerobic exercise may be involved in molecular and cellular mechanisms of arterial stiffness, inducing a favorable effect on the arterial wall elasticity. Regular aerobic exercise is currently considered an essential component of non-pharmacological treatment of arterial stiffness.
Key words: arterial stiffness, physical exercise, elderly people

Rezumat
Creşterea rigidităţii arteriale este o modificare caracteristică a vaselor, asociată procesului de îmbătrânire. Mecanismele patogenetice implicate în apariţia rigidităţii arteriale sunt complexe şi incomplet elucidate. Foarte multe date clinice şi experimentale susţin implicarea stresului oxidativ, a inflamaţiei sistemice şi a mecanismelor neuro-hormonale în alterarea peretelui vascular. Modificările structurale care însoţesc rigiditatea arterială interesează atât celulele cât şi matricea extracelulară a peretelui vascular, ducând la fragmentarea fibrelor de elastină, creşterea colagenului, formarea punţilor ireversibile între fibrele matriceale, prin compuşii finali de glicozilare avansată, fibrozarea şi calcifierea vasculară. S-a constatat că efortul fizic aerob poate interfera cu mecanismele moleculare şi celulare care induc rigiditatea arterială, cu consecinţe favorabile asupra elasticităţii peretelui arterial. Exerciţiul fizic aerob consecvent este considerat, în prezent, un component esenţial al tratamentului non-farmacologic al rigidităţii arteriale.
Cuvinte cheie: rigiditatea arterială, efortul fizic, vârstnici

Introduction

Cardiovascular diseases remain the main cause of morbidity and mortality in modern society, in both industrialized and developing countries. Aging is a major risk factor for cardiovascular diseases, including hypertension, stroke and heart failure (Najjar et al., 2005; Zieman et al., 2005; Lakatta & Levy, 2003; Lakatta, 1993; Cavalcante et al., 2011).

Aging leads to a multitude of morphological changes in the vasculature. These include dilatation of the central aorta and increase of arterial wall thickness, even in the absence of atherosclerotic disease. Degenerative changes in the wall of large arteries, such as rupture of elastic fibers, impairment of extracellular matrix components, accumulation of collagen fibers, necrosis of vascular smooth muscle cells (VSMCs), inflammation and calcification of the vascular wall, may induce arterial stiffness (Dao et al., 2005; Doyon et al., 2013), increasing the risk of cardiovascular events, dementia and death (Zieman et al., 2005).

Vascular aging is closely associated with vascular stiffness (Steppan et al., 2014; Vaitkevicius et al., 2002). Aorta stiffening with aging is accelerated by arterial hypertension (Cavalcante et al., 2011).

Habitual aerobic exercise is the first-line therapeutic strategy for reducing the risk of cardiovascular diseases

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with aging (Blair et al., 1989). Physical activity is associated with 35% reduction in cardiovascular diseases and 33% reduction in all-cause mortality (Nocon et al., 2008). This favorable effect of exercise on cardiovascular modifications with age may be partly due to reduction in large arterial stiffness.

Causes of arterial stiffness

Besides advanced age and hypertension, the increase in arterial stiffness has been associated with several physiological states such as low birth weight, menstrual status, menopause, sedentary life or high salt intake. Some known cardiovascular risk factors, including smoking, obesity, impaired glucose tolerance, type 1 and 2 diabetes mellitus, metabolic syndrome, hypercholesterolemia and chronic kidney disease may also induce arterial stiffness. Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and other pathological states including hyperhomocysteinemia and osteoporosis have also been associated with an increased risk of arterial stiffening (reviewed in Laurent et al., 2006).

Arterial stiffness in the elderly

Aging, according to the "theory of free radicals" formulated by Harman (1956), is the consequence of subcellular lesions caused by the progressive increase of reactive oxygen species (ROS), leading to oxidative damage of nucleic acids (DNA as the major substrate), lipid and protein oxidation. This process is accompanied by a decrease in antioxidant defense mechanisms and by a pro-oxidative action of environmental factors (Tache, 2001).

Changes in mechanical and elastic properties of the arterial wall, occurring as a consequence of age and disease, may be induced by oxidative stress, which may cause, directly or indirectly, a reduction in arterial elasticity and increased arterial stiffness (Uddin et al., 2003; Patel et al., 2011).

All layers of the vascular wall have enzyme systems that produce ROS. The most important vascular structures and mechanisms involved in oxidative stress augmentation with age are: NAD(P)H oxidase stimulation, responsible for ROS increase with age, the decrease in mitochondrial antioxidant superoxide dismutase activity, increase in xanthine oxidase production of superoxide ($\cdot O^{-}$) and reduction in endothelial NO synthase activity, which decreases NO bioavailability (Schulz et al., 2004; Cao et al., 2015; Gomez et al., 2015). VSMCs are hypersensitive to oxidative damage (Zhang et al., 2015). Proliferation of VSMCs, mediated by OS, contributes to plaque formation and progression of atherosclerosis (Ma et al., 2016). In an experimental model inducing OS in the arterial wall, the authors reported earlier apoptosis of smooth muscle fibers. Suppression of OS reduced the number of apoptotic cells and also, intima-media thickness (Gomez et al., 2015).

Stiffness in the elderly is more pronounced at the level of elastic arteries, the involvement of distal muscular arteries being less important (McEniery et al., 2008).

The main wall structures participating in vascular function are media and intima layers. The media of large arteries consists of VSMCs, elastic and collagen fibers, all included in an extracellular matrix, which contains glycoproteins and proteoglycans (Diez, 2007; Fleenor & Berrones, 2015). Arterial wall modifications associated with aging are complex and consist of:

- Wall alterations with increased intima-media thickness, increased collagen deposition and reduced elastin fibers, accumulation of advanced glycation end-products, with collagen cross-linking, and calcium deposits at the level of the media layer and also, increased fibrosis of adventitia (Fleenor & Berrones, 2015).
- Cellular modifications in VSMCs, endothelial cells, inflammatory cells and also, interactions between cells and the extracellular matrix.

Physiologically, VSMCs play an essential role in the mediation of vascular tone and synthesize the extracellular matrix (Lacolley et al., 2012). During the aging process, VSMCs may undergo important changes of the actin cytoskeleton, which may alter arterial wall elasticity (Sehgelet al., 2015; Fleenor & Berrones, 2015).

Endothelial cells form the internal layer of vessels, which is exposed to mechanical forces and humoral stimuli, performing an important function in arterial physiology. The endothelium has a determinant role in the regulation of vascular tone, leukocyte adhesion and VSMC proliferation. Endothelial cells synthesize various mediators:

- Vasodilator substances, such as nitric oxide (NO), prostacyclin I_2 (PGI_2), endothelial derived hyperpolarizing factor (EDHF)
- Vasoconstrictor substances such as endothelin-1 (ET-1), thromboxane A2 and angiotensin II (Ang II) (Sprague & Khalil, 2009)
- ROS, such as superoxide anion (O_2^{-}) and hydrogen peroxide (H_2O_2) (Schulz et al., 2004).

Arteries have important functions that contribute to hemodynamic homeostasis, such as:

- Elasticity, the property of the large central arteries, which dampens the rise in systolic pressure, transforming pulsatile flow, produced by each cardiac beat, into a continuous flow.
- Contractility, the property of the small vessels to modify their diameter, due to the contraction of smooth muscle fibers, caused by the influence of neural and humoral factors. It modulates peripheral vascular tone.
- Distensibility or extensibility, the property of large arteries to distend in response to blood volume or pressure variations.
- Secretory function, which can be induced by various stimuli and results in the release of: interleukins (IL-1, IL-6, IL-8, IL-11), γ-interferon (IFN-γ), granulocyte colony stimulating factor (GM-CSF), monocyte chemoattractant proteins (MCPS), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), macrophage migration inhibitory factors (MMIFs) type 1α and 1β, platelet-derived growth factor (PDGF), regulated on activation, normal T cell expressed and secreted (RANTES) (Sprague & Khalil, 2009), metalloproteinases, particularly MMP-2 and MMP-9 (Arun, 2016) and also, ROS (Schulz et al., 2004).

Aging of the arteries, characterized by increased arterial stiffness, is accompanied by some important processes, including:

a) The transformation of the VSMC, which has a key role in buffering pressure pulsatility, in central arteries, from a contractile to a secretory cell, producing matrix metalloproteinases with proinflammatory and procalcifying actions (Burton et al., 2008; Lacolley et al., 2012). VSMCs may also dedifferentiate to a more osteogenic phenotype and induce vascular calcification (Pikilidou et al., 2015). Increased stiffness and adhesiveness of VSMCs have also been reported and, recently, the concept of "smooth muscle cell stiffness syndrome" in the pathogenesis of arterial stiffness has been proposed (Sehgel et al., 2015).

b) Increase in extracellular matrix stiffness, due to an increase in collagen and a decrease in elastin and to irreversible cross-links between matrix fibers, produced by advanced glycation end-products (AGEs) (Bailey et al., 2001, Konova et al., 2004).

c) Activation of the renin-angiotensin-aldosterone system with the involvement of angiotensin II and aldosterone in:

- Stimulation of proinflammatory cytokines, (TNF-α, IL-6) (Belmin et al., 1995), and C-reactive protein (Pasceri et al., 2000).
- Activation of matrix metalloproteinases, particularly MMP-2, which stimulates TGF-1β, a profibrotic molecule, and also, the expression of adhesion molecules (Wang et al., 2006; Sehgel et al., 2015).
- Increase of ROS production and OS, which determines the reduction of NO bioavailability and endothelial dysfunction (Csiszar et al., 2002; Cockroft et al., 2007).
- Hyperproduction of fibronectin, VSMC hypertrophy and vascular fibrosis, due to increased aldosterone levels (Lacolley et al., 2012).
- Stimulation of medial calcification (London, 2013).

d) Reduction of mitochondrial antioxidant superoxide dismutase with age, which may be involved in vascular alterations (Li et al., 2006).

e) Endothelial dysfunction, which has been reported in the elderly, even in the absence of cardiovascular diseases (Cockroft et al., 2007).

Treatment of arterial stiffness

The main therapeutic interventions in arterial stiffness include:

- Antihypertensive medication, which indirectly decreases arterial stiffness by lowering the distending pressure.
- Therapy aimed at ameliorating arterial elasticity, by vascular remodeling and direct action on the arterial wall.

Methods of treatment

1. Non-pharmacological methods, including reduction in body weight, restriction in salt intake, moderate alcohol consumption, nutritional and non-nutritional supplements with antioxidant effects.

2. Pharmacological interventions, based mainly on antihypertensive medications, such as angiotensin converting enzyme inhibitors, angiotensin-2 receptor blockers, calcium-channel blockers and diuretics. Other medications including statins, aldosterone receptor antagonists, nitrates, phosphodiesterase 5 inhibitors, thiazolidinediones, LCZ696 - an angiotensin receptor neprilysine inhibitor (Williams et al., 2014), and advanced glycation end-product cross-link breakers have also been used, with some promising results (Zieman et al., 2005; Cavalcante et al., 2011).

Effects of physical exercise on arterial stiffness in the elderly

Numerous studies have shown the favorable effects of aerobic endurance exercise in reducing arterial stiffness in both elderly animals (Hanna et al., 2014; Gu et al., 2014; Roque et al., 2013; Steppan et al., 2014; Nosaka et al., 2003; Vaitkevicius et al., 1993; Tanaka et al., 2000) and elderly patients (Kingwell 2002; Ashor et al., 2014; Vaitkevicius et al., 2002).

The mechanisms underlying the effects of physical exercise on arterial stiffness are not completely elucidated, but the decrease in oxidative stress and systemic inflammation seems to play an important role.

A great number of experimental and clinical studies have investigated the effects of physical exercise in the treatment of diseases associated with the aging process (Tache, 2001). Exercise-induced antioxidant defense, with reduction of OS, has been associated with different types of activities, such as moderate repetitive aerobic exercise, prolonged low-intensity training and also, detraining, being correlated with the hyperregulation of antioxidant defense mechanisms (Tache & Staicu, 2010).

The decrease in OS could have favorable effects on the vascular wall, inducing a decrease in arterial stiffness in elderly people (Roque et al., 2013; Vaikevicius et al., 2002; Fleenor et al., 2010; Steppan et al., 2014). At a molecular and cellular level, exercise stimulates NO endothelial synthesis (Green et al., 2005) and the activity of antioxidant enzymes (Sharifi et al., 2014).

The anti-inflammatory effect of regular exercise has also been documented in clinical studies. Exercise may increase interleukins 4 and 10, which have anti-inflammatory effects, and decrease IL- 6 and TNF-α, two pro-inflammatory cytokines (Teixeira-Lemos et al., 2011; Ashor et al., 2014).

Physical exercise may decrease vasoconstrictor mediators (angiotensin II, endothelin-1) (Zieman et al., 2005) and sympathetic nervous tone (Mavritzakis, 2014), and reduce TGF-β1, involved in adventitial remodeling and fibrosis (Fleenor et al., 2010).

Histological research in animals has shown that elastin content is not influenced by exercise (Fleenor et al., 2010; Nosaka et al., 2003). The favorable effect of aerobic exercise seems to be mainly induced by a decrease in collagen fibers (collagen subtypes I and III) in both adventitia and media layers (Fleenor et al., 2010). However, in sedentary spontaneously hypertensive rats, a decrease in the elastic component has been found compared to spontaneously hypertensive rats subjected to physical training (Andrade et al., 2013).

Aerobic exercise may reverse arterial wall calcification (Fleenor et al., 2010).

A recent meta-analysis of studies investigating the effects of exercise on arterial stiffness confirms the clear

beneficial role of aerobic exercise on arterial stiffness. These favorable effects were more pronounced after higher intensity exercise, in subjects with more severe baseline arterial stiffness and with longer physical training programs (Ashor et al., 2014).

The favorable influence of aerobic exercise on arterial stiffness may persist over time in aging athletes. Masters endurance athletes may have more elastic arteries, preserved endothelial function and reduced arterial wall thickness when compared to untrained subjects, illustrating a model of "exceptional vascular aging" (DeVan & Seals, 2012).

Conclusions

Arterial stiffness in elderly patients requires an active therapeutic attitude. Besides the administration of antihypertensive therapy, aerobic exercise represents an important means to reduce arterial stiffness and cardiovascular risk.

Conflicts of interests

Nothing to declare.

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