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Review

*Corresponding author
Gustavo Santos Masson, PhD
Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of Sao Paulo
Av. Prof. Lineu Prestes, 1524 - ICB-I
05508-000 Butantan - Sao Paulo/SP
Brazil
E-mail: gsmasson@icb.usp.br

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Autonomic Dysfunction, Sympathetic Hyperactivity and the Development of End-Organ Damage in Hypertension: Multiple Benefits of Exercise Training

Gustavo Santos Masson* and Lisete Compagno Michelini

Department of Physiology and Biophysics, Biomedical Sciences Institute, University of Sao Paulo, Sao Paulo, SP, Brazil

ABSTRACT

Autonomic dysfunction is closely related to the development of hypertension, which is characterized by increased sympathetic activity, decreased vagal tonus and baroreflex dysfunction. The hypertension-induced maladaptive changes progressively lead to heart failure, myocardial infarction and stroke. Hypertrophic remodeling of brain arterioles, chemoreceptors activation, blood-brain barrier abnormalities, oxidative stress and pro-inflammatory cytokines production in autonomic brain areas increase neuronal activity and sympathetic outflow. These responses, together with increased baroreflex dysfunction-induced pressure variability, renin-angiotensin system hyperactivation and capillary rarefaction, increase blood pressure levels and act as a positive feedback mechanism to perpetuate hypertension and development of end-organ damage. Exercise training, a non-pharmacological tool, has been used as an adjuvant therapy to treat hypertension. Our recent data showed that moderate aerobic training in adult SHR completely normalizes oxidative stress and inflammation in autonomic brain areas involved in cardiovascular control and promptly corrects baroreflex dysfunction and increases cardiac vagal activity. The early (2-weeks) training-induced beneficial responses improve autonomic control even in the persistence of hypertension, since a partial reduction of pressure levels was observed after 8 weeks of exercise training, which was related to reversion of arteriolar hypertrophic remodeling and consequent decrease of peripheral vascular resistance.

KEYWORDS: Hypertension; Oxidative stress; Inflammation; Central nervous system; Baroreflex; Aerobic exercise training.

ABBREVIATIONS: ANG II: Angiotensin II; HMGB1: High-mobility group protein 1; HPLC: High Performance Liquid Chromatography; IL-1β: Interleukin 1 beta; MAPK: Mitogen-activated protein kinases; NADPH oxidase: Nicotinamide Adenine Dinucleotide Phosphate-oxidase; NF-Kb: Nuclear factor kappa-light-chain-enhancer of activated B cells; NOS: Nitric Oxide Synthase; NTS: tractussolitarii nucleus; PKC: Protein Kinase C; PVN: hypothalamic paraventricular nucleus; RAS: Renin-angiotensin system; RVLM: Rostroventrolateral medulla; SFO: Sub-fornicial organ; SHR: Spontaneously Hypertensive Rat; TGF-β: Transforming Growth Factor beta; TNF-α: Tumoral Necrosis Factor alpha.

INTRODUCTION

Central nervous system continuously monitors cardiovascular function through different types of receptors, which allow immediate and chronic hemodynamic adjustments evoked by endogenous and environmental stimuli. These adjustments are generated by the activation and/or inhibition of autonomic brain circuitry in the brain stem and the hypothalamus. Baroreceptors, chemoreceptors and cardiopulmonary receptors encode arterial pressure, partial pres-

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sure of blood gases and cardiac filling changes in frequency of action potentials of respective afferents. This information is integrated in the central nervous system, which modifies vagal and sympathetic activity to heart and vasculature and, consequently, corrects the initial alterations and keeps arterial pressure, PO_2 and PCO_2 and stroke volume at relatively constant levels. The imbalance between activation/inhibition of autonomic control areas promotes chronic adaptations in cardiovascular effectors that contribute to the establishment of arterial hypertension and the development of end-organ injuries.[1] The mechanisms underlying the establishment of autonomic dysfunction, sympathetic hyperactivity and the appearance of hypertensive dysfunctions will be briefly reviewed. In addition, we will address the benefits of aerobic training in an experimental model of primary hypertension, the Spontaneously Hypertensive Rat (SHR).

AUTONOMIC DYSFUNCTION IN ARTERIAL HYPERTENSION

Although hypertension *per sec* does not induce death, the pathological mechanisms associated with chronic arterial pressure elevation contribute to the development of end-organ injuries, as cardiac hypertrophy, stroke and glomerular sclerosis, which increase cardiovascular mortality. Since arterial hypertension is a multifactorial syndrome, many mechanisms overlapped to produce a positive feedback that facilitates cardiovascular dysfunction. Among these mechanisms, autonomic dysfunction seems to be a key factor in the pathophysiology of primary hypertension[2] and consists an important pharmacological target for blood pressure control and for the reduction of morbimortality.[3]

Autonomic dysfunction is characterized by the increased sympathetic nerve activity, decreased vagal nerve activity and abnormal reflex control of cardiovascular function, which are mediated by baroreceptors, chemoreceptors and cardiopulmonary receptors. Causative relation between autonomic dysfunction and elevated arterial pressure was primarily suggested in the 80's by Minami and co-authors[4] that identified reduced reflex bradycardia on juvenile SHR with normal arterial pressure. This finding indicated that autonomic dysfunction preceded the arterial pressure rise.

Many hypothesis have been proposed to explain the central nervous system abnormalities conditioning autonomic dysfunction in primary hypertension: baroreflex dysfunction itself, increased chemoreflex activation induced by reduced cerebral blood flow associated with arteriolar remodeling,[5] activation of peripheral chemosensitive cells,[6,7] increased brain Renin-angiotensin system (RAS),[8,9] as well increased blood-brain barrier permeability.[10] An elegant series of experiments developed by Julian Paton's group at the Bristol University identified the contribution of brain arteries/arterioles hypertrophic remodeling in the establishment of sympathetic hyperactivity. It was observed that neonates SHR had greater arterial wall thickness and elevated vertebral artery wall/lumen ratio with increased vascular resistance in the vertebro-basilar circuit, which determined reduced blood flow and, consequently, the rise of sympathetic activity and peripheral vasoconstriction.[5,11]

Although not well characterized as the role of brain vasculature hypertrophic remodeling, it was also suggested that activation of chemosensitive afferents by pro-inflammatory cytokines contributed to the activation of sympathetic activity.[6,12] Indeed, several studies demonstrated a direct correlation between plasma pro-inflammatory cytokines, increased arterial pressure[13] and autonomic dysfunction.[14] Mkrtchian and co-authors[15] identified, in humans, some inflammatory mediators (toll-like receptor 1 and 4, HMGB1, TNF-α and IL-1β receptors and transcription factor NF-κB) within the carotid bodies, where chemosensitive cells are located. Hyperactivity of chemosensitive afferents was also observed in young SHR, since denervation of the carotid body caused reduction of arterial pressure, sympathetic activity and macrophages infiltration in the smooth muscle tissue.[7] Together, these findings suggested that pro-inflammatory cytokines-induced activation of chemoreceptors contributed to establishment of autonomic dysfunction and, consequently, of hypertension.

Another contributor factor to the genesis of sympathetic hyperactivity is ANG II-induced AT_1 receptors activation in brain areas without blood-brain barrier, as the Sub-fornicial organ (SFO), which modulates other pre-autonomic areas, such as the hypothalamic Paraventricular nucleus (PVN) and the Rostroventrolateral medulla (RVLM). RAS inhibition in these areas abolishes arterial pressure increase, renal sympathetic hyperactivity, baroreflex dysfunction and attenuates the dipsogenic response. RAS inhibition also corrects the expression of pro-inflammatory cytokines and AT_1 receptors and reduces reactive oxygen species content in ANG II-dependent hypertension.[8,9,16] renovascular hypertension[17] and primary hypertension.[18] These data show that increased AT_1 receptor activation, *via* reactive oxygen species and pro-inflammatory cytokines, contribute to the development of autonomic dysfunction, sympathetic hyperactivity and hypertension. Activation of AT_1 receptors also disrupts blood brain barrier and facilitates the migration of monocytes and T cells into brain, thus contributing to local inflammation and to a further increase in sympathetic activity and arterial pressure.[10] It was demonstrated that hematopoietic cells bind to juncional adhesion molecule-1 to enter into the neural tissue, where they behaved as resident macrophages (activated microglia), acting as another important source for pro-inflammatory cytokines.[19]

MOLECULAR MECHANISMS OF SYMPATHETIC HYPERACTIVITY: THE IMPORTANCE OF REACTIVE OXYGEN SPECIES AND PRO-INFLAMMATORY CYTOKINES

Several mechanisms that induce autonomic dysfunction exhibit common factors: increased reactive oxygen species and pro-inflammatory cytokines in autonomic brain areas as the SFO, PVN, RVLM and tractus solitarii nucleus (NTS). The main intracellular signaling pathways in neurons and glia are activated by ANG II *via* AT_1 receptor, which activates NADPH oxidase through the Protein Kinase C (PKC) with the subsequent

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release of superoxide.[20-23] Increased superoxide production actives redox-sensitive pathways, as the Mitogen-Activated Protein Kinases (MAPK) that stimulate nuclear transcription factors (NF-κB and AP-1), thus increasing the gene expression of pro-inflammatory cytokines, as well as subunits of the NADPH oxidase and others RAS components.[22,24,25] Therefore, AT_1 receptors activation, oxidative stress and inflammation constitute important positive feedback mechanisms in autonomic dysfunction and sympathetic hyperactivity.

Besides the regulation of nuclear factors, reactive oxygen species directly increase sympathetic neuronal activity. In ANG II-dependent hypertension, Robin Davisson and Constatine Iadecola's groups, at the Cornell University, identified that NADPH oxidase-induced superoxide production increases the calcium influx and neuronal activation *via* glutamatergic NMDA receptors activation.[21,23,26] As calcium influx was abolished by antioxidant agents or nitric oxide donors,[26] the authors proposed that increased reactive oxygen species production decreased nitric oxide bioavailability and, consequently, NMDA receptor NR1 subunit nitrosylation,[27] thus increasing both neuronal activity and sympathetic activity. Several studies in ANG II-dependent hypertension,[28-30] renovascular hypertension[31-33] and primary hypertension,[34-36] identified that oxidative stress attenuation inhibits both arterial pressure and renal sympathetic activity elevation, decreases tissue RAS, pro-inflammatory cytokines and NADPH oxidase expression and reduces NF-κB e AP-1 transcriptional activity. These studies confirm the functional role of reactive oxygen species in autonomic dysfunction, sympathetic hyperactivity and, subsequently, in the development/establishment of arterial hypertension. In addition to sympathetic hyperactivity, reactive oxygen species also mediates lower parasympathetic activity and reduced baroreflex sensitivity after ANG II administration into the NTS.[37]

Tissue inflammation is another mechanism related to the establishment of autonomic dysfunction. It was described that healthy rats that received pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) into the PVN and NTS or through intracarotid injection,[38-40] exhibited autonomic dysfunction, increased renal sympathetic activity and elevated arterial pressure. In addition to these acute effects of cytokines, Joseph Francis's group, at Louisiana State University, demonstrated that chronic blockade of pro-inflammatory cytokines expression into autonomic control areas attenuated cardiac hypertrophy, renal sympathetic hyperactivity and the elevation of arterial pressure in ANG II-induced hypertension.[8,25]

SYMPATHETIC HYPERACTIVITY AND END-ORGAN DAMAGE IN HYPERTENSION

Adrenergic hyperactivity in hypertension was originally described by Amann, et al.[41] which identified increased forearm blood flow after α-adrenergic receptors blockade. The interaction between norepinephrine and α-adrenergic receptors in smooth muscle cells induced vasoconstriction through increased calcium influx and decreased nitric oxide bioavailability that elevated the peripheral vascular resistance and the arterial pressure.[42] Increased vascular sympathetic activity produced hypertrophic remodeling of arteries and arterioles,[43] since α-adrenergic stimulation increases the expression of adhesion molecules, leukocyte migration, activation of NADPH oxidase with reactive oxygen species formation and MAPKs stimulation, which drive hypertrophic vascular effects.[44]

In our group, neuronal recordings, dosage of norepinephrine content in vessels (HPLC) and tyrosine hydroxylase immunoreactivity in different tissues were used to demonstrate that increased sympathetic vasomotor tonus in SHR is not homogenous, since we observed increased sympathetic activity in cardiac and renal, but not in skeletal muscle arterioles.[45] Different sympathetic activation patterns, as increased renal and cardiac sympathetic nerve activity and unchanged lumbar nerve activity,[46] were described in others hypertensive models, defining a differential *sympathetic signature*. Interestingly the *sympathetic signature* of the SHR coincides with the sympathetic activation pattern observed in hypertensive patients.

Besides vascular hypertrophy, increased peripheral vascular resistance and elevated arterial pressure, sympathetic hyperactivity contributes significantly to the development of end-organ injuries. In the myocardium, the higher metabolic demand caused by sympathetic hyperactivity (increased vascular resistance and elevated heart rate) is an important factor to determine ventricular hypertrophy. Neurohormonal direct effects of sympathetic hyperactivity were described in the myocardium. It was observed that cardiac α- and β-adrenergic activation induced cardiac hypertrophy, augmented matrix metalloproteinase-2 activity, increased the expression of TGF-β and the synthesis of collagen I and III, in addition to intensify the production of reactive oxygen species and the infiltration of hematopoietic mononuclear cells.[47-49] Accordingly, Schlaich and co-authors[50] identified in hypertensive patients a direct correlation between cardiac norepinephrine spillover and cardiac hypertrophy.

Similar to cardiac and vascular tissues, adrenergic hyperactivation, by modifying sodium/water reabsorption[51] and renin secretion,[52] causes abnormalities in the renal function. Graham and co-authors[53] described increased renal α-adrenergic receptor concentration in the SHR. It was also demonstrated that subpressor doses of α- and β-adrenergic blockers decreased glomerular sclerosis and urinary albumin excretion in partial nephrectomized rats.[54] Besides these direct effects, increased renal sympathetic activity determined tissue and plasma RAS activation through juxtaglomerular cells that release renin. Acting in AT_1 receptors, ANG II induced reactive oxygen species and pro-inflammatory cytokines production that enabled renal remodeling and injury, as the glomerular sclerosis.[55] Renin also interacts with pro-renin receptors in several tissues being associated with additional activation of oxidative and inflammatory signaling pathways, and, consequently, with the worsening of end-organ injuries.[56,57] ANG II systemic and local effects in the cardiac[58]

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and renal[59] tissues add to brain RAS effects,[8,9,16,17,18,21,28,29] to facilitate sympathetic hyperactivity and to amplify the deleterious effects of hypertension.

Other mechanism closely related to end-organ injuries is the reduction of baroreflex sensitivity, which strengthens sympathetic hyperactivity. In this sense, Nosaka and co-authors[60] demonstrated that RVLM activation inhibited baroreceptors activation-induced reflex bradycardia, thus aggravating baroreflex dysfunction that is considered an independent prognostic marker in hypertension.[61] Baroreflex dysfunction decreases the ability of arterial baroreceptors to promptly correct venous return, heart rate, ventricular contractility and peripheral vascular resistance changes, which aggravate arterial pressure oscillations. High pressure variability, which increases hydrostatic pressure oscillations in the capillaries, expose tissues to brief periods of hyperperfusion or hypoperfusion interfering with normal tissue oxygenation. Hypoxia or partial oxygen pressure fall is a strong stimulus to drive endothelial cell injury and capillary apoptosis, which determine extensive capillary rarefaction and the consequent development of lesions in the various target organs.[62,63]

In summary, as illustrated in Figure 1, hypertension is associated to brain RAS hyperactivation, increased reactive oxygen species and pro-inflammatory cytokines in the autonomic brain areas that determine baroreflex dysfunction, decreased vagal cardiac activity and increased sympathetic activity to cardiac, vascular and renal tissues and increased pressure variability. These effects cause sympatho-vagal imbalance in the heart, activation of systemic and local RAS in peripheral tissues, vascular and tissue hypertrophic remodeling and end-organ damage. The deleterious adaptive responses potentiate the development/maintenance of hypertension and constitute a positive feedback mechanism to perpetuate the hypertensive disease.

AEROBIC TRAINING: AUTONOMIC BENEFITS TO HYPERTENSIVE INDIVIDUALS

Moderate intensity exercise training is one of the most important non-pharmacological strategies to decrease arterial pressure in hypertensive patients. A recent meta-analysis demonstrated that aerobic training decreases systolic and diastolic arterial pressure by 8 and 5 mm Hg, respectively.[65] Other works also recognized that aerobic training corrects autonomic dysfunction associated with hypertension, which contributes to the reduction of end-organ damage and cardiovascular mortality.[66-68]

Clinical[69] and experimental[70-74] studies have indicated that aerobic training is extremely efficient to revert autonomic dysfunction and to attenuate sympathetic hyperactivity, to normalize arterioles wall/lumen ratio and to decrease peripheral vascular resistance. On never-treated hypertensive patients, Laterza and co-authors[69] identified that aerobic training normalized reflex control of heart rate and decreased sympathetic activity. On SHR, several studies from our group demonstrated that aerobic training decreases sympathetic neuronal excitability into the PVN[75] and increased PVN density of oxytocin neurons and the density of oxytocinergic projections from PVN to NTS-DMV complex,[76] whose activation increase both baroreflex sensitivity and cardiac vagal activity and decrease peripheral vasomotor sympathetic activity. It was also demonstrated that the training-induced adaptive responses are significantly correlated with de-

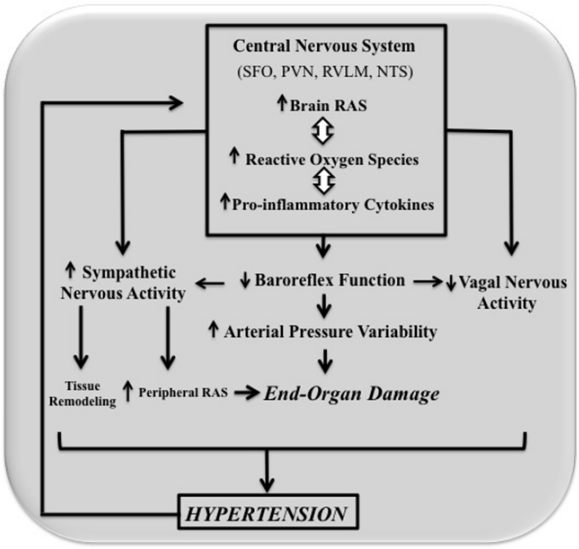

Figure1: Positive feedback mechanisms perpetuating hypertension. Increased RAS activation, reactive oxygen species and pro-inflammatory cytokines in autonomic brain areas of hypertensive individuals augments neuronal activity and sympathetic outflow and decreases both vagal activity and baroreflex sensitivity. The autonomic dysfunction increases arterial pressure variability and facilitates peripheral RAS activity and vascular and tissue remodeling, all these effects contributing to end-organ damage and to the maintenance of hypertension. NTS: Nucleus of the solitary tract; PVN: Paraventricular nucleus of the hypothalamus; RAS: Renin-angiotensin system; RVLM: Rostroventolateral medulla. Modified from Masson & michelini, 2014.[64]

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creased resting heart rate and exercise tachycardia.[77,78]

In a recent study,[70] we identified the sequential changes of autonomic and cardiovascular adaptations induced by aerobic training in SHR (Figure 2). Only 2-weeks of aerobic training were enough to normalize cardiac vagal activity and baroreflex sensitivity in the SHR. There was, at the same experimental time, a complete normalization of the oxidative stress and inflammatory profile into the PVN, which are the most prominent molecular mechanisms to normalize baroreflex dysfunction and sympathetic hyperactivity. It is important to note that these benefits were observed even in the persistence of hypertension, since a partial decrease of arterial pressure (~9%) was identified only after 8-weeks of aerobic training (Figure 2).[70] The temporal coincidence between the reversion of pro-inflammatory profile and oxidative stress in the PVN and the correction of autonomic dysfunction,[70] associated with previous findings proving the relationship among oxidative stress,[8,31,34] inflammation,[8,25] baroreflex dysfunction and sympathetic hyperactivity,[39,40] suggest a cause-effect relationship. In other words, aerobic training normalizes baroreflex function and decreases sympathetic hyperactivity through the correction of pro-inflammatory profile and oxidative stress within the PVN, an important autonomic area in cardiovascular control. This statement is corroborated by another study from our group that observed that aerobic training decreases neuronal excitability in the PVN of the SHR.[75]

It is important to note the temporal dissociation between a prompt normalization of both baroreflex function and cardiac vagal activity (significant at 2-weeks) and arterial pressure fall, which appeared only after 8-weeks of exercise training.[70] This dissociation suggests that training-induced normalization of baroreflex function is independent of pressure reduction, but may contribute to the subsequent pressure fall through the decrease of sympathetic vasomotor activity and the regression of vascular hypertrophy. Indeed, the contribution of increased baroreflex sensitivity to pressure fall was identified in clinical studies[79,80] that used chronic baroreflex stimulation to control refractory hypertension. The importance of augmented baroreflex function for a better cardiovascular control after aerobic training was also proved by other studies[71,72,77] demonstrating that sinoaortic denervation completely blocked autonomic and cardiovascular benefits induced by aerobic training in the SHR.

Besides the autonomic adaptive responses, arterial pressure fall observed in trained hypertensive individuals is also dependent on training-induced structural changes in the peripheral vasculature. Previous data from our group demonstrated that 8-12 weeks of moderate aerobic training normalize the wall/lumen ratio of skeletal muscle, heart and diaphragm arterioles that contributed to the attenuation of total peripheral resistance, thus reducing arterial pressure.[68,73,74] Increased nitric oxide and tetrahydrobiopterin bioavailability and decreased NOS uncoupling, superoxide formation and inducible NOS gene expression, were described as the cellular mechanisms related to vascular benefits of aerobic training in the SHR.[81]

CONCLUSIONS

Autonomic dysfunction, characterized by sympathovagal unbalance associated with baroreflex dysfunction, contributes widely to the establishment/maintenance of hypertension. Increased oxidative stress and pro-inflammatory profile observed in the SHR contribute to baroreflex dysfunction, augment sympathetic activity and cause vascular and tissue deleterious remodeling. Reduced baroreflex sensitivity implies in increased

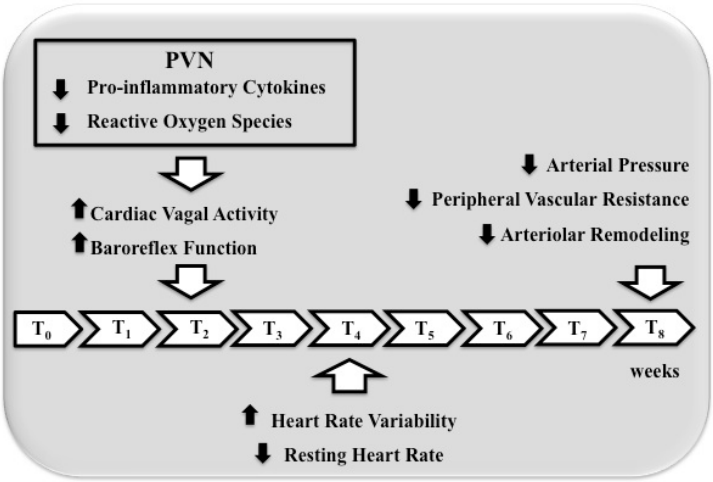

Figure2: Training-induced time-course adaptive changes on autonomic control and cardiovascular parameters in the SHR. Only 2 weeks of aerobic training (T) were enough to normalize oxidative stress and pro-inflammatory profile within the Paraventricular nucleus of the hypothalamus (PVN) and to correct both cardiac vagal activity and baroreflex dysfunction. These training-induced responses precede the augmentation of heart rate variability and the appearance of resting bradycardia (at the 4th week) as well as the partial reduction of peripheral vascular resistance (related to the reversion of arteriolar hypertrophic remodeling in exercised tissues) and a 9% fall in the arterial pressure (both occurring at the 8th week of training). Modified from Masson & Michelini, 2014.[64]

arterial pressure variability, sympathetic and RAS activation and the appearance of end-organ damage, which potentiate the development/maintenance of hypertension and constitute a positive feedback mechanism to perpetuate the hypertensive disease.

In the treatment of hypertension, it is crucial to promptly normalize autonomic dysfunction that decreases tissue injuries. It is important to note that aerobic training blocks oxidative stress and inflammation in the autonomic brain areas, normalizes baroreflex function and attenuates others autonomic and cardiovascular dysfunctions related to hypertension, even in the persistence of elevated arterial pressure. Thus, aerobic training constitutes an important therapeutic tool to decrease cardiovascular mortality in hypertensive patients.

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