Effects of aerobic exercise training in animal models of hypertension

Efeitos do treinamento físico aeróbio em modelos animais de hipertensão

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ABSTRACT

Background: Hypertension is one of the leading causes of death due to stroke, heart attack and kidney failure. The understanding of the pathophysiological mechanisms involved in its development and maintenance is critical to potential therapeutic interventions. Thus, animal models of hypertension have been used in the study of this disease for many years. **Objective:** To investigated the effects of dynamic aerobic exercise training as a non-pharmacological approach for the management of hypertension in animal models. **Method/Design:** This study is a literature review conducted in the *Medline* database. **Results:** The results demonstrated that aerobic exercise training may reduce blood pressure in different rat models of hypertension. **Conclusions:** The dynamic aerobic exercise can reduced blood pressure in different animal models of hypertension by mechanisms that involving neurohumoral changes, reinforcing the important role of this approach in the treatment of hypertension and its associated disorders.

Keywords: Hypertension; Aerobic exercise training; Rat; Blood pressure.

RESUMO

Introdução: A hipertensão arterial é uma das principais causas de morte na população mundial devido ao acidente vascular cerebral, infarto agudo do miocárdio e insuficiência renal. O entendimento dos mecanismos fisiopatológicos envolvidos no seu desenvolvimento e manutenção é fundamental para criação de estratégias terapêuticas. Neste sentido, há muitos anos modelos animais vêm sendo utilizados no estudo dessa doença. **Objetivo:** Abordar os efeitos do treinamento físico aeróbio dinâmico como estratégia não farmacológica de manejo da hipertensão em modelos animais. **Método:** Este estudo é uma revisão de literatura realizada na base de dados do *Medline.* **Resultados:** Os estudos publicados evidenciam que o treinamento físico aeróbio dinâmico pode reduzir a pressão arterial em diferentes modelos de hipertensão. **Conclusão:** O treinamento físico aeróbio dinâmico pode reduzir a pressão arterial em diferentes modelos de animais com hipertensão por mecanismos que envolvem alterações neurohumorais, reforçando o importante papel desta abordagem no tratamento da hipertensão e de suas disfunções associadas.

Palavras-chave: Hipertensão; Treinamento físico aeróbio; Rato; Pressão arterial.

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INTRODUCTION

In Brazil, approximately 32.6% of deaths and hospitalizations are due to cardiovascular disease. Between 1996 and 1999 cardiovascular disease accounted for 17% of hospitalizations in the public sector (SUS) of people aged between 40 and 59[1] and 27% over 60 years.[2] According to estimates by the Organization world Health (2012), one in three adults has hypertension, a condition that causes about half of all deaths from stroke and heart disease in the world.

Hypertension is a silent disease associated with poor living habits of modern society, it is often perceived as a cardiovascular event is manifested. This disease leads to high costs for health systems in many countries. In Brazil, for example, cardiovascular disease costs correspond to 1.74% of Gross Domestic Product.[3] Thus, strategies to prevent or mitigate the development of cardiovascular risk factors have been widely investigated because they can represent savings expressive in public health systems of many countries.

In this sense, experimental research provides significant contributions because it allows the control variables that are inherent in modern life, such as stress, for example. Furthermore, the use of animal models in research allows investigation of invasive parameters that are ethically unviable or very expensive or inaccessible methods for performing in humans. Because of the multifactorial etiology of hypertension, several experimental models of the disease have been developed over time, each involving one or more mechanisms, contributing to the investigation of changes resulting from the various etiological factors of hypertension.

Experimental models of hypertension can be grouped according to the disease etiology. Among the genetic models of hypertension, we can mention the mice with spontaneous hypertension (SHR) and the lineage of mice sensitive to sodium intake (Dahl). Moreover, there are models of environmentally induced hypertension, by stress or salt intake. Regarding the renal hypertension, there are renovascular hypertension, due to the partial occlusion of renal artery, and renopriva perinefrítica. Finally, there are the pharmacologically induced models, among them the model called L-NAME, due to the blockage in the formation of nitric oxide (NO).[4]

In recent years, these models of experimental hypertension underwent different strategies to control blood pressure levels. Among these strategies are the use of drugs, food control, and physical training. In this sense, this literature review presents the main effects of dynamic aerobic physical training (APT) in different experimental models of hypertension in mice, highlighting the importance of non-pharmacological approach in the management of disorders resulting from hypertension.

METHODS

This study is a literature review conducted in the Medline database undated limit until October 2014. The following terms were used; hypertension, rat, exercise training or physical training and high blood pressure or blood pressure in different forms combined in quotes in the title or abstract. Were considered for the review of the effects of aerobic exercise training in experimental hypertension only articles published in English that used dynamic training protocols (treadmill, swimming or wheel) in rats and evaluating cardiovascular variables.

RESULTS

Genetic hypertension - spontaneous

Spontaneously hypertensive rats (SHR)

Spontaneously hypertensive rats originated by selective breeding of the Wistar-Kyoto (WKY), with a tendency to high blood pressure, coming from the animal center of Kyoto University in Kyoto, Japan.[5] In SHR, between the fourth and sixth week old, there is increased blood pressure (BP) featuring, from that moment on, sustained hypertension. Hypertension of this model is characterized spontaneously, without any physiological, pharmacological or surgical intervention.[6]

The importance of the study in SHR model is due to the development of the pathophysiology be similar to that described for essential hypertension in humans, with hemodynamic and endocrine responses similar.[7] In addition, Sharma et al[8] state that this hypertension model has advantage over others, as it features a gradual increase in BP.

In vivo studies have shown that in the early stages of hypertension, the SHR rats showed an increase in cardiac output with normal peripheral resistance, progressing to established hypertension stage. During this period, the cardiac output returns to normal values, but the increase in BP is sustained, and due to the increase in total peripheral resistance[9].

In the temporal course of the pressure, the animal develops gradually SHR (between 6 and 24 months of age) cardiac morphological changes associated with the development of left ventricular hypertrophy (LVH),[10] which can assist in the maintenance of normal cardiac function, despite high systemic BP[11,12]. That genetic hypertension model is now very well documented the presence of sympathetic hyperactivity[13] and the renin-angiotensin system (RAS)[14].

Many studies address the effects of aerobic exercise training on BP control in SHR. At the end of the 70s, Evenwel and Struyker-Boudier[15] found that swimming APT with 11 weeks duration significantly reduced systolic blood pressure (SBP) in SHR group. Tipton et al[16], in a study using over 100 SHR of both genders, found that the resting pressure was significantly reduced in young rats SHR males who underwent moderate intensity APT (40-60% of VO2 max) on a treadmill for 24 weeks but not in those undergoing the training intensity of 75% of VO2 max. In this study it was possible to observe decreased antihypertensive dose (-85%) in SHR subjected

to moderate APT to obtain BP values of reduced or normal resting SHR males.

In addition, other beneficial effects of APT were also demonstrated between the decades of 80-90, as increased capillary surface area,[17] the improvement in the baroreflex control of BP and decreased resting heart rate.[18]

In the 90s, studies in SHR male rats observed beneficial effects after APT low intensity treadmill. Gava et al[19] observed BP reduction associated with reduced resting heart rate, and reduced sympathetic tone. Véras-Silva et al[20] also found a reduction of the sympathetic tone only APT low intensity (55% Vo_2max) as compared to high intensity (85% Vo_2max) without alteration of vagal tone or intrinsic heart rate, suggesting that the attenuation of sympathetic tone to the heart would be the main mechanism responsible for reducing BP in SHR males. Similarly, a swimming APT program in female SHR, besides the hypotensive effect was able to reduce activation of the sympathetic system and the concentration of prostaglandins kidney.[21]

Additionally, APT in treadmill was able to increase baroreflex sensitivity in SHR,[22] this being the benefit explained, at least in part, by increasing afferent this reflex arc after APT in SHR rats.[23] Other studies also suggest the reduction of oxidative stress (24), ultrastructural changes in renal morphology,[25,26] reduced expression of angiotensinogen central core,[27] the improvement of vascular compliance[28] and activation of the kallikrein-kinin system[29] could contribute to the improvement of baroreflex and reducing BP after APT in SHR.

Interestingly recent data show that cardiac beneficial changes, autonomic and vascular from APT are very attenuated by the withdrawal of the baroreflex, suggesting that this is an important mechanism in the modulation of adaptations to physical training.[30,31]

Zamo et al[32] reported a decrease of SBP and mean BP in addition to rest bradycardia in young male adult SHR after 8 weeks of swimming APT. These changes were associated with reduced circulating angiotensin II; however only in young SHR was decreased expression of the components of the renin angiotensin system (RAS) in the cardiac tissue. More recent studies show that this group a protocol of 10 weeks of aerobic swimming training promoted reduction of microRNA 16 and 21 levels (which regulator of vascular endothelial growth factor expression and vascular anti-apoptotic function, respectively), which may be involved in reducing vascular thinning of skeletal muscle caused by high blood pressure in hypertensive rats trained.[33]

Accordingly, it is suggested that one of the mechanisms by which generates APT hypotensive effects in SHR is the modulation of the RAS, which was demonstrated by increased protein expression of MAS receptor (angiotensin receptor 1-7) in the ventricular tissue of rats SHR submitted to swimming.[34] Furthermore, Bertagnoli e al[35] have observed that APT in mat

had the same heart benefits induced by treatment with an oral formulation agonist HPB-CD/Ang-(1-7) as a reducing BP and HR, improvement in left ventricular function and cardiovascular autonomic control.

Coimbra et al[36] demonstrated that treadmill APT induced cardiovascular different settings between SHR male and SHR female, suggesting that the hypotensive effect the training is linked to gender. In this regard, recently, we showed that SHR females submitted to ovarian hormone deprivation and APT for 8 weeks on a treadmill showed BP reduction, increased vagal tone and improved barroreflexa sensitivity, these benefits partly mitigated with the SHR animals that have undergone the chronic consumption of fructose[37].

Spontaneous hypertensive rats stroke - prone (shr-sp)

The model of stroke-prone rats (SHR-SP) was created from the SHR strain. These animals developed higher blood pressure levels that SHR with great tendency of mortality from cerebrovascular accident (CVA).[38]

Some studies have been conducted to verify the beneficial effects of APT to control BP in SHR-SP models. Lutgemeier et al[39] submeted SHR-SP to the swimming APT lasting 22 weeks, 6 times a week, performed twice a day for 1.5 hour. This physical training protocol was able to reduce BP of SHR-SP animals compared to control rats, perhaps by reducing the sympathetic tone - adrenal, reducing corticosterone levels, epinephrine and norepinephrine. Similarly, Song et al[40] found after 4 weeks of exercise training swimming duration of 1 hour a day, 5 times a week, a reduction in SAP in the SHR-SP males, as well as the increased insulin sensitivity and expression of GLUT4.

Rats dahl salt- sensitive

The Dahl salt-sentitive model was originally developed by Dahl from Sprague-Dawley rat strain, which was observed in some animals developing hypertension with high salt diet. Based on these findings, Dahl et al[41] selected from endo-crossing Sprague-Dawley rats and, based on the blood pressure induced by a diet high in sodium (NaCl 8%), two strains of different animals: Dahl salt-sensitive, which developed hypertension after high intake of salt and Dahl salt-resistant, which held the PA at normal levels with the same diet.

Shepherdet et al[42] demonstrated in Dahl salt-sensitive rats with 8% NaCl diet and concurrently subjected to APT in mat for 12 weeks attenuation of hypertension. However, it was not observed for those animals that started APT six weeks after the start of the intake. In addition, these authors have demonstrated that APT performed for 60 minutes per day was more effective than that with duration of 30 minutes per day, suggesting that the duration of APT may influence hypertension attenuation response.

Borderline hypertensive rats

The borderline hypertensive rat (BHR) is a genetic model environmentally hypertension induced by salt stress or ingestion[43] obtained by intersections between SHR and WKY.[44] The mechanism by which the environmental stress produces hypertension is not clarified in this model, however, the sympathetic nervous system seems to contribute to this development. The increase in plasma concentration of norepinephrine and changes in vascular reactivity induced by environmental stress BHR may contribute to the hemodynamic adaptations observed both in BHR.[45]

Cox et al[46] reported that the swimming APT with 12 weeks, attenuated the development of hypertension caused by stress on BHR, having reduced norepinephrine, suggesting an attenuation of the sympathetic nervous system for training. Lutgemeier et al[47] subjected to the BHR animals to swimming APT lasting 22 weeks, 6 times a week, performed twice a day for 1.5 hour. This physical training protocol was able to reduce the BP of BHR animals compared to control rats. Squire et al[48] found that the voluntary APT in wheel weeks in duration showed protective effects on hypertension induced by stress, only in older animals BHR. However, Melby et al[49] demonstrated that the swimming APT for 20 weeks to induce bradycardia in spite BHR with hypertension developed by high-sodium diet, did not cause a reduction in BP.

In association diet high in sodium and stress for the development of hypertension in BHR, there was a reduction of norepinephrine levels in the central nervous system of rats submitted to swimming APT for 2 or 6 months, highlighting the role of exercise in preventing hypertension induced by stress and high salt consumption.[50]

Hypertension renal

Renovascular hypertension

Renovascular hypertension is present in 2% of the hypertensive population.[51] In this sense, models of hypertension with reduced renal blood flow have been investigated. The first animal model was established by Goldblatt et al,[52] in which there was a progressive increase in BP in dogs by the partial constriction of the renal artery. The Goldblatt technique consists of constraining one or both renal arteries using a small silver clip[52] to draw most used forms of hypertension this model are: a clip two kidneys (2K1C, constriction of renal artery while the kidney contralateral remains integrate), a kidney and a clip (1R1C; constriction of renal artery and the contralateral kidney is removed) and two kidneys and two clips (2R2C; constriction of the aorta or both renal arteries).

Rodrigues et al[53] demonstrated that low intensity swimming APT (no overload weight tail) was able to reduce blood pressure and improve the sensitivity to baroreflex

bradycardic responses in 2K1C rats with hypertension. In a subsequent study the same group found that increasing the intensity of the swimming APT (weight overload 3% of body weight tail) did not improve the bradycardic response. Thus, the authors suggested that the increased intensity of exercise training would increase renal sympathetic activity, suppressing its benefits.[54]

On the other hand, some authors did not observe a reduction in blood pressure after APT in rats with severe hypertension (2K1C). Marcus et al[55] conducted an APT protocol in the wake of moderate intensity (50-70% Vo_2 max) lasting 8 to 12 weeks and showed no reduction in BP in 2K1C animals. Rakusan et al[56] underwent the mouse will 2K1C a swimming protocol with moderate intensity for only 6 weeks and did not observe BP reduction after training. Boissier et al[57] used 70% of maximum effort achieved on a treadmill for mice to prescribe 10 weeks of APT and did not obtain attenuation of hypertension in this model. However, it is important to note that there was a decrease in pulse pressure in two of the studies cited above, which could be associated will decrease in arterial stiffness, suggesting that APT may improve vascular compliance in this experimental model.[55,57]

Whereas Ang (1-7) presents a counter-regulatory role for angiotensin II in RAS, Shah et al (58) recently Demonstrated que the swimming TFA carried out for 4 weeks by 2K1C animals treated with Ang (1-7) to attenuated hypertension and cardiac hypertrophy evidenced by the smaller diameter of myocytes and fibrosis in the trained animals.

Renopriva hypertension

The renopriva hypertension is induced by bilateral nephrectomy at different species, including human beings, especially if the lifetime of the animal or human being, is prolonged after complete removal of kidneys.[59]

The unilateral nephrectomy does not cause hypertension or cardiovascular injuries. The removal of a kidney, and approximately two thirds of the other kidney leads to a slow rise in BP. In this model, the increased intravascular volume results in hypertension and may have the same renopriva pathogenesis of hypertension.[60]

SHR animals subjected to 5/6 nephrectomy for removal of the left kidney and removal of two-thirds of right kidney, underwent APT treadmill for 4 weeks of moderate intensity, observing attenuation of proteinuria and protection to increased glomerular sclerosis.[61] However, the APT associated with enalapril or losartan reduced the BP and induced significant additional protection against an increase in glomerular sclerosis.[61] runs on voluntary racing TFA did not induce BP normalization in Wistar rats[62,63] or Sprangue- Dawley rats subjected to 5/6 nephrectomy, although reducing oxidative stress in heart tissue[64] to improve vascular function.[63]

Inhibition in hypertension chronicle of nitric oxide

Ribeiro et al[65] and Baylis et al[66] first described a sustained hypertension induced by inhibition of nitric oxide (NO) by means of an inhibitor of the enzyme NO synthase, the L-arginine-methyl nittro ester (L-NAME). These findings demonstrate the importance of NO in the regulation of systemic vascular resistance, exercising a vasodilator tonic effect.

This hypertension model is associated with an intense peripheral vasoconstriction and a consequent increase in peripheral vascular resistance. Kassab et al[67] demonstrated that the reduced cardiac output even during the chronic inhibition of NO synthase. In addition, they observed tachycardia associated with hypertension induced by sympathetic hyperactivity, no change in intrinsic heart rate.[68] The direct effect of L-NAME preventing endothelial synthesis of NO and reducing the tonic vasodilation is an important mechanism in the genesis of this model experimental hypertension.[69] The pressure in this experimental model was also associated with kidney damage, characterized by glomerulosclerosis, glomerular ischemia and renal interstitial infiltrate.[65,66]

Studies from our group showed that 10 weeks of APT mild-moderate intensity treadmill in hypertensive rats by L-NAME administration did not induce reduction in BP.[70] However, an improvement of peripheral insulin sensitivity occurred[69] and reduction of blood pressure levels (unpublished data) after a training session in the L-NAME trained animals compared to the sedentary group.

Kuru et al[71] found the answer to the TFA treadmill with 4 weeks duration in rats that were submitted to L-NAME administration. The groups that protocol were divided into short (4 weeks of administration) and long term (10 weeks of administration). The short-term group started the APT concomitant administration of L-NAME and the long-term group started the APT at six weeks of L-NAME administration. As a result BP reduction was observed in rats subjected to APT in both groups as well as the prevention of increased thickness of the aortic wall when compared to sedentary hypertensive rats, suggesting that this morphofunctional alteration of the aorta wall may be associated with reduction BP. In a later study, the research team observed after APT that there were no differences in response contraction and relaxation of vascular smooth muscle, but there was a difference in the response of endothelial resistance of the aorta and normalization of acetylcholine response in the trained group.[72]

According to Husain[73] the APT associated with administration of L-NAME was able to enhance the synthesis of NO by activation of endothelial NO synthase enzyme promoting an increase in the vascular endothelial growth factor (VEGF) and in capillary density, which should have contributed to the restoration of blood flow, reducing the concentration of plasma lactate and oxidative stress in plasma observed in the L-NAME sedentary group.

Recently, Cardoso et al[74] suggested that APT swimming improves dyslipidemia caused by administration of L-NAME, having a protective effect against oxidative stress and renal damage generated by hypertension. Thus, this could be a mechanism associated with BP reduction in rats treated with L-NAME.

Moreover, Rossi et al[75] showed no attenuation of hypertension after APT in mat 10 weeks, although it has been demonstrated attenuation of the sympathetic predominance noted in L-NAME sedentary animals.

FINAL CONSIDERATIONS

New approaches have been used to mitigate the pathophysiology of hypertension in animal models, among them the APT. There is good evidence that APT plays a key role in mitigating a number of factors involved in the development and maintenance of hypertension in animal models. In this sense, many of the published studies shows that the moderate APT shown to be effective in reducing BP in different models of hypertension.

However, in most models of severe hypertension, or associated complications of hypertension the attenuation is not a consensus. In this respect, it is important to emphasize that the divergence of results published in relation to the hypotensive effects of APT may be related to the early period of application of this approach (before, during or after the establishment of hypertension), the variations of the hypertension model (2K1C vs. 1R1C, L-NAME dose, etc.), applied to the type of training (treadmill vs. swimming vs. wheel), the training characteristics (intensity and session duration, frequency and duration of training), the association other approaches (antihypertensive treatment, removal of the baroreflex, etc.), the bpmeasurement method (awake vs. anesthetized, direct vs. indirect), among others.

In addition, experimental models have helped since the first reports of beneficial effects of APT in hypertensive in understanding the mechanisms involved in mitigation of disorders associated with hypertension. Among these mechanisms we highlight the improved vascular and cardiac autonomic control/modulation and baroreflex, resting bradycardia, the attenuation of SARS hyperactivity, improved vascular compliance, increased capillarity, and other neuro-humoral and molecular mechanisms yet little studied.

CONCLUSION

In conclusion, the results of published studies show that the dynamic APT can reduce BP in different models of animal hypertension by mechanisms involving neurohumoral changes, reinforcing the important role of this approach in the treatment of hypertension and its associated disorders.

AUTHORS CONTRIBUTION
RKP preparation of the manuscript, CM preparation of the manuscript, GLS formatting the manuscript, ICS formatting the manuscript, KDA reviewing the manuscript.

COMPETING INTERESTS
The authors declare no conflicts of interest.

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