Resistance Training Controls Arterial Blood Pressure in Rats with L-NAME- Induced Hypertension

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Abstracts

Background: **Arterial hypertension is a multifactorial chronic condition caused by either congenital or acquired factors.**

Objective: **To evaluate the effects of Resistance Training (RT) on arterial pressure, and on vascular reactivity and morphology, of L-NAME-treated hypertensive rats.**

Methods: **Male Wistar rats (200 – 250 g) were allocated into Sedentary Normotensive (SN), Sedentary Hypertensive (SH) and Trained Hypertensive (TH) groups. Hypertension was induced by adding L-NAME (40 mg/Kg) to the drinking water for four weeks. Arterial pressure was evaluated before and after RT. RT was performed using 50% of 1RM, 3 sets of 10 repetitions, 3 times per week for four weeks. Vascular reactivity was measured in rat mesenteric artery rings by concentration-response curves to sodium nitroprusside (SNP); phenylephrine (PHE) was also used for histological and stereological analysis.**

Results: **Resistance training inhibited the increase in mean and diastolic arterial pressures. Significant reduction was observed in Rmax (maximal response) and pD_2 (potency) of PHE between SH and TH groups. Arteries demonstrated normal intima, media and adventitia layers in all groups. Stereological analysis demonstrated no significant difference in luminal, tunica media, and total areas of arteries in the SH and TH groups when compared to the SN group. Wall–to-lumen ratio of SH arteries was significantly different compared to SN arteries ($p<0.05$) but there was no difference when compared to TH arteries.**

Conclusions: **RT was able to prevent an increase in blood pressure under the conditions in this study. This appears to involve a vasoconstrictor regulation mechanism and maintenance of luminal diameter in L-NAME induced hypertensive rats (Arq Bras Cardiol. 2013;100(4):339-346).**

Keywords: **Hypertension / physiopathology; Exercise; Rats; Arterial Pressure / drug effects; Vasodilatation / physiology.**

Introduction

Arterial hypertension (AH) is a multifactorial chronic condition[1], caused by either congenital or acquired factors[2]. Its treatment involves pharmacological and non-pharmacological methods[3]. Among non-pharmacological methods, physical training (PT) has been one of the most important interventions indicated for preventing or controlling AH[4,5].

There is a positive relationship between hypertension and sedentary lifestyle[6]. Beunza et al[6] demonstrated that the interaction of sedentary behaviors, such as driving and computer use, was associated with a higher risk of hypertension. On the other hand, the noninteractive subtype, such as television viewing and sleeping, was not associated with AH. This data shows the great importance of long-term PT for the primary prevention and treatment of high blood pressure[4].

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Many studies have focused on the effects of aerobic exercise[2-5], and it has been recommended as an adjuvant treatment for hypertension; however, knowledge regarding the benefits of resistance training (RT) has been increasing. Positive effects of long-term RT, such as increased skeletal muscle tone, inhibition of risk factors and prevention of obesity have been found[7]. Studies suggest the adoption of a moderate strength training program and assert that it can have a positive effect on chronically increased BP[8].

According to Pollock et al[9], there is some trepidation about the prescription and implementation of RT due to the possibility of vascular brain or cardiac events. On the other hand, in normotensive individuals, Ciolac and Guimarães[10] indicate that there is no justification for fearing RT implementation as many negative effects on blood pressure before the execution of RT have been observed. Furthermore, acute dynamic resistance exercise in spontaneously hypertensive rats decreased resting BP and reactivity to PHE, in addition to increasing endothelium-dependent relaxation[11,12]; however, the long-term effect of RT on BP and reactivity and morphology

of the vasculature have not yet been documented. Thus, the purpose of the present study was to determine the chronic effects of RT on arterial blood pressure, vascular reactivity and changes in arterial luminal diameter of L-NAME-treated hypertensive rats.

Methods

Animals

Thirty male Wistar rats (200 - 250 g) were obtained from the breeding colony at the Sergipe Federal University. Animals were housed four to a cage under controlled temperature conditions (22 ± 2 ºC) and a light-dark cycle of 12 hours. Food and water were provided *ad libitum*. The animals received filtered water and were fed rodent-specific food (Labina, Purina®, Paulínia-SP, Brazil). All procedures described in the present study were approved by the Animal Research Ethics Committee of Sergipe Federal University, Brazil (Protocol number 02/2010). Animals were arranged into three groups with ten animals each: sedentary normotensive (SN), sedentary hypertensive (SH) and training hypertensive (TH). SN and SH groups were kept in their cages without undergoing RT, while animals in TH group were subjected to four weeks of RT.

Drugs

Acetylcholine chloride (ACh), L-phenylephrine (Phe), N$^{\omega}$-nitro-L-arginine methyl ester hydrochloride (L-NAME) and sodium nitroprusside (SNP) were utilized in this study, all obtained from SIGMA-Aldrich (St. Louis, Missouri, USA)

Blood pressure measurements

Blood pressure was obtained upon the animal awakening and 48 hours after the induction and training periods. Animals were allowed to adapt to the environment for three days before the measurement of blood pressure. Mean, systolic and diastolic blood pressures were determined by tail cuff method (LETICA, LE5002, Barcelona, Spain). Animals were placed in a heated chamber at a temperature of 38 – 40 °C for ten minutes and blood pressure values (10-15) were recorded from each animal.

Hypertension induction and maintenance

During the induction period, the animals were given L-NAME in their drinking water at a concentration of 0.4 mg/ml for a total daily intake of 40 mg/kg[13] for four weeks[14]. During the experimental period, AH was maintained by the administration of L-NAME dissolved in water to accumulate a daily intake of 25 mg/Kg for a duration of more than four weeks, which was sufficient to maintain the hypertensive state. The concentration of L-NAME was adjusted daily for water consumption and total weight of the animals in each cage.

Training protocol

The training protocol was initiated after detection of hypertension in the subjects. RT was performed in a squat-training apparatus following a model adapted from Tamaki et al[15]. TH animals, following one week of adaptation, were trained with three sets of ten repetitions with a 60 second resting period at a 50% training load set by one repetition maximum test (1RM), three times per week. The training load and intensity were adjusted every two weeks with a new 1RM.

Parameters of electrical stimulation were fulfilled as described by Barauna et al[16] and Pinter et al[17]. Animals were encouraged to perform the series through the application of electrical stimulation (20 V, 0.3 s duration, 3 s intervals) with electrodes (ValuTrode, Model CF3200, Axelgaard, Fallbrook, CA, USA) attached at the tail and connected to an electrostimulator (BIOSET, Physiotonus Four, Model 3050, Rio Claro, SP, Brazil).

In vitro studies

Following animal sacrifice the superior mesenteric artery was removed, stripped of connective and fatty tissues and sectioned into rings (1–2 mm). Rings were suspended from fine stainless steel hooks, connected to a force transducer (Letica, Model TRI210; Barcelona, Spain) with cotton threads in organ baths containing 10 ml of Tyrode's solution (composition in mM: NaCl 158.3, KCl 4.0, $CaCl_2$ 2.0, $NaHCO_3$ 10.0, $C_6H_{12}O_6$ 5.6, $MgCl_2$ 1.05 and NaH_2PO_4 0.42). This solution was continually gassed with carbogen (95% O_2 and 5% CO_2) and maintained at 37 ºC under a resting tension of 0.75 g for 60 minutes (stabilization period). During this time, the nutrient solution was changed every 15 minutes to prevent the interference of metabolites[18]. Isometric tension was recorded through the force transducer (TRI210, Letica, Barcelona, Spain) coupled with an amplifier-recorder (BD-01, AVS, SP, Brazil).

When necessary, endothelium was removed by gently rubbing the intimal surface of the vessels with a fine stainless wire; its functionality was assessed by the ability of ACh (1 μM) to induce more than 75% relaxation of Phe (1 μM) tonus. The absence of relaxation in reaction to ACh was taken as evidence that the rings were functionally denuded of endothelium[19]. Changes in vascular reactivity were assessed by obtaining concentration-response curves for the contractile agents Phe (10^{-8} - 10^{-3} M), an α_1-adrenergic agonist; and the relaxant agent SNP (10^{-9} - 10^{-4} M), a donor nitric oxide (NO). Relaxing agents were tested on rings pre-contracted with Phe (1 μM).

Histological examination of tissues

Three rings from each artery were immersed in a 4% paraformaldehyde in phosphate-buffered saline (PBS; 0.1 M pH 7.4) and kept at 4 °C for 24 hours. Rings were then rinsed in distilled water and kept in 70% ethanol for 12 hours, followed by standard histological protocol.

Sections of 5-6 μm thickness were obtained using a microtome and were mounted on slides coated with gelatin. For morphological analysis, sections were stained with hematoxylin and eosin (H.E) for further observation under bright field microscopy.

Arterial stereological analysis was performed by using a test-area comprising a system of equidistant points containing a total of 1000 μm^2 performed in the Image J

program. Two random and non-consecutive sections of each arterial ring (four animals per group) were analyzed by overlaying images of test-area and the arterial section. The number of total points falling into the area of interest was estimated. A periphery to the center direction was considered, including artery lumen and arterial wall (intima and tunica media). The adventitia layer was discarded because there was incongruity in the definition of the limits of the supportive adjacent tissue. Thus, the total sectional area of the artery, the sectional area of the lumen of the vessel and the sectional area of the arterial wall were estimated, allowing the calculation of density areas of the arterial lumen and arterial wall over the full reference.

Statistical analysis

Values are expressed as mean ± standard error of mean (SEM). The potency of the *in vitro* experiments were expressed in pD_2 values and calculated by the negative logarithm of EC_{50} (effective concentration able to induce 50% of maximal response) obtained by nonlinear regression of concentration-response curves. When necessary, Student's t test or ANOVA repeated measures followed by Bonferroni post-test were performed to evaluate the significance of differences between means. Values were considered statistically significant when $p < 0.05$. For all of these procedures we used the statistical program GraphPad Prism™ version 3.02 (GraphPad Software, San Diego, CA, USA).

Results

Effects of treatment with L-NAME on body weight and blood pressure during the induction period

L-NAME-treated rats appeared generally healthy and gained weight similarly to the untreated rats. L-NAME significantly increased MAP, SBP and DBP ($p < 0.001$). There was no significant elevation of blood pressure levels in the untreated group (control) (Table 1).

Effects of resistance training on body weight and blood pressure values in hypertensive rats

The animals in the SN and SH groups showed a significant increase ($p<0.001$ and $p<0.05$ respectively) in body weight at four weeks of treatment. However, the body weight of the TH group was unchanged following training. L-NAME elevated the MAP, SBP and DBP in the SH group during the experimental period. However, RT was effective in preventing this increase. Before the training protocol there were no significant differences in MAP, SBP and DBP between the TH and SH groups. After four weeks of training, RT significantly reduced MAP ($p < 0.05$) and DBP ($p < 0.05$) (Table 2).

Effect of resistance training on the response to phenylephrine

Phenylephrine was able to induce contraction in the rings from all groups. The concentration-response curve to phenylephrine was significantly shifted to the left in the

Table 1 - Body weight and mean (MAP), systolic (SBP) and diastolic (DBP) arterial pressures of rats at baseline (week 0) and end (week 4) of the induction period with L-NAME (control and L-NAME groups)

	CONTROL (n = 6)		L-NAME (n = 10)	
WEEK	**0**	**4**	**0**	**4**
WEIGHT (g)	254.3 ± 2.9	289.0 ± 4.8	249.2 ± 2.4	283.9 ± 1.8
MAP (mmHg)	108.8 ± 1.7	108.2 ± 2.0	117.3 ± 1.0***	142.0 ± 0.2***,c
SBP (mmHg)	125.8 ± 1.9	131.5 ± 2.2	135.9 ± 1.3***	157.9 ± 0.3***,c
DBP (mmHg)	101.0 ± 1.7	97.6 ± 2.5	108.5 ± 1.0**	132.6 ± 0.6***,c

*n: number of animals; the results were expressed as mean ± SEM; statistical differences between means were determined by Student's t test (intra-group) or by repeated measures ANOVA followed by the post-test (inter-group) *** p<0.001 vs CONTROL and [c] p < 0.001 vs 0 week.*

Table 2 - Body weight and mean (MAP), systolic (SBP) and diastolic (DBP) arterial pressures of rats at baseline (week 0) and end (week 4) of the experimental period in animals of the sedentary normotensive (SN), sedentary hypertensive (SH) and trained hypertensive (TH) groups

	SN (n = 6)		SH (n = 3)		TH (n = 3)	
WEEK	**0**	**4**	**0**	**4**	**0**	**4**
WEIGHT (g)	289.0 ± 12.0	325.2 ± 12.1[c]	280.7 ± 9.8	315.3 ± 12.5[a]	297.3 ± 7.3	316.6 ± 15.0
MAP (mmHg)	108.5 ± 5.1	121.7 ± 4.8	135.9 ± 1.2**	143.2 ± 1.5*,[a]	137.8 ± 1.8	132.7 ± 1.8##
SBP (mmHg)	131.5± 5.4	146.5 ± 6.5	149.8 ± 1.8	157.7 ± 1.6[a]	156.5 ± 3.4	150.8 ± 0.4
DBP (mmHg)	97.6 ± 6.3	110.1 ± 5.4	129.5 ± 0.9**	136.7 ± 1.7*,[a]	128.7 ± 4.5	124.3 ± 2.5#

*n: number of animals; the results were expressed as mean ± SEM. Statistical differences between means were determined by Student's t test (intra-group) or by repeated measures ANOVA followed by the post-test (inter-group).*p < 0.05; ** p < 0.01 vs SN, and ##p < 0.01 vs SH, [a]p < 0.05 and [c]p < 0.001vs 0 week.*

H group (pD_2 = 5.35 ± 0.07, n = 9) in relation to the SN group (pD_2 = 4.36 ± 0.04, n = 6) with change in Rmax. RT significantly reversed the increase in the potency, since its concentration-response curve to phenylephrine was significantly ($p < 0.001$) shifted to the right (pD_2 = 4.36 ± 0.10, n = 9) compared to SH (pD_2 = 5.35 ± 0.07, n = 9), without change in Rmax (Figure 1).

Effect of resistance training on the response to sodium nitroprusside

The concentration-response curve to SNP was significantly ($p < 0.05$) shifted to the right in the SH group (pD_2 = 4.85 ± 0.14; n = 3) in relation to the SN group (pD_2 = 6.18 ± 0.13; n = 3) without change in Rmax. RT partially reversed the decrease in the potency, since its concentration-response curve to SNP was significantly ($p < 0.01$) shifted to the left (pD_2 = 5.42 ± 0.06; n = 3) compared to SH (pD_2 = 4.85 ± 0.14; n = 3). Furthermore, the Rmax of TH group was significantly ($p < 0.05$) larger than SH group (Figure 2).

Effect of resistance training on vascular morphology

Analysis of arterial segments demonstrated a standard arrangement of intima, media and adventitia layers in all groups (SN, SH, TH) (Figure 3 A-D). Endothelium in the tunica intima consisted of simple squamous epithelial tissue (Figure 3B) supported by loose connective tissue scattered in the subendothelial layer, followed by the internal elastic membrane that separates the tunica intima from the tunica media. In the tunica media, there were concentric layers of smooth muscle fibers intermingled with elastic fibers (Figure 3B). The presence of the external elastic membrane was also noted, which delimits the tunica media from the tunica adventitia. The tunica adventitia was comprised of loose connective tissue (Figure 3B) with collagen and elastic fibers, blood vessels and sparse fat cells.

Stereological results demonstrated no significant difference in the lumen, tunica media and the total area of the arteries of SH and TH groups in relation to SN group. The wall-to-lumen ratio of the arteries of SH group ($p < 0.05$) was significantly different from SN group (Table 3).

Discussion

The main purpose of this study was to evaluate the cardiovascular effects of RT on L-NAME hypertensive rats. The current study showed that RT is effective in preventing an increase in blood pressure levels in L-NAME hypertensive rats, possibly by changing the α_1-adrenergic receptor sensibility.

It is well established in the literature that the synthesis and the availability of nitric oxide (NO) by endothelial cells play an important role in vasorelaxation, thus contributing to the modulation of vascular tone. Furthermore, NO has been identified as an important agent in the proliferation of smooth muscle cells[20].

It is also known that the chronic inhibition of NO synthesis by L-NAME, and the consequent decreased availability of NO, causes an increase in arterial blood pressure[21,22], reduces the internal arterial diameter, increases response to components of

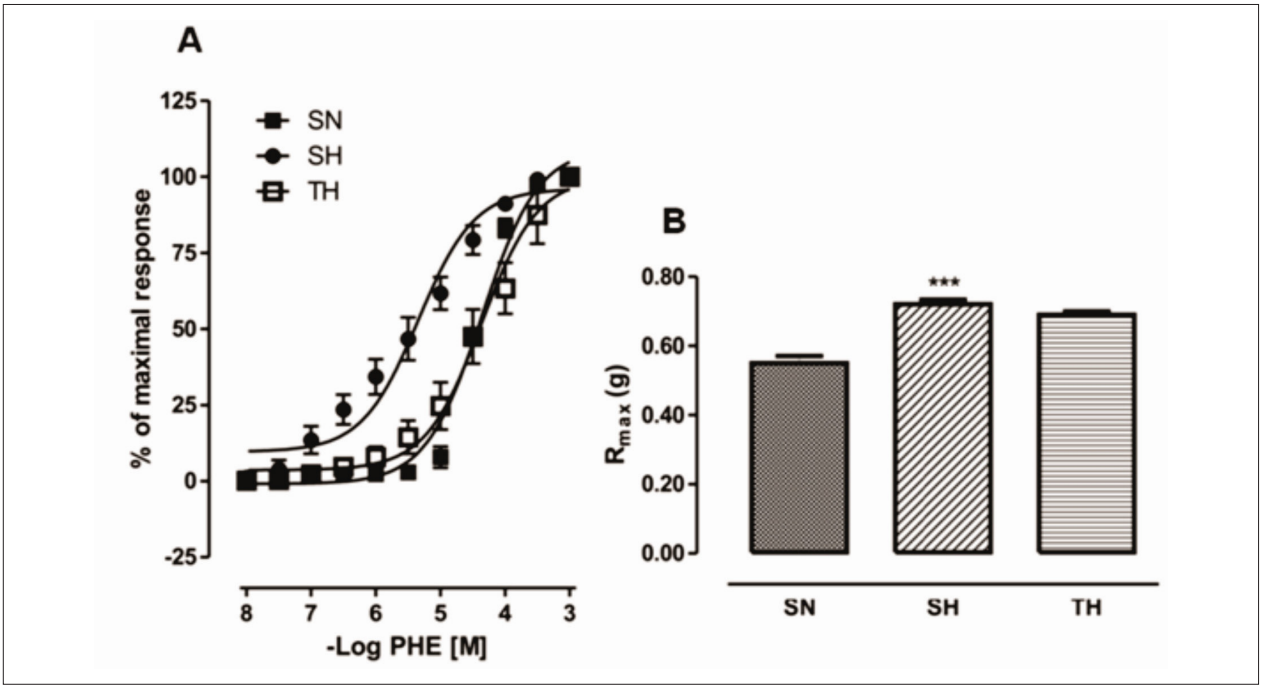

Figure 1 - *Concentration-response curves for phenylephrine (10^{-8} – 10^{-3} M) in rings isolated from the superior mesenteric artery without functional endothelium (A). The rings were obtained from sedentary normotensive (SN) n = 6, sedentary hypertensive (SH) n = 9 and trained hypertensive (TH) n = 9 groups. The bars indicate the means ± SEM of Rmax (g) of the Phe-induced contractions (B). Data represent the mean ± SEM. Statistical differences were determined by the one-way ANOVA followed by the Bonferroni post-test *** p < 0.001 vs SN.*

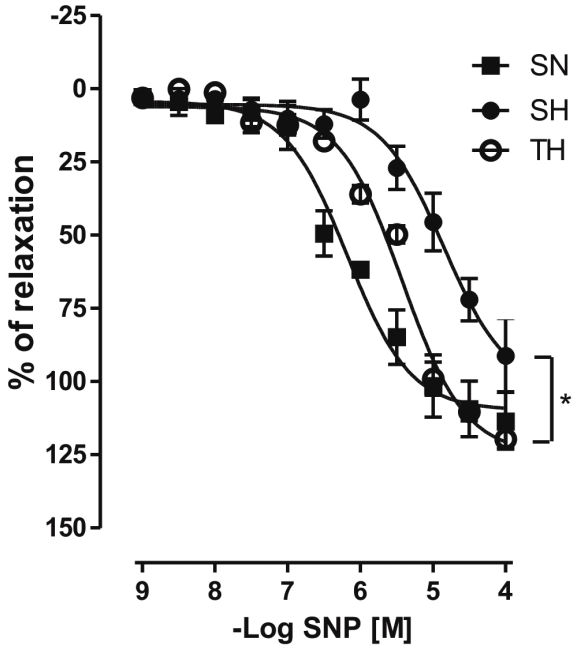

Figure 2 - *Concentration-response curves for sodium nitroprusside (SNP, 10^{-9} – 10^{-4} M) in rings isolated from the superior mesenteric artery without functional endothelium and pre-contracted with Phe (1μM). The rings were obtained from sedentary normotensive (SN) n = 3, sedentary hypertensive (SH) n = 3 and trained hypertensive (TH) n = 3 groups. Data represent the mean ± SEM. Statistical differences were determined by the one-way ANOVA followed by the Bonferroni post-test * p < 0.05 vs SH.*

the endothelium-derived contracting factors, increases peripheral resistance[13] and causes vascular remodeling and endothelial dysfunction[21]. Because of this, the L-NAME-induced hypertension method has been used as a reliable model for morphological and functional studies of the cardiovascular system.

In our study, L-NAME was able to induce hypertension. The increase in arterial pressure induced by L-NAME was inhibited in the animals that underwent RT. Furthermore, RT was not able to reduce the weight gain of the hypertensive animals. This result is in agreement with a study by Barauna et al[16], in which a reduction of 14% in DBP and 13% in MAP of normotensive rats was observed, and a study by Tamaki et al[15], which demonstrated that RT for four weeks did not alter weight gain of animals.

There is evidence that both short and long-term physical training significantly reduces blood pressure in humans[23,24] and in hypertensive rats[11], but little is known about the mechanisms involved in this reduction[25].

Reports in the literature indicate that physical training (PT) has a very strong relationship with vascular function, being able to modify the structure and function of vascular cells[26]. Studies suggest that PT increases blood flow and therefore the stress on the vascular wall, providing an increase in endothelium-derived NO production and thereby improving the vasodilator response[27,28].

Therefore, in order to better understand the possible mechanism involved in arterial blood pressure control promoted by RT in L-NAME hypertensive rats, we investigated the effects of RT on the vascular reactivity and morphology of these animals.

First, we evaluated the vascular contractile response to Phe, an α_1-adrenergic agonist. The results showed that the sensitivity of α_1-adrenergic receptors was significantly increased in L-NAME hypertensive rats. Similar results were also found by Sekiguchi[29], who demonstrated an increase in the effects of PHE on different vascular beds from animals subjected to forced swimming.

Interestingly in our study, the PHE effect on arterial rings from L-NAME hypertensive rats treated with RT was reduced. It is possible that RT is able to induce an adjustment in the blood flow distribution[30]. Furthermore, according to Convertino[31], changes in the sensitivity of these receptors may be primarily dependent on the intensity, duration and frequency of the exercise. Although more experiments are needed to clarify the mechanisms by which RT promotes vascular changes, this study suggests that the changes caused by RT on the hemodynamics of trained animals could be related to a reduced sensitivity of adrenergic receptors.

To evaluate the vascular relaxant response, we used SNP, a NO donor that mimics an endogenous response related to NO. This set of experiments revealed that the sensitivity of the NO pathway was significantly decreased in L-NAME hypertensive rats and that RT was able to partially reverse this effect. Packer[32] demonstrated that blocking NO production, such as occurs when using L-NAME, reduces the eNOS expression. Furthermore, it is possible that the output of endothelium-derived constricting factor (EDCF) increases in the presence of L-NAME in peripheral arteries[22].

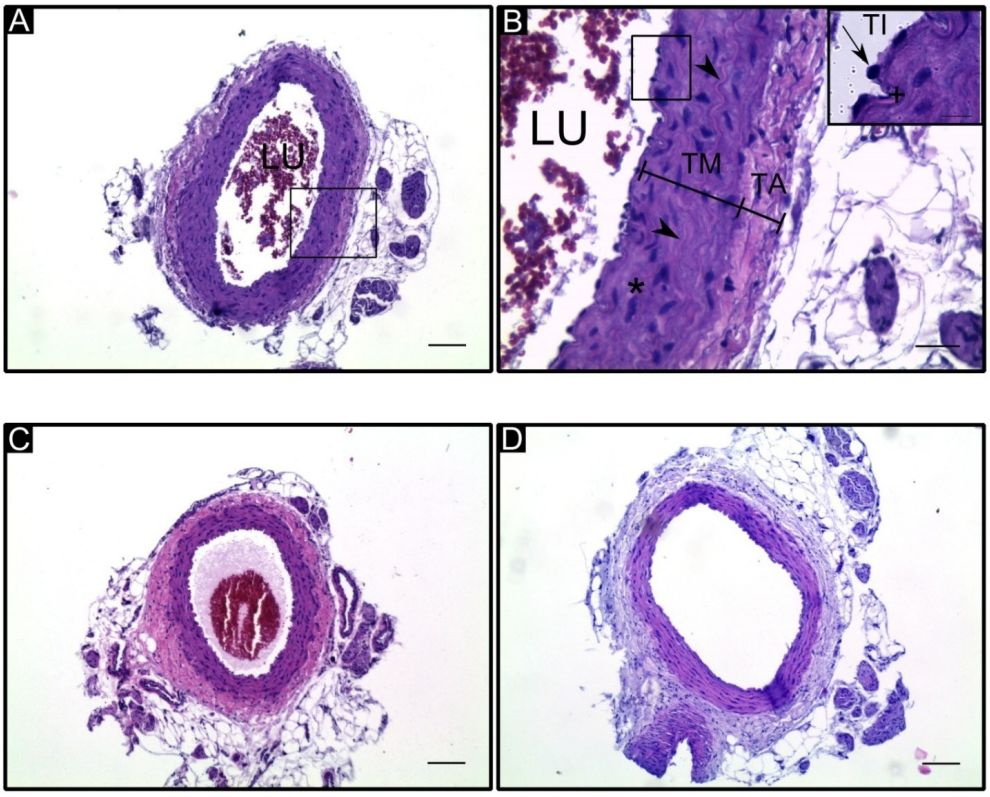

Figure 3 - *Representative photomicrographs of superior mesenteric arteries in the normotensive group (A and B), sedentary hypertensive (C) and trained hypertensive (D). [B]: Detail of the artery in which it is possible to visualize the lumen (LU), the tunica intima (TI), tunica media (TM) and tunica adventitia (TA). In the TI it is possible to visualize the endothelium (detail, arrow) and the internal elastic lamina (+). A TM is composed of smooth muscle (*) and elastic fibers (arrowheads). In the TA there is loose connective tissue. Sections of paraffin, HE. Bar: 100µm (A, C, D), 30µm (B), 10µm (detail B).There was no difference in histologic aspects among the groups.*

Table 3 - Lumen, wall and total areas of the superior mesenteric artery of animals in sedentary normotensive (SN), sedentary hypertensive (SH) and trained hypertensive (TH) groups

	SN (n = 4)	SH (n = 4)	TH (n = 4)
LUMEN AREA (µm²)	124125 ± 11538	74375 ± 8285	119750 ± 31886
WALL AREA (µm²)	99625 ± 8730	90875 ± 7703	113625 ± 17814
TOTAL AREA (µm²)	223750 ± 15421	165250 ± 15336	133375 ± 49242
WALL-TO-LUMEN RATIO	0.77 ± 0.08	1.32 ± 0.08*	1.11 ± 0.17

*n: number of animals; the results were expressed as mean ± SEM; *p <0.05 vs SN group.*

The wall-to-lumen ratio of the arteries is increased due to rearrangement of the medial layer of the vessel lumen[33]. Our results showed an increase of the wall-to-lumen ratio in the arteries of SH group, but the RT protocol used did not cause significant changes in the reduction of this ratio. Melo et al[34] found a similar result when they showed that aerobic training at 50% intensity in SHR decreased MAP and the wall-to-lumen ratio of the arteries when compared to the sedentary group, proving that anaerobic training can be a possible adjuvant therapy for hypertension. This reinforces the importance of studies on the effects of RT as a preventive or recuperative therapy for hypertension, because it shows that RT is not only effective in preventing changes in blood pressure but may also protect against vascular changes, as shown in the model of L-NAME-induced hypertension.

In conclusion, long-term resistance training, under the tested conditions in this study, is able to prevent an increase in blood pressure. This effect appears to involve a mechanism of vasoconstrictor regulation and maintenance of the luminal diameter in L-NAME- induced hypertensive rats.

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Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Obtaining funding, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Araujo AJS, Santos ACV, Souza KS, Aires MB, Santana-Filho VJ, Fioretto ET, Mota MM, Santos MRV; Acquisition of data: Araujo AJS, Santos ACV, Souza KS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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