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Research article

Exercise Training Improves Cardiovascular Autonomic Activity and Attenuates Renal Damage in Spontaneously Hypertensive Rats

Octávio Barbosa Neto [1,3]✉, Débora T.R.S. Abate [2], Moacir Marocolo Júnior [1], Gustavo R. Mota [1], Fábio L. Orsatti [1], Renata C. Rossi e Silva [2], Marlene A. Reis [2] and Valdo J. Dias da Silva [3]
[1] Department of Sport Sciences, Institute of Health Sciences; [2] Discipline of General Pathology and [3] Discipline of Physiology, Institute of Natural and Biological Sciences, Federal University of Triangulo Mineiro, Brazil

Abstract
Experiments were performed to determine the influence of exercise training by swimming on cardiovascular autonomic control and renal morphology in spontaneously hypertensive rats (SHR) and Wystar-Kyoto (WKY) rats. Sedentary normotensive (SN), trained normotensive (TN), sedentary hypertensive (SH), and trained hypertensive (TH) rats were included in this study. Arterial pressure (AP), heart rate (HR), means of power spectral analysis of HR (HRV) and systolic AP variability (SAPV) were recorded in baseline conditions. Following, the HR baroreflex and autonomic tonus control were assessed. At the end, all animals were euthanized and their kidneys were excised to evaluate renal damage. Resting bradycardia was observed in TH and TN rats compared with their respective sedentary animals ($p < 0.05$). Exercise training attenuated AP in TH *vs*. SH ($p < 0.001$). The LF component of HRV and SAPV were lower in TH than SH ($p < 0.05$). The LF/HF relation was lower in TH than SH and SN ($p < 0.05$). TN and TH rats showed a sympathetic tonus reduction in comparison to SN and SH rats ($p < 0.001$). The TH presented an increased vagal tonus compared to SH ($p < 0.05$). Exercise training improved baroreflex control of HR in TH group *versus* SH ($p < 0.05$). The TH showed a lower number of sclerotic glomeruli compared to SH ($p < 0.005$). The exercise training decreases the glomerular indexes in TN and TH ($p < 0.05$). Further analysis showed a significant correlation between sympathetic nervous activity and AP levels ($p < 0.05$). A positive association was also found between sympathetic nervous activity and glomerular index ($p < 0.05$). Therefore, the exercise training reduces AP and attenuates renal damage. In addition, the attenuation of renal injury was associated with lower sympathetic activity. These findings strongly suggest that exercise training may be a therapeutic tool for improving structure and renal function in hypertensive individuals.

Key words: Exercise training, hypertension, cardiovascular autonomic dysfunction, glomerulosclerosis, renal damage.

Introduction

Kidney disorders may be the cause or a consequence of hypertension. Substantial evidence supports the notion that elevated arterial pressure (AP) plays a pivotal role in the development of renal disease. Moreover, is considered the most important risk factor for the progression of kidney failure. In this context, hypertension and kidney function are strongly linked (Johnson et al., 2005; Whitworth, 2005).

In healthy kidneys, the renal autoregulation mechanisms maintain a balance of level of renal blood flow and glomerular pressure. In a situation where the AP increases, the afferent arteriole constricts, thereby limiting the transmission of the increased pressure to the glomerular capillaries (Bidani et al., 2009). However, if AP was maintained elevated for a long period, this regulatory mechanism is lost, resulting in renal autoregulation impairment (Palmer and Fenvez, 2010).

It is well established that increases in physical activity produces beneficial effects on the cardiovascular system in normal and diseased individuals via alterations in neural control of the circulation (Cornelissen and Fagard, 2005; Zucker et al., 2004). These effects include reductions in AP, sympathetic outflow in humans (Iwasaki et al., 2003; Roveda et al., 2003), as well as in animal models of exercise training (Collins et al., 2000; Kramer et al., 2002) and vascular resistance (Gando et al., 2010; Thijssen et al., 2010). Because morbidity and mortality in cardiovascular disease are often associated with elevations in sympathetic nervous system (SNS) activity (Benedict et al., 1996; Zoccali et al., 2002), the beneficial effects of physical activity are likely related, in part, to reductions in sympathetic activity (Cornelissen and Fagard, 2005; Roveda et al., 2003).

It has been suggested that exercise training improves renal function in patients with chronic kidney disease (Henrique et al., 2010). In addition, exercise training provokes a reduction of the fatigue in patients' physically inactive (Chang et al., 2010).

If there is relation between exercise training and renal function, the mechanisms by which chronic exercise training improves renal morphology, are not still completely elucidated. We hypothesized that the exercise training decreases AP and consequently attenuates renal injury in spontaneously hypertensive rats (SHR). A second hypothesis was that there was an association between renal damage and sympathetic activity levels. Therefore, the aim of the present investigation was to evaluate the effects of the exercise training on autonomic nervous system and structural renal morphology in normotensive rats and SHR.

Methods

Animal care and exercise training protocol

Twenty normotensive male Wistar-Kyoto (WKY) rats (48-50 weeks-old) and twenty male age-matched SHR were obtained from the breeding facility of the Federal University of Triangulo Mineiro (Uberaba, MG, Brazil).

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Animals were fed standard laboratory chow and water *ad libitum* while housed (3 to 5 per cage) in a temperature-controlled room (22°C) and 12-hour dark/light cycles. All animal protocols were approved by the local Experimental Animal Use Committee. These rats were randomly assigned to 4 experimental groups: sedentary normotensive (SN, n = 10), exercise-trained normotensive (TN, n = 10), sedentary hypertensive (SH, n = 10) and exercise-trained hypertensive (TH, n = 10) rats.

The exercise training sessions were performed in a glass tank with warm water at ~ 30º ± 1ºC (Tanno et al., 2002). The trained groups were submitted to adaptation period and consisted in 20 min on the first day and were increased 10-min each day until reaching 60 minutes on the fifty day (Seo et al., 2006). Following, these animals trained 5 days/week with a gradual progression toward a 120-min session for 9 wk. This protocol is defined as an aerobic endurance training and low-intensity, as the animals swam without additional work load, this method correspond the intensity below the anaerobic threshold in rats (Gobatto et al., 2001). Sedentary animals were placed in the swimming tank for 1 min in the same period of exercise training protocol to mimic the water stress with the experimental protocol. All procedures were followed in accordance with institutional guidelines.

Surgical procedure and arterial pressure and heart rate recording

Twenty-four hours after the last training session, 2 polietilene catheters (PE-50 welded to PE-10) filled with saline solution (0.9%) and heparin (500 $IU \cdot ml^{-1}$) were implanted into the femoral artery and vein of the anesthetized rats (sodium pentobarbital - 40 $mg \cdot kg^{-1}$ *i.p.*) to direct recordings of pulsatile AP and drug administration, respectively. Followed, the polietilene catheters were exteriorized at the posterior neck region of the animal. Rats received food and water ad libitum and were studied 1 day after catheter placement. On the day of the experiments, the rats were conscious in their cages and allowed to move freely during the experiments. The arterial catheter was connected to a strain-gauge transducer (P23Db, Gould-Statham), and pulsatile AP signals were recorded in baseline conditions over a 30-minute period by a microcomputer equipped with an analog-to-digital converter board (CODAS, 4-kHz sampling frequency, Di220 Dataq Instruments, Inc., Akron, OH, USA). During the experimental procedure, the mean AP (MAP) and HR were derived from the pulsatile AP.

Spectral analysis of heart rate and arterial pressure variability

Pulsatile AP was processed with customized software that determines beat-by-beat values of systolic AP (SAP) and HR. The SAP (SAPV) and HR (HRV) variability in the frequency domain was assessed by autoregressive spectral analysis as described elsewhere (Malliani et al., 1991). Briefly, a modeling of the oscillatory components present in the time series of SAP and HR was calculated based on the Levinson–Durbin recursion, with the order of the model chosen according to Akaike's criterion (Malliani et al., 1991). This procedure allows an automatic quantification of the center frequency and power of each relevant oscillatory component present in the time series. The oscillatory components were labeled as very low (VLF), low (LF) or high frequency (HF) when their central frequency was located in a band of 0.01–0.25 Hz, 0.25–0.75 Hz or 0.75–2.50 Hz, respectively. The power of the LF and HF components of HRV was also expressed in normalized units, obtained by calculating the percentage of the LF and HF variability with respect to the total power (all components from zero to 2.5 Hz) after subtracting the power of the very-low-frequency component (frequencies 0.25 Hz). The normalization procedure tends to minimize the effect of the changes in total power on the absolute values of LF and HF components of HRV (Malliani et al., 1991).

Baroreflex sensitivity, sympathetic-vagal tonus and pacemaker IHR assessment

After recording the basal pulsatile AP the animals received, randomly, injections of phenylephrine (2 $\mu g \cdot kg^{-1}$; *i.v.*) or sodium nitroprusside (2 $\mu g \cdot kg^{-1}$; *i.v.*) to elicit changes in AP to measure baroreflex sensibility, which was evaluated by the slope of the regression line obtained by best-fit points relating changes in HR (bpm) and MAP (Head and McCarty, 1987).

Following, all experimental groups received atropine (4 $mg \cdot kg^{-1}$ *i.v.*) and propranolol (5 $mg \cdot kg^{-1}$ *i.v.*), through a catheter in the femoral vein, to block the vagal and sympathetic influence on the heart. After atropine injection, HR was recorded for 15 minutes to evaluate the effect of the vagal blockade on the HR. Subsequently, propranolol was injected in the same animal and the HR was recorded for 15 more minutes to determine the intrinsic HR (IHR). In another animal subgroup, the sequence was inverted to propranolol/atropine, following the same recording procedure (15/15 minutes) for each drug. Vagal tonus was estimated by the difference between the maximal bradycardia achieved after sympathetic blockade with propranolol (double blockade by atropine and propranolol) and the pacemarker IHR. Sympathetic tonus was evaluated by the difference between the highest tachycardia observed after vagal blockade with atropine and the pacemarker IHR.

Renal damages evaluation

All animals were euthanized and their kidneys were excised to make color slides with Hematoxylin/Eosin (HE) and Picrosirius (PS). In the analysis of the slides a light microscope coupled to a camera and a computer were used. The KS-300 software technique was used (Koltron-Zeiss). The counting (score) of tubulointerstitial fibrosis, perivascular and inflammatory focus were done per analysed field. A final 800x increase of the microscope was done and they were quantified to the fullest extent of the cut. In order to count the number of glomeruli a 10x objective was used and the number of normal and sclerotic glomeruli was done. The glomerular index was calculated by relation sclerotic glomeruli / total glomeruli number.

Statistical analysis

Data are presented as mean ± standard error (±S.E.M).

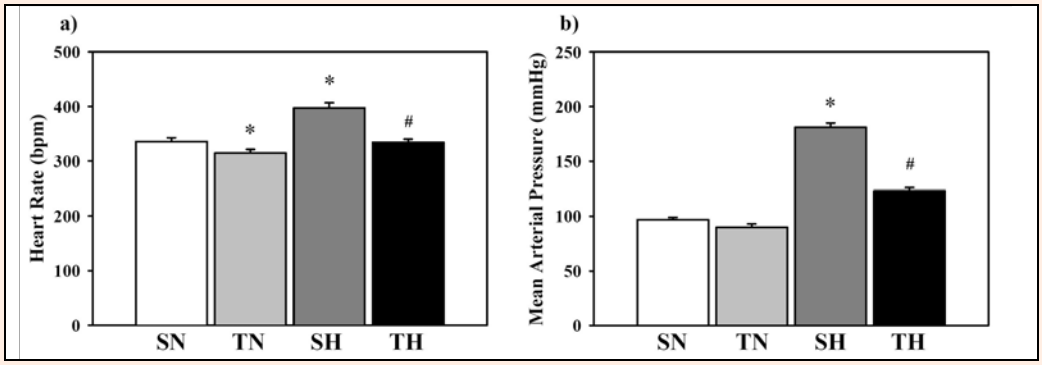

Figure 1. Hemodynamic parameters at baseline conditions (N = 10 each group). SN (sedentary normotensive); TN (exercise-trained hypertensive); SH (sedentary hypertensive); TH (exercise-trained normotensive). Data are means ±S.E.M * $p < 0.05$ *vs*. SN; # $p < 0.05$ *vs*. SH.

Statistical comparisons of the effect of exercise-training on the several measured parameters between groups was evaluated by two-way analysis of variance test followed by the *post hoc* Tukey test or Mann-Whitney in agreement with presence or not of distribution normality and/or homogeneity of the variance, respectively. Pearson correlation coefficient was used to test the correlation between sympathetic activity with AP and glomerular index. The level of significance was set at $p \leq 0.05$ were considered to be statistically significant (SigmaStat® SPSS, Chicago, IL).

Results

At baseline we found a significantly resting bradycardia for both trained groups (Figure 1A) compared with their respective sedentary groups ($p < 0.05$). The Figure 1B shows that the exercise training attenuated AP in TH *vs*. SH ($p < 0.001$).

The HR and AP variability are showed in Table 1. The variance of HRV was higher in TH than SH animals ($p < 0.05$). On the other hand, the variance of SAPV decreased in comparison to SH ($p < 0.05$). The LF component of HRV and SAPV were lowers in TH than SH ($p < 0.05$). In addition, the LF component of HRV was lower in TH compared to SN ($p < 0.05$). The normalized values of HF component of HRV were lowers in TH compared to SH. Considered a hallmark of sympatho-vagal balance, the LF/HF relation was significantly lower in TH animals in comparison to SH and SN groups ($p < 0.05$).

The exercise training improved baroreflex control of HR significantly in normotensive and hypertensive rats. Consequently, at the end of the 2-month intervention period, the reflex taquicardic sensitivity in both trained groups exceeder that observed in their respective sedentary groups ($p < 0.001$). The reflex bradycardic sensitivity was also significantly higher in TH than SH ($p < 0.001$) and was similar to that observed in SN (Figure 2).

The Figure 3 shows that the normotensive and hypertensive trained rats presented a sympathetic tonus reduction in comparison to their respective sedentary groups ($p < 0.001$). The sympathetic tonus was lower in TH *vs*. SN ($p < 0.05$). The TH presented an increased vagal tonus compared to SH ($p < 0.05$).

The number of sclerotic glomeruli and the glomerular index were significantly lower ($p < 0.05$) in TN and TH when compared to the both sedentary groups (Table 2).

In kidneys of hypertensive animals (Figure 4), the sedentary group (a,b,c) showed patterns of abnormalities compared to the trained group (d,e). This morphologic scenery of renal injury found in SH was more evident when compared to TH.

Further analysis showed a significant association between sympathetic nervous activity and MAP levels (Figure 5), demonstrated by correlation of sympathetic tonus and MAP ($r = 0.79$, $p < 0.001$; Figure 5a) and LF component of SAPV and MAP ($r = 0.57$, $p < 0.001$;

Table 1. Baseline values of variance (time domain) and spectral parameters (frequency domain) calculated for the heart rate (HR) and systolic arterial pressure (SAP) time series using autoregressive spectral analysis. Values are expressed as means (±SEM).

		SN (n=10)	TN (n=10)	SH (n=10)	TH (n=10)
HR	Variance, ms^2	12.7 (1.6)	18.6 (2.3)	10.3 (1.5)	21.7 (1.4) #
	VLF, ms^2	10.0 (1.8)	7.6 (1.4)	5.6 (1.3)	8.4 (1.6)
	LF, ms^2	2.4 (.7)	1.1 (.1)	6.0 (.6) *	.8 (.2) *#
	LF, nu	21.2 (3.5)	14.7 (1.4)	12.9 (2.4)	14.3 (2.0)
	HF, ms^2	4.9 (.6)	4.7 (.4)	4.7 (2.0)	6.2 (1.5)
	HF, nu	77.9 (3.4)	85.0 (1.4)	73.8 (2.3)	84.3 (1.9) #
	LF/HF	.4 (.1)	.2 (.0)	3.6 (1.0) *	.1 (.0) *#
SAP	Variance, $mmHg^2$	11.1 (1.3)	9.7 (1.2)	38.8 (6.9) *	28.4 (3.4) *
	LF, $mmHg^2$	3.6 (.4)	3.6 (.6)	17.3 (2.4) *	5.3 (.9) #
	HF, $mmHg^2$	4.6 (.2)	5.4 (.6)	3.9 (.2)	4.9 (.4) #

Abbreviations: VLF; very low-frequency component, LF; low-frequency component, HF; high-frequency component, nu indicates normalized units. * $p < 0.05$ *vs*. SN and # $p < 0.05$ *vs*. SH.

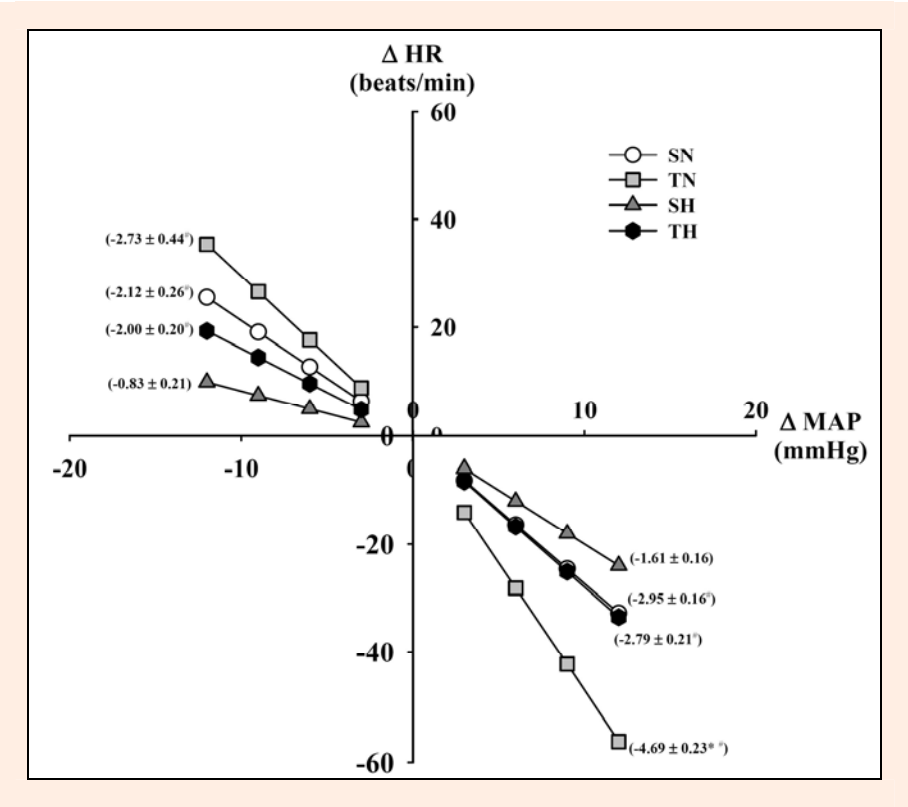

Figure 2. Baroreflex sensitivity (MAP/mmHg) evaluated for bradycardia and tachycardia reflex. The slope of each linear regression (baroreflex gain) is expressed as mean ± S.E.M. (N = 10 each group). SN (sedentary normotensive); TN (exercise-trained hypertensive); SH (sedentary hypertensive); TH (exercise-trained normotensive). * $p < 0.05$ *vs*. SN and $^{\#}p < 0.05$ *vs*. SH.

Figure 5b). The Figure 5c show a correlation between MAP and glomerular index ($r = 0.55$, $p < 0.05$) In addition, a positive association was also found between sympathetic tonus and glomerular index ($r = 0.46$, $p < 0.05$; Figure 5d).

Discussion

Our main finding was that exercise training triggered-beneficial effects in structure of the kidneys in hypertensive rats, decreasing the degree of renal damage and, to our knowledge, this is one of the first reports to evidence association between attenuation renal injury and sympathetic tonus.

The morphologic renal analysis employed in our study revealed that the sclerotic glomeruli were more preserved in trained SHR compared to sedentary animals of the same lineage. Increasing intraglomerular pressure is a possible explanation for how hypertension affects the glomerular ultrastructure of the kidneys in the SHR

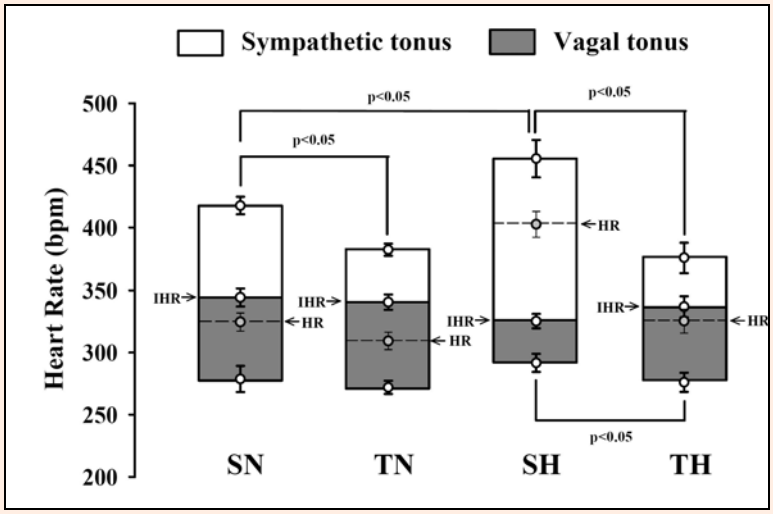

Figure 3. Sympathetic (ST) and vagal (VT) tonus and intrinsic heart rate (IHR) (N = 10 each group). SN (sedentary normotensive); TN (exercise-trained hypertensive); SH (sedentary hypertensive); TH (exercise-trained normotensive). Data are means ±S.E.M.

Table 2. Quantitative analysis of renal parameters. All values are expressed as means (±SEM).

	SN (n = 10)	TN (n = 10)	SH (n = 10)	TH (n = 10)
Glomerulosclerosis	13.8 (1.9)	6.1 (1.3) *	16.6 (4.2)	9.2 (3.7) #
Glomerular index (%)	.09 (.01)	.07 (.02) *	.20 (.05) *	.11 (.03) *#
Inflammatory focus (%)	.6 (.6)	1.5 (.6)	3.6 (.8) *	3.8 (1.1) *

* $p < 0.05$ *vs.* SN and # $p < 0.05$ *vs.* SH.

(Martinez-Maldonado, 1987). Previous study demonstrated by transmission electron microscopy that the basal membranes in the sedentary SHR had a thickened appearance. In addition, these authors showed that the basal membrane, the slit diaphragm and pedicel were more preserved in the both sedentary and trained normotensive rats and trained SHR compared to the sedentary SHR (Garcia-Pinto et al., 2011). The decrease in proteinuria would support this concept. Some studies had reported a decreases in proteinuria (Heifets et al., 1987), reduction of AP and ameliorates progressive renal disease in rats with subtotal nephrectomy submitted the exercise training (Kohzuki et al., 2001).

Resting bradycardia is considered to be an excellent hallmark for exercise training adaptation in humans and rats (Nelson et al., 1986; Negrão et al., 1992; Sugawara et al., 2001; Tipton et al., 1991). Thus, the bradycardia found in trained rats clearly demonstrates the effectiveness of exercise protocol here used.

In our investigation we found that chronic exercise attenuated glomerulosclerosi index and it was associated with decreased sympathetic nerve activity and reduction of AP. An important question in this study is that our results were due solely to the reduced hypertension caused by the physical activity or could be due to the attenuated sympathetic activity? In this sense, data of literature have demonstrated that renal functional and structural changes can occur in response to alterations in renal sympathetic nervous activity. In the context, it is established that the majority of the input to the kidney from the SNS derives from the efferent renal sympathetic nerves. The kidneys have a dense afferent sensory and efferent sympathetic innervation and are thereby strategically positioned to be origin as well as target of sympathetic activation (Gabbai et al., 1995).

Sympathetic hyperactivity has considerable adverse consequences for the renal systems. Sympathetic activation further aggravates hypertension contributes to glomerulosclerosis (Adamczak et al., 2002). If sympathetic activation is a fundamental process in chronic renal failure, then one would expect inhibition of adrenergic drive to antagonize the progression of renal damage. This simple fact could explain the association between the decreased sympathetic tonus and the reduction of the glomerulosclerosis index found in this present study. In fact, several experimental studies revealed that the use of β-blockade in subtotal nephrectomy reduced glomerulosclerosis and progression of kidney failure (Amann et al., 2001). Besides, there are several studies that has showed anti-hypertensive pharmacological tool are effective in reduce sympathetic nervous activity and, consequently, improves renal damage (Amann et al., 2000; Bohmann et al., 1994; Brooks et al. 1993; Klein et al., 2003; Ligtenberg et al., 1999; Nagasu et al., 2012; Strojek et al., 2001; Van Zwieten, 1997) and our study are in line with this results but using a non-pharmacological therapy (i.e. exercise).

Effects of exercise training on sympathetic nerve activity can reflect a generalized normalization of all known cardiovascular reflexes. In this way, another important finding in our research was that there was restoration of the baroreflex bradycardia and tachycardia

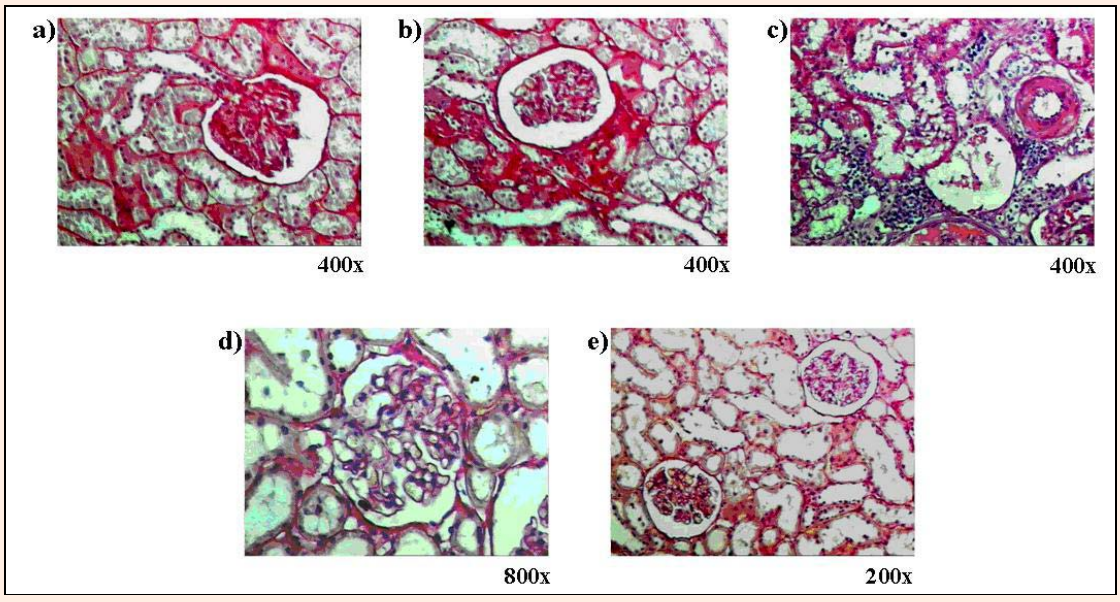

Figure 4. Kidney sections of renal histopathology showing glomerulosclerosis and interstitial fibrosis in sedentary hypertensive rats (Figure a, b and c) and typical glomeruli in exercise-trained hypertensive rats (Figure d and e).

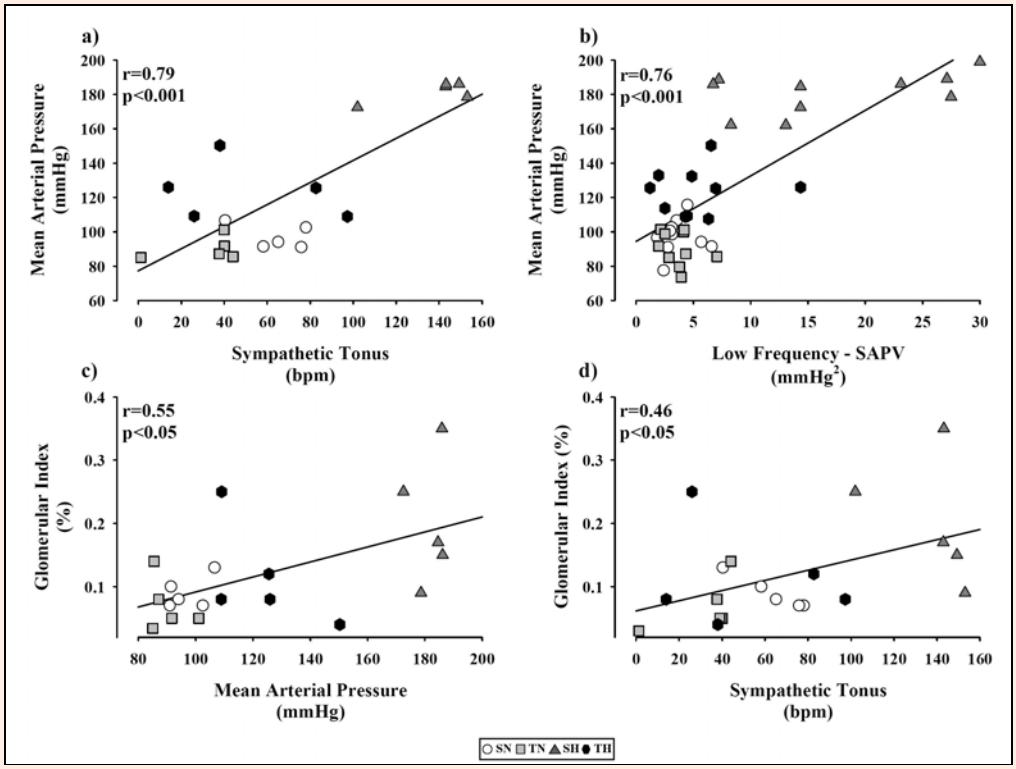

Figure 5. Correlation coefficient between MAP and ST (a), MAP and LF component of SAPV (b), glomerular index and MAP and (c), and glomerular index and ST (d).

corroborating with others investigators that demonstrated that physical training also improves the baroreflex control (Liu et al., 2002), chemoreflex, and the Bezold-Jarisch reflexes (Pliquett et al., 2003; Zhao et al., 1996) in experimentally induced heart failure, and hypertensive humans and rats (Brum et al., 2000; Somers et al., 1988).

Conclusion

Considering our findings, we can conclude that endurance exercise training was effective in reducing arterial pressure and improving kidney morphology in SHR models. In sum, these data strongly suggests that this improvement was associated with decreases sympathetic nerve activity. In conclusion, exercise is an important non-pharmacological tool for improving structure and renal function in hypertensive individuals.

Acknowledgements

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Key points

- Endurance training.
- Decrease of the sympathetic activity.
- Attenuation of renal injury.
- Decrease of blood pressure in SHR.

AUTHORS BIOGRAPHY

Octávio BARBOSA NETO
Employement
Professor, Institute of Health Sciences, Federal University of Triangulo Mineiro, Brazil, Department of Sport Sciences.
Degree
PhD
Research interests
Hypertension, hemodynamics and blood pressure regulation, cellular therapy, heart rate variability and exercise physiology.
E-mail: octavio@ef.uftm.edu.br

Débora Tavares de Resende e Silva ABATE
Employement
Institute of Natural and Biological Sciences, Federal University of Triangulo Mineiro, Brazil, Discipline of General Pathology.
Degree
PhD
Research interests
Experimental pathology.
E-mail: deboratavares.silva@hotmail.com

Moacir MAROCOLO JÚNIOR
Employement
Professor, Institute of Health Sciences, Federal University of Triangulo Mineiro, Brazil. Department of Sport Sciences.
Degree
PhD
Research interests
Exercise physiology
E-mail: isamjf@gmail.com

Gustavo Ribeiro da MOTA
Employement
Professor, Institute of Health Sciences. Federal University of Triangulo Mineiro, Brazil. Department of Sport Sciences.
Degree
PhD
Research interests
Exercise physiology
E-mail: grmotta@gmail.com

Fábio Lera ORSATTI
Employement
Professor, Institute of Health Sciences, Federal University of Triangulo Mineiro, Brazi, Department of Sport Sciences.
Degree
PhD
Research interests
Exercise physiology
E-mail: fabiorsatti@gmail.com

Renata Calciolari ROSSI SILVA
Employement
Professor, University of Paulista West.
Degree
PhD
Research interests
Experimental pathology.
E-mail: renata@unoeste.br

Marlene Antônia dos REIS
Employement
Professor, Institute of Natural and Biological Sciences, Federal University of Triangulo Mineiro, Brazil, Discipline of General Pathology.
Degree
PhD
Research interests
Experimental pathology and renal morphology.
E-mail: mareis.pat@dcb.uftm.edu.br

Valdo José DIAS DA SILVA
Employement
Professor, Institute of Natural and Biological Sciences. Federal University of Triangulo Mineiro, Brazil. Discipline of Physiology.
Degrees
MD, PhD
Research interests
Cardiovascular physiology, stem cells, cardiovascular variability, hypertension and congestive heart failure.
E-mail: valdo@mednet.com.br

✉ **Octávio Barbosa Neto**
Department of Sport Sciences - Institute of Health Sciences, Federal University of Triangulo Mineiro, Centro Educacional, Rua Getúlio Guaritá, 159 Abadia 38025-440 - Uberaba, MG - Brazil