

Original article (short paper)

Resistance training attenuates the effects of aging in the aorta of Wistar rats

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Abstract—The objective of the present study was to follow the structural modifications of the aortic wall in middle-aged rats submitted to a resistance training protocol for a period of four months. Three groups of 8 animals per group were considered: middle-aged group (MA), old control group (OC) and old trained group (OT). Training consisted in to climb a 1.1-m vertical (80° incline) ladder with weights tied to their tail. Aortic wall structural modifications were studied through light and electron microscopy and morphometry. The mean arterial blood pressure at rest was similar in the three experimental groups ($p = .07$). At the beginning of the experiment, the OC and OT groups had similar repetition maximums, ranging from 1.6-fold to 1.9-fold the body weight. At the end of the experiment, the repetition maximum of the OT group was 5-fold greater than the body weight ($p = .03$). The LV weight was 15% larger in the OT group than in the MA group and 12% larger than in the OC group ($p = .02$). The LV wall thickness of the OT group was significantly larger than that of both, the MA group and the OC group ($p = .03$). The LV internal diameter in the OT group was significantly smaller than that observed in the MA and OC groups ($p = .02$). Resistance training diminished the alterations associated with aging improving aortic wall structure by reducing the thickness, normalising the elastic material, the collagen and the smooth muscle cells. Resistance training seems to be a potential treatment for reducing the deleterious effects of aging on the aortic wall.

Keywords: aortic structure, anaerobic training, remodeling, stereology

Resumo—“O treinamento resistido atenua os efeitos do envelhecimento na aorta de ratos Wistar.” Este estudo teve por objetivo avaliar as modificações da parede da aorta de ratos Wistar de meia-idade, submetidos a treinamento resistido por 4 meses. Foram utilizados 3 grupos de animais com oito animais por grupo: meia idade (MI), idoso controle (IC) e idoso treinado (IT). Os ratos subiam uma escada vertical inclinada (80°) com pesos atrelados à cauda. A parede da aorta foi avaliada através de microscopia de luz e eletrônica e morfometria. A pressão arterial média no repouso foi similar nos três grupos experimentais ($p = 0,07$). No início, os grupos IC e IT tiveram treinamento de repetições máximas semelhantes, variando de 1,6 a 1,9 vezes o valor do peso corporal. No final o treinamento de repetição máxima do grupo IT foi 5 vezes maior que o peso corporal ($p = 0,03$). O peso do ventrículo esquerdo do grupo IT foi 15% maior do que o do grupo MI e 12% maior do que o do grupo IC ($p = 0,02$). A espessura da parede do ventrículo no grupo IT foi significativamente maior do que nos grupos MI e IC ($p = 0,03$). O diâmetro interno da cavidade do ventrículo foi significativamente menor no grupo IT do que nos demais grupos ($p = 0,02$). O treinamento diminuiu as alterações associadas com o envelhecimento melhorando a estrutura da parede da aorta através da redução da sua espessura, normalização quantitativa do material elástico, colágeno e das fibras musculares lisas. O treinamento resistido parece ser um tratamento potencial para reduzir os efeitos deletérios do envelhecimento na parede da artéria aorta.

Palavras-chave: estrutura aórtica, treinamento anaeróbico, remodelação, estereologia

Resumen—“El entrenamiento de resistencia minimiza los efectos del envejecimiento en la aorta del ratón.” El objetivo fue evaluar, por morfometria, los cambios estructurales de la aorta de ratones (Wistar) en la mitad de la vida, cuando se someten a entrenamiento de resistencia. Se utilizaron 3 grupos de animales con ocho animales por grupo: de edad media (EM), de viejos control (VC) y de viejos entrenados (VEn). Los animales subieron una escalera vertical inclinada (80°) con pesos atados a la cola. Al comienzo del experimento, los grupos de VC y VEn tenían entrenamientos de repetición máximos similares, que van desde 1,6 hasta 1,9 veces el peso corporal. Al final del experimento, el entrenamiento de repetición máxima en el grupo VEn era 5 veces mayor que el peso del cuerpo ($p = 0,03$). El peso del ventrículo izquierdo del grupo de VEn fue de 15% mayor que en el grupo EM y 12% mayor que en el grupo VC ($p = 0,02$). El espesor de la pared ventricular en el grupo de VEn fue mayor que en los grupos, EM y VC ($p = 0,03$). El diámetro de la cavidad del ventrículo fue significativamente menor en el grupo VEn ($p = 0,03$) en relación a los otros grupos. El entrenamiento de resistencia disminuyó los cambios asociados

con el envejecimiento, mediante la mejora de la estructura de la pared de la aorta, mediante la reducción de su espesor, normalización cuantitativa del material elástico, colágeno y de las fibras musculares lisas. El entrenamiento de resistencia parece ser un tratamiento potencial para reducir los efectos perjudiciales del envejecimiento en la pared de la aorta.

Palabras claves: estructura de la aorta, entrenamiento anaeróbico, remodelación, estereología

Introduction

The collagen and elastic fibers are important components of the aortic wall for maintenance of the aortic functioning. Elastic fibers confer elasticity, while collagen acts in the wall stiffening, limiting its extensibility (Horta, Carvalho, & Mandarim-de-Lacerda, 2005). The density of both, collagen and elastic fibers is important in conferring adequate mechanical properties to the aortic wall (Bruehl & Oxlund, 2002). The increase of collagen-elastic ratio characterizes the hardening of the artery wall (Robert, 1999), resulting in loss of elasticity of the vessel wall, promoting myocardial fibrosis and heart failure in the elderly (Besse *et al.*, 1993). This is because it affects the so called 'secondary heart' that is an important mechanism which is closely dependent on the elastic aortic enlargement at every systole and the energy-less recoil during diastole pumping the blood volume ejected into the aorta (Robert, 1996).

The aging process in the aortic wall brings about a number of morphological changes, such as the deposition of collagen and elastic material and loss of smooth muscle cells (Gaballa *et al.*, 1998; Matsuda, Nosaka, Sato, & Oshima, 1993). These alterations characterize the arterial stiffness. When examined with the electron microscope, important changes were found mainly in the tunica media (Kojimahara, 1985). These changes can ultimately result in aortic stiffening, which impairs the buffering capacity in relation to arterial pressure and flow, contributing to systolic hypertension and an increased cardiac after load (Belz, 1995; Kass, Saeki, Tunin, & Recchia, 1996). On the other hand, several studies have shown that arterial stiffening may be favorably modified through exercise training (Mourot *et al.*, 2009; Naka *et al.*, 2003).

Several studies confirm the beneficial effects of habitual aerobic training to minimize the effects of aging on the cardiovascular system (Horta, Carvalho, & Mandarim-de-Lacerda, 2005; Kokkinos, Narayan, & Papademetriou, 2001; Pinheiro, Cunha, Aguila, & Mandarim-de-Lacerda, 2007; Marques, Fernanda, Nascimento, Mandarim-de-Lacerda & Aguila, 2006; Mourot *et al.*, 2009; Naka *et al.*, 2003; Tanaka, Dinunno & Monahan, 2000; Tsai *et al.*, 2004; Wallace, 2003). However, nothing is known about the influence of resistance training on the effects of aging on the aortic wall. Therefore, the aim of the present investigation was to determine if resistance training would attenuate the aortic changes normally seen with aging in Wistar rats.

Methods

Sample and procedures

Twenty four male Wistar rats 12 months of age were obtained from São Judas Tadeu University (São Paulo) and

randomly divided among one of the three groups: (1) middle-aged group (MA, $n = 8$), sacrificed at the beginning of the experiment; (2) old control group (OC, $n = 8$), or (3) old trained group (OT, $n = 8$). The rats in groups OC and OT were sacrificed at 16 months of age. Rats were housed three to a cage and provided standard laboratory chow and water *ad libitum* throughout the investigation. The animal room was maintained at $21 \pm 1^\circ\text{C}$ and had an artificial 12: 12 light and dark cycle.

Resistance training

After a period of adaptation (1 week) to the motorized devices, the rats in the OT group were trained to climb a 1.1 m vertical (80 degree incline) ladder with weights tied to their tails (Heyward, 1998; Hornberger & Farrar, 2004). The rats were trained once a day throughout five days per week during 16 weeks. Each training session consisted of six climbs. Over the course of 16 weeks, the amount of weight carried by each rat was equivalent to 60% of its body weight (BW). The BW was measured at the beginning of each week of the experiment and the new weight to be carried by the animals during that week was adjusted according to their BW (Hornberger & Farrar, 2004). No external stimulus was necessary so that the animals conduct the training. The animals from OC group were also trained once a day throughout five days per week during 16 weeks, but each training session consisted of just one climb. The animals' handling was approved by our University Ethics Committee, in adherence to the International Guiding Principles for Biomedical Research involving animals.

Assessments of aortic remodelling

At the end of the experiment, each animal was anesthetized with Pentobarbital sodium (3 mg/100 g body weight, intra peritoneal) and, then, killed by exsanguination. The ascending aorta was excised after thoracotomy, and an arterial ring (5 mm long) was immediately isolated and cleaned from adipose and connective tissue.

Light microscopy. Eight pieces from each group were immersed in the fixative (freshly prepared 4% w/v formaldehyde in 0.1M phosphate buffer, pH 7.2 for 48 h (Carson, Martin, & Lynn, 1973). The arterial rings were sectioned according to the vertical sections method (Baddeley & Cruz-Orive, 1986) and processed according to the routine histological procedures and embedded in Paraplast plus (Sigma Chemical Co., St Louis, USA).

Quantitative study

The thickness of the aorta wall in four fields, located at 0°, 90°, 180°, 270°, was measured in five non consecutive sections stained with haematoxylin and eosin (Figure 1).

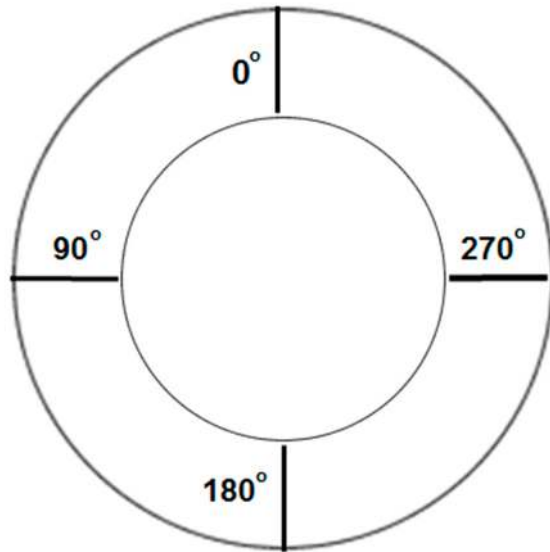


Figure 1. Schematic representation of a cross section of the aorta showing the locations where measurements of the wall thickness were taken.

The numerical density of smooth muscle cell nuclei per area ($QA[nuc]$) was obtained by counting the number of the myocyte nuclei in a two dimensional $1225 \mu m^2$ frame in five non consecutive histological sections per animal. The number of elastic lamellae of the aorta wall was counted in sections stained with Verhoeff. The lamellae surface area per volume ($Sv[lam]$) was quantified according to the stereological method described by Horta, Carvalho, and Mandarim-de-Lacerda (2005). A test system with 16 cycloids arcs was put upon the monitor screen and calibrated (Zeiss micrometer 1mm/100). The minor axes of the cycloids were arranged parallel with the defined vertical axis. The number of elastic lamellae intersections with the cycloid arcs (L) was counted, allowing to estimate the lamellae surface area per volume ($Sv[lam]$) according to the formula ($Sv[lam] = 2 \cdot L$).

The collagen content was determined in four fields of 5 histological non serial sections of $5 \mu m$ stained with the Picrosirius technique and examined under polarised light. When studied with this method, tissues containing collagen fibres show intensely birefringent thick and thin fibres (Junqueira, Bignolas, & Brentani, 1979). To determine the collagen content range in the three groups, histological sections were entered into a KS-400 digital analysing computer program (Zeiss, Germany), which quantified the area percentage (of $12,000 \mu m^2$) of the collagen fibres. The sections were analysed using a microscope equipped with appropriate polarisation lenses. In each section, 4 randomised fields were selected, and the area percentage of collagen fibres was quantified in each field.

The maximum and minimum diameters of collagen fibrils were determined in ten electron micrographs of each aorta at a final magnification of $\times 130,000$ obtained from regions where the fibrils were transversely sectioned. The diameters of each fibril were measured using the image analyser program. By commencing at one corner of each field and radiating outward in an arc, the diameters of the fibrils present in the field were determined. A total of 1 500 fibrils were measured in the three groups.

Statistical analysis

Computer program InStat was used for data analysis. Descriptive statistics were given as mean \pm standard error mean (SEM). All data were not normally distributed. The aortic parameters of three groups of rats were compared using the ANOVA and Tukey's test. When not specified, $p < .05$ was considered significant.

Results

No significant difference was observed between groups for body weight during the period of experiment (Table 1)

One repetition maximum

Figure 1 shows an increase in the absolute values for weight lifted by the trained group obtained during the repetition maximum test. The OC and the OT rats had similar values for repetition maximum at the beginning of the experiment (day 0). After 8 weeks, the load lifted by the OT group was higher than that of the OC group and 55% higher than that lifted in the first repetition test. At the end of 16 weeks, OT rats lifted 1250 ± 45 g which represents 3.1 fold the body weight for 16 weeks.

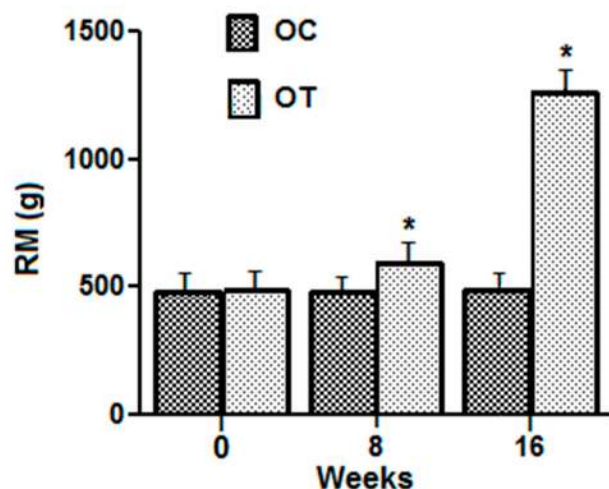


Figure 2. Values for 1 repetition maximum (RM) test. Results are mean \pm SEM.* $p < .05$, compared with the previous test. Groups were compared using one way ANOVA.

Effects of training on cardiac growth

Results from cardiac growth in MA, OC and OT groups of rats are showed in Table 1. The LVW, LV wall thickness and LV internal diameter of the OT group were significantly higher than that of the MA and OC groups. These results may indicate the development of concentric hypertrophy by hearts from OT group of rats.

Table 1. Body weight, LV weight, LV wall thickness and LV internal diameter of MA, OC and OT groups of rats.

Parameter/Groups	MA	OC	OT
BW (g)	399 ± 43	434 ± 20	388 ± 14
LVW (g)	0.81 ± 0.02	0.84 ± 0.01	0.93 ± 0.03*
LV wall thickness (mm)	1.42 ± 0.04	1.51 ± 0.03	1.83 ± 0.06*
LV internal diameter	0.74 ± 0.06	0.75 ± 0.06	0.68 ± 0.04*

Results are presented as mean ± SEM. **p* < .05, OT vs. OC and vs. MA.

Aorta morphometry

Resistance training attenuated the effects of aging in all parameters studied. The aortic wall thickness was larger in OC group than in MA and OT groups and it was larger in OT group than in MA group (in both cases, *p* < .05) (Figure 3). *N*[lam] and *S_v*[lam] was greater in OC group than in MA and OT groups (*p* < .05), and it was greater in OT group than in MA group (*p* < .05) (Table 2 and Figure 4). MA group showed more than 38 % greater *Q_A*[nuc] than OC group and more than 9 % greater than OT group (Table 2, Figure 5). The amount of collagen was higher in the OC group compared with the MA group but it was lower in the OT group compared with the OC group (Figure 6). In the MA group aortas, collagen fibres were composed by fibrils of small, medium and large diameter predominating that of small diameter (Figure 7A). In the OC group the collagen fibres were composed mainly by fibrils of large diameter (Figure 7B). In the OT group aortas, the collagen fibres were formed by small, medium and large diameter, predominating that of medium diameter (Figure 7C). Histograms showing collagen fibril diameter distribution in MA, OC and OT aortas are presented in Figure 8. It was observed a clear deviation of the values to the right in the OC group.



Figure 3. Photomicrographs of aortic wall sections from MA (A), OC (B) and OT (C) groups of rats stained with haematoxylin and eosin and taken with the same magnification. The OC group of rats (B) presented the highest aorta thickness, followed by the OT group (C).

Table 2. Aortic structure of the MA, OC and OT groups of rats during the 4 month training period.

Parameter/Groups	MA	OC	OT
Thickness (µm)	121.31 ± 1.25	204.94 ± 2.65*	167.08 ± 2.05**
<i>N</i> [lam]	11.71 ± 0.24	14.06 ± 0.24*	12.20 ± 0.23**
<i>S_v</i> [lam]	36.44 ± 0.77	40.4 ± 0.77*	38.32 ± 0.78**
<i>Q_A</i> [nu]	3260 ± 73	1993 ± 139*	2943 ± 95**

*Significant vs. MA and OT (*p* < .05); **Significant vs. MA (*p* < .05. *N*[lam]: number of elastic lamellae per field; *S_v*[lam]: Surface density of lamellae. *Q_A*[nu]: Numerical density of nuclei per area; Values are means±SEM.

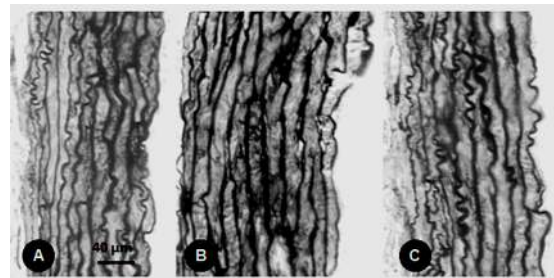


Figure 4. Photomicrographs of the ascending aorta cross-sections showing elastic lamellae (Verhoeff stain). The number and thickness of elastic lamellae (arrows) in OC group (B) was greater than in MA (A) and OT (C) groups. The endothelium is on the right side.

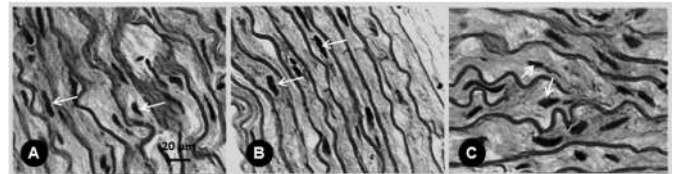


Figure 5. Photomicrographs of the aortic wall sections stained with hematoxylin-eosin. The numbers of cell nuclei (arrows) in OC (B) and OT (C) groups are greater than in MA group (A).

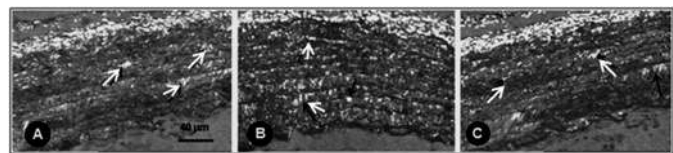


Figure 6. Cross-sections of rat aorta stained in Picrosirius and photographed with crossed polarizing filters. The amount of collagen (arrows) is higher in the OC group (B) compared with the MA group (A) and it is lower in the OT group (C) compared with the OC group (B).

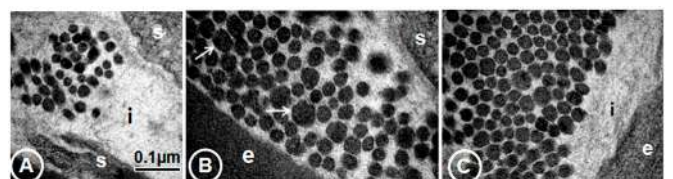


Figure 7. Transverse section of collagen fibres of a MA aorta (A), of an OC aorta (B) and of an OT aorta (C). The constituent fibrils (arrows) in (B) are of significantly larger diameter than those shown in (A) and (C). S-Smooth muscle cell; i-interstitium; e-elastic fibre.

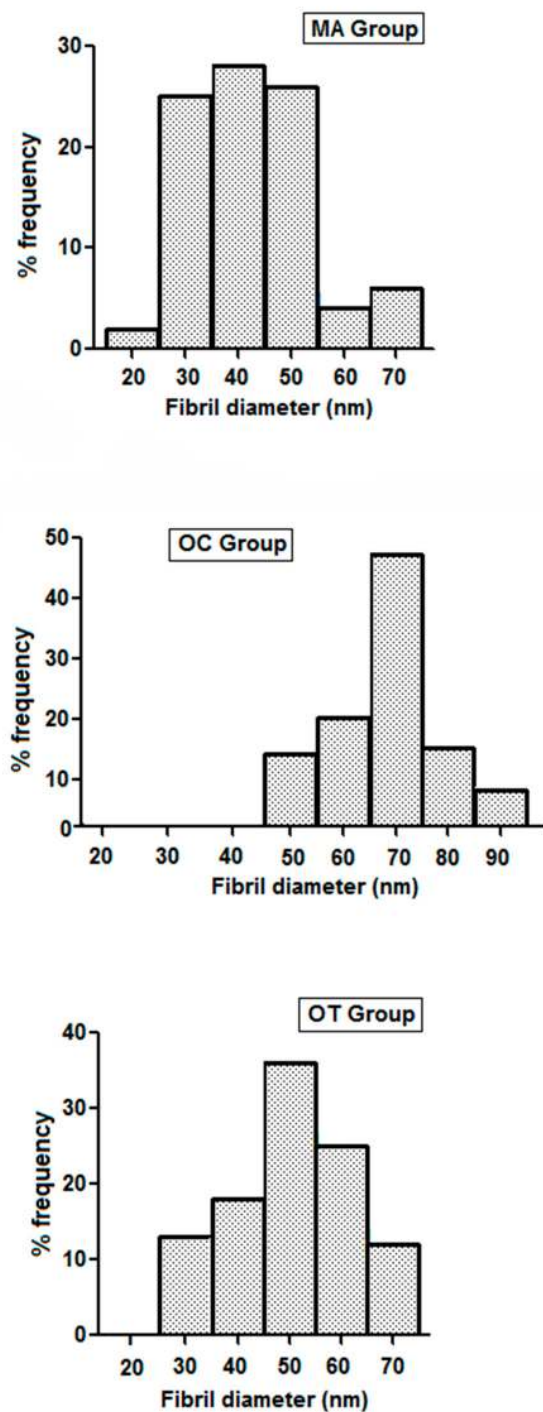


Figure 8. Histograms showing collagen fibril diameter distribution in the aorta of the MA, OC and OT groups. Observe deviation of the values to the right in the OC group.

Discussion

There are two major findings in the present study. First, the changes associated with aging include a decrease in the number of nuclei of smooth muscle cells, the increasing in tunica media

thickness, increase in the number and density of elastic lamellae and increase in collagen content and diameter of collagen fibrils. These alterations characterize the aorta stiffness which is a major contributor to cardiovascular disease. Second, the model of resistance training used in this experiment has been proved to be successful in producing an exercise response (Hornberger & Farrar, 2004; Lee, Barton, Sweeney & Farrar, 2004) in heart and aorta of aging rats.

In the present study, age-related changes were characterized as degenerative changes in the smooth muscle cells of the tunica media. The decreasing cellularity of the media with aging could be attributed in part to the increasing cell degeneration and necrosis identified with age (Gaballa *et al.*, 1998; Niederhoffer *et al.*, 2000). Degenerative changes involving both nucleus and cytoplasm of the cells were identified. The cytoplasm changes involved accumulation of lipids with foam-cell appearances developing at times. In addition, various granular and vesicular forms of cytoplasm degeneration occurred and resulted in similar debris being liberated into the extracellular space where it remained without producing any detectable reaction (Cliff, 1970). As aging occurs, smooth muscle cells progressively migrate from the tunica media and accumulate into the tunica intima. Aging also associates with changes of smooth muscle cells proliferative and apoptotic behavior and response to growth factors, such as transforming growth factor- β 1 (Yildiz, 2007).

The present work demonstrated the increasing in tunica media thickness with aging. The exaggerated deposition of collagen, elastin, and proteoglycans could explain the thickening observed in arterial wall from aged sedentary animals (Virmani *et al.*, 1991). Furthermore, numerous substances involved in inflammatory and/or atherosclerotic processes such as adhesion molecules, matrix metalloproteinases, transforming growth factor- β , and others, such as pro inflammatory cytokines, are also abundant in aging arterial intima (Challat *et al.*, 1997; Li, Frölich, Galis, & Lakatta, 1999).

In the present study, the number and density of elastic lamellae increased significantly with aging. Despite of the increase in the number and thickness of the elastic fibers with aging, there is a reduction in their elasticity since there is a diminution of the elastic material (elastin) due to calcification and fragmentation of the elastic fibers with aging (Lakatta, 2003).

The present study demonstrated that the percent aortic collagen increased with age. These results imply reduced collagen turnover with aging, with degradation rates falling faster than simultaneously declining synthesis rates (Bishop & Laurent, 1995; Laurent, 1987). This is consistent with the finding of impairment of distensibility, the fundamental age-related change in aortic function (Van der Heijden, Fagard, Hoeks Boudier, & Van Bortel, 2000). These age-related alterations are also present in atherosclerotic vessels. Thus, because aging and atherosclerosis run along very similar biochemical pathways and determine many similar vascular alterations, aortic alterations observed in this work with aging may be viewed as representing the prodromal stage of atherosclerotic disease (Ferrari, Radaeli, & Centola, 2003). According to Dobrin (1978) the progressive vessel rigidity observed with aging are related to the inversion of the elastin/collagen ratio. Muscle cells are responsible of the biosynthesis of

collagen. The factor responsible for collagen increase is unknown. The loss of muscle cells could be one cause and another cause could be an inhibition of collagen degradation (Eghbali, 1990).

The present study showed that the changes of aortic wall structure observed with aging were attenuated in rats subjected to resistance training for 16 week compared to sedentary controls, indicating that resistance training had an effect in the changes of aortic wall observed with aging.

The LVW, LV wall thickness but not LV internal diameter of the OT group was significantly higher than that of the MA and OC groups. These results indicate the development of concentric hypertrophy by hearts from OT group (Pluim, Zwinderman, Van der Laarse, & Van der Wall, 2000) providing a consistent evidence of an increase of myocardial aging tissue associated with resistance training. The results also suggest a continuous response of cardiac tissue to training, beyond the adult life. The improvement in cardiac structure was associated with a reduction in aortic resistance promoted by training. The increasing rigidity and changes in the mechanical properties of the aorta wall which is related to the elastic/collagen changes (Lévy, 1992; Quiu *et al.*, 2007) was attenuated by resistance training.

In the present study animals receiving resistance training exhibited a significant reduction in aortic wall thickening, in the number of elastic lamellae, lamellae surface area per volume, the collagen content and in the diameter of collagen fibrils compared with the matched sedentary. This suggests that exercise training was efficient in preventing adverse aortic wall remodeling (Tanaka, Dineno & Monahan, 2000; Thomas, Schlatemann, Facc, & Becker, 1977; Toda, Tsuda, Nishimori, & Kummerow, 1980).

The present study demonstrated that animals receiving resistance training showed a significant enhancement in the number of smooth muscle cells compared with sedentary controls. The 38% reduction in the number of smooth muscle cells that was detected in OC rats was not observed in the OT animals indicating that training could prevent the effect of aging in smooth muscle cells.

The effects of resistance training on expression of message for collagens seem to be of preserving the decline in expression of mRNAs for collagen seen with aging (Thomas, Zimmerman, Hansen, Martin, & McCormick, 2000). Whether the alterations in hemodynamic load on the aorta provided the stimulus for the observed decline in collagen mRNA in trained compared with sedentary rats in the older age group is a question requiring further investigation. The issue of collagen degradation process and its regulation during resistance training is not known. It is possible that it is related to the increase of systolic blood pressure during resistance training. Then, the increase of aortic collagen may represent a response to increased loading conditions imposed by resistance training in the aortic wall. Alternatively, it is possible that TGF- β 1 increases with pressure overload, which could explain the increase of collagen transcription in the trained aorta.

Conclusion

Resistance-trained displayed improved aortic structure in rats, decreasing the adverse age-related remodeling in the aorta.

The aortic adaptation to resistance training was associated with reduction of smooth muscle cell loss, and collagen and elastic increasing in the aortic wall.

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Manuscript received on May 4, 2014

Manuscript accepted on August 25, 2015



Motriz. The Journal of Physical Education. UNESP. Rio Claro, SP, Brazil
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