

# Impact of Malnutrition and Moderate Aerobic Training on the Structure of Arterial Wall in Aging Rats



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## ABSTRACT

We evaluated the late effects of multi-needly malnutrition imposed during lactation and the possible effects and / or changes to both the aging process as of moderate aerobic training on the luminal diameter and the tunica media area of the left common carotid artery, horizontal aorta and thoracic aorta of rats in the aging process. Twenty-four Wistar male rats were separated according to diet and physical training: SNG – Sedentary Nourished Group, TNG - Trained Nourished Group, SMG- Sedentary Malnourished Group and TMG – Trained Malnourished Group. At 10 months, the TNG and TMG were submitted to aerobic training in water for 8 weeks. Then the mice were anesthetized and sacrificed and the arterial fragments were collected for histological processing. The area of the tunica media was measured by the difference between external and internal areas of the arterial wall and luminal diameter was measured from the average of two diameters measured from four points marked on the internallayer of the vessel. The area of tunica media decreased in the horizontal aorta when compared groups SNG x SMG ( $p = 0.015$ ) and increased in left common carotid artery between groups SNG and TNG ( $p < 0.001$ ). The thoracic aorta showed an increase in luminal diameter when comparing the SMG with the TMG ( $p = 0.041$ ). Multi-needly malnutrition induced both to partial changes in the horizontal aorta wall, as well as physical training was able to promote changes in the tunica media area of the left common carotid artery and luminal diameter of the thoracic aorta.

**Keywords:** aerobic moderate training, arterial remodeling, aorta, carotid artery.

## INTRODUCTION

The tissues and organs have “critical” development periods<sup>(1)</sup>, which are characterized by fast growth, replication, cellular differentiation and maturation of organs and systems, and are decisive for the determination of the morphofunctional characteristics in adults<sup>(2)</sup>. Disorders occurred during this period may determine permanent or long-term alterations in different organs<sup>(3)</sup>. Among these disorders, we can stress the nutritional deficiencies which, associated with unfavorable socioeconomic conditions<sup>(4)</sup>, may be related to high risk of development of defects in metabolism, as well as trigger diseases such as type diabetes, obesity<sup>(5)</sup>, systemic arterial hypertension (SAH), as well as cardiovascular diseases in more advanced ages<sup>(6,7)</sup>.

The type, duration as well as phase of development at which malnutrition occurs may determine the type of interference on the organic structure<sup>(3,5)</sup>. Thus, malnutrition has been mentioned as one of the main non-genetic factors which can interfere in the normal development of the organs<sup>(2)</sup>. During the neonatal development, malnutrition may reflect on alterations such as growth delay<sup>(8)</sup>, low weight<sup>(9)</sup>, alterations in the arteries straight muscle tissue<sup>(10)</sup>, hemodynamic alterations<sup>(11)</sup> as well as cardiovascular problems<sup>(8,12)</sup>. Several experimental studies showed that a hypoprotein and hypocaloric diet or food restriction in initial phases of life, may cause adverse remodeling of the tunica media of the throacic aorta, hyperplasia of the straight muscle cells and consequently, increase of wall thickness of this artery<sup>(7)</sup>, endothelial dysfunctions such as increase of basal tonus of the left internalthoracic artery<sup>(13)</sup>, increase of the contraction strength of the femoral arteries<sup>(14)</sup>, insufficiency in the

relaxation of the vascular endothelium<sup>(15)</sup> leading to increase of systolic blood pressure<sup>(7)</sup>.

Some studies have shown that the cardiovascular function may be significantly improved by the practice of physical training<sup>(16,17)</sup>, which contributes to reduction on the cardiovascular morbimortality indices<sup>(16)</sup>.

Physical training generally speaking, increases the energetic need of the body, causing expressive alterations in the cellular metabolism, implying in a series of physiological responses in the body systems, and especially in the cardiovascular system<sup>(18)</sup>. Frequent and regular exposure to physical training result in adaptations to the organism typically represented by alterations in the heart rate. The increase in venous return and improvement in myocardic contrability<sup>(16,19)</sup>, induced by physical training, can result in relative rest bradycardia<sup>(19)</sup>. This alteration of heart rate is also related to improvement in cardiac chronotropism due to alterations occurred in the atrioventricular conduction system<sup>(16)</sup>. The peripheral arteries adapt with alterations in their structure induced by physical training in a trial to correspond to the metabolic needs of the skeletal musculature supplied by these vessels. These adaptations are represented by the increase of the vessels diameter as well as in the arterial walls diameter<sup>(20)</sup>.

Thus, the study aims to analyse the late effects of the alterations early caused by a multi-needly malnutrition status on the vascular structure of the left common carotid, horizontal aorta and thoracic aorta arteries. Additionally, to demonstrate how aerobic physical training (AT), with moderate intensity can interfere in this process.

## METHODS

All experiments were performed according to the guidelines suggested by the Brazilian Committee of Animal Experimentation (COBEA). The study was submitted to and approved by the Ethics in Animal Experimentation Committee (CEEA) of the Center of Biological Sciences of UFPE (protocol # 21931/2008 – 29).

24 male albino Wistar rats from the animal facility of the Nutrition Department of the Federal University of Pernambuco-UFPE were used. The animals were randomly sorted in two groups: Nourished group N (n = 12), composed of pups which received LABINA diet® and Malnourished group – M (n = 12), composed of pups which received basic regional diet (RBD) from the first to the 21<sup>st</sup> day of life, and after this period, also started being fed with standard diet (LABINA®).

At 10 months, the animals were randomly distributed according to performance or not of physical training, in four subgroups: Sedentary Nourished Group (SNG), Trained Nourished Group (TNG), Sedentary Malnourished Group (SMG) and Trained Malnourished Group (TMG). Each experimental subgroup was composed of six animals.

The animals from TNG and TMG were submitted to the aerobic physical training protocol with moderate intensity<sup>(21)</sup>. The training modality used was swimming in a plastic round tank with water temperature kept between 30 and 32°C through a digital thermostat. The trained animals were submitted to an adaptation period which lasted 10 minutes on the first day. On the following days, 10 minutes were added to the training until total time would reach 40 minutes on the fourth day and remaining with this duration until the end of the first week. Subsequently, 40min/day were kept until the eighth training week. The animals of the SNG and SMG limited to activities inside their cage.

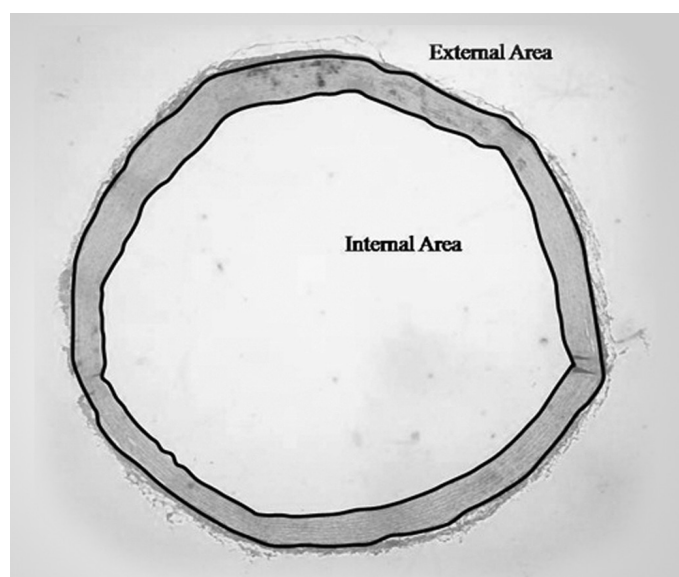
At the end of the training period, the animals received intramuscular anesthesia of Xylazine Chloridate (Rompum® – Bayer) and Ketamine. The thoracic and abdominal cavities were then opened and the hearts were perfused with cannulation of the left ventricle for introduction of 250ml of saline solution at 0.9% with 1ml of heparin per liter of saline solution. The right atrium was opened for draining of the perfusion solutions. After washing of the system, the tissues were treated with glutaraldehyde 4% diluted in phosphate buffer at 0.5 molar with pH = 7.2. Fragments of the left common carotid artery (5mm proximal to the horizontal aorta) and horizontal aorta (portion between the arterial brachiocephalic trunk and the left common carotid artery) were dissected for removal of the adhering tissues, treated with alcohol 70% and transversal cuts of 3µm were stained by Verhoeff-Van Gienson method.

The histological preparations of the left common carotid artery were submitted to histomorphometric analysis through photomicrography performed with help of a system composed of the Tv Turner Application software, a Samsung video camera (model SHC-410NAD) attached to the Olympus optical microscope (model Bx-50) with final increase of 40x, all integrated to a micro computer. The photomicrografies of the horizontal aorta and thoracic arteries were performed with the aid of a Sony digital camera (model DSC-H7) directly attached to the lenses of an Olympus BX-50 optical microscope with final increase of 40x.

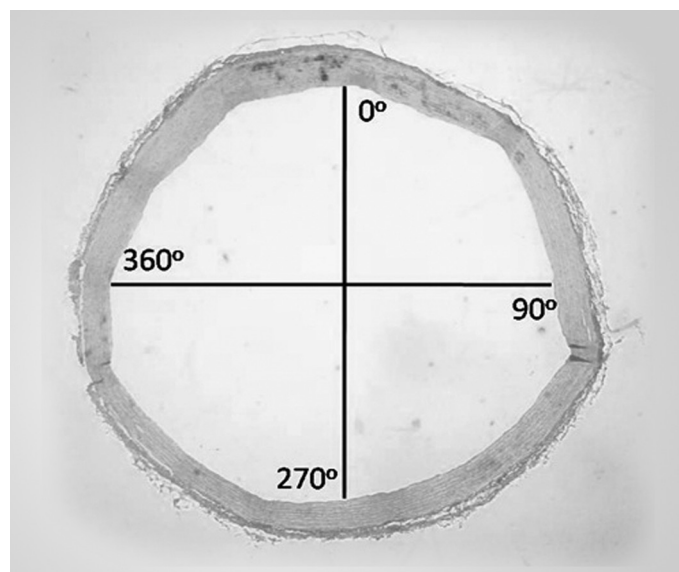
Having these photomicrografies as starting point, the difference between the value of the external and internal areas of the vessel wall was performed for determination of the area of the tunica media of the arterial wall (figure 1).

The 0°, 90°, 270° and 360° points were determined for measurement of the luminal diameter of the vessels. Two straight lines were drawn in a way they crossed each other and formed a 90 degree angle from these points. Subsequently, the diameter values were summed and divided by two, so that a mean value could be found for the luminal diameter of the vessels<sup>(22)</sup> (figure 2).

Measurement of both luminal diameter and area of tunica media of the arteries was performed with the Scion Image software for Windows (Beta 4.0.3 version for Windows). A scale of 0.564 pixels/micrometer was used for the left common carotid artery values and for the horizontal and thoracic aorta arteries, the scale of 0.279 pixels/micrometers was used.



**Figure 1.** Illustration of the measurement of the tunica media area of the left common carotid artery wall, horizontal aorta and thoracic with aid of the Scion Image software for Windows. Increase of 40x.



**Figure 2.** Illustration of the measurement of the internal diameter of the left common carotid artery, horizontal aorta and thoracic with the aid of the Scion Image software for Windows. Increase of 40x.

Histomorphometric analysis of the arteries was done with the SPSS 11.5 program for Windows and, for comparison between groups, the Student's t test for independent and parametric samples as well as Mann-Whitney test for non-parametric samples, with significance level of  $p < 0.05$  were used; data were presented in mean  $\pm$  standard deviation.

## RESULTS

Concerning the area of the tunica media, the horizontal aorta artery presented decrease when SNG and SMG are compared ( $335.566.83 \pm 58.149.13 \mu\text{m}^2$  and  $259.487.72 \pm 51.742.44 \mu\text{m}^2$ , respectively,  $p = 0.015$ ), demonstrating partial influence of nutritional deficiency, since neither the left common carotid nor the thoracic aorta arteries presented significant differences. Still concerning the area of the tunica media, the left common carotid artery presented significant increase between TNG ( $36.531.42 \pm 4.164.45 \mu\text{m}^2$ ) and SNG ( $23.663.72 \pm 3.036.43$ ) ( $p \leq 0.001$ ), indicating a partial effect of physical training over the structure of the arterial wall. The remaining arteries under study did not present alterations in the normonourished animals (table 1).

Regarding the luminal diameter, only the thoracic aorta artery presented significant increase when the SMG ( $798.98 \pm 69.83 \mu\text{m}^2$ ) and TMG ( $980.35 \pm 154.62 \mu\text{m}^2$ ) were compared ( $p = 0.041$ ), demonstrating that aerobic physical training with moderate intensity partially influenced the structure of the wall of this artery. The left common carotid and horizontal aorta did not suffer influence of the moderate aerobic training on the luminal diameter (table 2).

**Table 1.** Mean values concerning area of the arterial tunica media. Data as mean  $\pm$  SD.

	SNG	SMG	TNG	TMG
LCCA, $\mu\text{m}^2$	23.663.72 $\pm$ 3.036.43	23.401.44 $\pm$ 5.065.86	36.531.42 $\pm$ 4.164.45**	24.198.87 $\pm$ 6.042.24
HAA, $\mu\text{m}^2$	335.566.83 $\pm$ 58.149.13	259.487.72 $\pm$ 51.742.44*	318.906.49 $\pm$ 34.584.25	255.195 $\pm$ 65.154.98
TAA, $\mu\text{m}^2$	162.885.15 $\pm$ 24.159.60	151.805.18 $\pm$ 37.903.60	187.409.81 $\pm$ 48.669.94	156.037.69 $\pm$ 49.166.12

\*Difference between groups SNG and SMG,  $p = 0.015$  – Student's t test. \*\*Difference between groups SNG and TNG,  $p \leq 0.001$  – Student's t test. LCCA: left common carotid artery, HAA: horizontal aorta artery, TAA: thoracic aorta artery and  $\mu\text{m}^2$ : micrometer to the square.

**Table 2.** Mean values concerning the luminal diameter of the arteries. Data as mean  $\pm$  SD.

	SNG	SMG	TNG	TMG
LCCA, $\mu\text{m}^2$	358.16 $\pm$ 29.73	331.41 $\pm$ 43.98	367.02 $\pm$ 26.44	355.64 $\pm$ 18.32
HAA, $\mu\text{m}^2$	1.041.63 $\pm$ 67.56	934.15 $\pm$ 53.44	1.107.95 $\pm$ 56.73	1.080.92 $\pm$ 166.28
TAA, $\mu\text{m}^2$	843.23 $\pm$ 42.02	798.98 $\pm$ 69.83	892.41 $\pm$ 89.70	980.35 $\pm$ 154.62***

\*\*\*Difference between groups SMG and TMG,  $p = 0.041$  – Mann-Whitney test. LCCA: left common carotid artery, HAA: horizontal aorta artery, TAA: thoracic aorta artery and  $\mu\text{m}^2$ : micrometer to the square.

## DISCUSSION

Studies with laboratory animals have suggested the hypothesis that the uterine phase and the lactation period are critical stages for the development of many tissues and body systems, among them, the cardiovascular system<sup>(7,23)</sup>. Therefore, factors

which may interfere in the development phases, such as malnutrition, may favor the onset of cardiovascular pathologies in late phases of life. The mechanisms which promote such alterations have not been totally elucidated<sup>(3)</sup>, although such vascular pathologies have already been related to alterations in the structure of vessels, notably to alterations on the arterial wall<sup>(24)</sup>.

The multi-needly malnutrition used in this study during the lactation period promoted reduction in the area of the tunica media of the horizontal aorta artery of 12-month rats, demonstrating that, although malnutrition has occurred in a very early phase of the animal's life, the alterations caused by it remained, reducing hence the thickness of the arterial wall. A study with rats submitted to protein malnutrition during gestation and lactation also demonstrated reduction in the thickness of the tunica media of the aorta artery<sup>(23)</sup>. However, this same author in another study<sup>(24)</sup>, observed increase of thickness of arterial wall of the abdominal aorta in neonatal pups, attributing this divergence in results to the different models of fetal malnutrition. In addition to this, a previous study carried out in our laboratory in rats with 80 days of life whose mothers were fed with hypoprotein diet during the gestational and neonatal periods, demonstrated reduction of thickness of the left common carotid artery<sup>(25)</sup>. It has also been demonstrated that in humans and adults (mean of 58 years) whose mothers were not fed with hypoprotein diet presented reduction of thickness of the left common carotid artery<sup>(26)</sup>. According to Barker and Hanson<sup>(27)</sup>, these data divergences may occur due to the structural differences of the artery walls. For example, the coronary arteries are much more sensitive to alterations of the structure components (proteins, straight muscle tissue) derived from nutritional aggression, which may imply in increase of thickness of their walls as well as reduction in luminal diameter, increasing hence the risk of cardiovascular diseases, especially of ischemic order<sup>(27)</sup>. These structural alterations may have not occurred with the arteries of our study, demonstrating that the multi-needly diet may have caused loss of structural components, ended with reduction of thickness of the arterial wall found in our study.

Khorram et al.<sup>(28)</sup> using rats with one day of life and whose mothers had been submitted to food restriction (50% of food intake compared to control group) on the 10th Day of gestation, and Pires and Mandarim-de-Lacerda<sup>(7)</sup>, using animals with 36 weeks submitted to protein restriction during lactation, on the other hand observed increase of thickness of tunica media of aorta artery of these animals. This increase of arterial thickness could be related to the increase of systolic blood pressure found by these authors in their studies.

At basal conditions, the vascular endothelium secretes relaxing factors (nitric oxide, NO; prostacyclins) and contractile factors (endoperoxides, thromboxane  $A_2$  and endothelins, ET)<sup>(29)</sup>. The increase of contraction strength of the arteries as well as the insufficiency in the endothelial relaxation are related to decrease of NO availability in the vascular endothelium<sup>(14,15)</sup>. NO induces to relaxation of the straight muscle layer of the arterial wall through increase of conduction of  $K^+$  ions to the cellular interior, hyper polarizing the cells and inhibiting the intracellular flow of  $Ca^{++}$  ions, altering hence the contraction mechanism of the straight musculature of the arteries. Rats submitted to protein restriction in initial pha-

ses of life, presented disorders in the endothelial relaxation of the thoracic aorta<sup>(14,15)</sup>, implying in increase of vascular tonus, which could explain the fact these animals present increase in thickness of arterial wall.

Cardiovascular diseases, such as arteriosclerosis and SAH, may be related to increase of vascular tonus derived from disorders in endothelial relaxation<sup>(29)</sup>. The natural aging process can also induce to alterations in the vascular endothelium<sup>(30)</sup>. Large arteries as the aorta are mainly constituted by straight muscle tissue, which, among other functions, produces the components of the extracellular matrix<sup>(31)</sup>. Alterations on the arterial wall consequent from aging may occur due to alterations in the components of the extracellular matrix such as decrease of elastin biosynthesis, increase of elastane enzyme activity, collagen deposition, hypertrophy and hyperplasia of the straight muscle cells<sup>(32)</sup>. Thus, the arterial wall becomes more rigid, due to higher concentration of collagen fibers, increasing even more the probability of cardiovascular diseases in older subjects<sup>(33)</sup>.

The maternal nutrition status during gestation and lactation are more important and decisive to the body development than the genetic constitution itself<sup>(34)</sup>. Gestational and neonatal malnutrition causes negative impact on the development of the organs and systems which cannot be reverted in the long term, even with suitable diet after the critical period of development<sup>(35)</sup>, which, in rats, comprehends the 21 first days of life<sup>(2)</sup>. Our study demonstrated that the multi-need diet administered in the neonatal period induced alterations in the vascular system which persisted during the entire life of the animal, despite they have been fed immediately after weaning with a balanced diet.

Physical training has been recommended as an excellent prevention factor of cardiovascular diseases<sup>(36)</sup> for promoting hemodynamic and autonomous adaptations, structural alterations on the arterial vessel walls as well as decrease in sympathetic tonus<sup>(17,18,21)</sup>. However, in the present study, aerobic physical training with moderate intensity using swimming did not influence on the tunica media area of the wall of the horizontal and thoracic aorta arteries. Maux et al.<sup>(25)</sup> did not observe alterations on the arterial wall of horizontal aorta of rats submitted to protein malnutrition in gestation and lactation which performed physical training from the age of 60 days, during eight weeks. Likewise, Huonker et al.<sup>(20)</sup>, using athletes of different sports modalities, demonstrated there are not dimension alterations in the aorta artery, possibly due to the predominance of elastic fibers in this artery. According to the same authors, the aorta artery is a central vessel responsible for collecting the blood flow ejected by the left ventricle, through a passive dilatation caused by the expansion of the elastic structures of the artery. Such expansion allows an elastic detachment of the vessel wall during the ventricular diastole<sup>(20)</sup>. Since the aorta arterial wall is highly elastic, it may not give away to the increased blood flow due to cardiac adaptations derived from physical exercise<sup>(18)</sup>, which could explain the fact that we had not found difference in thickness of the horizontal and thoracic aorta arteries.

However, swimming physical training promoted increase of the tunica media of the left common carotid artery. Similar data have been demonstrated by Maux et al.<sup>(25)</sup> using the left common carotid artery of malnourished rats in the gestational and neonatal phases with hypoprotein diet which performed swimming training during eight weeks. On the other hand, the study by Tanaka et al.<sup>(37)</sup> did not demonstrate differences in the thickness of the arterial wall of the

common carotid in young (18-37 years), adults (38-57 years) and older (58-77 years) sedentary individuals and who have practiced regular physical training for three months. These authors attribute the lack of differences to the intensity of the used training protocol. Aerobic physical training works as a stimulus to the proliferation of endothelial progenitor cells and of straight muscle fibers, leading to increase in the endothelial and muscular layers of the artery, and can result in increase of its thickness<sup>(26)</sup>. Moreover, the present study used animals in aging process, which are more sensitive to present increase of thickness of the arterial wall.

It is believed that the natural aging process associated with nutritional aggressions may promote increase in stiffness and thickness of the arterial wall. Such alterations may lead to reduction of luminal diameter of some arterial vessels<sup>(38)</sup>. Conversely, the present study observed increase in luminal diameter of the thoracic aorta artery in the malnourished animals which practiced training compared with the sedentary malnourished animals. Maux et al.<sup>(25)</sup>, also using swimming as physical training, observed increase in the diameter of left common carotid artery in malnourished animals. Huonker et al.<sup>(20)</sup> obtained different results concerning the luminal diameter of different arterial vessels: while the aortic arch and the abdominal aorta in trained and non-trained athletes did not present differences, the subclavian artery presented wider diameter in the dominant limb of athletes from tennis modality.

The tunica media of the muscular arteries is predominantly constituted by straight muscular cells, with scattered elastic membranes and few collagen fibers<sup>(38)</sup>. Due to this display, the arterial wall would be more prone to alterations in its lumen caused by the alterations in the tonus of the straight muscle cells of the tunica media according to the variation in the demand flow of a given organ, such as the skeletal muscle during training<sup>(20)</sup>. Moreover, since the arterial wall in malnourished animals is normally thinner than in normonourished animals, it would be more vulnerable to distension and consequently, increase of demand promoted by the exertion resulting from physical training could cause increase in the vessel diameter. This fact could explain the increase in luminal diameter of the thoracic aorta artery in the malnourished animals submitted to physical training with moderate intensity observed in the present study. We speculate that during swimming training the animals use more the lower limbs, and need greater blood flow for this region and thus can cause more pressure on the thoracic aorta walls and increase in the luminal diameter of this artery.

The nutritional aggression occurred during the lactation period was efficient in partly inducing alterations in the structure of the arterial wall, which remained during the entire life of the animals. However, aerobic physical training with swimming in later phases of the malnourished animals lives during lactation was partially a factor which can contribute to revert the alterations caused by malnutrition since exercising promotes increase of luminal diameter of the thoracic aorta. Nevertheless, it was not able to revert the structural alterations derived from malnutrition and the aging process on the horizontal aorta artery wall.

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All authors have declared there is not any potential conflict of interests concerning this article.

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