

Nandrolone Decanoate Increases the Left Ventricular Wall but Attenuates the Cavity Increase Caused by Swimming Training in Rats



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ABSTRACT

Anabolic androgen steroids (AAS) are drugs synthesized from testosterone. Their anabolic action is mainly due to increased synthesis and reduced degradation of muscle proteins. The purpose of this study was to investigate the effects of swimming training associated to nandrolonedecanoate treatment on the blood pressure, the myocardial dimensions, vascular reactivity. Forty Wistar male rats, aged 60 days, were divided into 4 groups (n = 10): sedentary (SN), sedentary treated (ST), trained (TN) and trained treated (TT). TN and TT animals performed a swimming training during 12 weeks and ST and TT animals received weekly nandrolonedecanoate (15mg/kg). The heart and testicles were removed and weighted. The left ventricular diameter (LVD) and left ventricular wall thickness (LVWT) had been measured with an electronic pachymeter. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was weekly measured, while the mesenteric arteries vascular reactivity was studied for its response to noradrenaline. There were no alterations in the heart weight, but the LVD increased ($p < 0.05$) in TN rats, while the LVWT increased ($p < 0.05$) in ST and TT rats, both in relation to SN. Testicle weight decreased ($p < 0.05$) in the ST and TT animals in relation to SN. There was no alteration in blood pressure, neither in vascular reactivity. It was concluded that swimming training increased the left ventricular diameter, while nandrolonedecanoate treatment increased mainly the left ventricular wall thickness, suggesting concentric hypertrophy.

Keywords: physical exercise, anabolic steroids, blood pressure, cardiac muscle.

INTRODUCTION

Anabolic androgen steroids (AAS) are drugs synthesized from testosterone and, likewise, present effects which stimulate the protein anabolism, besides promoting androgen action. Their anabolic action is mainly due to the synthesis increase and reduction in degradation of the muscle proteins^(1,2).

AAS are used in medical clinics as well as with the purpose to improve physical performance of individuals submitted to physical training. However, the AAS non-therapeutic use in humans is related to many health problems⁽³⁾. Chronic treatment with high doses of AAS causes reduction in the antioxidant enzymes activity induced by exercise, and, consequently, reduces the cardioprotective mechanisms during an ischemia⁽⁴⁾.

Endurance training caused physiological hypertrophy of the left ventricle in the cardiovascular system of humans, which was associated with increase of the cavity diameter⁽⁵⁾, while resistance training produced concentric hypertrophy⁽⁶⁾. AAS reduced complacence of the left ventricle with no alteration in the cardiac contrality of rats⁽⁷⁾, and their simultaneous administration with training increased collagen concentration on the wall of the right ventricle in dogs⁽⁸⁾.

Physical training is known to be an efficient means used in the regulation of the blood pressure (BP) and peripheral vascular resistance⁽⁹⁾, while the treatment with nandrolone decanoate may reduce reactivity of the thoracic aorta in rabbits⁽¹⁰⁾. However,

increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) was verified in individuals submitted to high AAS doses^(11,12).

There is massive controversy concerning the physical training benefits when associated with the use of anabolic steroids, as well as when the AAS are independently used, especially when referring to their effects on the heart and its dimensions^(3,5). The physiological alterations provided by physical training may be more or less evident, depending on its kind, duration, frequency, exercise intensity and also on the individual characteristics^(9,13).

Thus, the AAS effects depend on the kind, dose, treatment duration as well as drug administration, besides being related to the user age and performance level and varies according to the animal species to which they have been administered. Therefore, this investigation tries to study the effects of the aerobic swimming training and the androlone decanoate on the heart weight, cardiac dimensions, blood pressure and reactivity of the mesenteric artery of rats.

MATERIAL AND METHODS

Animals

40 male Wistar rats (219 ± 4g), from the Animal Facility of the Federal University of Maranhão were used. The animals were kept in standard boxes, in a room with mean temperature of 20°C under

standard illumination conditions (12:12 hours light/dark cycle), with free food and water access and were randomly divided in four groups: trained and treated with nandrolonedecanoate (TT), trained which received the vehicle (TN), sedentary and treated with nandrolone decanoate (ST) and the sedentary group which received the vehicle (SN). This study was carried out according to the guidelines established for the use of animals in research, approved by the Ethics Committee of the State University of Maranhão under the number 22/05.

Physical training and steroid treatment

The swimming training protocol lasted 12 weeks and was carried out in a 1m x 1m x 0.5m clear glass swimming pool with frequency of five times a week. On the first week the animals were placed in the pool with a small quantity of water for adaptation, while the sessions' duration was increased in five minutes at each week until reaching 60 minutes of training.

The animals were weekly weighed on a digital scale. Nandrolone decanoate (Deca-Durabolin) subcutaneous injection in the dose of 15mg/kg was administered during the 12 swimming training weeks, before the last session of each week. The drug was diluted in vegetable oil (vehicle) and administered to the animals from groups TT and ST, while the animals from the untreated groups (TN and SN) received the volume corresponding to the vehicle.

Blood pressure determination

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was evaluated twice a week, during seven weeks, by the non-injury method⁽¹⁴⁾, in which the rats were previously warmed-up during 10 minutes at 45°C and placed in contensors to the pressure cuff and the piezoelectric crystal (Korotkoff), for recording of the arterial pulse in electro sphygmograph of one polygraph Norcotrace 40.

Evaluation of the mesenteric artery reactivity

The animals were anesthetized with ethyl ether 48 hours after the protocol end. The mesenteric arteries were dissected in a ring shape (0.5cm long) and were carefully placed on stainless steel threads (50µm diameter), suspended on an isolate organ chamber (5.0ml), containing Krebs solution (pH 7.4; 37°C) and balanced with carbogenic mixture (CO₂ 5% and O₂ 95%). The tension variations of the preparations were recorded on a Narcotrace 40 poligraph (Narco Bios systems). The rings of the mesenteric artery were initially balanced for one hour under 1.0g tension and washed every 10 min. The concentration-response curves for the noradrenaline (1nM to 1µM) were performed in the mesenteric arteries of the animals from the many experimental groups after preparations stabilization^(15,16).

Body weight and organs determination

After sacrifice, the heart was removed, fixed in formalin at 10% and after fixing, it was weighed on a high precision digital

scale (Bel Engineering). The diameter of the left ventricle cavity (LVD) was measured in the laterolateral direction, in the biggest circumference, while the left ventricle wall thickness (LVWT) was measured using a *Stainless Hardener* digital pachymeter similarly to what has been described by Pfeffer *et al.*⁽¹⁷⁾.

STATISTICAL ANALYSIS

The results were submitted to analysis of variance (two-way ANOVA) and the means compared by the *Student's Newman-Keulstest* of multiple comparisons, where significant values were $p \leq 0.05$. The values are presented in means \pm SEM.

RESULTS

The results showed that the nandrolone decanoate reduced body weight of the ST animals compared with the others, while training increased weight in the TN animals compared with the SN ones (table 1). Testicle weight was reduced by the steroid in the ST and TT groups compared with the SN group (table 1). There was no significant difference in the heart weight; however, the left ventricular cavity increased ($p < 0.05$) only in the trained animals (TN) and the ventricular wall thickness increased in the treated sedentary animals (ST) and trained (TT) animals compared with the sedentary untreated (table 1).

Heart weight presented in percentage values of the body weight increased ($p < 0.05$) in the ST animals compared with the others, while testicle weight, corrected by the body weight, decreased ($p < 0.05$) in the treated trained (TT) and sedentary treated with nandrolone decanoate (ST) animals compared with the sedentary untreated ones (figure 1).

SBP was not altered by the steroid neither the treatment in any of the groups. On the other hand, DBP of the animals from groups TT and TN reduced ($p < 0.05$) on the fourth week of observation, compared with groups SN and ST (figure 2). Vascular reactivity was not significantly altered by training or nandrolone decanoate when independently applied (figure 3).

Table 1. Body weight (BW), testicle weight (WTest), heart weight (Wheart), left ventricle diameter (LVD) and left ventricular wall thickness(LVWT) of the animals from the sedentary (SN), sedentary treated (ST), trained (TN) and trained and treated (TT) groups after 12 weeks of swimming physical training and/or nandrolonedecanoate treatment.

Groups	BW (g)	Wtest (g)	Wheart(g)	LVD (mm)	LVWT mm)
SN	336 \pm 7	1.73 \pm 0.03	1.09 \pm 0.05	2.48 \pm 0.19	2.56 \pm 0.11
ST	305 \pm 6*	1.32 \pm 0.04†	1.21 \pm 0.04	2.69 \pm 0.21	3.03 \pm 0.13#
TN	357 \pm 4#	1.60 \pm 0.04	1.07 \pm 0.03	3.49 \pm 0.13#	2.76 \pm 0.16
TT	346 \pm 7	1.34 \pm 0.02†	1.09 \pm 0.02	3.32 \pm 0.38	3.11 \pm 0.13#

n = 10, mean values (\pm SEM). * $p < 0.05$ concerning SN, TN and TT; # $p < 0.05$ concerning SN; † $p < 0.05$ concerning SN and TN.

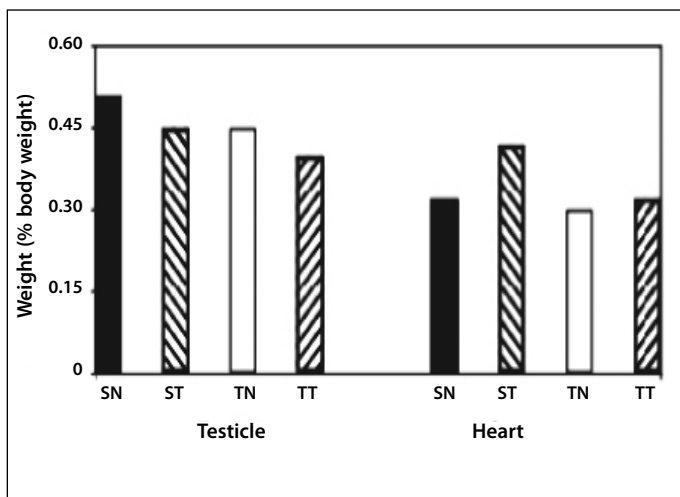


Figure 1. Weight percentage (mean \pm SEM) of the testicle and heart compared to the body weight obtained in the animals from the sedentary (SN), sedentary treated with nandrolone decanoate (ST), trained (TN) and trained and treated (TT) experimental groups, after 12 weeks of swimming physical training and/or nandrolone decanoate treatment. $n = 10$. * $p < 0.05$ concerning SN and TT. # $p < 0.05$ compared to the remaining groups.

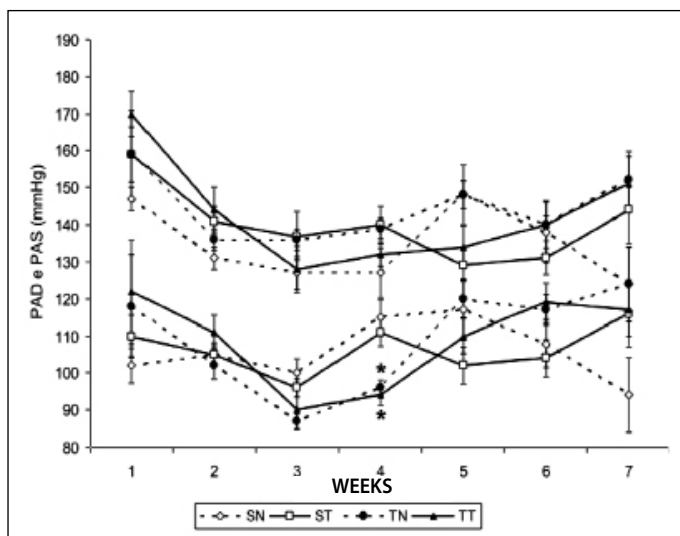


Figure 2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) during seven weeks of protocol, of the animals from the sedentary (SN), sedentary treated with nandrolone decanoate (ST), trained (TN) and trained and treated with nandrolone decanoate (TT) experimental groups. $n = 10$, mean values (\pm SE). * $p < 0.05$ of DBP on the fourth week of protocol.

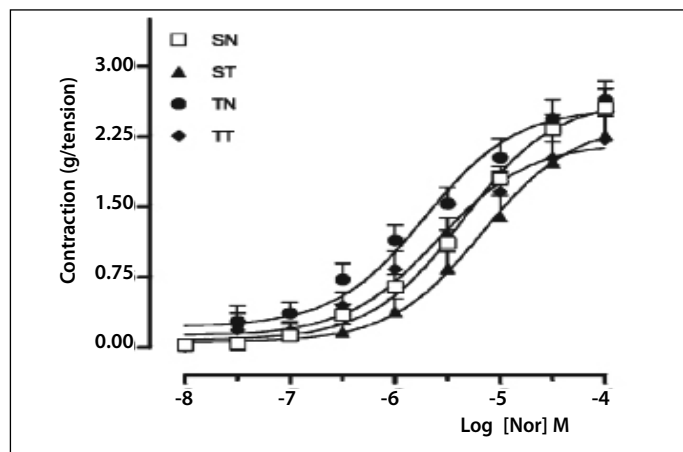


Figure 3. Mesenteric arteries reactivity to noradrenaline (NOR) in sedentary (SN), sedentary treated with nandrolone decanoate (ST), trained (TN) and trained and treated with nandrolone decanoate (TT) rats during 12 weeks, $n = 10$, the symbols and vertical lines represent the mean \pm SEM.

DISCUSSION

This study demonstrated that the nandrolone decanoate increased heart weight and the left ventricular wall, while aerobic training especially increased the cavity. However, training and steroid independently, as well as the association of both, did not cause BP alteration nor in the vascular activity of the mesenteric artery.

Significant reduction ($p < 0.05$) of testicular mass was observed in the animals treated with nandrolone decanoate, both in absolute values and (table 1) and in values related body weight (figure 1), when compared with the SN animals. This decrease makes the androgen effect of the drug very evident in the treated animals, which is certainly associated with the nandrolone decanoate exogenous administration, which causes dysfunction in the endogenous production of the gonadotropic hormones (FSH and LH) as well as testosterone⁽¹⁸⁾.

The treatment with testosterone reduced body weight in rats⁽¹⁹⁾. In our study, despite the significant reduction (9%) in body weight of the ST animals compared with the other animals, the nandrolone decanoate effect on the body weight decrease was not every evident (table 1), since there was not significant alteration between the trained animals (TN versus TT). However, body weight was increased by training when we compared the trained animals with the sedentary ones (TN versus SN). Such reduction in body weight caused by the steroid may be related with the reduction in food ingestion during the night period, since the rats treated during 14 days with different doses of nandrolone decanoate (5, 15 and 45mg/kg) presented lower weight gain⁽²⁰⁾. A similar result concerning body weight gain of rats caused by training was noted by Woodiwisset *al.*⁽²¹⁾. In the present body weight gain among trained rats is certainly related with increase in lean mass, since data (not published) from our laboratory demonstrated clear reduction in body fat of the animals after physical training.

Training and steroid treatment did not significantly alter the heart weight (table 1), although the increase observed in the ST group compared with the SN animals (10%) and TN (11%) suggests that there could have been concentric cardiac hypertrophy, an alteration which despite not being statistically different, is relevant from the physiological point of view. This increase is corroborated when the heart weight is related to body weight (figure 1), since in this situation the ST animals present higher values (30%) than the SN ones. Nevertheless, this difference was not observed between the trained animals (TN versus TT).

In a study carried out by Yeater *et al.*⁽²²⁾ there was no difference on the ventricular wall, nor on the interventricular septum in individuals who used AAS compared with others who performed resistance training. However, the left ventricular mass was higher in individuals who used the drugs than in the trained ones. Moreover, this same result was verified when the ventricular mass was corrected by the body weight. Pereira Júnior *et al.*⁽²³⁾ have also verified in treated rats that there was not significant alteration in the heart weight. However, when the heart weight is considered in values relative to the body weight, both Pereira Júnior *et al.*⁽²³⁾ and Woodiwisset *et al.*⁽²¹⁾ found results similar to

ours, using different doses. In addition to that, Nahrendorf *et al.*⁽¹⁹⁾ verified increase in the left ventricle mass in rats treated with testosterone during 10 weeks.

The diameter of the left ventricular cavity was increased by training; however, this increase of 29% was only observed in the TN animals compared with the SN ones, while increase in the TT animals compared with the ST ones was not significant. Increase in the ventricular cavity, without corresponding increase in the wall thickness, verified in the trained and untreated animals, suggests a cardioprotector effect caused by training. Hypertrophy of the left ventricle, caused by physical training, is associated with increase of the cavity size⁽⁵⁾.

The steroid increased the wall thickness in the treated animals, both sedentary and trained. The cardioprotector effect of the aerobic training is again observed when we verify that the ventricular cavity of the TT animals is relatively higher than in the ST animals. In an echocardiographic study⁽²⁴⁾, the AAS increased the left ventricular wall thickness of elite athletes in more than 13mm, while mean increase in the cavity diameter was of 16mm. AAS stimulating effects on these cardiac dimensions have also been verified, including when compared with individuals who performed moderate resistance training⁽²²⁾.

AAS cause stiffness on the cardiac muscle in trained and sedentary rats⁽²¹⁾, an alteration which may be attributed to the myofibrillar destruction. In our study the main training effect was the increase of the left ventricular cavity, while the nandrolone decanoate effect occurred more in increasing the thickness of the ventricular wall.

Since SBP and DBP significant alterations in humans have already been reported with only three weeks of moderate training⁽²⁵⁾, blood pressure in the present study was assessed only during the first seven weeks. During this period there was no alteration in the SBP between groups; however, the DBP of the TT and TN groups was reduced on the fourth week. Despite being transitory, this reduction evidenced the physical training effect, since only the animals from the trained groups presented reduced DBP, an effect which was not verified in the ST group. Nevertheless, since this reduction only occurred on the fourth week of the protocol, it is not possible to state that this was an effect specific to training.

In a meta-analysis study in adult humans (47 years), Fangard⁽⁹⁾ verified that endurance training performed three days/week with 40-minute duration reduced blood pressure. Significant blood pressure reduction was also reported by Wiley *et al.*⁽²⁵⁾ in individuals submitted to moderate isometric training. Further studies, also with humans, verified SB increase when AAS were associated with physical training^(12,18). The mechanism through which the drug induces BP increase is not known yet; however, there is a hypothesis that the high level of 11-deoxy corticosterone may be involved⁽²⁶⁾, increase which must be a consequence of the direct inhibition of the 11- β -hydroxylase enzyme by the androgen. Furthermore, the androgens can also increase renin secretion by the kidneys, a fact which would also lead to BP increase⁽¹¹⁾.

Spontaneously hypertensive rats when treated with nandrolone (20mg/kg) during six weeks presented SBP increase compared to the control group⁽²⁷⁾. Lenders *et al.*⁽²⁸⁾ and Friedlet *et al.*⁽²⁹⁾ verified acute BP increase in individuals who used AAS, while Hartgens *et al.*⁽³⁰⁾ did not observe BP alteration in athletes who used AAS supra physiological doses for a period longer than 16 weeks. The majority of the results is conflicting concerning SBP and DBP in experiments with anabolic steroids and physical training due to the diversity of variables which are involved in the experiment.

In order to evaluate the physical training effect and/or nandrolone decanoate treatment in the arterial responsiveness, the mesenteric artery reactivity to noradrenaline was analyzed. There was not alteration in the responsiveness of this artery to the adrenergic agonist. The nandrolone treatment in rabbits (12 weeks) produced small or none reduction of response induced by agonists such as noradrenaline, 5-hydroxytryptamine and angiotensin II in mesenteric artery. On the other hand, in thoracic aorta, the nandrolone treatment reduced the contraction reduced by the noradrenaline and especially by 5-hydroxytryptamine and angiotensin II⁽¹⁰⁾.

However, in the present study, although there has been a transitory DBP reduction in the trained rats (TN) and trained and treated with nandrolone decanoate rats (TT), it was not possible to conclude whether it was really due to an alteration in responsiveness of the mesenteric arteries.

The physical training effects on the cardiovascular system as well as other tissues, has been well evidenced in many studies with animals and humans. However, studies^(18-23,31,32) on the influence of the AAS use on these variables, especially concerning the cardiovascular system, have presented different results since the effect of these drugs depend on, for instance, the kind of anabolic steroid, dose, period of use and administration means of the drug, besides the species, age, sex, training level and other variables associated with the animal.

It was observed in this study that swimming training with nandrolone decanoate did not alter BP or mesenteric artery responsiveness. Nevertheless, training increased body weight, probably due to the increase of lean mass, and presented positive effects on the cardiac dimensions, increasing mainly the left ventricle cavity diameter. The anabolic effect of the nandrolone decanoate was a sign to the onset of concentric cardiac hypertrophy, with increase of wall thickness, without corresponding increase in the size of the left ventricular cavity.

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