Heart Reaction to Nandrolone Decanoate plus Two Different Intensities of Endurance Exercise: Electrocardiography and Stereological Approach

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Abstract

Background: Regarding the negative effects of androgenic anabolic steroids (AASs) abuse, the long-term effect of nandrolone decanoate with/without two intensities of endurance exercise training was investigated on heart tissue and electrocardiogram (ECG) in rats.

Methods: The experiment was conducted on 63 male Wistar rats, which were 4 months old. The rats were divide into groups of control (CTL), arachis oil as nandrolone solvent (Ar), nandrolone (Nan) (received a dose of 5 mg/kg twice/week for 8 weeks), mild swimming exercise training (mEx), severe exercise (sEx), sEx + Nan, mEx + Nan, mEx + Ar, and sEx + Ar. During the 8 weeks of swimming exercise, the animals carried dumbbells equivalent to 2% of their body weight, which was gradually increased and reached 5% and 8% in the 6th week for mild and severe exercises, respectively. Finally, ECGs recording and samplings were done.

Findings: Both types of exercise, without nandrolone, significantly reduced the heart rate and increased the RR interval of ECG. Nandrolone alone and with mild (P < 0.050) and intense exercise (P < 0.010 vs. CTL) increased the left ventricular hypertrophy (LVH) index. Left ventricular volume was significantly higher in the Nan group (P < 0.050) compared to the CTL group and all exercise groups (P < 0.010) compared to the Nan, CTL, and Ar groups. Myocytes volume increased in the presence of both of mild and high-intensity exercise plus nandrolone (P < 0.050 vs. CTL and Ar groups). Hydroxyproline value of the heart was significantly higher in the nandrolone group compared to all other groups (P < 0.001). Exercise prevented the effect of nandrolone on hydroxyproline.

Conclusion: Both levels of swimming exercise prevent the effect of nandrolone on the production of hydroxyproline and fibrotic cardiac remodeling.

Keywords: Nandrolone decanoate; Exercise; Electrocardiography; Histology

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Heart Response to Exercise plus Nandrolone

Introduction

Nandrolone, 19-Nortestosterone, is a synthesized androgenic anabolic steroid (AAS) that is derived from testosterone. In addition to androgenic properties, AASs have significant anabolic activity. These properties enhance the motivation for the use of these agents among athletes. However, at high doses, androgenic and anabolic activities of these agents are accompanied with harmful effects on the mammalian body.

Regular appropriate exercise has been proven to be one of the cheapest and most effective interventions for promoting cardiovascular health. Exercise can improve the resistance of the heart against ischemia-reperfusion injury and can protect the mechanical function of the heart during post-ischemia-reperfusion periods in animals. Regular physical exercise can reduce mortality by reducing cardiovascular risk factors such as plasma cholesterol, hypertension, overweight, and intolerance to glucose.

Several studies have associated AASs alone or along with exercise with cardiovascular side effects such as wall thickness, ventricular hypertrophy associated with diastolic dysfunction, cardiac arrhythmias, and sudden death. Previously we reported that the combination of exercise and nandrolone decanoate increases the risk of lethal ventricular arrhythmia. The interpretation of the results of post-mortem tissue autopsy, and histopathological and toxicological studies of AASs users are difficult and no exact conclusions can be made. Because they are associated with many limitations such as case series and small sample volume, variety in the type, form, dose, and frequency and period of use of steroids, and commonly, the use of various steroid-accessory drugs. Therefore, as the main objective of this study, we explored and compared the chronic effects of nandrolone decanoate along with low and high intensity endurance exercise on heart morphology and electrocardiogram (ECG) in an empirically controlled study without the above confounding factors.

Methods

The experiment was done based on the Guide for the Care and Use of Laboratory Animals (ethics committee permission of Kerman University of Medical Sciences, Kerman, Iran; No: K/94/615). The experiment was conducted on 63 male rats which were 4 months old, weighed 220–270 g, were kept under normal environmental conditions, had free access to water, and were fed normal rat chow. They were divided into the 9 groups of (a) sedentary or control (CTL), (b) sedentary vehicle-treated (Ar), which received arachis oil as nandrolone decanoate solvent; (c) sedentary nandrolone-treated (Nan), which was treated with nandrolone decanoate, (d) low intensity exercise (mEx), (e) low-intensity trained arachis oil-treated (mEx + Ar), which received arachis oil plus low-intensity exercise, (f) low-intensity trained nandrolone-treated group (mEx + Nan), which underwent nandrolone decanoate and low-intensity exercise, (g) high-intensity exercise trained (sEx), (h) high-intensity trained vehicle-treated (sEx + Ar), which received arachis oil along with high-intensity exercise, and (i) high-intensity trained nandrolone-treated group (sEx + Nan), which were treated with nandrolone decanoate and high-intensity exercise. Nandrolone decanoate (Gedeon Richter, Hungary) was administered through intramuscular injection (5 mg/kg) twice a week for 8 weeks, and its volumetric equivalent (0.2 ml/kg) was considered for arachis oil (Henry Lamotte, Germany). The selected dose of nandrolone is comparable to the dosage consumed by heavy AAS abusers.

Swimming exercise training: The swimming exercise training was conducted based on the protocols reported by Joukar et al. The rats swam in a pool containing warm water (30–32 °C) with a depth of 50 cm. The exercise period was 8 weeks, 5 days per week at 60-minute intervals. On the first day, the training started with 20 minutes of swimming. It was extended 10 minutes every following day, so that on the last day of the first week the swimming period was 60 minutes. During the other weeks, the duration of the exercise schedule was constant (60 minutes/day for 5 days/week); however, while swimming, the animals also carried dumbbells equivalent to 2% of their body weight. With gradual increase in weight during study, the low-intensity trained rats carried dumbbells weighing 5% of their body weight on the sixth week and the dumbbell was kept attached to them constantly from that point on. The high-intensity swimming exercise program was similar to the low-intensity exercise protocol exception in terms of the weight of the caudal dumbbells. Namely, the
weight of the dumbbells was increased gradually from 2% to 8% of their body weight between the 2nd and 6th weeks of the experiment and was kept constant from then onwards. To adjust the weight of the dumbbells based on body weight variations, all animals were weighed weekly. Each tired animal that could not continue the exercise was brought out from the water and, after a 2-minute rest, was returned back into the water.13 Animals that could not continue the exercise protocol were eliminated from the study. Sedentary rats were placed in the pool for 10 minutes two times per week to simulate the pool and water stress among groups.13,14

**ECG recording and hypertrophy and collagen indices measurement:** Finally, 24 hours after the end of the experiment, the animals were weighed and were anesthetized with sodium thiopental (Sandoz, Austria) (50 mg/kg, IP). Limb lead II of the ECG was recorded by the connection of animals to the PowerLab Physiograph system. Moreover, the heart rate, RR interval (the interval time between two consecutive R waves of ECG), the PR interval (the interval time from the P-wave onset to QRS complex onset), the JT interval (the interval from junction point J to T wave end), and QT interval (the earliest Q or R-wave onset to the end of T wave) of the basal ECG were determined by a mean of 2 minutes of ECG recorded strip. To prevent the dependence of QT interval on heart rate, corrected QT (QTc) interval was measured using Bazett’s formula normalized as

$$QTc-B = QT / (RR/f)^{1/2},$$

where RR is R–R interval and f = 150 ms.19 Then, the animals were sacrificed and the heart was harvested, rinsed in 1 × PBS, and weighed. Furthermore, a small piece of the heart muscle was frozen and its hydroxyproline value was measured using a standard kit (Shanghai Crystal day Biotech Company, China) and considered as an index of heart muscle collagen. The left ventricle (LV) of the heart was removed, weighed, and the ratio of the left ventricular weight (mg)/body weight of animal (g) was considered as the left ventricular hypertrophy (LVH) index.

**Heart stereological study**

A) Estimation of the volume of the cardiomyocytes and vessels: The volume of LV of the heart was estimated using Scherle’s method.20 In brief, the LV was immersed in a jar filled with isotonic saline and weighted. The volume was calculated by the difference in the weight of the filled jar before and after ventricular immersion by the specific gravity of isotonic saline (1.0048 g/cm³). Then, the LV was divided into 8-12 isotropic uniform random (IUR) sections generated using the orientator method21 and embedded in paraffin. Sections of 4 μm thickness were cut and stained with Heidenhain’s AZAN trichrome stain. The point-counting method, as described previously, was used to estimate the volume density of the myocardium and vessels.20 It consists of an overlying grid of points upon the images of the ventricle sections viewed on the monitor. Then, the volume density “Vv (structure/ref)” of these mentioned parameters were obtained using the following formula: Vv (structure/ref) = P(structure)/P(ref) where “P(structure)” and “P(ref)” represent the total number of the points hit the structures of interest (myocytes and capillaries) and the LV sections, respectively. The total volume of each of the parameters was estimated by multiplying the volume density of the desired parameter by the last ventricular volume (Figure 1).20,21

![Figure 1. Point-counting method to estimate the volume density of the myocytes and vessels (The number of the points hit the desired structure was divided by the total number of points.)](http://ahj.kmu.ac.ir)

The results were expressed as means ± standard error (SE). The normality of data was analyzed using the Shapiro-Wilk test. Comparisons were made using the analysis of variance (ANOVA) followed by Tukey’s post hoc test. All P values of < 0.05 were considered statistically significant.

**Results**

The hypertrophy index of LV significantly
increased in the Nan group in comparison with the CTL and Ar groups (P < 0.050). Low-intensity exercise alone or in combination with nandrolone had no significant additional effect on LVH index; however, when high-intensity exercise was combined with nandrolone, the hypertrophy index was more enhanced (P < 0.010 vs. CTL and Ar groups) (Figure 2).

**Figure 2.** The left ventricular hypertrophy (LVH) index in different animal groups
LVH index = Ratio of left ventricular weight (mg)/body weight of animal (g)
CTL: Control; Ar: Animal group which received vehicle (arachis oil); Nan: Animal group which received nandrolone decanoate 5 mg/kg/day two times each week; mEx: Animal group which underwent mild swimming exercise; mEx + Ar: Animal group which received arachis oil and mild swimming training; mEx + Nan: Animal group which received nandrolone decanoate and mild swimming training; sEx: Animal group which underwent severe swimming exercise; sEx + Ar: Animal group which received arachis oil and severe swimming training; sEx + Nan: Animal group which received nandrolone decanoate and severe swimming training
*P < 0.050 and **P < 0.010 vs. CTL and Ar groups, Values are mean ± SE, n = 6-7

Hydroxyproline value was significantly higher in the nandrolone group compared to all other groups (F(8, 49) = 37.3, P < 0.001). Low-intensity and high-intensity swimming exercise diminished the effect of nandrolone on the amount of this amino acid in the heart, so that the value of this marker in the mEx + Nan and sEx + Nan groups had no significant difference with the control, Ex, and Ar groups (Figure 3). Left ventricular volume was greater in the nandrolone group (P < 0.050) compared to the CTL group and all exercise training groups (F(8, 36) = 8.99, P < 0.010) compared to the CTL, Ar, and Nan groups (Figure 4).

**Figure 3.** The hydroxyproline value as the index of heart tissue collagen in different experimental groups
CTL: Control; Ar: Animal group which received vehicle (arachis oil); Nan: Animal group which received nandrolone decanoate 5 mg/kg/day two times each week; mEx: Animal group which underwent mild swimming exercise; mEx + Ar: Animal group which received arachis oil and mild swimming training; mEx + Nan: Animal group which received nandrolone decanoate and mild swimming training; sEx: Animal group which underwent severe swimming exercise; sEx + Ar: Animal group which received arachis oil and severe swimming training; sEx + Nan: Animal group which received nandrolone decanoate and severe swimming training
***P < 0.001 vs. all others groups, Values are mean ± SE, n = 6-7

Moreover, myocytes volume only increased with nandrolone plus both mild and high-intensity exercise (F(8, 36) = 3.27, P < 0.050) compared to the CTL and Ar groups (Figure 5) and vessels volume did not show significant differences among different groups (Figure 6).

**Figure 4.** Left ventricular volume in the studied animal groups
CTL: Control; Ar: Animal group which received vehicle (arachis oil); Nan: Animal group which received nandrolone decanoate 5 mg/kg/day two times each week; mEx: Animal group which underwent mild swimming exercise; mEx + Ar: Animal group which received arachis oil and mild swimming training; mEx + Nan: Animal group which received nandrolone decanoate and mild swimming training; sEx: Animal group which underwent severe swimming exercise; sEx + Ar: Animal group which received arachis oil and severe swimming training; sEx + Nan: Animal group which received nandrolone decanoate and severe swimming training
Values are mean ± SE, n = 6-7, *P < 0.050 vs. CTL group, **P < 0.010 vs. CTL, Ar, and Nan groups
Nandrolone alone had no significant effect on ECG parameters. However, in the exercise training groups, the RR interval was longer ($F_{(8, 58)} = 4.07$, $P < 0.01$ in sEx and $P < 0.050$ in other training groups vs. CTL group) and heart rate was lower ($F_{(8, 58)} = 4.62$, $P < 0.010$ vs. CTL group) and nandrolone had no significant effect on the other variables (Table 1).

Table 1. The effects of nandrolone, mild, and high-intensity endurance exercise and their combination on the heart rate and PR, RR, QRS, and QTc intervals of the electrocardiogram (ECG)

| Groups         | RR interval (ms) | HR (Beat/Min) | PR interval (ms) | QTc-n interval (ms) | QTc interval (ms) | QRS interval (ms) |
|----------------|------------------|---------------|------------------|---------------------|-------------------|-------------------|
| CTL            | 148 ± 4          | 407 ± 9       | 45.3 ± 1.1       | 54.6 ± 1.6          | 144 ± 4.6         | 18.1 ± 0.6        |
| Ar             | 159 ± 2          | 377 ± 5       | 45.7 ± 2.0       | 53.3 ± 3.0          | 133 ± 15          | 16.4 ± 1.0        |
| Nan            | 159 ± 3          | 378 ± 7       | 44.8 ± 1.7       | 54.6 ± 2.2          | 141 ± 6           | 17.9 ± 0.8        |
| mEx            | 173 ± 9*         | 354 ± 18**    | 43.3 ± 2.0       | 52.6 ± 4.1          | 145 ± 7           | 16.9 ± 1.5        |
| mEx + Ar       | 169 ± 2*         | 355 ± 4**     | 46.5 ± 2.1       | 64.6 ± 3.4          | 167 ± 9           | 19.2 ± 2.0        |
| mEx + Nan      | 179 ± 8*         | 338 ± 14**    | 46.7 ± 0.9       | 52.7 ± 3.9          | 136 ± 10          | 16.2 ± 1.0        |
| sEx            | 183 ± 7**        | 331 ± 13**    | 47.0 ± 1.0       | 56.6 ± 2.1          | 146 ± 5           | 17.9 ± 0.5        |
| sEx + Ar       | 160 ± 7*         | 366 ± 12**    | 43.8 ± 1.2       | 56.2 ± 2.7          | 145 ± 7           | 19.3 ± 1.3        |
| sEx + Nan      | 173 ± 4*         | 354 ± 6**     | 47.7 ± 1.9       | 61.1 ± 1.9          | 153 ± 4           | 17.3 ± 1.6        |

Nandrolone alone had no significant effect on ECG parameters. However, in the exercise training groups, the RR interval was longer ($F_{(8, 58)} = 4.07$, $P < 0.01$ in sEx and $P < 0.050$ in other training groups vs. CTL group) and heart rate was lower ($F_{(8, 58)} = 4.62$, $P < 0.010$ vs. CTL group) and nandrolone had no significant effect on the other variables (Table 1).

Discussion

The present study was conducted to assess the effect nandrolone along with two different levels of endurance exercise on ECG parameters and structural elements of rat heart.
The CTL results showed that nandrolone both alone and along with low-intensity and high-intensity endurance exercise increased the LVH index. The volume of the left ventricular muscle increased in nandrolone group and all exercise groups with, and without nandrolone; however, myocytes volume only enhanced in the presence of exercise plus nandrolone. Moreover, hydroxyproline as the index of collagen tissue of the heart increased following nandrolone treatment, but low-intensity and high-intensity exercise prevented this increase.

The findings regarding LVH are in line with previous human studies on athletes and bodybuilders who used high doses of AASs. In addition, varying degrees of myocardial fibrosis have been reported in human autopsy studies of AASs users. Video densitometry of myocardial texture of weightlifters showed that the ‘cyclic variation index’ of the interventricular septum and the left ventricular posterior wall was significantly lower in AASs users versus the control groups. This finding reflects a focal increase in myocardial collagen in AASs users, which could predispose them to cardiac arrhythmias. However, previous studies have shown that consumers are often unaware of the side effects of these drugs. In a case report, using cardiovascular magnetic resonance (CMR), myocardial scarring with severe LVH was observed in a patient with normal coronary arteries after long-term abuse of AASs. Animal studies have also provided further insights into the cardiac remodeling of AASs. In agreement with the present study, previous evidence revealed that nandrolone alone and independent of exercise training induces cardiac hypertrophy and increases the collagen index of the heart in rats. Interestingly, the cardiac hypertrophic effect of nandrolone was maintained or strengthened by both resistance and endurance training. However the increasing effect of nandrolone on heart collagen can be reinforced by resistance training and may be maintained or attenuated by endurance training; this also confirmed the present study findings. In this study, nandrolone consumption was associated with increase in left ventricular volume, but not cardiac myocytes volume. In addition, as noted above, the value of hydroxyproline increased in the presence of nandrolone. This may be the cause of the hypertrophic effect of nandrolone being pathologic and mostly originating from collagen deposition as also demonstrated by others. The nandrolone induced collagen deposition was attributed to increasing renin angiotensin system activity and pro-inflammatory cytokines/anti-inflammatory cytokines ratio. Collagen deposition can reduce the heart contractility and its compliance, and thus, lead to heart failure.

In addition, the strengthening of the heart hypertrophy index in the presence of nandrolone plus severe exercise confirmed the cardiac hypertrophy effect of high-intensity endurance training which has been reported in previous studies. It has been indicated that long-term swimming induced physiological cardiac hypertrophy through increasing the cardiac myocytes volume without increase in collagen tissue. However, many factors such as the intensity, duration, frequency, and mode of the exercise regimen affect exercise-induced cardiac hypertrophy. That in turn provides a reasonable explanation for the different impacts of the two levels of exercise in our study regarding cardiac hypertrophy. Apparently, a part of physiological LVH induced by swimming exercise is regulated by local renin-angiotensin system independent of the systemic renin-angiotensin system. Changing the expression of specific miRNAs targeting the PI3K/AKT/mTOR signaling pathway and its negative regulators has also been proposed. Moreover, exercise decreased the heart rate and increased the RR interval of ECG. However, nandrolone had no significant effect on ECG parameters. The results of the present study are in line with previous findings. For example, Bissoli et al. showed that long-term consumption of high doses of nandrolone had no significant effect on heart rate in rats. Similar findings were reported in other studies. Furthermore, in agreement with our findings, previous evidence confirmed that endurance exercise can increase RR interval, and hence, decrease heart rate. Chronic endurance exercise is associated with vagal tone and structural atrial remodeling. Exercise induced a reduction in the number of β-adrenergic receptors without any change in the number of muscarinic cholinergic receptors of the right atrial membrane that partly contributed to the bradycardic effect of exercise. In addition, exercise increases the stimulatory G-protein content of the heart that in turn reduces the maximal response to
sympathomimetic drugs such as isoproterenol.\(^{47,48}\) Moreover, intrinsic atrial adaptation, independent of autonomic nervous system receptors-mediated signals transduction mechanisms, is suggested.\(^{49}\)

**Conclusion**

In summary, the present study revealed the effects of two different endurance exercise intensities on heart histology and hypertrophy index and also on ECG as lengthening of RR interval and decreasing of heart rate. Nandrolone increased the cardiac hypertrophy effect of exercise through enhancing the tissue collagen, and both types of exercise changed the hypertrophy quality by increasing myocytes volume and decreasing collagen deposition. There was no significant difference in cardiac parameters between groups with different intensities of endurance exercise. However, the influence of high-intensity swimming training plus nandrolone, especially in the case of ventricular hypertrophy, was dominant.

**Conflict of Interests**

The Authors have no conflict of interest.

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چکیده
مقیده‌ها: با توجه به اثرات منفی سوء مصرف استروپلدیه‌های آنتروپلیک، اثر طولانی مدت ناندرولون دکانوات با و بدون دو سطح از شدت تمیز در موس‌های صحرا اثر بر سر فارگرفت.

ارجاع: جوکار سیاوش، بوسفنیا مهدیه، نادری بلدوجی ویدا، نصری حمیدرضا، رفیعی فروزان (1398) واکنش قلب به ناندرولون دکانوات همراه با دو شدت مختلف ورزش استقامتی: الکتروکاردیوگرافی و روش استریولوژیک. مجله اعتیاد و تحقیقات، شماره‌ی 189، صفحات 3-12.

مقدمه
هفته‌های ناندرولون همراه با ورزش سبک و شدید، حیات قلبی‌ای گردید. حیات قلبی ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح ناندرولون، دکانوات با و بدون دو سطح N

نتیجه‌گیری
هر دو سطح ورزش، از انسپنی ناندرولون بر تولید هیپرکوپرین پرولین و بار ساختنی فیبروزی قلب جلب‌گری می‌کند.

واژگان کلیدی: ناندرولون، دکانوات، ورزش، قلب، هیپرکوپرین، هیستولوژی

ایران

ملاحظه: با توجه به اثرات منفی سوء مصرف استروپلدیه‌های آنتروپلیک، اثر طولانی مدت ناندرولون دکانوات با و بدون دو سطح از شدت تمیز در موس‌های صحرا اثر بر سر فارگرفت.