Steroids xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Acute interruption of treatment with nandrolone decanoate is not sufficient to reverse cardiac autonomic dysfunction and ventricular repolarization disturbances in rats

Moacir Marocolo[a,*], Julio A. Silva-Neto[b], Octávio Barbosa Neto[c]

[a] Physiology and Human Performance Research Group, Department of Physiology, Institute of Biological Sciences, Federal University of Juiz de Fora, Juiz de Fora, Brazil
[b] "Paes de Carvalho" Laboratory of Biophysics of Heart, Department of Physiology, Federal University of Sergipe, Aracaju, Brazil
[c] Department of Sport Sciences, Federal University of Triângulo Mineiro, Uberaba, Brazil

ARTICLE INFO

Keywords:
Heart rate variability
Anabolic steroids
Cardiac autonomic control
Heart
Electrocardiographic ventricular parameters
QT dispersion
QT interval

ABSTRACT

Anabolic androgenic steroids are a class of synthetic compounds derived from testosterone, eventually used by athletes, to improve physical performance. However, anabolic steroids can also modify normal cardiovascular function. Thus, we investigated cardiac electrophysiological and autonomic abnormalities in rats, through a electrocardiographic variability protocol during and after interruption of administration of nandrolone decanoate (DECA) anabolic steroid. Twenty male Wistar rats (60–70 days old) received DECA (10 mg. kg^{-1} *i.m*) once a week or vehicle, during eight weeks. Electrocardiogram was recorded in conscious rats by a noninvasive method, and time and domain analysis of heart rate variability as well as electrocardiogram intervals (QTc / QTd) were performed. Body mass was lower in treated rats compared to control after 4th and 8th weeks, but not at the end of 14th week. QTc and QTd were longer in DECA group compared to control on 4th, 8th, 11th, but equal on 14th week. Cardiac autonomic dysfunction (vagal attenuation) was present on DECA group after 4th week and did not normalize after interruption of treatment. The animals of DECA group showed a correlation between attenuated parasympathetic modulation and increased correct QT interval. Our data allow us to conclude that long-term treatment with DECA impairs autonomic cardiac physiology, predisposing to cardiovascular risk and sudden death, and interruption of administration does not recovery the normality immediately.

1. Introduction

Anabolic androgenic steroids (AAS) are synthetic derivatives of the testosterone Wagman, Curry and Cook [1], often used to promote body growth effect, also enhancing strength, power, physical performance and muscular mass. More than three million people have used supra-physiologic doses of illicit AAS, including testosterone and its synthetic relatives, to gain muscle mass for athletics or personal appearance [2]. Nandrolone decanoate (DECA) is one of the mainly AAS are widely consumed by athletes and non-athletes due its relative low androgenic properties and great anabolic effects [3–5] that is related to dysfunction in physiology of the heart [6,7].

AAS action mechanism occurs through nuclear pharmacological receptor, when activated, promotes migration of it steroid-receptor complex from cytoplasm to nucleus, where transcriptional genic process happens to protein synthesis testosterone-induced [8,9]. Nonetheless, high-doses of AAS have been attributed to several cardiovascular disorders, including arterial hypertension [10,11], lipid profile abnormalities [12], heart failure [13], hypertrophic cardiomyopathy [14], cardiac arrhythmia [15], changes in membrane potential [16] and sudden death [17,18], generating serious public health problem [19].

These kinds of disturbances are detected on electrocardiogram signal and consequently by heart rate variability (HRV) analysis [20], which may be used as an indirect evaluation of cardiac autonomic alterations, associated for instance to immune dysfunction, inflammation, impairment in baroreceptors response [6] and mainly a large group of cardiovascular diseases and sudden death [21–24].

We have recognized that the attenuated parasympathetic (vagal) function leads to cardiovascular risk [24,25], and HRV analysis may provide a noninvasive method for estimating sympathovagal balance at the sinoatrial level [23,26], representing prognostic information about ventricular arrhythmia [27–29] and cardiac electrical instability.

Nevertheless, while marked reductions in the vagal activity were associated to cardiac autonomic impairment after treating with DECA [29], the functionality of the autonomic nervous system, changed by AAS effects are not still completely elucidated. In addition, to our

* Corresponding author at: Rua José Lourenço Kelmer, s/n, Campus Universitário – Juiz de Fora, MG 36036-900, Brazil.
E-mail address: isamjf@gmail.com (M. Marocolo).

https://doi.org/10.1016/j.steroids.2018.01.005
Received 8 November 2017; Received in revised form 10 January 2018; Accepted 16 January 2018

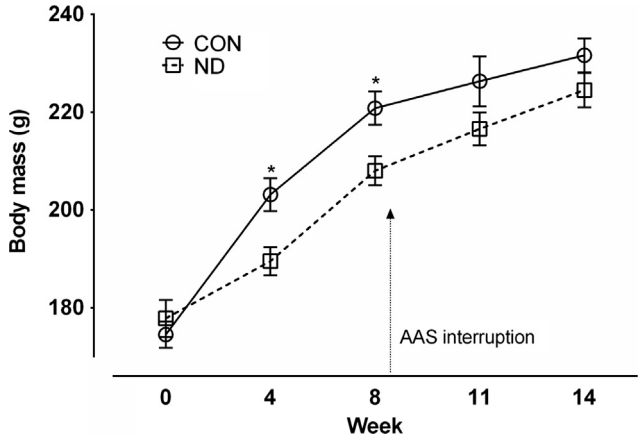

Fig. 1. Temporal series showing rat corporal body mass range among control (circles) and treated groups (squares) during 14 weeks. Trace vertical line indicates that nandrolone decanoate administration was interrupted after eight weeks. $^{*}p < .05$.

knowledge, few studies have attempted to investigate the effects of interruption of the DECA use on cardiac electrophysiological and autonomic abnormalities, as well as an association between parasympathetic activity and ventricular depolarization (QT interval).

Since that the most common way of AAS administration is non-continuous, e.g., individuals use for a certain time and stop on the other, our purpose was to evaluate the sustained effects of DECA administration by HRV and QT interval measurements and their recovery after interruption of treatment, providing information about cardiocirculatory loses and risks due androgenic steroids supplementation. Our hypothesis is that the possible deleterious effects caused by steroid administration would reverse after treatment discontinuation.

2. Materials and methods

2.1. Animals and procedures

Experiments were carried out on male Wistar rats (60–70 days old) kept at conditioned environment (25 ± 2 °C, 12/12 h day/night cycle and free access to rat chow and water). All protocols occurred in accordance to Canadian Council on Animal Care (CCAC) and the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health - NIH publication 85-23, revised 1985). The Local Institutional Animal Care and Use Committee (n. 202/2011) also approved experimental protocol.

The animals were randomly divided into two experimental groups: Control (CON, n = 10) and treated (ND, n = 10), while received during 8 weeks respectively peanut oil plus benzyl alcohol (90:10, V/V) or DECA (Deca Durabolin, Organon®; 10 mg kg^{-1}), always on the gluteus medium (*via* intramuscular) once a week [30,31].

2.2. Electrocardiogram acquisition and measurement

For HRV and QT analysis, ECG recordings were made by non-invasive method [32] in a lead close to DII bipolar derivation

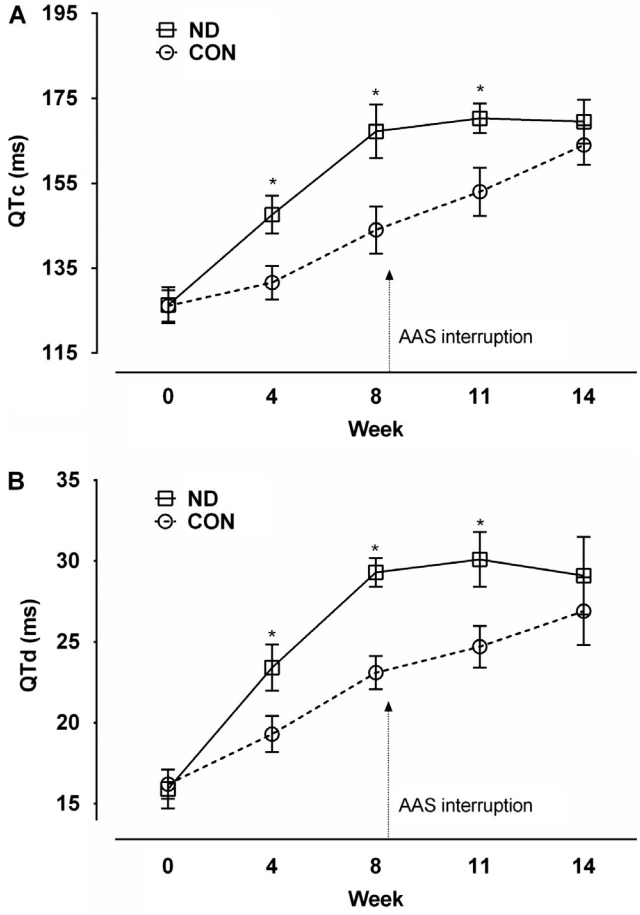

Fig. 2. Graphics showing QTc and QTd variability noted during 14 weeks in rats which received vehicle (circles), n = 10 and rats that received nandrolone decanoate 10 mg kg^{-1} (squares), n = 10. Trace vertical line indicates that nandrolone decanoate administration was interrupted after eight weeks. $^{*}p < .05$ vs. CON.

maintaining prominent R wave peaks, keeping the animals singly inside the cages. After carefully shaving the ventral thoracic region of animals, they were clothed with a custom-made elastic cotton jacket developed to fit the rat's mean thoracic circumference. Two rectangular pieces of platinum electrodes (7.0 × 3.0 mm) were attached to the jacket's inner surface. A conductive ECG gel was applied over each electrode, with care being taken to avoid the establishment of a gel bridge between them [32].

The electrodes were connected to a differential A/C amplifier and the signal digitized by 16 bits A/D interface converter (FE22400, ADInstruments, Sydney, Australia) at 2 kHz sample rate (LabChart Pro, Australia). The ECG recorder started 4 min after the animal was restrained and it was lasting for 10 min, always conducted in the same environment and time (between 9 and 11 a.m.), even without anesthesia to avoid physiological fluctuate.

Table 1
Effects of AAS treatment on body, fat and heart weights.

Group	Body weight (g)		Retroperitoneal fat (g)	Heart weight	
	Before	After 14 weeks		Absolute (g)	Relative (mg g^{-1})[a]
CON	174.5 ± 2.7	231.6 ± 3.4	3.69 ± 0.37	1.6 ± 0.032	6.8 ± 0.4
ND	177.8 ± 3.8	224.5 ± 3.6	2.34 ± 0.26*	1.9 ± 0.065*	8.1 ± 0.3*

Values as mean ± standard error.
[a] Absolute heart weight divide by body weight multiplied by 1000.$^{*}p < .001$ *control (CON) versus treated group (ND).*