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Abnormal cardiac repolarization in anabolic androgenic steroid users carrying out submaximal exercise testing

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SUMMARY

1. The aim of the present study was to investigate the cardiovascular effects of anabolic androgenic steroid (AAS) abuse by comparing the electrocardiographic parameters before and after submaximal exercise between AAS users and non-AAS users.

2. A total of 22 men who regularly engaged in both resistance and aerobic exercise at fitness academies volunteered for the study (control group: $n = 11$, age 25 ± 4 years; AAS group: $n = 11$, age 27 ± 5 years). All subjects were submitted to submaximal exercise testing using an Astrand–Rhyming protocol. Heart rate and electrocardiography parameters were measured at rest and at the third minute of the post-exercise recovery time.

3. AAS users presented higher QTc and QTd at rest (10% and 55%, respectively) and at the post-exercise period (17% and 43%, respectively), compared with control subjects. The maximal and minimum QTc interval of the AAS group was significantly prolonged at the post-exercise period (12% and 15%, respectively). The haemodynamic parameters were similar in both groups ($P > 0.05$). The AAS group showed a lower heart rate recovery at the first minute after the test ($P = 0.0001$), and a higher exertion score ($P < 0.0001$) at a lower workload, compared with the control group.

4. Our results show that the QTc interval and dispersion are increased in individuals who abuse AAS, suggesting the presence of ventricular repolarization abnormalities that could potentially increase the risk of cardiac arrhythmias and sudden cardiac death.

Key words: anabolic androgenic steroid, electrocardiographic ventricular parameters, QT dispersion, QT interval, ventricular repolarization.

INTRODUCTION

Self-administration of high doses of anabolic androgenic steroids (AAS) is widespread among young athletes aiming to optimize strength and gain muscle mass.[1,2] Furthermore, AAS abuse is increasing, particularly among non-athletes at fitness centers, with an aesthetic purpose.[3]

Several adverse cardiovascular effects of AAS have been reported.[1–8] Sudden death among athletes was predominantly as a result of cardiovascular diseases, mainly hypertrophic cardiomyopathy.[9] However, several case reports of sudden death in athletes indicate an association between chronic AAS abuse and increased risk of arrhythmias and sudden cardiac death.[10,11]

Electrocardiographic ventricular repolarization QT parameters, as the rate-corrected QT interval (QTc), the maximum QTc (QTcmax) and the QT interval dispersion (QTd), have been used as predictors of increased risk of ventricular arrhythmias and sudden death in patients with myocardial infarction,[12] Chagas' disease,[13,14] long QT syndromes[15,16] and diabetes mellitus.[17,18] Further, alterations in the QT interval and in the dispersion of the QT interval reflect heterogeneity of ventricular repolarization in adjacent areas of the heart.[19] An increased QT interval has been associated with abnormally depressed parasympathetic activity after exercise.[20] Despite the known adverse cardiovascular effects of high-doses of AAS, few studies have used QT parameters to assess cardiovascular risk associated with AAS abuse. Some of them have reported short QT intervals,[21,22] whereas Chung *et al.*[23] have found no change in the QTc interval of AAS users. Thus, because such issues have not been clarified, the present study was designed to evaluate the QT interval and dispersion during recovery from submaximal exercise in subjects using AAS.

METHODS

Subjects

A total of 22 male subjects who regularly engaged in strength training (mean 6 days per week) and low aerobic training (mean 2 days per week) at fitness academies in Niteroi city (Rio de Janeiro state, Brazil) volunteered to participate in the present study. All experimental procedures were carried out in accordance with the Declaration of Helsinki and were approved by the ethical committee of the Fluminense Federal University. All subjects gave written informed consent. Individuals were selected based on the results of a screening questionnaire and all of them were non-smokers, non-alcoholics

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and non-users of cocaine, marijuana or heroin. Eleven subjects, included in the AAS group, were individuals who declared they had taken AAS for periods as long as 4 years. The reported self-administration regimens were in cycles of 6.7 ± 1.1 weeks, with the use of two or more drugs in the same cycle. The orally self-administered drugs were oxymetholone and stanozolol, and the injectable steroids were nandrolone, stanozolol and testosterone propionate. The control group consisted of 11 individuals who declared that they did not use and had never before taken AAS. To indirectly assess anabolic steroid use, hormonal examinations were taken from blood samples. Serum testosterone, estradiol, follicle stimulating hormone and luteinizing hormone were measured by electrochemiluminescence immunoassays (Roche Diagnostics, Basel, Switzerland). The subjects' bodyweight and height were measured and the body mass index (BMI) was calculated as bodyweight divided by squared height (kg/m^2). No clinical problems occurred during the study.

Submaximal exercise testing

Exercise testing was carried out on a cycloergometer (Monark 828 E, Stockholm, Sweden) at submaximal workload using the Astrand–Rhyming protocol.[24] The test protocol was initiated after a rest period of 10 min in the supine position. The testing comprised of a 3-min warm-up at a workload of 50 W, followed by a constant workload at 100–130 W for 6–7 min until the subjects met the steady-state heart rate (140–150 b.p.m., with less than five beats of difference between the heart rates of the fifth and sixth minute or the sixth and seventh minute). This was followed by a 3-min recovery period with the workload set at 50 W, followed by a 10-min rest period in the supine position. Subjects were allowed sufficient practice during preliminary testing to become familiar with the cycloergometer. Ambient air temperature was 22–24°C. The rating of perceived exertion (RPE) during the testing was identified through the Borg's exertion score (scale from 6 to 20). All testing was carried out between 1300 and 1500 hours. Before testing, subjects avoided intake of coffee, tea or alcohol for 12 h and strenuous exercise for at least 48 h. A light lunch was provided to individuals 2 h before the test. Blood pressure (BP) was determined by sphygmomanometry before, during and after the exercise testing. Mean arterial blood pressure (MBP) was calculated from systolic (SBP) and diastolic (DBP) pressures using the equation: DBP + (SBP-DBP)/3 and rate pressure product (RPP) as HR × SBP. The percentage of arterial O_2 haemoglobin saturation ($\%SpO_2$) was continuously monitored with a fingertip oximeter (model CMS-50D; CONTEC, Qinhuangdao, China).

Electrocardiogram recording and QT interval measures

Electrocardiogram (ECG) was continuously recorded at a sampling rate of 1 kHz with 12-bit resolution using a 12-lead ECG monitor system (model 8000D; CONTEC). Heart rate (HR) was measured from the ECG recording and the %HR reserve was calculated as ((maximum HR at test − rest HR)/rest HR) × 100. The QT interval was measured manually in each of the 12 ECG leads as the time interval between the initial deflection of the QRS complex and the point at which a tangent drawn to the steepest portion of the terminal part of the T wave crossed the isoelectric line. When U waves were present, the QT interval was measured to the nadir between the T and U waves, and when the end of the T wave could not be identified, the lead was discarded from analysis. Mean values of QT and QTc intervals in each lead were calculated from five consecutive cycles. The preceding RR intervals to the target heart cycles were measured and used to calculate the mean heart rate-corrected QT interval with Bazett's formula[25]:

$$QTc = QT/\sqrt{RR}$$

Repolarization parameters analysed from QT measurements were: QT and QTc intervals obtained from lead II, maximal QTc (QTcmax) and minimum QTc (QTcmin), and QT dispersion (QTd) obtained from simultaneous 12-lead ECG recordings. QTcmax and QTcmin were defined as the largest and the shortest QTc interval duration, respectively, measured in any of the 12 leads. QT dispersion was defined as the difference between maximum and minimum values of QT interval obtained in any of the 12 leads. All measurements were carried out by two independent observers.

Statistical analysis

Data are expressed as mean ± SEM. Comparisons between groups were carried out using unpaired *t*-tests. Repeated measures analysis of variance (ANOVA) and paired *t*-tests (rest × post-exercise) were used to analyse group differences in response to exercise testing. Interobserver variability of QT interval and dispersion was assessed by both Student's *t*-test and intraclass correlation coefficient (ICC). The correlation between QT dispersion and RR interval was assessed by Pearson's correlation coefficient. A P-value <0.05 was considered significant. All statistical analysis was carried out using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Table 1 shows the baseline characteristics of subjects. Age, bodyweight, height and BMI were not significantly different between groups (Table 1). The concentration of follicle stimulating hormone and luteinizing hormone were significantly lower in the AAS group in comparison with the control group, as expected in individuals who use exogenous anabolic androgenic steroids. Furthermore, the total testosterone was higher in the AAS group when compared with the control group (Table 1). Control subjects had been training for 5.2 ± 1.3 years (4.2 ± 1.2 h per week), whereas the AAS users had been training for 5.4 ± 1.8 years (4.0 ± 1.2 h per week).

Figure 1 shows RR interval, QTc interval and QTd for both groups at rest and during the post-exercise recovery period. The RR interval of AAS group was significantly shorter compared with the control group, in both the rest and post-exercise period. For both groups, the post-exercise RR interval was shorter than the rest RR interval. The QTc was significantly prolonged in the AAS group compared with the control group. No statistical difference between rest and post-exercise QTc was observed in the control group. However, in the AAS group, the post-exercise QTc was significantly prolonged ($P = 0.0006$) compared with rest QTc. The QT dispersion of the AAS group was significantly greater than that of the control group in both the rest and post-exercise period. The post-exercise QT dispersion was significantly decreased in both groups, compared with the rest value. The QT dispersion of the AAS group did not show a significant correlation with RR intervals at rest ($r = 0.46$; $P < 0.15$) and at post-exercise period ($r = 0.39$; $P < 0.22$). The mean intra- and

Table 1 Baseline characteristics of the anabolic androgenic steroids users and non-user (control) subjects

Variable	Control ($n = 11$)	AAS ($n = 11$)	P-value
Age (years)	25 ± 4	27 ± 5	0.4512
Height (cm)	179 ± 7	174 ± 6	0.5285
Body mass (kg)	82 ± 8	85 ± 7	0.3334
Body mass index (kg/m^2)	26 ± 2	28 ± 3	0.7938
Total testosterone (ng/dL)	541 ± 41	667 ± 28	0.0476
LH (mUI/mL)	6.2 ± 0.6	3.0 ± 0.3	0.0008
FSH (mUI/mL)	4.4 ± 0.6	2.6 ± 0.2	0.0153
Oestradiol (pg/mL)	28 ± 3	50 ± 20	0.4054

Values are expressed as mean ± SEM. Unpaired *t*-test.

AAS, anabolic androgenic steroids; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

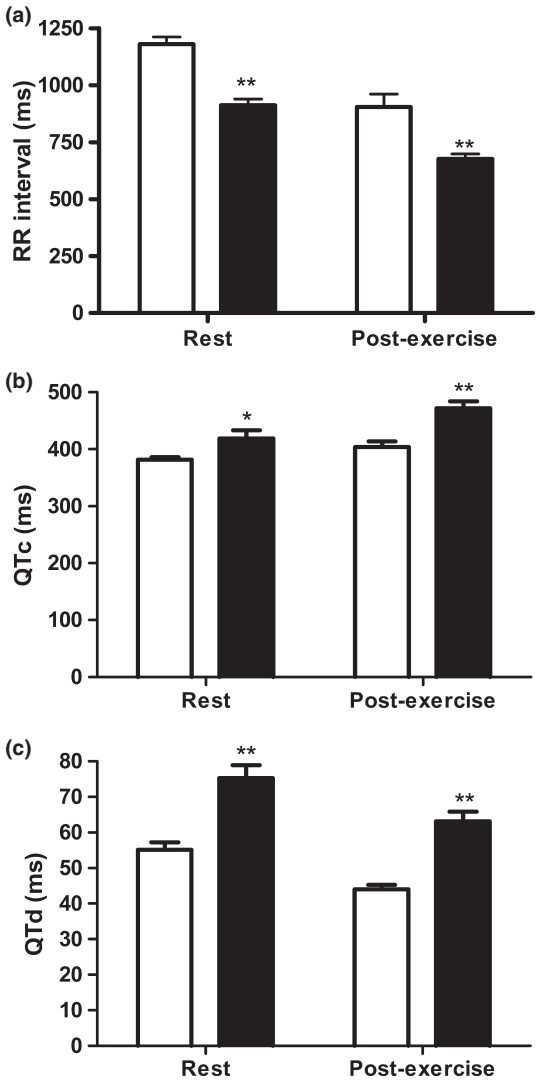

Fig. 1 RR interval, QTc interval, and QT dispersion determined before exercise testing (rest) and at the third minute of the recovery period (post-exercise) in anabolic androgenic steroids (AAS) users (AAS group, $n = 11$, ■) and non-AAS users (control group, $n = 11$, □). Values are expressed as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.001$ versus control group.

interobservers absolute error for QT parameters measurements was between 3 and 5 ms. The intraclass correlation coefficients (ICC) for each individual observer was 0.92 ($P < 0001$), whereas correlations among readers was 0.91 ($P < 0.001$).

Table 2 shows maximal and minimum QTc at rest and after a 3-min post-exercise recovery. Post-exercise maximal and minimum QTc were significantly prolonged in the AAS group compared with the control group and compared with the rest QTc of the AAS group. At rest, the minimum QTc did not show any difference between groups, whereas the maximal QTc was significantly prolonged in the AAS group. Table 3 presents the haemodynamic parameters assessed at rest and during the exercise testing. There was no significant difference between the groups for HR, SBP, DBP, MBP, RPP and SpO_2 at rest and during exercise.

Heart rate recovery at the first minute (ΔHR_{1min}) was significantly lower in the AAS user group (66.5%) compared with the control group (Table 4). Furthermore, the workload to reach steady state HR during the submaximal test was significantly higher in the control group than in the AAS group. However, the control group showed a lower Borg's exertion score when compared with the AAS group.

Table 2 QT interval characteristics at rest and post-exercise

Parameters	Control ($n = 11$)	AAS ($n = 11$)
QTcmax rest (ms)	407 ± 4	452 ± 14*
QTcmax post-exercise (ms)	427 ± 10	505 ± 13***,#
QTcmin rest (ms)	357 ± 4	386 ± 17
QTcmin post-exercise (ms)	381 ± 10	440 ± 13**,#

Values are expressed as mean ± SEM. Measurements were obtained before exercise testing (rest) and at the third minute of the recovery period (post-exercise).

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ versus control group. $^{\#}P < 0.001$ versus anabolic androgenic steroids (AAS) rest value.

Table 3 Haemodynamic variables

Variables	Control ($n = 11$)		AAS ($n = 11$)	
	At rest	Exercise	At rest	Exercise
SBP (mmHg)	119 ± 3	193 ± 6	125 ± 4	200 ± 6
DBP (mmHg)	74 ± 3	78 ± 2	77 ± 3	76 ± 4
MBP (mmHg)	89 ± 3	116 ± 2	93 ± 3	117 ± 4
RPP (b.p.m. mmHg)	7061 ± 264	28603 ± 876	8001 ± 432	29603 ± 1155
SpO_2	99 ± 0.2	98 ± 0.2	98 ± 0.2	98 ± 0.3

Values are expressed as mean ± SEM. Rest variables were determined before exercise testing. Exercise variables were determined at the sixth or seventh minute of exercise testing, when the heart rate reached 140–150 b.p.m.

AAS, anabolic androgenic steroids; DBP, diastolic blood pressure; MBP, medium blood pressure; RPP, rate pressure product; SBP, systolic blood pressure; SpO_2, blood oxygen saturation.

Table 4 Exercise test variables

Variables	Control ($n = 11$)	AAS ($n = 11$)	*P*-value
ΔHR_{1min} (b.p.m.)	36 ± 3	22 ± 2	0.0001
% of HR reserve (b.p.m.)	76 ± 1	77 ± 2	0.5827
ΔSBP_{1min} (mmHg)	35 ± 5	27 ± 4	0.1879
MET (unit)	7 ± 0.4	8 ± 0.6	0.2804
Workload (W)	133 ± 5	114 ± 5	0.0164
Borg's exertion score	12 ± 0.3	14 ± 0.3	0.0001

Values are expressed as mean ± SEM. ΔHR_{1min} and ΔSBP_{1min} were determined at the first minute of the recovery period.

AAS, anabolic androgenic steroids; HR, heart rate; MET, metabolic equivalent; SBP, systolic blood pressure.

DISCUSSION

This study presents an evaluation of the electrocardiographic and haemodynamic parameters achieved at rest and after exercise testing at a fixed submaximal heart rate in a small sample of mens' fitness academies users. The principal new findings from the present study are that subjects who are AAS users have a significantly longer QTc

interval and higher QT dispersion, at rest and after moderate exercise training, when compared with AAS-free subjects. Because QT prolongation and increased QT dispersion are predictors of risk of arrhythmias in different patient populations,[12–18] our data suggest AAS induced repolarization ventricular abnormalities in AAS users and could contribute to the early identification of AAS users with high risk of ventricular arrhythmias and sudden death.

In adult males, the normal values for QTc are shorter than 430 ms, with a borderline value ranging from 430 to 450 ms.[16] QT dispersion usually ranges from 40 to 50 ms, and a value of 65 ms is regarded as the upper limit of normality by some authors.[26] Nevertheless, a measurement of QT dispersion > 90 ms identified patients at increased risk of cardiac death.[20] Salles *et al.*[13] showed for patients with Chagas' disease, that a maximal dispersion of the QT interval greater than 65 ms and a maximum corrected QT interval longer that 465 ms are independent predictors of sudden death. In the present study, the AAS group had a rest QTd > 65 ms and although the maximum QTc was below 465 ms at rest, it increased to a value > 465 ms at the post-exercise recovery time. In subjects who submitted to moderate exercise testing, it was observed that a parasympathetic blockade might provide an arrhythmic effect during the post-exercise time, with a significantly increased QT interval.[20] In the present study, AAS users and non-user subjects showed a lengthening in QTc after exercise; however, the AAS group presented a higher increment in QTc interval than the control group. Furthermore, the AAS group presented increased QTd compared with the control group, with a rest value higher than 65 ms, suggesting abnormal ventricular repolarization in those AAS users.

The present results are in contrast to the study by Chung *et al.*[23] that has found no effect of AAS on QTc interval and those of Stolt *et al.*[21] and Bigi *et al.*,[22] which found that athletes who were AAS users had significantly shorter QT intervals than AAS-free athletes. Bigi *et al.*[22] examined only the QTc interval duration in 165 male professional bodybuilders and they found that those who subjected themselves to AAS abuse had a shorter QTc interval than AAS-free bodybuilders and healthy sedentary men. Stolt *et al.*,[21] in contrast, evaluated 30 AAS-free endurance athletes, 15 power athletes who were AAS users and 15 AAS-free sedentary men, and found that endurance athletes with physiological adaptive left ventricular hypertrophy had prolonged QT duration, but their QT dispersion was similar to that of sedentary men. In contrast, power athletes using anabolic steroids had increased QT dispersion and short QT intervals. However, the mean value of QTd found by Stolt *et al.*[21] in the AAS-using power athletes was below 65 ms. The discrepancy between our findings and those from previous studies[21–23] could be a result of differences among the groups of AAS-users included in these studies and AAS dosage. We evaluated amateur bodybuilders in fitness academies, whereas the other two studies evaluated professional bodybuilders subjected to different exercise modes and higher intensity, frequency and duration of exercise regimen. The self-reported AAS dosage in the present study was 410 ± 79 mg/week in cycles of 7 ± 1 week, whereas Stolt *et al.*[21] reported AAS dosage ranging from 63 to 174 mg/day. In contrast, Chung *et al.*[23] evaluated non-athletes treated with 200 mg/week of testosterone or nandrolone decanoate for only 4 weeks.

Bigi *et al.*[22] hypothesized that the androgen-induced QT interval shortening could be mediated by the potassium current I_{K1}, because experimental studies in androgen-treated castrated animals reported an increase in I_{K1} current[27] and Kir2.1 protein expression.[28] Liu *et al.*[27] also reported an increase in I_{Kr} current, but without any change in the ether-a-go-go-related gene RNA, suggesting a possible non-genomic effect of androgen. However, in a recent study,[29] we observed longer QTc was associated with left ventricle action potential prolongation, I_{to} density reduction, and downregulation of Kv1.4, Kv4.3 and KChIP2 mRNA in sedentary rats treated with nandrolone decanoate, suggesting the participation of the potassium current I_{to} in the genesis of the nandrolone decanoate-induced prolonged QTc and action potential duration.

The present study showed increased QTd, at rest and post-exercise, in the AAS-user group. Increased QTd is found in various cardiac diseases and reflects cardiac autonomic imbalance and greater susceptibility to complex ventricular arrhythmias.[30,31] An increase in QTd is also a marker of inhomogeneity in ventricular repolarization.[32] The correlation between QT dispersion and RR interval was not significantly different at rest and after cessation of exercise in the AAS group, showing a non-association of the exercise-induced increase in heart rate with the increased QTd.

We did not observe any significant differences in the haemodynamic parameters between the groups. These results were similar to that reported by Grace *et al.*,[33] who did not observe high blood pressure levels in the AAS user group. In addition, in the present study, the AAS users had a lower heart rate recovery at the first minute, in comparison with the AAS-free subjects. It has previously been shown in asymptomatic subjects that a heart rate recovery of < 25 b.p.m. had 2.1 times more risk of sudden death compared with the highest-percentile heart rate recovery group (> 40 b.p.m.).[34] Another study found that patients with an impaired heart rate recovery at 1-min had more severe myocardial ischaemia.[35] Because the decrease in heart rate during the first minute after the cessation of exercise is primarily related to parasympathetic reactivation,[34,35] it has been proposed that a delayed heart rate recovery might be a prognostic marker for abnormal or delayed parasympathetic reactivation.[20,36] The impairment of vagal activity is a risk factor for sudden death,[37] and thus, an attenuated heart rate recovery after exercise might be an important predictor of sudden death.[34,36] The results of the present study, showing decreased heart rate recovery in the subjects with AAS abuse could suggest an AAS-induced impairment of parasympathetic activity.

Exercise capacity is known to be an important prognostic factor in patients with cardiovascular disease.[38,39] In the present study, the AAS group had a higher exertion score and a lower workload at a fixed heart rate, but the MET was similar to that of the control group. A low workload at a fixed submaximal heart rate has been associated with an increased risk of cardiovascular disease.[40]

In conclusion, the present results show that the QTc interval and dispersion are increased in subjects who abuse AAS, suggesting the presence of ventricular repolarization abnormalities. Evaluation of electrocardiographic repolarization parameters at rest and at post-exercise could provide diagnostic and prognostic information about the risk of cardiac arrhythmias and sudden cardiac death in apparently healthy subjects who chronically use supraphysiological doses of AAS.

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