ORIGINAL ARTICLE

The Effect of Chronic Anabolic–Androgenic Steroid Use on Tp-E Interval, Tp-E/Qt Ratio, and Tp-E/Qtc Ratio in Male Bodybuilders

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Background: The chronic consumption of androgenic anabolic steroids has shown to cause atrial arrhythmias. Several studies have suggested that the interval from the peak to the end of the electrocardiographic T wave (Tp-e) may correspond to the transmural dispersion of repolarization and that increased Tp-e interval and Tp-e/QT ratio are associated with malignant ventricular arrhythmias. The aim of this study was to evaluate repolarization dispersion measured from the 12-lead surface electrocardiogram (including Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio) in bodybuilders who are using anabolic androgenic steroids (AAS).

Methods: We selected a population of 33 competitive bodybuilders, including 15 actively using AAS for ≥ 2 years (users) and 18 who had never used AAS (nonusers), all men.

Results: QT, cQT, QTd, cQTd, JT, and cJT were significantly increased in AAS users bodybulders compared to the nonusers (all $P < 0.001$). Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio were also significantly higher in AAS user group compared to the nonuser group (all $P < 0.001$). QRS duration was not different between the groups. There were negative correlation between E_m and Tp-e, Tp-e/QT ratio, Tp-e/cQT ration ($r = -0.657$, $P < 0.01$; $r = -0.607$, $P = 0.02$; $r = -0.583$, $P = 0.02$; respectively).There were also negative correlation between S_m and Tp-e, Tp-e/QT ratio, Tp-e/cQT ration ($r = -0.681$, $P < 0.01$; $r = -0.549$, $P = 0.03$; $r = -0.544$, $P = 0.023$; respectively).

Conclusion: In conclusion, we have presented a strong evidence suggesting that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were increased in AAS users, which suggest that there might be a link between AAS use and ventricular arrthymias and sudden death.

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Anabolic androgenic steroids (AAS) are group of doping drugs used by bodybuilders to increase lean body mass and muscle strength. Long-term illicit use of supraphysiologic doses of AAS may cause several adverse cardiovascular effects.[1–3] There are several case reports of sudden death (SD) in athletes indicate an association between chronic AAS abuse and increased risk of arrhythmias and sudden cardiac death.[4,5]

Concentric left ventricular hypertrophy (LVH) occurs due to the direct effect of AAS on the heart muscle.[6] In contrast to the physiological

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LVH caused by endurance training, LVH in pathological conditions like systemic hypertension and hypertrophic cardiomyopathy is characterized by impaired diastolic function.[7–9] In addition, pathologic LVH with impaired diastolic function secondary to the illicit use of supraphsiologic doses of AAS was also described.[10–13] It is known that, pathologic LVH is a risk factor for ventricular arrhythmias and SD. Pathological hypertrophy is associated with alterations of the electrophysiological properties of cardiomyocytes, thus became more susceptible to malignant tachyarrhythmias. The combination of interstitial fibrosis with pathologic hypertrophy leads to abnormalities in ventricular repolarization.[14,15] Several mechanisms have been proposed to explain the vulnerability of the hypertrophied ventricle to life-threatening arrhythmias, but the factors actually predisposing long-term AAS users with pathologic LVH to electrical instability and sudden cardiac death are not well established.

Myocardial repolarization has been evaluated by various methods including QT dispersion (QTd), corrected QT dispersion (cQTd), and transmural dispersion of repolarization. Recent studies indicated that Tp-e interval, which is the interval between the peak and the end of T wave on electrocardiogram (ECG), can be used as an index of total (transmural, apicobasal, and global) dispersion of repolarization.[16,17] Also, increased Tp-e interval might be a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality.[18,19] Recently, a new index, the Tp-e/QT ratio has been suggested to be more accurate measure for the dispersion of ventricular repolarization compared to QTd, cQTd, and Tp-e intervals, which is independent of alterations in heart rate.[20,21] Although ventricular repolarization was evaluated in long-term AAS users by using T wave and QT interval measurements previously,[22] the novel repolarization indexes like Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio are not studied in these groups before.

The aim of this study was to evaluate repolarization dispersion measured from the 12- lead surface electrocardiogram (including Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio) in bodybuilders who are using AAS.

METHODS

Study Population

We selected a population of 33 competitive bodybuilders, including 15 actively taking AAS for ≥2 years (users) and 18 who had never used AAS (nonusers), all men. Prior to data collection written informed consent was obtained from each patient, and the study had been approved by the appropriate institutional ethics review committee. Patients with coronary artery disease, chronic renal failure, chronic liver disorders, chronic lung disease, moderate or severe valvular heart disease, diabetes mellitus, congenital heart disease, left ventricular systolic dysfunction on echocardiography (EF < 50%), recent acute coronary syndrome, anemia, obstructive sleep apnea, secondary hypertension, hematological disorders, known malignancy, thyroid dysfunction, hypercholesterolemia, electrolyte imbalance and bundle branch block, atrio-ventricular conduction abnormalities on ECG, and ECGs without clearly analyzable QT segment were excluded from the study. The subjects who had LVH by means of Cornell voltage criteria were not included into the study. In addition, subjects with ST-segment elevation, ST-T changes, T wave inversion, wide QRS complexes, and ventricular preexcitation were excluded. All the patients were in sinus rhythm and none of them was taking medications such as anti-arrhythmics, tricyclic antidepressants, anti-histaminics, and antipsychotics.

Training Protocols

All participants had trained intensively for >10–15 h/wk for >5 years. AAS users and nonusers had started bodybuilding at approximately the same age (19.44 ± 2.91 years vs 21.47 ± 3.24 years, respectively, P = nonsignificant) and completed the same anaerobic isometricstatic exercises (4.81 ± 1.72 h/wk vs 4.5 ± 2.06 h/wk, P = NS). Maximum self-reported one-repetition squat results were significantly greater among AAS users (144.5 kg ± 19.49 vs 111.37 ± 21.2 kg, P < 0 .001).

AAS Abuse

An anonymous, self-administered questionnaire was used to investigate each athlete's clinical

(diseases and medication) and drug intake history (type and timing of steroid use and other performance-enhancing drugs). In addition, urine testing was performed by high-performance liquid chromatography coupled to mass spectrometry to confirm or exclude any recent consumption of anabolic steroids. Each AAS user admitted the current use of multiple AAS administered by intramuscular injection and/or orally. The orally self-administered drugs were oxymetholone and stanozolol, and the injectable steroids were nandrolone, stanozolol, and testosterone propionate. The mean duration of AAS use was 5.73 ± 3 years (range, 3–20 years). The mean weekly dosage of AAS was 1085.5 ± 354 mg.

Physical Examination and Laboratory Tests

All subjects were examined on an empty stomach. Height, weight, body mass index (BMI), body surface area (BSA), body fat mass, heart rate, and blood pressure were measured. Venous blood samples were drawn from each subject, always in the afternoon between 1 and 2 PM, to evaluate serum hormone levels (testosterone, luteinizing hormone, follicle-stimulating hormone, insulin, T3, and T4), hematology (hematocrit, hemoglobin), and blood lipids (total cholesterol, high-density lipoprotein). The subjects' body weight and height were measured and the BMI was calculated as body weight divided by squared height (kg/m^2).

Echocardiographic Measurements

Echocardiography was performed in left lateral decubitus position with an ultrasound machine GE-Vingmed Vivid 7 system (General Electric Vingmed Ultrasound AS, Horten, Norway) and 3S-RS (3.5 MHz) probe. Examinations were performed by a cardiologist who was blinded to the clinical details of each subject. Single-lead ECG was recorded continuously during the echocardiographic examination. Two-dimensional, M-mode, and tissue Doppler images were acquired from the parasternal long and short axis and apical four-chamber views at end-expiratory apnea, and were transferred to a customized dedicated software package (EchoPAC, General Electric Vingmed Ultrasound) for off-line analysis of stored data. All measurements were averaged from three cardiac cycles. Two-dimensional echocardiographic measurements were performed according to standards outlined by the American Society of Echocardiography.[23] Left atrial (LA), LV dimensions, and wall thickness were obtained from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the ventricle. LV end-diastolic diameter (LVEDD) and end-systolic (LVESD) diameter, thickness of the interventricular septum (IVS), and posterior wall of the left ventricle (PW) were measured. LV ejection fraction was calculated according to the Simpson method.[23] For determination of left ventricular mass (LVM), the Devereux formula was used: LVM (g), 1.04 [(LVID + PWT + IVST)3 − LVID3] − 14 (LVID indicates LV internal dimension; PWT, PW thickness; IVST, IVS thickness). Left ventricular mass index was calculated by dividing LVM by body surface area. LV hypertrophy was defined as an LV mass index $> 115\ g/m^2$ in men, as recommended by the American Society of Echocardiography and the European Association of Echocardiography.[23] Mitral inflow velocities were evaluated by pulsed-wave Doppler echocardiography with the sample volume placed at the tip of the mitral leaflets from the apical four-chamber view. Diastolic peak early (E) and peak late (A) transmittal flow velocity, peak E to peak A velocities (E/A), deceleration time of peak E velocity (EDT), and isovolumetric relaxation time (IVRT) were measured.[24]

The tissue Doppler imaging (TDI) was performed in the apical four-chamber view using a 5-mm pulsed Doppler sample volume with as minimum optimal gain as possible to obtain the best signal-to-noise ratio. Care was taken to align the echo image so that the annular motion was parallel to the TDI cursor. Spectral pulsed-wave Doppler signal filters were adjusted until a Nyquist limit of 15–20 cm/s was reached. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. In apical four-chamber view, the pulsed Doppler sample volume was subsequently placed at the level of LV lateral mitral annulus, septal mitral annulus, and right ventricular (RV) tricuspid annulus. The myocardial peak systolic (S_m), and early diastolic (E_m) velocity, and late diastolic (A_m) velocity were obtained from the septum, the lateral wall of the left ventricle, and the annulus of the right ventricle. The S_m global, E_m global, and A_m global velocities were derived by averaging the velocities from the two mitral annular sites. Global E_m/A_m ratio and E/E_m ratio were calculated.[25]

Table 1. Clinical Characteristics and Training Programs of the AAS User and Nonuser Bodybuilders

	AAS Nonusers (n = 18)	AAS Users (n = 15)	P Value
Age (year)	33.8 ± 4.1	32.5 ± 6.6	NS
Height (cm)	180.4 ± 6.9	179.9 ± 7.3	NS
Weight (kg)	87.4 ± 10.3	90.8 ± 6.3	NS
BMI (kg/m^2)	26.3 ± 3.2	29.1 ± 4.4	<0.05
BSA (m^2)	2.08 ± 0.14	2.1 ± 0.14	NS
Blood pressure (mmHg)	120 ± 13.37/80.37 ± 6.49	118.51 ± 9.88/78.51 ± 6.9	NS
Heart rate (beats/min)	68.74 ± 10.45	72.22 ± 13.40	NS
Sessions per week	3.92 ± 0.86	3.67 ± 0.84	NS
Years	8.64 ± 2.11	9.03 ± 1.94	NS
Starting age	22.34 ± 3.68	21.61 ± 3.04	NS
Anaerobic exercise (h/wk)	4.73 ± 2.02	4.94 ± 1.82	NS
Aerobic exercise (h/wk)	3.11 ± 3.03	1.94 ± 1.82	NS
Maximal weight (kg)	120.67 ± 21.61	142.67 ± 19.09	<0.05

NS, nonsignificant.

Electrocardiographic Measurements

The 12-lead ECG was recorded at a paper speed of 25 mm/s at rest in the supine position. Resting heart rate was measured from the ECG taken during the patient evaluation. To decrease the percentage of error during measurements, QT and Tp-e intervals were measured manually with calipers and magnifying glass. Subjects with U waves on their ECGs were excluded from the study. An average value of three readings was calculated for each lead. The QRS interval was measured from the start of the Q wave, or, in the absence of the Q wave, from the start of R wave to the end of S (to its return to the isoelectric line). The QT interval was defined as the time from the onset of the QRS complex to the end of the T wave at which the isoelectric line intersected a tangential line drawn at the maximal down slope of a positive T wave, and was corrected for heart rate using the Bazett's formula: $cQT = QT/\sqrt{(R\text{–}R \text{ interval})}$. The QTd was defined as the difference between the maximum and minimum QT interval of the 12 leads.[26] The JT interval was derived by subtracting the QRS duration from the QT interval. JT measurement was also corrected for heart rate using the Bazett's formula. The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of Tp-e interval were performed from precordial leads.[18] Tp-e/QT ratio and Tp-e/cQT ratio was calculated from these measurements. All measurements were performed by 2 experienced investigator unaware of the clinical characteristics of the study participants. Intraobserver and interobserver coefficients of variation (standard deviation [SD] of differences between two observations divided by the mean value and expressed as percent) were found to be 1.1% and 2.1%, respectively.

Statistical Analysis

The SPSS 15.0 statistical program (SPSS Inc., Chicago, IL, USA) was used for the statistical study. All values are given as mean ± standard deviation. Mean values of continuous variables were compared between groups using the Student t test or Mann–Whitney U test, according to whether normally distributed or not, as tested by the Kolmogorov–Smirnov test. The chi-square test was used to assess differences between categorical variables. Pearson's correlation coefficients were used to assess the strength of relationship between continuous variables. A P value of < 0.05 was considered significant.

RESULTS

Clinical Characteristics of the Study Population

The characteristics of the subjects are listed in Table 1. No differences between groups emerged in age, height, weight, BSA, blood pressure, or heart rate. However, AAS users had higher BMIs compared with AAS nonusers.

Echocardiographic Analysis

Table 2 shows the details of the echocardiographic analysis. LV mass index, interventricular

Table 2. Comparison of the Echocardiographic Parameters of the Subjects Both AAS User and Nonuser Bodybuilders

	AAS Nonusers (n = 18)	AAS Users (n = 15)	P Value
Two dimensional echocardiographic parameters			
LA dimension (mm)	33.1 ± 0.3	34.2 ± 0.2	NS
LA volume index (mL/m^2)	26.2 ± 2.3	27.6 ± 2.4	NS
LV end-systolic diameter (mm)	31.9 ± 4.4	33.2 ± 3.2	NS
LV end-diastolic diameter (mm)	49.7 ± 1.9	51.2 ± 3.1	NS
Septal wall thickness (mm)	11.5 ± 1.2	12.4 ± 1.3	<0.01
Posterior wall thickness (mm)	9.8 ± 0.9	11.3 ± 0.7	<0.01
RWT	0.39 ± 0.03	0,44 ± 0,02	<0.01
LV mass index (g/m^2)	90.9 ± 10.8	113.6 ± 13.6	<0.01
LV ejection fraction (%)	61.37 ± 1.6	60.87 ± 2.3	NS
Doppler parameters			
Peak E velocity (m/s)	79.8 ± 9.4	77.6 ± 11.6	NS
Peak A velocity (m/s)	55.7 ± 8.9	50.7 ± 6.8	NS
E/A ratio	1.47 ± 0.3	1.54 ± 0.2	NS
IVRT (ms)	80.7 ± 5.8	83.58 ± 11.7	<0.01
E_m septal (cm/s)	12.1 ± 1.5	10.1 ± 1.3	<0.01
A_m septal (cm/s)	9.4 ± 1.2	9.5 ± 0.7	NS
E/E_m septal (cm/s)	6,7 ± 1,2	7,8 ± 1,7	<0.01
E_m/A_m septal (cm/s)	1.29 ± 0.2	1.06 ± 0.2	<0.01
E_m lateral (cm/s)	16.2 ± 1.5	11.6 ± 1.2	<0.01
E_m global (cm/s)	13.05 ± 1.8	10.86 ± 1.27	<0.01
S_m (cm/s)	7.04 + 1.16	6.23 ± 0.63	<0.01
A_m lateral (cm/s)	9.9 ± 1.2	9.4 ± 1.3	NS
E/E_m lateral (cm/s)	4.9 ± 0.8	6.8 ± 1.3	<0.01
E_m/A_m lateral (cm/s)	1.6 ± 0.3	1.2 ± 0.2	<0.01
E/E_m global (cm/s)	5.8 ± 0.9	7.3 ± 1.5	<0.01
E_m/A_m global (cm/s)	1.5 ± 0.2	1.6 ± 0.1	<0.01

NS, nonsignificant.

septal thickness, LV posterior wall thickness, and relative diastolic wall thickness were significantly greater in AAS users than in nonusers and sedentary controls ($P < 0.01$). No significant differences were found in LA, LA volume index, LV end-systolic, end-diastolic dimensions, and LV ejection fraction among the groups.

Transmitral Doppler echocardiography data of LV diastolic function are listed in Table 2. No significant differences were found in peak E and peak A between AAS user and nonusers. However, drug-using bodybuilders exhibited longer isovolumetric relaxation times and lower ratio of E/A than their drug-free counterparts.

When comparing the diastolic functions obtained by measuring the TDI velocities, lateral and septal E_m were significantly lower in AAS users than in nonusers (11.6 ± 1.2 vs. 16.2 ± 1.5, $P < 0.01$; 10.1 ± 1.3 vs. 12.1 ± 1.5, $P < 0.01$; respectively), whereas, lateral and septal A_m were not a significant difference in AAS users than in nonusers (9.4 ± 1.3 vs 9.9 ± 1.2, $P > 0.05$; 9.5 ± 0.7 vs 9.4 ± 1.2, $P > 0.05$; respectively). Global E/E_m and E_m/A_m were significantly difference in ASS users than in nonusers (7.3 ± 1.5 vs 5.8 ± 0.9, $P < 0.01$; 1.6 ± 0.1 vs 1.5 ± 0.2, $P < 0.01$; respectively). In addition, S_m was significantly lower in AAS users than in nonusers (6.23 ± 0.63 vs. $7.04 + 1.16$, $P < 0.01$).

Electrocardiographic Parameters

Electrocardiographic parameters of the groups are shown in Table 3. QT, cQT, QTd, cQTd, JT, and cJT were significantly increased in AAS users bodybuilders compared to the nonusers (all $P < 0.001$). Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio were also significantly higher in AAS user group compared to the nonuser group (all $P < 0.001$). QRS duration was not statistically different between the groups. There was a positive correlation between LV mass index and Tp-e, Tp-e/QT ratio, and Tp-e/cQT ration. There were negative correlation between E_m and Tp-e, Tp-e/QT ratio, Tp-e/cQT ration ($r = -0.657$, $P < 0.01$; $r = -0.607$,

Table 3. Comparison of Electrocardiographical Features of AAS User and Nonuser Bodybuilders

	AAS Nonuser (n = 18)	AAS User (n = 15)	P Value
QT (milliseconds)	370.3 ± 22.5	421.1 ± 22.7	<0.01
QTd (milliseconds)	39.5 ± 7.9	57.9 ± 7.1	<0.01
cQT	395.6 ± 42.7	459.7 ± 41.3	<0.01
cQTd	42.1 ± 7.9	63.3 ± 9.4	<0.01
QRS (milliseconds)	93.8 ± 10.1	97.3 ± 9.1	NS
JT (milliseconds)	276.6 ± 18.6	323.7 ± 25.3	<0.01
cJT	294.7 ± 32.6	352.8 ± 35.9	<0.01
Tp-e	77.1 ± 9.5	102.7 ± 9.2	<0.01
Tp-e/QT	0.21 ± 0.02	0.24 ± 0.02	<0.01
Tp-e/cQT	0.20 ± 0.03	0.22 ± 0.03	<0.01

P = 0.02; r = - −0.583, P = 0.02; respectively). There were also negative correlation between S_m and Tp-e, Tp-e/QT ratio, Tp-e/cQT ration (r = −0.681, P < 0.01; r = −0.549, P = 0.03; r = −0.544, P = 0.023; respectively). Moreover, LV mass index well correlated with Tp-e and Tp-e/QT ratio (r = 0.605, P <0.001; r = 0.355, P = 0.04; respectively).

Discussion

In our study, we found that mean Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio that are known to be related to various ventricular arrhythmias and SD are significantly prolonged in AAS using bodybuilders compared with non-AAS users. Also, these electrocardiographic parameters were significantly and negatively correlated with pathologic LVH, which is known to be a consequence of long term use of AAS.

Previous studies have reported that hypertrophic cardiomyopathy, SD, cardiovascular morbidity, and mortality rates are significantly increased in long-term AAS using bodybuilders than nonusers.[27] In addition, ventricular arrhythmic events were described secondary to the long-term intake of AAS.

Echocardiographic studies show that concentric LVH is common morphologic changes of the heart in both long-term use of supraphysiologic doses of AAS users and nonuser bodybuilder athletes. There are some studies related to the differences between pathologic and physiologic adaptative LVH in AAS using and nonusing athletes.[28–30] In contrast to the physiological LVH caused by endurance training, LVH in pathological conditions like systemic hypertension and hypertrophic cardiomyopathy is characterized by impaired diastolic function.[7–9] In addition, long-term illicit use of supraphysiologic doses of AAS induced pathologic LVH with impaired diastolic function has also been described.[10–13] In our study, we found that E/E_m ratio was significantly higher in AAS users than in nonusers. In addition, the E_m/A_m ratio was significantly lower in AAS users than in nonusers. Also we found that IVRT prolonged in AAS using group, indicating the impairment of diastolic function.

Although standard Doppler echocardiography has been widely used to distinguish athlete's heart from pathological LVH, recent studies indicate that Doppler tissue imaging techniques, in particular PWTDI, are also useful in assessing myocardial systolic and diastolic function and differentiating pathologic ventricular hypertrophy from the physiologic one.[28,31–33] Shan et al., comparing Doppler tissue imaging and histologic findings in patients affected by coronary artery disease, demonstrated that S_m and E_m are strongly dependent on the number of myocytes, myocardial β-adrenergic receptor density, and the amount of interstitial fibrosis.[34] D'Andrea et al. and other studies observed lower myocardial early diastolic peak velocities of the interventricular septum and the lateral LV wall in AAS users when compared to AAS free athletes.[28–30] Confirming previous findings, we observed low S_m velocity and low early diastolic peak velocities (E_m) at the interventricular septum and the lateral LV wall that indicate pathologic LVH in AAS users. Moreover, it is known that, pathologic LVH is a risk factor for ventricular arrhythmias and SD.[14,15]

Increased heterogeneity of ventricular myocardial repolarization favors susceptibility to reentrant ventricular tachyarrhythmias. Myocardial repolarization has been evaluated by various methods including QTd, cQTd, and transmural dispersion

of repolarization.[35] Several studies indicated that prolongation of QTd and cQTd are associated with ventricular arrythmias and sudden cardiac death. An increased QTd and cQTd have been found in patients with pathologic LVH, such as hypertrophic cardiomyopathy and hypertension.[36,37] In our study, we found significant difference in QTd and cQTd between AAS using bodybuilders than in nonusers. Also, our findings are consistent with those of Maior and Stolt et al. that power training combined with use of large doses of anabolic steroids is associated with increased QTd and cQTd.[38,39] However, in these studies and our present findings, QTd and cQTd were not changed in physiologic adaptive LVH group. Past studies also demonstrated that QTd and cQTd were normal in training-induced LVH both in young and elderly athletes. However, in these studies, only QTd and cQTd were used to access homogeneity of cardiac repolarization, and no information about the relation between transmural dispersion of repolarization and long-term AAS using athletes.[40,41]

Transmural dispersion of repolarization, calculated as the interval between the peak and the end of T wave on electrocardiogram, has been related to ventricular arrhythmias and sudden cardiac death.[18,19,35] Recent studies indicated that Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio can be used as an index of total (transmural, apicobasal, and global) dispersion of repolarization.[16,17] Also, these markers may be used as an electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death.[18,19,35] Previous studies showed that Tp-e interval and Tp-e/QT ratio were associated with increased risk for malignant ventricular arrhythmias in a variety of conditions, including long-QT syndrome (acquired and congenital), Brugada syndrome, acute ST-segment elevation myocardial infarction, and hypertrophic cardiomyopathy.[18,42,43] Moreover, Zhao et al.[44] demonstrated that Tp-e interval and Tp-e/QT ratio were increased in LVH. However, Braschi et al.[45] denoted that athlete's heart is not associated to any alteration in ventricular repolarization homogeneity and physiologic adaptative LVH does not affects duration of Tp-e interval and Tp-e/QT ratio. As far as we know, there is no study available in the literature about the association between AAS using athletes and nonuser groups. In this study, we showed for the first time that Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio were significantly prolonged in AAS using bodybuilders compared to nonusers.

The possible mechanism for increasing QTd, cQTd, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in AAS using athletes is LV pathological hypertrophy. LV pathological hypertrophy induced by AAS appears to be generated by a direct action on cardiac androgen receptors, whose effects are directly proportional to the doses, time, and duration of drug administration.[46,47] In our study, as indicators of pathological hypertrophy we have found impaired diastolic functions, S_m and E_m values in long-term AAS using athletes. It is known that pathological hypertrophy is associated with alterations of the electrophysiological properties of cardiomyocytes, closely related to a higher susceptibility toward malignant tachyarrhythmias.[14,15,48] In pathological LVH, alterations of the electrophysiological properties can be related to a myocardial architecture deformity such as myocardial disarray, interstitial fibrosis, and inhomogeneous cardiac myocyte hypertrophy.[14,15,39,49,50] In fact, the effects of chronic consumption of AAS on myocardial structural alterations are inhomogeneous myocardial hypertrophy, focal myocyte damage with myofibrillar loss, and interstitial fibrosis, which may produce a significant prolongation ventricular action potential duration that promotes a marked increment in transmural dispersion of repolarization.[14,15,48] In our study, LV wall thickness and LV mass index were enlarged in AAS using athletes compared to nonusers. In addition, we found that S_m and E_m velocities that evaluated by DMI are directly dependent on myocardial structure, characterized by the percentage of interstitial fibrosis have negative correlation with Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio. Furthermore, we also found positive correlation between LV mass index and Tp-e, and Tp-e/QT ratio. Therefore, we can speculated that pathologic LVH induced by chronic consumption of supraphyiologic doses of AAS in athletes may be the reason underlying the prolongation of Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio.

Study Limitations

Our study has several limitations. The most important limitations of our study are the small sample size and cross-sectional design of the study, in which we could not follow up the patients prospectively for future arrhythmic events. We

did not observe any arrhythmias in the study population. Therefore, we do not know whether prolongation of Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio predicts ventricular arrhythmias in chronic AAS using athletes. Further studies need to be conducted with a larger number of patients and a longer follow-up time in order to increase the accuracy of the results.

We were dealing with young individuals. Thus, the impact of AAS in older individuals is unknown. The same idea can be used for gender. There is no guarantee that the effects of AAS on Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in women will be similar to those found in men. The information about the intake of steroids was self-reported, but it is difficult to assess this in an objective manner. It seems unlikely that the small differences in AAS intake could explain our results. Finally, training-related influences are also improbable as an explanation for the differences between the AAS users and nonusers in our study, as the training protocol was the same for all the athletes.

CONCLUSION

In conclusion, in this cross-sectional study, we have presented an strong evidence suggesting that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were increased in AAS users, which suggest that there might be a link between AAS use and ventricular arrthymias and SD. Furthermore, pathologic LVH induced by chronic consumption of supraphyiologic doses of AAS may be the reason underlying the prolongation of Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio. These findings may be markers of subclinical cardiac involvement in AAS using bodybuilders. Finally, this implication deserves further studies for clarifying the possible linkage between long-term consumption of supraphyiologic doses of AAS and ventricular arthymias/SD.

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