Cardiac Effects of Anabolic Steroids: Hypertrophy, Ischemia and Electrical Remodelling as Potential Triggers of Sudden Death

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Abstract: Anabolic-androgenic steroids (AAS) are synthetic testosterone derivatives developed to maximise anabolic activity and minimise androgenic activity. AAS abuse is widespread among both athletes and non-athletes at fitness centres and is becoming a public health issue. In addition to their atherogenic, thrombogenic and spastic effects, AAS have direct cardiotoxic effects by causing hypertrophy, electrical and structural remodelling, and contractile dysfunction and by increasing the susceptibility to ischemic injuries. All of these factors contribute to an increased risk of ventricular arrhythmias and sudden cardiac death.

Keywords: Anabolic steroid, hypertrophy, sudden cardiac death, myocardial ischemia, electrical remodelling, dysautonomia.

INTRODUCTION

Anabolic-androgenic steroids (AAS) are synthetic testosterone derivatives developed to maximise anabolic activity and minimise androgenic activity [1-3]. They are used in clinical settings to treat catabolic conditions, such as hypogonadism, osteoporosis, and cachexia, associated with conditions including burns, HIV, hepatic and renal failure [1,4]. Although various side effects secondary to high doses of AAS have been reported, illicit AAS abuse is widespread among athletes aiming to optimise their strength and maximize muscle mass [5-7]. AAS abuse has become a public health issue in recent years, because AAS self-administration is particularly widespread among non-athletes at fitness centres who have aesthetic goals [8-10].

The adverse effects of chronic consumption of supraphysiological doses of AAS include behavioural, cardiovascular, dermatologic, endocrine and hepatic abnormalities [11,12]. However, special attention has been paid to AAS-induced adverse cardiovascular effects, including lipoprotein alterations, thrombosis, vasospasms, hypertension, hypertrophy, heart failure, arrhythmia and sudden cardiac death [5,13-16].

Melchert and Welder [17] classified the effects of AAS on the cardiovascular system into four categories of activities: atherogenic, thrombotic, and vasospastic activities and direct myocardial injuries. The first three categories have been discussed in different reviews about the vascular effects of AAS, including changes in lipid metabolism and lipoprotein levels, which increase the risk of atherosclerosis; polycythemia and enhanced platelet aggregation, which increase the risk of thrombus formation; and arterial vasospasms, which increase the risk of ischemia and the occurrence of an infarct or stroke [13, 14,17].

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Therefore, in this review, we will focus on the direct cardiotoxic effects of AAS and discuss the evidence for the potential mechanisms involved in these phenomena.

MYOCARDIAL ISCHEMIA

Chronic use of supraphysiological doses of AAS has been associated with ischemic heart disease and myocardial infarction [13]. Various pathological mechanisms have been proposed to contribute to the higher risk of myocardial ischemia and infarct in AAS users. (1) AAS abuse increases the serum level of LDL cholesterol and reduces the level of HDL cholesterol [13,18]. High LDL and low HDL are associated with a high risk of atherosclerosis, which contributes to the risk of death from ischemic coronary heart disease [19]. (2) AAS causes polycythemia, which increases the blood viscosity [20] and elevates platelet aggregation [13]. Both induce thrombus formation, which increases the risk of a myocardial infarct or stroke [13]. (3) AAS-induced impairment of endothelial function causes vasospasms and contributes to ischemic heart disease, associated with AAS abuse [17]. (4) AAS pathologically alter the normal physiological adaptations that occur after exercise, from compensated to uncompensated hypertrophy [13]. Uncompensated hypertrophy is associated with ventricular dilatation, heart failure and reduced tolerance to ischemia [21]. Tagarakis *et al.* [22] have shown that AAS induce cardiomyocyte hypertrophy with decreased capillary density and increased spacing between capillaries in exercised mice. This impairment of the exercise-induced cardiac capillarisation could impair the myocardial oxygen supply, subjecting the myocardium to ischemia. Consistent with these data, Du Toit *et al.* [23] have shown that swimming rats treated with AAS lost their exercise-induced improvement of cardiac tolerance to ischemic events. Moreover, our group has demonstrated that exercise-induced antioxidant enzymes activity is impaired by supraphysiological doses of AAS in rats, leading to reduced myocardial tolerance of ischemic events [24]. Other intrinsic mechanisms may contribute to the AAS-induced increase in

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myocardial susceptibility to ischemic injury and merit future studies.

CARDIAC HYPERTROPHY

Prolonged use of supraphysiological doses of AAS induces ventricular hypertrophy. Data from echocardiographic studies in athletes using AAS found an increase in left ventricular mass [25-28]. The hypertrophic effect of AAS is thought to occur *via* androgen receptor activation, because AAS have a high affinity for these receptors [29], which are expressed by atrial and ventricular myocardial cells [30,31]. Marsh *et al*. [31] reported direct hypertrophic effects of testosterone and its metabolites in cultured rat ventricular myocytes. Evidence from a study of Altamirano *et al*. [32] demonstrated that, in cultured cardiomyocytes, testosterone-induced cardiomyocyte hypertrophy is mediated by the activation of the mammalian target of rapamycin (mTOR) signalling pathway. mTOR is a key element in the regulation of protein synthesis and cell growth [33,34]. Other studies have shown that pressure overload-induced cardiac hypertrophy can be prevented [35] or reversed [36] by rapamycin, a selective mTOR inhibitor.

Some authors have proposed that, at a physiological concentration of testosterone, androgen receptors are saturated, and the anabolic effects of supraphysiological doses of AAS occur *via* the interaction of these synthetic androgens with glucocorticoid receptors [37,38]. AAS have a low affinity for glucocorticoid receptors, but, at high concentrations, they can inhibit the binding of glucorticoids and block their catabolic effects [38,39].

AAS have also been associated with abnormalities in left ventricular (LV) structure with possible impaired diastolic relaxation [28] and, in a single case, the onset of dilated cardiomyopathy [40]. Structural alterations in the myocardium, the presence of focal myocardial fibrosis and contraction band necrosis were reported [15,41]. Behrendt and Boffin [42] observed structural disarray in the myofibrils and mitochondria in the myocardium of rats treated with AAS for three weeks. In fact, our group has found low numbers of cardiac nuclei and an increase in nuclear area in rats after 8 weeks of AAS treatment [43]. These data suggest a possible direct cardiotoxic effect mediated by AAS. In this context, Zaugg *et al.* [44] described that AAS induce apoptotic cell death in a dose-dependent manner in adult rat ventricular myocytes *in vitro*. Other evidence for this phenomenon has been published by Fanton *et al.* [45], whose histopathological examinations of hearts from treated rabbits revealed coronary thrombosis associated with left ventricular hypertrophy in 3 cases and lesions analogous to toxic or adrenergic myocarditis in all of the other treated animals. These findings were very similar to those observed after cardiac sudden death in 6 athletes with histories of anabolic steroid abuse. In addition, elevated caspase-3 activity in the hearts of treated rabbits (compared to controls) suggests that apoptosis is involved in the induction of norethandrolone-induced cardiac lesions, as described above. This finding is similar to previous data published by Norton *et al.* [46] who treated rats with high doses of AAS for three months. The perfusion of isoproterenol in an isolated heart preparation resulted in left-shifted LV systolic and diastolic pressure-volume (P-V) relationships, suggesting a decrease in the myocardial contractile response to adrenergic stimulation.

Because cardiac hypertrophy is frequently associated with sudden death and arrhythmias in endurance athletes and AAS users [47], the heart weight/body weight ratio is a useful index for assessing cardiac hypertrophy [48]. For example, in animals chronically treated with nandrolone decanoate, Andrade *et al*. [49] found an increase in heart weight and the heart weight/body weight ratio, and Rocha *et al.* [50] only found an increase in the heart weight/body weight ratio. Furthermore, Andrade *et al*. [49] have observed modest but significant myocyte hypertrophy in histological and morphometric analyses of haematoxylin-eosin stained tissue. These data are reinforced by our previous work that has showed the down-regulation of the gene expression of the Kv4.3 and KChIP2 subunits of the Ito channel, which are strongly associated with cardiac heart failure and hypertrophy, respectively [51-53].

In contrast, our histological analysis did not reveal an increase in the tissue collagen content or in the mRNA expression level of type-I or type-III collagen. These data partially disagree with the data by Rocha *et al.* [50], who found an increase in heart collagen content but not mRNA expression.

ELECTRICAL REMODELLING AND SUDDEN CARDIAC DEATH

Sudden cardiac death has frequently been associated with anabolic steroid abuse [45]. For example, a 12-year human longitudinal study comparing a group of bodybuilders who abused AAS to an age-matched control group composed of individuals from the general population found a 4.6-fold greater mortality in the former group. Cardiovascular damage was identified as the cause of death in 37.5% of these individuals [54]. However, the body of evidence supporting a direct cause-effect relationship among AAS abuse, ventricular arrhythmia and sudden cardiac death has not yet been clearly established, and little is known about the possible mechanisms responsible for arrhythmogenesis and sudden death in AAS abusers. Nevertheless, differential electrical, structural and autonomic changes have been found in animal models, in subjects using AAS and in the hearts of individuals that have died suddenly. These findings might help us understand the possible mechanisms involved in the sudden cardiac death.

In an animal model, our group has recently demonstrated cardiac electrical remodelling in rats that were treated with a supraphysiological dose of AAS (nandrolone decaonate) for 8 weeks. Two subunits that determine the transient outward potassium current (Ito), Kv1.4 and Kv4.3, were down-regulated in the AAS group (compared with the control group). The Ito density current was also diminished in these animals. The consequences of this electrical remodelling were manifested as a long action potential duration (APD) and a prolonged QT interval [43]. Together, all of these could create an environment that might lead to the development of several ventricular arrhythmias and sudden death. In this context, we have found electrical disturbances in human AAS users, both under basal conditions and after exercise

[55]. AAS users have a higher QT and QT dispersion (QTd) at rest (10% and 55%, respectively) and after exercise (17% and 43%, respectively), as compared to control subjects [55]. These data are consistent with the work by Sculthorpe *et al*. [56], who, using signal-averaged ECG (SAECG), found a higher incidence of abnormal SAECG immediately after exercise in the AAS group. All of these electrical disturbances strongly contribute to increased risk for ventricular arrhythmias and sudden cardiac death. However, Chung *et al*. [57] did not find changes in the QT intervals of AAS users, whereas Bigi *et al.* [58] and Stolt *et al*. [59] found short QT intervals in human AAS users. A short QT interval would help trigger re-entry ventricular arrhythmias that increase the risk of sudden cardiac death. Bigi *et al.* [58] hypothesised that androgen-induced QT-interval shortening could be mediated by the potassium current I_{K1}, because experimental studies on androgen-treated castrated animals reported increase in this potassium current [60] and Kir2.1 protein expression [61]. Liu *et al*. [60] also reported an increase in the I_{Kr} current but with no change in the ERG mRNA level, suggesting that androgens may have non-genomic effects.

The discrepancy found in the QT interval when comparing these results to our previous results [55] could be due to the different kind and/or dose of AAS. However, it appears inconsistent that both our study and the work published by Stolt [59] found an increase in the QTd (compared to AAS non-users). The QTd is a parameter that directly reflects an increase in ventricular electrical heterogeneity that is one of the most important predictors of sudden death in the ECG [62,63].

An increased QTd is found in various cardiac diseases and reflects cardiac autonomic imbalance and a greater susceptibility to complex ventricular arrhythmias (64,65).

In contrast, the decrease in the heart rate in the first minute after the cessation of exercise is primarily related to parasympathetic reactivation [66,67]. It has been proposed that delayed heart rate recovery might be a prognostic marker for abnormal or delayed parasympathetic reactivation [68,69]. A decrease in vagal activity is a risk factor for sudden death [70], and, thus, attenuated heart rate recovery after exercise might be an important predictor of sudden death [66,68]. In this context, our group has recently published that AAS users have slower heart rate recovery in the first minute compared with AAS-free subjects, suggesting that AAS impair parasympathetic activity [55]. In agreement with these results in humans, our group has previously shown that AAS-treated rats have a marked decrease in parasympathetic cardiac modulation, with a decreased high frequency (HF) power component of heart rate variability (HRV) compared to the

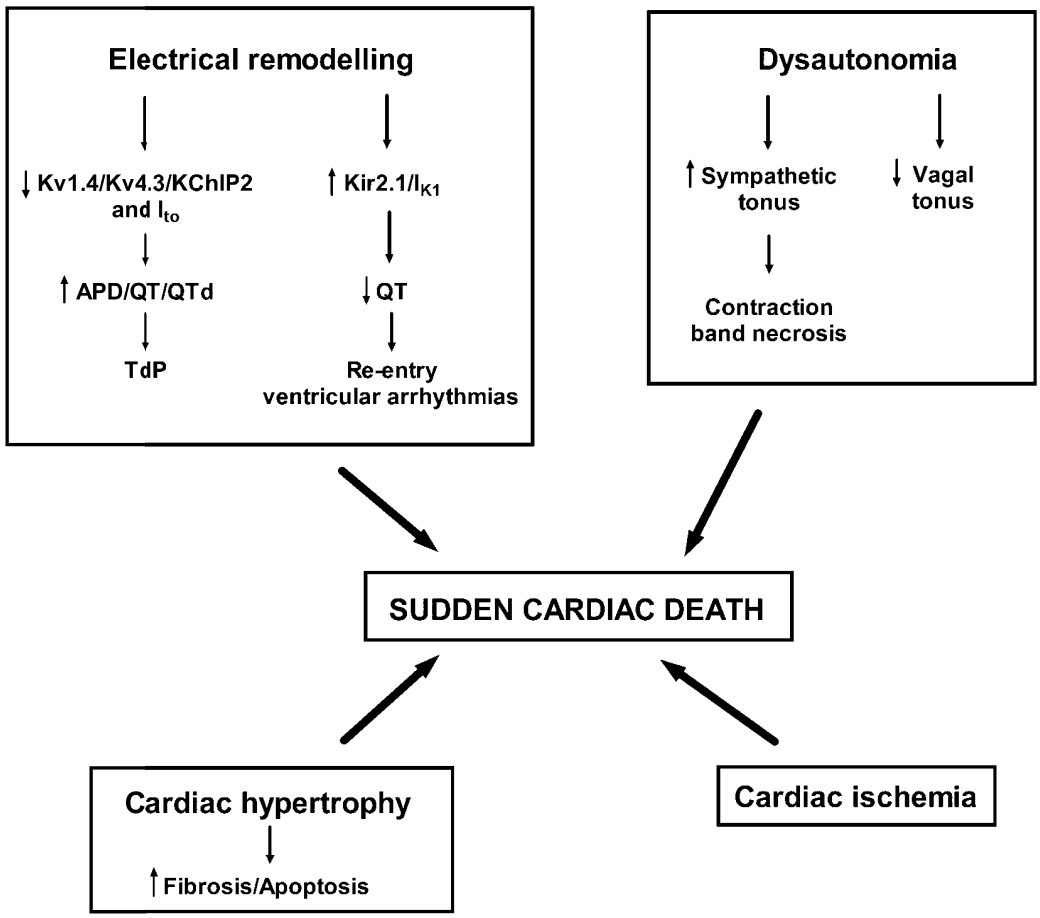

Fig. (1). AAS induces sudden cardiac death. APD: action potential duration; QT: QT interval; QTd: QT interval dispersion; TdP: torsades de pointes; I_{to}: transient outward potassium current channel; KChIP2: I_{to} β-subunit; Kv1.4 and Kv4.3: I_{to} α-subunits; Kir2.1: I_{K1} α-subunit.

control group. In the AAS group, the time-domain parasympathetic indexes RMSSD and pNN5 were also reduced, which corroborates the parasympathetic cardiac dysfunction found by the spectral analysis. Muscarinic blockade data reinforce the role of parasympathetic modulation in HF power and confirm the reliability of the HRV analysis methodology [48].

The results of HRV analyses in human and animal models with AAS-induced cardiac autonomic imbalances with reductions in parasympathetic cardiac modulation and increases in sympathetic cardiac modulation agree with *post mortem* histopathological data from AAS users, because the presence of contraction band necrosis in the myocardium is associated with adrenergic overstimulation [15,71].

In Fig. (**1**)**,** we summarise the topics discussed above. Thus, the scientific work that has been published to date, to the best of our knowledge, strongly supports the hypothesis that AAS abuse increases the risk of sudden cardiac death and induces autonomic, mechanical, electrical and morphological cardiac remodelling.

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REFERENCES

[1] Strauss, R.H.; Yesalis, C.E. Anabolic steroids in the athlete. *Annu. Rev. Med*., **1991**, *42*, 449-457.

[2] Schänzer, W. Metabolism of anabolic steroids. *Clin. Chem*., **1996**, *42*(7), 1001-1020.

[3] Kicman, A.T. Pharmacology of anabolic steroids. *Brit. J. Pharmacol*., **2008**, *154*, 502-521.

[4] Shahidi, N. T. A review of the chemistry, biological action, and clinical applications of anabolic-androgenic steroids. *Clin. Therapeutics*., **2001**, *23*, 1355-1390.

[5] Kennedy, M. C.; Lawrence, C. Anabolic steroid abuse and cardiac death. *Med. J. Aust.*, **1993**, *158*, 346-348.

[6] Yesalis, C.E.; Kennedy, N.J.; Kopstein, A.N.; Bahrke, M.S. Anabolic-androgenic steroid use in the United States. *JAMA*, **1993**, *270*, 1217-1221.

[7] NIDA. *Anabolic steroid abuse*. NIH Publication 06-3721. **2006**.

[8] Hartgens, F.; Kuipers, H. Effects of androgenic-anabolic steroids in athletes. *Sports Med.*, **2004**, *34*, 513-554.

[9] Payne, J.R.; Kotwinski, P.J.; Montgomery, H.E. Cardiac effects of anabolic steroids. *Heart*, **2004**, *90*, 473-475.

[10] Silva, P.R.P.; Machado-Junior, L.C.; Figueiredo, V.C.; Cioffi, A.P.; Prestes, M.C.; Czepielewski, M.A. Prevalência do uso de agentes anabólicos em praticantes de musculação de Porto Alegre. *Arq Bras Endocrinol Metab*., **2007**, *51*, 104-110.

[11] Evans, N.A. Current Concepts in Anabolic-Androgenic Steroids. *Am. J. Sports Med*., **2004**, *32*, 534-542.

[12] Casavant, M.J.; Blake, K.; Griffith, J.; Yates, A.; Copley, L.M. Consequences of use of anabolic androgenic steroids. *Pediatr. Clin. N. Am.*, **2007**, *54*, 677–690

[13] Sullivan, M.L.; Martinez, C.M., Gennis, P., Gallagher, E.J. The cardiac toxicity of anabolic steroids. *Prog. Cardiovasc. Dis.*, **1998**, *41*, 1-15.

[14] Kuipers, H. Anabolic steroids: side effects. In: *Encyclopedia of Sports Medicine and Science*, T.D.Fahey (Editor). Internet Society for Sport Science: http://sportsci.org. 7 March 1998.

[15] Fineschi, V.; Baroldi, G.; Monciotti, F.; Reattelli, L. P.; Turillazzi, E. Anabolic steroid abuse and cardiac sudden death: A pathologic study. *Arch. Pathol. Lab. Med*., **2001**, *125*, 253–255

[16] Yavari, A. Abuse of anabolic androgenic steroids. *J. Stress Physiol. Biochem.*, **2009**, *5*(3), 22-32.

[17] Melchert, R.B.; Welder, A. A. Cardiovascular effects of androgenic-anabolic steroids. *Med. Sci. Sports Exerc.*, **1995**, *27*, 1252-1262.

[18] Hartgens, F.; Rietjens, G.; Keizer, H.A.; Kuipers, H.; Wolffenbuttel, B.H. Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein. *Brit. J. Sports Med*., **2004**, *38*(3), 253-259.

[19] Grundy, S. M. Small LDL, atherogenic dyslipidemia, and metabolic syndrome. *Circulation*, **1997**, *95*, 1-4.

[20] Stergiopoulos, K.; Brennan, J.J.; Mathews, R.; Setaro, J.F.; Kort, S. Anabolic steroids, acute myocardial infarction and polycythemia: A case report and review of the literature. *Vasc. Health Risk Manag*., **2008**, *4*, 1475–1480.

[21] Friehs, I.; del Nido, P. J. Increased susceptibility of hypertrophied hearts to ischemic injury. *Ann. Thorac. Surg*., **2003**, *75*, S678–S684.

[22] Tagarakis, C. V. M.; Bloch, W.; Hartmann, G.; Hollmann, W.; Addicks, K. Anabolic steroids impair the exercise-induced growth of the cardiac capillary bed. *Int. J. Sports Med*., **2000**, *21*, 412-418.

[23] Du Toit, E. F.; Rossouw, E.; van Rooyen, J.; Lochner, A. Proposed mechanisms for the anabolic steroid-induced increase in myocardial susceptibility to ischaemia/reperfusion injury. *Cardiovasc. J. South. Afr.*, **2005**, *16*, 21–28.

[24] Chaves, E. A.; Pereira-Junior, P. P.; Fortunato, R. S.; Masuda, M. O.; Campos de Carvalho, A. C.; Carvalho, D. P.; Oliveira, M. F.; Nascimento, J. H. M. Nandrolone decanoate impairs exercise-induced cardioprotection: Role of antioxidant enzymes. *J. Steroid Biochem. .Mol. Biol*., **2006**, *99*, 223–230.

[25] Nieminen, M. S.; Ramo, M. P.; Viitasalo, M.; Heikkilaf, P.; Karjalainen, J.; Mantysaarii, M.; Heikkila, J. Serious cardiovascular side effects of large doses of anabolic steroids in weight lifters. *Eur. Heart J.*, **1996**, *17*, 1576-1583.

[26] McKillop, G.; Todd, I.C.; Ballantyne, D. Increased left ventricular mass in a bodybuilder using anabolic steroids. *Brit. J. Sports Med*,. **1986,** *20*(4), 151-152.

[27] Karila, T.A.M.; Karjalainen, J.E.; Mäntysaari, M.J.; Viitasalo, M.T.; Seppaälä, T.A. Anabolic androgenic steroids produce dose-dependent increase in left ventricular mass in power athletes, and this effect is potentiated by concomitant use of growth hormone. *Int. J. Sports Med*., **2003**, *24*, 337-343.

[28] Nottin, S.; Nguyen, L-D.; Terbah, M.; Obert, P. Cardiovascular effects of androgenic anabolic steroids in male bodybuilders determined by tissue Doppler imaging. *Am. J. Cardiol,*. **2006**, *97*, 912–915.

[29] Jänne, O. A.; Bardin, C. W. Androgen and antiandrogen receptor binding. *Ann. Rev. Physiol.*, **1984**, *46*, 107-18.

[30] McGill, H.C.; Anselmo, V.C.; Buchanan, J.M.; Sheridan, P. J. The heart is a target organ for androgen. *Science*, **1980,** *207*, 775-777.

[31] Marsh, J.D.; Lehmann, M.H.; Ritchie, R.H.; Gwathmey, J.K.; Green, G.E.; Schiebinger, R.J. Androgen receptors mediate hypertrophy in cardiac myocytes. *Circulation*, **1998**, *98*, 256-261.

[32] Altamirano, F.; Oyarce, C.; Silva, P.; Toyos, M.; Wilson, C. Lavandero, S.; Uhlén, P.; Estrada, M. Testosterone induces cardiomyocyte hypertrophy through mammalian target of rapamycin complex 1 pathway. *J. Endocrinol.*, **2009,** *202*, 299–307.

[33] Schmelzle, T.; Hall, M. N. TOR, a central controller of cell growth. *Cell*, **2000**, *103*, 253-262.

[34] Proud, C. G. Ras, PI3-kinase and mTOR signaling in cardiac hypertrophy. *Cardiovasc. Re*s., **2004**, *63*, 403-413.

[35] Shioi, T.; McMullen, J. R.; Tarnavski, O.; Coverso, K.; Sherwood, M. C. Rapamycin attenuates load-induced cardiac hypertrophy in mice. *Circulation*, **2003**, *107*, 1664-1670.

[36] McMullen, J.R.; Sherwood, M.C.; Tarnavski, O.; Zhang, L.; Dorfman, A.L.; Shioi, T.; Izumo, S. Inhibition of mTOR signaling with rapamycin regresses established cardiac hypertrophy induced by pressure overload. *Circulation*. **2004**, *109*, 3050-3055.

[37] Mayer, M.; Rosen, F. Interaction of anabolic steroids with glucocorticoid receptor sites in rat muscle cytosol. *Am. J. Physiol.*, **1975**, *229*, 1381-1386.1975;

[38] Jänne, O.A. Androgen interaction through multiple steroid receptors. In: Geraline C. Lin and Lynda Erinoff. Anabolic steroid abuse. Research Monograph 102, **1990**. U. S. Department of Health and Human Services, National Institute on Drug Abuse, Rockville, USA. P178-186.

[39] Rockhold, R. W. Cardiovascular toxicity of anabolic steroids. *Annu. Rev. Pharmacol. Toxicol*., **1993**, *33*, 497-520.

[40] Ferrera, P.C.; Putnan, D.L.; Verdlle, V.P. Anabolic steroid use as a possible precipitant of dilated cardiomyopathy. *Cardiology*, **1997**, *88*, 218–220,

[41] Fineschi, V.; Riezzo, I.; Centini, F.; Silingardi, E.; Licata, M.; Beduschi, G.; Karch, S. B. Sudden cardiac death during anabolic steroid abuse: morphologic and toxicologic findings in two fatal cases of bodybuilders. *Int. J. Legal Med*., **2007**, *121*, 48–53.

[42] Behrendt, H.; Boffin, H. Myocardial Cell Lesions Caused by an Anabolic Hormone. *Cell Tiss. Res.*, **1977**, *181*, 423-426.

[43] Medei, E.; Marocolo, M.; Rodrigues, D.C.; Arantes, P.C., Takiya, C.M.; Silva, J.; Rondinelli, E.; Goldenberg, R.C.S.; Campos de Carvalho, A.C.; Nascimento, J.H.M. Chronic treatment with anabolic steroids induces ventricular repolarization disturbances: cellular, ionic and molecular mechanism. *J. Mol. Cell. Cardiol.*, **2010**, *49*, 165-75.

[44] Zaugg, M.; Jamali, N. Z.; Lucchinetti, E.; Xu, W.; Alam, M.; Shafiq, S. A.; Siddiqui, M. A. Anabolic-androgenic steroids induce apoptotic cell death in adult rat ventricular myocytes. *J. Cell. Physiol.*, **2001**, *187*(1), 90-95.

[45] Fanton, L.; Belhani, D.; Vaillant, F.; Tabib, A.; Gomez, L.; Descotes, J.; Dehina, L.; Bui-Xuan, B.; Malicier, D.; Timour, Q. Heart lesions associated with anabolic steroid abuse: comparison of post-mortem findings in athletes and norethandrolone-induced lesions in rabbits. *Exp. Toxicol. Pathol*., **2009,** *61*(4), 317-23.

[46] Norton, G.R.; Trifunovic, B.; Woodiwiss, A.J. Attenuated beta-adrenoceptor-mediated cardiac contractile responses following androgenic steroid administration to sedentary rats. *Eur. J. Appl. Physiol.*, **2000,** *81*, 310-316.

[47] Maron, B. J. Sudden death in young athletes. *N. Engl. J. Med*., **2003**, *349*, 1064-1075

[48] Pereira-Junior, P.P., Chaves, E.A.; Costa-e-Sousa, R. H.; Masuda, M. O.; de Carvalho, A. C., Nascimento, J. H. Cardiac autonomic dysfunction in rats chronically treated with anabolic steroid. *Eur. J. Appl. Physiol*., **2006**, *96*, 487-94

[49] Andrade, T. U.; Santos, M. C.; Busato, V. C.; Medeiros, A. R.; Abreu, G. R.; Moysés, M. R., Bissoli, N.S. Higher physiological doses of nandrolone decanoate do not influence the Bezold-Jarish reflex control of bradycardia. *Arch. Med. Res*., **2008**, *39*, 27-32.

[50] Rocha, F.L.; Carmo, E.C.; Roque, F.R.; Hashimoto, N.Y.; Rossoni, L.V.; Frimm, C.; Anéas, I.;, Negrão, C.E., Krieger, J.E., Oliveira, E.M. Anabolic steroids induce cardiac renin-angiotensin system and impair the beneficial effects of aerobic training in rats. *Am. J. Physiol. Heart Circ. Physiol*., **2007**, *293*, H3575-H3583.

[51] Dixon, J.E.; Shi, W.; Wang, H-S.; McDonald, C.; Yu, H.; Wymore, R.S.; Cohen, I.S.; McKinnon D. Role of the Kv4.3 K+ channel in ventricular muscle. A molecular correlate for the transient outward current. *Circ. Res*., **1996**, *79*, 659–668.

[52] Radicke, S.; Cotella, D.; Graf, E.M., Banse, U.; Jost, N.;Varró, A.; Tseng, G.N.; Ravens, U.; Wettwer E. Functional modulation of the transient outward current Ito by KCNE beta-subunits and regional distribution in human non-failing and failing hearts. *Cardiovasc. Res.*, **2006**, *71*, 695–703.

[53] Jin, H.; Hadri, L.; Palomeque, J.; Morel, C.; Karakikes, I.; Kaprielian, R.; Hajjar, R.; Lebeche, D. KChIP2 attenuates cardiac hypertrophy through regulation of I(to) and intracellular calcium signaling. *J. Mol. Cell. Cardiol.* **2010**, *48*, 1169-1179.

[54] Parssinen, M.; Kujala, U.; Vartiainen, E.; Sarna, S.; Seppala, T. Increased premature mortality of competitive powerlifters suspected to have used anabolic agents. *Int. J. Sports Med*., **2000**, *21*, 225-227.

[55] Maior, A. S.; Menezes, P.; Pedrosa, R.C.; Carvalho, D.P.; Soares, P. P.; Nascimento, J. H. M. Abnormal cardiac repolarization in anabolic androgenic steroid users carrying out submaximal exercise testing. . *Clin. Exp. Pharmacol. Physiol*., **2010**, *37*, 1129-1133.

[56] Sculthorpe. N.; Grace, F.; Jones, P.; Davies, B. Evidence of Altered Cardiac Electrophysiology Following Prolonged Androgenic Anabolic Steroid Use. *Cardiovasc Toxicol*., **2010**, *10*, 239-243.

[57] Chung, T., Kelleher, S.; Liu, P.Y.; Conway, A.J.; Kritharides, L.; Handelsman, D. J. Effects of testosterone and nandrolone on cardiac function: a randomized, placebo-controlled study. *Clin. Endocrinol*. **2007**, *66*(2), 235-45.

[58] Bigi, M.A.; Aslani, A., Aslani, A. Short QT interval: A novel predictor of androgen abuse in strength trained athletes. *Ann. Noninvasive Electrocardiol*., **2009**, *14*(1), 35-9.

[59] Stolt, A.; Karila, T.; Viitasalo, M., Mäntysaari, M.; Kujala, U.M.; Karjalainen, J. QT interval and QT dispersion in endurance athletes and in power athletes using large doses of anabolic steroids. *Am. J. Cardiol*., **1999**, *84*(3), 364-366.

[60] Liu, X-K.; Katchman, A., Whitfield, B.H.; Wan, G.; Janowski, E.M.; Woosley, R.L.; Eber,t S. N. *In vivo* androgen treatment shortens the QT interval and increases the densities of inward and delayed rectifier potassium currents in orchiectomized male rabbits. *Cardiovasc. Res*., **2003**, *57*, 28-36.

[61] Fülöp, L.; Bányász, T.; Szabó, G.; Tóth, I.B.; Biró, T.; Lôrincz, I.; Balogh, Á.; Petô, K.; Mikó, I.; Nánási, P.P. Effects of sex hormones on ECG parameters and expression of cardiac íon channels in dogs. *Acta Physiol*., **2006**, *188*, 163-171.

[62] Lonati, L. M.; Magnaghi, G.; Bizzi, C.; Leonetti, G. Patterns of QT dispersion in athletic and hypertensive left ventricular hypertrophy. *Ann. Noninvasive Electrocardiol*., **2004**, *9*(3), 252-256.

[63] Salles, G.; Xavier, S.; Sousa, A.; Hasslocher-Moreno, A.; Cardoso, C. Prognostic value of QT interval parameters for mortality risk stratification in Chagas' disease: results of a long-term follow-up study. *Circulation*, **2003**, 108, 305-312.

[64] Anastasiou-Nana, M.I.; Nanas, J.N.; Karagounis, L.A.; Tsagalou, E.P.; Alexopoulos, G.E.; Toumanidis, S.; Gerali, S.; Stamatelopoulos, S.F., Moulopoulos, S.D. Relation of dispersion of QRS and QT in patients with advanced congestive heart failure to cardiac and sudden death mortality. *Am. J. Cardiol*., **2000**, *85*, 1212-1217.

[65] Piccirillo, G.; Viola, E.; Nocco, M.; Santagada, E.; Durante, M., Bucca, C.; Marigliano, V. Autonomic modulation and QT interval dispersion in hypertensive subjects with anxiety. *Hypertension*, **1999**, *34*, 242-246.

[66] Jouven, X.; Empana, J.P.; Schwartz, P.J.; Desnos, M.; Courbon, D.; Ducimetière, P. Heart-rate profile during exercise as a predictor of sudden death. *N. Engl. J. Med*., **2005**, 352, 1951-1958.

[67] Georgoulias, P.; Orfanakis, A.; Demakopoulos, N.; Xaplanteris, P.; Mortzos, G.; Vardas, P.; Karkavitsas, N. Abnormal heart rate recovery immediately after treadmill testing: correlation with clinical, exercise testing, and myocardial perfusion parameters. *J. Nucl. Cardiol*., **2003**, *10*, 498-505.

[68] Cole. C.R.; Blackstone, E.H.; Pashkow, F.J.; Snader, C.E.; Lauer, M.S. Heart-rate recovery immediately after exercise as a predictor of mortality. *N. Engl. J. Med*., **1999**, *341*, 1351-1357.

[69] Sundaram, S.; Carnethon, M.; Polito, K.; Kadish, A.H.; Goldberger, J.J. Autonomic effects on QT- RR interval dynamics after exercise. *Am. J. Physiol. Heart Circ. Physiol*., **2008**, *294*: H490-H497.

[70] Lahiri, M.K.; Kannankeril, P.J.; Goldberger, J.J. Assessment of Autonomic Function in Cardiovascular Disease Physiological Basis and Prognostic Implications. *J. Am. Coll. Cardiol.*, **2008**, *51*, 1725-1733.

[71] Baroldi, G.; Mittleman, R.E.; Parolini, M.; Silver, M. D.; Fineschi, V. Myocardial contraction bands: Definition, quantification and significance in forensic pathology. *Int. J. Legal Med*., **2001**, *115*, 142-151.

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