

Position Paper

ESC Study Group of Sports Cardiology Position Paper on adverse cardiovascular effects of doping in athletes

Asterios Deligiannis^a, Hans Björnstad^b, Francois Carre^c, Hein Heidbüchel^d, Evangelia Kouidi^a, Nicole M. Panhuyzen-Goedkoop^e, Fabio Pigozzi^f, Wilhelm Schänzer^g and Luc Vanhees^h on behalf of the ESC Study Group of Sports Cardiology

^aLaboratory of Sports Medicine, Aristotle University, Thessaloniki, Greece, ^bDepartment of Heart Disease, Haukeland University Hospital, Bergen, Norway, ^cUnité Biologie et Médecine du Sport, Hôpital Pontchaillou, Rennes, France, ^dUniversity Hospital Gasthuisberg, Leuven, Belgium, ^eDepartment of Cardiology, Radboud University Hospital and Department of Sports Cardiology and Cardiac Rehabilitation, St Maartens Kliniek, Nijmegen, The Netherlands, ^fSports Medicine Department, University Institute of Movement Sciences, Roma, Italy, ^gInstitute of Biochemistry, German Sport University, Cologne, Germany and ^hDepartment of Rehabilitation Sciences, Leuven, Belgium.

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The use of doping substances and methods is extensive not only among elite athletes, but also among amateur and recreational athletes. Many types of drugs are used by athletes to enhance performance, to reduce anxiety, to increase muscle mass, to reduce weight or to mask the use of other drugs during testing. However, the abuse of doping substances and methods has been associated with the occurrence of numerous health side-effects. The adverse effects depend on the type of the consumed drug, as well as the amount and duration of intake and the sensitivity of the body, since there is a large inter-individual variability in responses to a drug. Usually the doses used in sports are much higher than those used for therapeutic purposes and the use of several drugs in combination is frequent, leading to higher risk of side-effects. Among biomedical side-effects of doping, the cardiovascular ones are the most deleterious. Myocardial infarction, hyperlipidemia, hypertension, thrombosis, arrhythmogenesis, heart failure and sudden cardiac death have been noted following drug abuse. This paper reviews the literature on the adverse cardiovascular effects after abuse of prohibited substances and methods in athletes, aiming to inform physicians, trainers and athletes and to discourage individuals from using drugs during sports. *Eur J Cardiovasc Prev Rehabil* 13:687–694 © 2006 The European Society of Cardiology

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Introduction

Doping is defined as ‘the presence of a Prohibited Substance or its Metabolites or Markers in an Athlete’s bodily Specimen and the Use or Attempted Use of a Prohibited Substance or a Prohibited Method to increase athletic performance’ [1]. In 1967, for the first time, the International Olympic Committee (IOC) made up a list

of banned substances, which has been updated and adapted to changes in the use of doping substances or methods in sports ever since. Since 2004 the World Anti-Doping Agency (WADA) has been coordinating the anti-doping fight. In the WADA 2005 list of prohibited substances and methods [2], the following categories of substances are included:

- (1) anabolic agents, hormones and related substances, beta-2 agonists, agents with anti-estrogenic activity, and diuretics and other masking agents are always prohibited;

Correspondence and requests for reprints to Dr Asterios Deligiannis MD, Professor of Sports Medicine, 26 Agias Sofias Street, 546 22 Thessaloniki, Greece.
Tel: +30 2310 992181; fax: +30 2310 992183;
e-mail: stergios@med.auth.gr

- (2) stimulants, narcotics, cannabinoids and glucocorticosteroids are prohibited in competition; and
- (3) alcohol and beta-blockers are prohibited in particular sports.

In terms of prohibited methods the following categories are included: enhancement of oxygen transfer; pharmacological, chemical and physical manipulation; and gene doping.

All these are considered as doping and therefore are forbidden, practically because of two main reasons: performance enhancing and, thus, unfair competition, and health risks. The health side-effects of doping depend on the type of the consumed drug, as well as the amount and duration of intake and the sensitivity of the body. Additionally, athletes often use a combination of several drugs at high doses, which are constantly changing, leading to interactions and counteractions. Among biomedical side-effects of doping, the cardiovascular ones are the most deleterious, with the potential to lead to increased morbidity and mortality (Tables 1 and 2). It is important to stress, and easy to understand, that only sparse data and isolated clinical cases are actually available. Thus, despite the recent increase in the number of publications, it is difficult to know the real hazard and effects of doping drugs and methods upon the cardiovascular system, particularly during acute exercise.

Table 1 WADA doping list of drugs affecting cardiovascular system

Prohibited in competitive sports	Prohibited in certain competitive sports	Not prohibited
Stimulants	Beta blockers	Antihypertensive drugs
amphetamine	atenolol	calcium blockers
cocaine	bisoprolol	ACE Inhibitors
ephedrine	carvedilol	AR Blockers
fencamfamin	esmolol	Local anesthetic
modafinil	labetolol	xylocaine
nikethamide	metoprolol	Analgesics
Narcotics	pindolol	acetylsalicylic acid
morphine	propranolol	Cholesterol-reducing drugs
pethidine	sotalol	fluvastatin
Beta-2 agonists		clofibrate
reproterol		colestipol
isoprenaline		ezetimibe
Masking drugs (diuretics)		gemfibrozil
amiloride		atorvastatin
chlortalidone		acipimox
etacrynic acid		colestyramine
furosemide		pravastatin
Anabolic steroids		simvastatin
testosterone		
nandrolone		
stanozolol		
metandienone		
Glucocorticosteroids		
betamethasone		
triamcinolone		

ACE, angiotensin-converting enzyme; AR, angiotensin II type 1 receptor.

Table 2 Cardiac side-effects of prohibited substances

	Hyper-tension	Arrhyth-mias	LVH	CAD	MI	HF	SCD
AAS	+	+	+	+	+	+	+
hGH		+	+			+	+
EPO	+					+	+
Beta-2 agonists		+			+	+	+
Diuretics		+					
Amphetamines	+	+			+	+	+
Cocaine	+	+		+	+	+	+
Ephedrine	+	+		+	+	+	+
Narcotics							+
Cannabinoids		+			+		+
Glucocorticosteroids	+			+			
Alcohol	+	+			+	+	+

+ Indicates an effect on a parameter; LVH, left ventricular hypertrophy; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; SCD, sudden cardiac death; AAS, androgenic-anabolic steroids; hGH, human growth hormone; EPO, erythropoietin.

Substances and methods prohibited at all times

Androgenic-anabolic steroids

The use of androgenic-anabolic steroids (AASs) is common among all kind of athletes, amateur, elite and recreational. Anabolic steroids have the potential to increase lean muscle mass and strength under certain conditions [3]. Tetrahydrogestrinone is a recently identified compound, being developed as a potent androgen [4]. Several reports associate AAS abuse with serious cardiovascular disorders, such as ischemic heart disease, arterial hypertension, cardiomyopathy, heart failure, QT dispersion, arrhythmias, ventricular thrombosis, etc. [5,6]. Myocardial infarction and sudden cardiac death are reported as the most dramatic manifestations in athletes who had taken massive amounts of AASs [5,7-9]. Melchert and Welder [10] demonstrated four hypothetical models of anabolic-induced adverse cardiovascular effects:

- (1) an 'atherogenic' model involving the effects of AASs on lipoprotein concentrations;
- (2) a 'thrombogenic' model involving the effects of AASs on clotting factors and platelets;
- (3) a 'vasospasm' model involving the effects of AASs on the vascular nitric oxide system;
- (4) a 'direct myocardial injury' model involving the effects of AASs on myocardial cells.

Lipoprotein profile and atherogenesis AAS administration is found to cause a marked reduction of high-density lipoprotein (HDL) cholesterol that ranges from 39 to 70% [11]. The effects are dose dependent and vary with types of substances used. The most pronounced decrease is shown within a few days after starting the intake and after about 8 weeks no further alteration is observed [12,13]. Particularly, HDL₂-cholesterol seems to be most affected [12,13]. It is found that the orally taken 17 α -alkylated substances are most potent in this respect [12].

The stimulation of hepatic triglyceride lipase that regulates serum lipids is responsible for this reduction [14]. In parallel, there is an increase of low-density lipoprotein (LDL) cholesterol, especially caused by oral administration [12]. Additionally, AASs induce a decline in apolipoprotein B-1 and increases of apolipoprotein A [12,13]. On the other hand, most studies in athletes found no changes of either cholesterol or triglyceride levels due to AAS administration [12,13]. There is evidence that several AASs in high doses beneficially alter lipoprotein (a) levels [15]. However, there is a complete recovery of serum lipid and lipoproteins after AAS withdrawal within a few months, which depends on the duration of intake [13]. Androgens may also be pro-atherogenic, promoting cell adhesion [16]. Additionally, they are found to promote monocyte adhesion to endothelial cells and macrophage lipid loading [17,18].

Thrombogenesis AASs have been demonstrated to decrease fibrinolytic activity and synthesis of prostacyclin and to increase platelet aggregation and endothelium release of proteins C and S [19–21]. Additionally, AAS abuse is found to affect the hemostatic system, causing its accelerated activation, as evidenced by increased generation of both thrombin and plasmin [21,22]. These changes could reflect a thrombotic diathesis that may contribute to vascular occlusion. These adverse effects are exacerbated in cases of dehydration and catecholaminergic stress which are often associated with physical exercise.

Coronary vasoconstriction Testosterone has been found to inhibit extraneuronal uptake of neuroamines and increase the vascular response to norepinephrine. Sader *et al.* [23] found that the use of AASs is associated with impaired vascular reactivity, but not with arterial thickening or endothelial dysfunction. AASs are associated with impaired arterial reactivity and enhanced endothelium-dependent dilatation in adult men [24,25]. However, the use of AASs was not associated with significant arterial thickening and endothelial dysfunction in healthy young men [23].

Direct myocardial injury AAS intake leads to myocyte hypertrophy [26,27] with changes in the contractile apparatus, with disintegration and Z-band distortions or dissolution in the sarcomere, to disturbances in the mitochondria (like swelling damage), change of myofibril/mitochondria ratio and to intracellular lipid accumulation [28]. Moreover, cellular swelling and increased intercellular collagen deposition have been reported [29]. Luke *et al.* [30] found extensive myocardial fibrosis, foci of necrosis and myocytes with contraction band necrosis in a weight-lifter using anabolic steroids. Also, lack of blood supply in a hypertrophic myocardium may contribute to myocardial fibrosis [31]. Additionally, there is evidence that AASs induce apoptotic cell death in adult ventricular myocytes, affecting cardiac contractility [32].

The effects of AASs on global left ventricular (LV) structure and function are still unequivocal. A majority of echocardiographic studies have shown larger posterior wall and interventricular septal thickness, as well as an increased LV mass and mass index with the use of AASs [33–35]. On the contrary, some studies have not observed any differences in the echocardiograms between AAS users and non-users in strength athletes [36,37]. Additionally, AAS intake was not found to affect LV systolic and possibly diastolic function [34–36]. However, there is evidence that the use of AASs leads to a decrease in the contribution of LV passive filling to LV filling associated with a decrease in LV relaxation properties [38,39].

AASs may influence LV structure through direct adverse myocardial effects (as mentioned above) reinforced by mineralocorticoid-like effects causing hypertension. Thus, unlike the physiological cardiac hypertrophy observed after physical training, cardiac hypertrophy induced by AAS is pathological, with an increased fibrosis and an inadequate myofibril/arterial vessel ratio. When cardiac hypertrophy is observed it persists after the cessation of AAS abuse [40].

Cardiac arrhythmias AASs are pro-arrhythmic through the myocardial structural changes they may induce, as described above. Moreover, they have electrophysiological effects. They cause a profound and prolonged depression of the stimulation threshold of the heart [41]. Additionally, they influence electrolyte concentrations, increasing levels of potassium, sodium, calcium and phosphate, which can ultimately result in atrial and ventricular fibrillation [42,43]. Nieminen *et al.* [21] reported the increased automaticity as the possible electrophysiological mechanism of ventricular fibrillation, which was observed in an athlete using anabolics. AASs also affect the cardiac sympathetic nervous system, causing transient depletion and degeneration of sympathetic axon terminals [44]. Anabolic agents have been shown to increase the pressor response to catecholamines in animals [45]. All these alterations may lead to an increased vulnerability to serious dysrhythmias.

Blood pressure An elevation of either systolic and or diastolic blood pressure (BP) has been observed as a result of AAS abuse in many studies [46,47]. Androgens seem to have a more intense effect on BP than anabolics, mainly due to sodium and water retention [46]. On the other hand, there are studies that could not detect any significant alteration of BP in athletes who used AASs [35,48].

Peptide hormones, mimetics and analogues

The most commonly used substances from this class are human growth hormone (hGH) and insulin-like growth factor 1 (IGF-1), as well as erythropoietin (EPO).

Human growth hormone (hGH) and insulin-like growth factor 1 Chronic hGH excess leads to cardiomyopathy, characterized by myocardial hypertrophy with interstitial fibrosis, lympho-mononuclear infiltration and areas of monocyte necrosis. Additionally, hGH excess increases the incidence of arrhythmias and thus cardiovascular mortality [49].

Erythropoietin There is a dose-dependent increase in hematological parameters after administration of recombinant human erythropoietin (rHuEPO) [50]. Its effects last several days after its last intake, when the erythropoietin concentrations are in the range of normal values [51]. The misuse of rHuEPO causes increased viscosity of the blood which, in combination with the elevated hematocrit, leads to increased risk of thrombosis and embolisms [52]. Additionally, increased afterload, elevated blood viscosity and the loss of hypoxia-induced vasodilation lead to arterial hypertension and perhaps to cardiac dysfunction [53]. A fatal reduction of heart rate during the night has also been reported [54].

Beta-2 agonists

Beta-2 agonists, such as clenbuterol and salbutamol, when administered orally, appear to improve muscular strength due to their potential role in increasing muscle mass. Clenbuterol is also popular for its reduction of subcutaneous fat [55]. It is well known that formoterol, salbutamol, salmeterol and terbutaline are widely used in treating asthma. Thus, they are allowed to be administered by inhalation, if the athlete has applied in advance for a therapeutic use exception (TUE). Use of beta-2 agonists has been found to increase the risk for adverse cardiovascular events. They may precipitate ischemia, congestive heart failure, arrhythmias and sudden death [56]. They activate cardiac and peripheral beta-2 adrenoceptors, inducing positive chronotropic and inotropic effects and vasodilation with coronary blood flow redistribution [56,57]. Additionally, initiation of treatment reduces potassium concentrations and causes other metabolic and electrical changes, including prolonged QT interval [57]. Chodorowski and Sein-Anand [58] described a case of acute, unintentional intoxication with clenbuterol in a bodybuilder, who appeared with tachycardia, headache, dizziness, tremor, sweats, muscle weakness and agitation.

Diuretics and other masking agents

Diuretics may be taken mainly to mask drug contents in the urine [3]. Diuretics may cause imbalance of electrolytes leading to arrhythmias. Especially, inhibition of hydroxysteroid dehydrogenase is found to cause an increase in cholesterol and triglyceride levels [59]. In athletes with silent genetic mutations of sodium and potassium channels, electrolytic imbalance may lead to subsequent QT prolongation and arrhythmias.

Substances and methods prohibited only in competition **Stimulants**

Stimulants, like amphetamines and cocaine, act on the central nervous system through dopamine, norepinephrine and serotonin secretion.

Amphetamines Amphetamines may increase time to exhaustion by masking the physiological response to fatigue [3]. Amphetamine intoxication or long-term exposure can result in stroke, hypertension, tachycardia or bradycardia, cardiac rhythm disturbances, coronary events, coma and death [3,60,61]. Smoking of crystal methamphetamine, as well as chronic oral abuse of dextroamphetamine, are reported to have caused cardiomyopathy [62,63]. In another case, smoking of crystal methamphetamine has produced diffuse vasospasm that resulted in acute myocardial infarction, cardiogenic shock and death [63].

Cocaine Cocaine is an alkaloid extracted from the erythroxyton coca. Cocaine and other sympathomimetic drugs seem to have little or no effect on athletic performance [3]. Myocardial ischemia and infarction in individuals with normal or atherosclerotic coronary arteries have previously been described as an important causative factor of morbidity and mortality [64,65]. Cocaine has a local anesthetic property on the heart, due to its ability to block sodium and potassium channels, as well as a potent sympathomimetic and a vagolytic effect [66,67]. Moreover, it increases adenyl cyclase activity [65]. Interestingly, development of myocardial infarction is independent of cocaine dose [65]. The possible mechanisms by which cocaine causes myocardial ischemia and coronary artery thrombosis include an increase in myocardial oxygen demand (increasing heart rate and blood pressure), a decrease in oxygen supply as a result of coronary vasospasm and, also, an ingressive thrombogenesis [65–68]. Ventricular arrhythmias, QT- and PR-interval prolongation, and A-V conduction disorders are a precursor to sudden death in cocaine users [69]. It is likely that cocaine induces ventricular arrhythmias with or without underlying myocardial pathology [65,66]. Rapid adrenergic stress, local anesthetic properties and a direct toxic effect of cocaine on the myocardium are related with the arrhythmic potential of the drug [65,66]. Pulmonary edema mediated by increased endothelial permeability of the capillaries is seen commonly in crack abuse [68]. Other cardiovascular adverse reactions include the appearance of myocarditis and dilated cardiomyopathy, infective endocarditis, ruptured aortic aneurysm, vascular thrombosis, hypertension and cerebrovascular accidents [64,65]. Death from cocaine can occur within some minutes, suggesting direct cardiac toxicity, fatal arrhythmia and depression of medullary respiratory centers [67].

Ephedrine alkaloids Ephedrine is effective orally and appears to have longer-acting potency than catecholamines.

Ephedrine-containing preparations, such as ma-huang, 'herbal Ecstasy' and others, in small dosages stimulate the heart, increasing the rate and force of contraction [70]. Moreover, ephedrine raises the blood pressure by constriction of blood vessels [70]. Several studies have shown that ephedra abuse may lead to acute constriction and thrombosis of the coronary and other arteries [70,71]. Moreover, the adrenergic effects of ephedrine may lead to the development of cardiac arrhythmias [70,71]. Therefore, cardiovascular complications, such as acute myocardial infarction, severe hypertension, myocarditis, stroke, arrhythmias and sudden cardiac death, have become a recognized problem due to ephedrine use in athletes [70–73].

Narcotics

Some preparations (for example, morphine, heroin, codeine) are derived directly from opium, while others are semi-synthetic or entirely synthetic. Narcotic analgesics are not necessarily ergogenic but their use can be harmful in cases where they allow the participation of an athlete with a severe injury [3]. Opium is a strong respiratory depressant, but affects heart rate and blood pressure to only a minor degree [74,75]. The main toxic effects are respiratory depression, coma and death [75].

Cannabinoids

The most commonly used preparations of cannabis are marijuana and hashish. Maximal blood concentrations of the main active ingredient, tetrahydrocannabinol (THC), are attained 3–8 min after a cigarette smoke and the peak effect in 2–4 h, lasting for 4–6 h [76]. Concentrations of the main metabolite, carboxy-THC > 15 µg/l in urine samples are considered as doping. THC acts primarily via β -adrenergic stimulation and possibly also by parasympathetic blockade. It increases heart rate and decreases cardiac stroke volume. The increased sympathetic activity in combination with interference with the integrity of the peripheral vascular reflex responses and arterial vasospasm effects leads to the appearance of tachycardia, and, also, vascular reflex failure [77]. These pathophysiologic mechanisms are responsible for increased myocardial oxygen demand and decreased oxygen delivery and, thus, can result in acute ischemia and/or arrhythmias [65,77]. Therefore, myocardial infarction, stroke and sudden cardiac death may occur from using cannabis preparations [77].

Glucocorticosteroids

Glucocorticosteroids may be used by topical, inhalation or intra-articular routes of administration. For the use of non-systemic preparations a therapeutic use exception (TUE) has to be applied. All kinds of systematic application (oral, i.m. and i.v. injections) are not allowed. The long-term use of glucocorticosteroids is associated with serious and sometimes irreversible side-effects.

These include suppression of the hypothalamic–pituitary axis, osteoporosis, reduced bone growth in the young, opportunistic infections, behavioral alterations, and disorders of lipid metabolism, such as elevations of total plasma cholesterol, triglycerides and LDL cholesterol [78]. Dyslipidemia is caused by increased plasma insulin levels, impaired lipid catabolism and increased lipid production by the liver [79]. Hypertension is a major adverse effect of high doses and prolonged intake of glucocorticoids [79]. The possible mechanism is increased systemic vascular resistance, increased extracellular volume and increased cardiac contractility [79].

Substances prohibited in particular sports

Alcohol

Alcohol is the oldest social beverage and principal drug of abuse in the USA and other countries [80]. Alcohol does not possess an ergogenic effect. However, it may be used to reduce anxiety or tremor prior to competition [3]. Moderate drinkers consume one or two drinks per day, while heavy drinkers consume more than five drinks per day, each of which contains 13 g of alcohol [81]. Initially, alcohol consumption may lead to increased heart and respiratory rate, superficial vasodilation and a rise in blood pressure [66,82]. Adverse consequences of alcohol use are hypertension, stroke, coronary events, cardiac arrhythmias and dilated cardiomyopathy [65,66,83]. The precise mechanism by which alcohol produces hypertension and stroke is unknown. Moreover, the effects of alcohol consumption on coronary artery disease are controversial [65]. Adrenergic activity in heavy drinkers causes hypertension, tachycardia and coronary spasm, leading to increased risk for ischemic heart disease and sudden cardiac death [84]. On the other hand, there is a lower incidence of coronary atherosclerosis in moderate drinkers [85]. The cardio-protective effect of moderate alcohol consumption is partly due to its favorable effect on HDL level and fibrinolytic activity [86]. Additionally, alcoholics may have low LDL levels. However, moderate alcohol consumption is found to increase apolipoproteins (apo) A-I, A-II and high-density lipoprotein subfraction (HDL₃) without affecting other lipoproteins [86,87].

Beta-blockers

The use of beta-blockers in endurance sports causes a decrease of physical capacity due to the negative effect on energetic metabolism [88]. The reduction in endurance capacity is found to be related mainly to lipid metabolism and possibly to K⁺ efflux, but not to hemodynamics [89,90].

However, in the case of high psychological strain, beta-blockers lead to a decrease of stress caused by competition [91]. Their use leads to significant decreases of heart rate and blood pressure [91]. As a possible reason for increased physical capacity after sympathicolysis, changes

of cardiovascular parameters as well as central influences are conceivable [91].

Prohibited methods

Blood doping, artificial oxygen carriers or plasma expanders

Blood doping increases red blood cell mass to deliver more oxygen to muscle, leading to an increase of physical capacity. Erythrocytosis results in tachycardia and an increased afterload, which may lead to hypertension, myocardial infarction and cardiac insufficiency [53]. Additionally, there is an increased risk of blood clots.

Substance abuse in sports

There are substances, such as nicotine, antidepressants, caffeine, etc., which are often used by athletes as a part of their lifestyle and abused in an attempt to improve athletic performance, although they are not considered prohibited. Many of the abused agents may, however, have adverse effects on the cardiovascular system.

Caffeine

Caffeine may improve the utilization of fatty acids as a fuel source, thereby sparing muscle glycogen [3]. Caffeine enhances the cardiovascular and central nervous system effects of ephedrine. It acts competitively, antagonizing the receptors for adenosine and augments the release of catecholamines [3,65,92]. Large doses of caffeine increase cardiac activity and cause peripheral vasodilation [83]. Rarely, adverse reactions to caffeine are severe; for example, hypertension, cholesterol abnormalities, arrhythmias, coma and death [65,92]. More often, caffeine abuse leads to palpitations and chest pain [65,66,85]. Caffeinism is a syndrome resulting from the excessive ingestion of caffeine, characterized by respiratory alkalosis with cardiovascular and central nervous system disorders [93].

Smokeless tobacco

Tobacco products may produce psychomotor effects or control appetite, which may be beneficial to some athletes [3]. The use of smokeless tobacco in sports is increasing, with adolescents accounting for the majority of users [94]. It is well known that nicotine abuse may lead to elevation of total cholesterol and depression of HDL [95]. Moreover, it causes intense vasoconstriction of diseased and normal coronary artery segments [65,66]. In addition to atherogenic and vasospasm effects, nicotine has thrombogenic actions resulting in increased coagulability [65]. Another adverse effect of smokeless tobacco is adrenergic stimulation, which may cause cardiac arrhythmias. Also, a reduced threshold for ventricular fibrillation following tobacco consumption has been reported [65]. Thus, it is recommended that tobacco is avoided for 2 h before and after a sports session or practice.

Nutritional supplements

Nutritional supplementation, such as proteins, creatine, vitamins or carnitine, is commonly used by both athletes and people engaged in recreational sports. No strong evidence linking nutritional supplementation to cardiac side-effects has been found. In fact, most reports on side-effects remain anecdotal because the case studies do not represent well-controlled trials. Additionally, data with regard to long-term safety of nutritional supplementation are lacking. Nutritional or herbal supplements may have harmful effects on arrhythmias [96]. The use of cesium chloride as a dietary supplement is potentially hazardous as it may induce fatal ventricular arrhythmias [97]. Moreover, chronic excess of calcium intake may also contribute to dysrhythmias.

In practice, several drugs are frequently used in combination, which may lead to interactions and a higher risk of cardiovascular side-effects than described for any of the substances above. For example, the intake of anabolic steroids, amphetamines, frumil and potassium supplements caused myocardial infarction, hyperkalemia and ventricular tachycardia in a young bodybuilder [98]. Moreover, herbal preparations containing both ephedrine and caffeine, as 'herbal Ecstasy', or other compositions may often lead to adverse reactions, ranging from minor to major, such as palpitations, hypertensive crises and severe ventricular arrhythmias [71,99]. When examining an athlete with unexpected cardiac symptoms, physicians should suspect the abuse of substances. Testing to detect abused substances by systematic sampling of urine or blood is important to prevent adverse events and to ensure fair competition. The target is to obtain a highly accurate and sensitive assessment of the used substances in urine, long enough after the intake.

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References

- 1 World Anti-Doping Agency. *The International Olympic Committee Anti-Doping Rules applicable to the Games of the XXVIII Olympiad in Athens in 2004*. Lausanne: WADA; June 2004, p. 3. Available at website <http://www.wada-ama.org/> [Accessed 26 December 2005]
- 2 World Anti-Doping Agency. *The World Anti-Doping Code – The 2005 prohibited list, International standard*. Lausanne: WADA; September 2004. Available at website <http://www.wada-ama.org/> [Accessed 26 December 2005]

- 3 Wagner J. Enhancement of athletic performance with drugs. An overview. *Sports Med* 1991; **12**:250–265.
- 4 Labrie F, Luu-The V, Calvo E, Martel C, Cloutier J, Gauthier S, *et al.* Tetrahydrogestrinone induces a genomic signature typical of a potent anabolic steroid. *J Endocrinol* 2005; **184**:427–433.
- 5 Sullivan ML, Martinez CM, Gennis P, Gallagher EJ. The cardiac toxicity of anabolic steroids. *Prog Cardiovasc Dis* 1998; **41**:1–15.
- 6 McCarthy K, Tang AT, Dalrymple-Hay MJ, Haw MP. Ventricular thrombosis and systemic embolism in bodybuilders: etiology and management. *Ann Thorac Surg* 2000; **70**:658–660.
- 7 Thiblin I, Lindquist O, Rajs J. Cause and manner of death among users of anabolic androgenic steroids. *J Forensic Sci* 2000; **45**:16–23.
- 8 Fineschi V, Baroldi G, Monciotti F, Paglicci Reattelli L, Turillazzi E. Anabolic steroid abuse and cardiac sudden death: a pathologic study. *Arch Pathol Lab Med* 2001; **125**:253–255.
- 9 Deligiannis A. Cardiac side effects of anabolics. *Osterreichisches J Sportsmedizin* 2002; **2**:35–37.
- 10 Melchert RB, Welder AA. Cardiovascular effects of androgenic-anabolic steroids. *Med Sci Sports Exerc* 1995; **27**:1252–1262.
- 11 Glazer G. Atherogenic effects of anabolic steroids on serum lipid levels. A literature review. *Arch Intern Med* 1991; **151**:1925–1933.
- 12 Thompson PD, Cullinane EM, Sady SP, Chenevert C, Saritelli AL, Sady MA, *et al.* Contrasting effects of testosterone and stanozolol on serum lipoprotein levels. *JAMA* 1989; **261**:1165–1168.
- 13 Hartgens F, Rietjens G, Keizer HA, Kuipers H, Wolffenbuttel BH. Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a). *Br J Sports Med* 2004; **38**:253–259.
- 14 Applebaum-Bowden D, Haffner SM, Hazzard WR. The dyslipoproteinemia of anabolic steroid therapy: increase in hepatic triglyceride lipase precedes the decrease in high density lipoprotein2 cholesterol. *Metabolism* 1987; **36**:949–952.
- 15 Cohen LI, Hartford CG, Rogers GG. Lipoprotein (a) and cholesterol in body builders using anabolic androgenic steroids. *Med Sci Sports Exerc* 1996; **28**:176–179.
- 16 Kennedy MC, Lawrence C. Anabolic steroid abuse and cardiac death. *Med J Aust* 1993; **158**:346–348.
- 17 McCrohon JA, Jessup W, Handelsman DJ, Celemajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. *Circulation* 1999; **99**:2317–2322.
- 18 McCrohon JA, Death AK, Nakhla S, Jessup W, Handelsman DJ, Stanley KK, *et al.* Androgen receptor expression is greater in macrophages from male than from female donors. A sex difference with implications for atherogenesis. *Circulation* 2000; **101**:224–226.
- 19 Ferenchick G, Schwartz D, Ball M, Schwartz K. Androgenic-anabolic steroid abuse and platelet aggregation: a pilot study in weight lifters. *Am J Med Sci* 1992; **303**:78–82.
- 20 Pernot C, Hartgens F, Keizer HA. Effects of self-administration of high doses androgenic-anabolic steroid on fibrinolytic activity in non elite bodybuilders. *Fibrinolysis* 1996; **10**(suppl 2):53–54.
- 21 Nieminen MS, Ramo MP, Viitasalo M, Heikkilä P, Karjalainen J, Mantysaari M, *et al.* Serious cardiovascular side effects of large doses of anabolic steroids in weight lifters. *Eur Heart J* 1996; **17**:1576–1583.
- 22 Ferenchick GS, Hirokawa S, Mammen EF, Schwartz KA. Anabolic-androgenic steroid abuse in weight lifters: evidence for activation of the hemostatic system. *Am J Hematol* 1995; **49**:282–288.
- 23 Sader MA, Griffiths KA, McCredie RJ, Handelsman DJ, Celemajer DS. Androgenic anabolic steroids and arterial structure and function in male bodybuilders. *J Am Coll Cardiol* 2001; **37**:224–230.
- 24 McCredie RJ, McCrohon JA, Turner L, Griffiths KA, Handelsman DJ, Celemajer DS. Vascular reactivity is impaired in genetic females taking high-dose androgens. *J Am Coll Cardiol* 1998; **32**:1331–1335.
- 25 Herman SM, Robinson JT, McCredie RJ, Adams MR, Boyer MJ, Celemajer DS. Androgen deprivation is associated with enhanced endothelium-dependent dilatation in adult men. *Arterioscler Thromb Vasc Biol* 1997; **17**:2004–2009.
- 26 Appell HJ, Heller-Umpfenbach B, Feraudi M, Weicker H. Ultrastructural and morphometric investigations on the effects of training and administration of anabolic steroids on the myocardium of guinea pigs. *Int J Sports Med* 1983; **4**:268–274.
- 27 Takala TE, Ramo P, Kiviluoma K, Vihko V, Kainulainen H, Kettunen R. Effects of training and anabolic steroids on collagen synthesis in dog heart. *Eur J Appl Physiol Occup Physiol* 1991; **62**:1–6.
- 28 Behrendt H, Boffin H. Myocardial cell lesions caused by an anabolic hormone. *Cell Tissue Res* 1977; **181**:423–426.
- 29 Hausmann R, Hammer S, Betz P. Performance enhancing drugs (doping agents) and sudden death—a case report and review of the literature. *Int J Legal Med* 1998; **111**:261–264.
- 30 Luke JL, Farb A, Virmani R, Sample RH. Sudden cardiac death during exercise in a weight lifter using anabolic androgenic steroids: pathological and toxicological findings. *J Forensic Sci* 1990; **35**:1441–1447.
- 31 Karch SB, Billingham ME. Myocardial contraction bands revisited. *Hum Pathol* 1986; **17**:9–13.
- 32 Zaugg M, Jamali NZ, Lucchinetti E, Xu W, Alam M, Shafiq SA, *et al.* Anabolic-androgenic steroids induce apoptotic cell death in adult rat ventricular myocytes. *J Cell Physiol* 2001; **187**:90–95.
- 33 McKillop G, Todd IC, Ballantyne D. The effects of body building and anabolic steroids on left ventricular structure and function. *J Cardiovasc Technol* 1989; **8**:23–29.
- 34 Dickerman RD, Schaller F, Zachariah NY, McConathy WJ. Left ventricular size and function in elite bodybuilders using anabolic steroids. *Clin J Sport Med* 1997; **7**:90–93.
- 35 Karila TA, Karjalainen JE, Mantysaari MJ, Viitasalo MT, Seppala TA. Anabolic androgenic steroids produce dose-dependant 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.
- 36 Palatini P, Giada F, Garavelli G, Sinisi F, Mario L, Michieletto M, *et al.* Cardiovascular effects of anabolic steroids in weight-trained subjects. *J Clin Pharmacol* 1996; **36**:1132–1140.
- 37 Deligiannis A, Zahopoulou E, Mandroukas K. Echocardiographic study of cardiac dimensions and function in weight lifters and bodybuilders. *Int J Sports Cardiol* 1988; **5**:24–32.
- 38 Stolt A, Karila T, Viitasalo M, Mantysaari M, Kujala UM, 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**:364–366.
- 39 Nottin S, Nguyen LD, 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.
- 40 Urhausen A, Albers T, Kindermann W. Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? *Heart* 2004; **90**:496–501.
- 41 Svorcik C, Bicikova L. Effect of drugs on the stimulation threshold of the human heart. *Cor Vasa* 1978; **20**:184–195.
- 42 Neumann F, Schneck B. Pharmakotherapie mit hormonem. In: Forth W, Henschler D, Rummel W, editors. *Pharmakologie und Toxikologie*. Mannheim, Wien, Zurich: Bibliographisches Institut und FA Brockhaus; 1987. pp. 396–423.
- 43 Sullivan ML, Martinez CM, Gallagher EJ. Atrial fibrillation and anabolic steroids. *J Emerg Med* 1999; **17**:851–857.
- 44 Hartmann G, Addicks K, Donike M, Schanzer W. Testosterone application influences sympathetic activity of intracardiac nerves in non-trained and trained mice. *J Auton Nerv Syst* 1986; **17**:85–100.
- 45 Baker PJ, Ramey ER, Ramwell PW. Androgen-mediated sex differences of cardiovascular responses in rats. *Am J Physiol* 1978; **235**:H242–246.
- 46 Kuipers H, Wijnen JA, Hartgens F, Willems SM. Influence of steroids on body composition, blood pressure, lipid profile and liver function in bodybuilders. *Int J Sports Med* 1991; **12**:413–418.
- 47 Grace F, Sculthorpe N, Baker J, Davies B. Blood pressure and rate pressure product response in males using high-dose anabolic androgenic steroids (AAS). *J Sci Med Sport* 2003; **6**:307–312.
- 48 Hartgens F, Cheriex EC, Kuipers H. Prospective echocardiographic assessment of androgenic-anabolic steroids effects on cardiac structure and function in strength athletes. *Int J Sports Med* 2003; **24**:344–351.
- 49 Colao A, Marzullo P, Di Somma C, Lombardi G. Growth hormone and the heart. *Clin Endocrinol* 2001; **54**:137–154.
- 50 Audran M, Gareau R, Matecki S, Durand F, Chenard C, Sicart MT, *et al.* Effects of erythropoietin administration in training athletes and possible indirect detection in doping control. *Med Sci Sports Exerc* 1999; **31**: 639–645.
- 51 Kicman AT, Cowan DA. Peptide hormones and sport: misuse and detection. *Br Med Bull* 1992; **48**:496–517.
- 52 Vergouwen PC, Collee T, Marx JJ. Haematocrit in elite athletes. *Int J Sports Med* 1999; **20**:538–541.
- 53 Wagner KF, Katschinski DM, Hasegawa J, Schumacher D, Meller B, Gembbruch U, *et al.* Chronic inborn erythrocytosis leads to cardiac dysfunction and premature death in mice overexpressing erythropoietin. *Blood* 2001; **97**:536–542.
- 54 Noakes TD. Tainted glory. Doping and athletic performance. *N Engl J Med* 2004; **151**:847–849.
- 55 Prather ID, Brown DE, North P, Wilson JR. Clenbuterol: a substitute for anabolic steroids? *Med Sci Sports Exerc* 1995; **27**:1118–1121.

- 56 Fisher AA, Davis MW, McGill DA. Acute myocardial infarction associated with albuterol. *Ann Pharmacother* 2004; **38**:2045–2049.
- 57 Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; **125**:2309–2321.
- 58 Chodorowski Z, Sein-Anand J. Acute poisoning with clenbuterol—a case report. *Przegl Lek* 1997; **54**:763–764.
- 59 Fuster D, Escher G, Vogt B, Ackermann D, Dick B, Frey BM, et al. Furosemide inhibits 11- β hydroxysteroid dehydrogenase type 2. *Endocrinol* 1998; **139**:3849–3854.
- 60 Laties V, Weiss B. The amphetamine margin in sports. *Federation Proc* 1981; **40**:2689–2692.
- 61 George A. Central nervous system stimulants. *Bailliere's Clin Endocrinol Metab* 2000; **14**:79–88.
- 62 Smith HJ, Roche AH, Jausch MF, Herdson PB. Cardiomyopathy associated with amphetamine administration. *Am Heart J* 1976; **91**:792–797.
- 63 Hong R, Matsuyama E, Nur K. Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991; **265**:1152–1154.
- 64 Cregler L, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986; **315**:1495–1500.
- 65 Cregler L. Substance abuse in sports: The impact of cocaine, alcohol, steroids, and other drugs on the heart. In: Williams RA, editor. *The athlete and heart disease: diagnosis, evaluation and management*. Philadelphia: Lippincott Williams and Wilkins; 1999. pp. 131–153.
- 66 Covert J. Illicit drugs and the athlete. *Am Pharm* 1986; **26**:39–45.
- 67 O'Leary ME. Inhibition of human ether-a-go-go potassium channels by cocaine. *Mol Pharmacol* 2001; **59**:269–277.
- 68 Brody S, Slovis C, Wrenn K. Cocaine – related medical problems. Consecutive series of 233 patients. *Am J Med* 1990; **88**:325–331.
- 69 Billman GE. Cocaine: a review of its toxic actions on cardiac function. *Crit Rev Toxicol* 1995; **25**:113–132.
- 70 Haller C, Benowitz NN. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; **343**:1833–1838.
- 71 Zahn K, Li R, Pursell R. Cardiovascular toxicity after ingestion of 'Herbal Ecstasy'. *J Emerg Med* 1999; **17**:289–291.
- 72 Zaacks S, Klein L, Tan C, Rodriguez E, Leikin J. Hypersensitivity myocarditis associated with ephedra use. *J Toxicol Clin Toxicol* 1999; **37**:485–489.
- 73 Samenuk D, Link MS, Homoud MK, Contreras R, Theoharides TC, Wang PJ, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc* 2002; **77**:12–16.
- 74 Chyka P, McCommon S. Reporting of adverse drug reactions by poison control centres in the US. *Drug Saf* 2000; **23**:87–93.
- 75 Erjavec M, Coda B, Nguyen Q, Donaldson G, Rister L, Shen D. Morphine-fluoxetine interactions in healthy volunteers: analgesia and side effects. *J Clin Pharmacol* 2000; **40**:1286–1295.
- 76 Campos DR, Yonamine M, de Moraes Moreau RL. Marijuana as doping in sports. *Sports Med* 2003; **33**:395–399.
- 77 Bachs L, Morland H. Acute cardiovascular fatalities following cannabis use. *Forensic Sci Int* 2001; **124**:200–203.
- 78 Belvisi MG, Brown TJ, Wicks S, Foster ML. New glucocorticosteroids with an improved therapeutic ratio? *Pulm Pharmacol Ther* 2001; **14**:221–227.
- 79 Sholter DE, Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. *Can J Cardiol* 2000; **16**:505–511.
- 80 Spence J, Gauvin L. Drug and alcohol use by Canadian University athletes: a national survey. *J Drug Educ* 1996; **26**:275–287.
- 81 Kagan A, Yano K, Rhoads GG, McGee DL. Alcohol and cardiovascular disease: the Hawaiian experience. *Circulation* 1981; **64**:III 27–31.
- 82 Wadler G, Hainline B. *Drugs and the athlete*. Philadelphia: F.A. Davis; 1989.
- 83 Williams M. *Beyond training*. Champaign, Illinois: Leisure Press; 1989.
- 84 Deutscher S. The effects of heavy drinking on ischemic heart disease. *Prim Cardiol* 1986; **12**:40–48.
- 85 Stason WB, Neff RK, Miettinen OS, Jick H. Alcohol consumption and nonfatal myocardial infarction. *Am J Epidemiol* 1976; **104**:603–608.
- 86 Vogel RA. Alcohol, heart disease, and mortality: a review. *Rev Cardiovasc Med* 2002; **3**:7–13.
- 87 Taskinen MR, Nikkila EA, Valimaki M, Sane T, Kuusi T, Kesaniemi A, et al. Alcohol-induced changes in serum lipoproteins and in their metabolism. *Am Heart J* 1987; **113**:458–464.
- 88 Clarkson PM, Thompson HS. Drugs and sport. Research findings and limitations. *Sports Med* 1997; **24**:366–384.
- 89 Vanhees L, Fagard R, Lijnen P, Amery A. Effect of antihypertensive medication on endurance exercise capacity in hypertensive sportsmen. *J Hypertens* 1991; **9**:1063–1068.
- 90 Vanhees L, Defoor JG, Schepers D, Lijnen P, Peeters BY, Lacante PH, et al. Effect of bisoprolol and atenolol on endurance exercise capacity in healthy men. *J Hypertens* 2000; **18**:35–43.
- 91 Schmid P. Use of beta receptor blockers in performance sports. *Wien Med Wochenschr* 1990; **140**:184–188.
- 92 Graham T. Caffeine and exercise: metabolism, endurance and performance. *Sports Med* 2001; **31**:785–807.
- 93 Josephson G, Stine R. Caffeine intoxication: a case of paroxysmal atrial tachycardia. *JACEP* 1976; **5**:776–778.
- 94 Glover ED, Edmundson EW, Edwards SW, Schroeder KL. Implications of smokeless tobacco use among athletes. *Physician Sports Med* 1986; **14**:95–105.
- 95 Connolly G, Orleans C, Kogan M. Use of smokeless tobacco in major-league baseball. *N Engl J Med* 1988; **318**:1281–1284.
- 96 Chung MK. Vitamins, supplements, herbal medicines, and arrhythmias. *Cardiol Rev* 2004; **12**:73–84.
- 97 Saliba W, Erdogan O, Niebauer M. Polymorphic ventricular tachycardia in a woman taking cesium chloride. *Pacing Clin Electrophysiol* 2001; **24**:515–517.
- 98 Appleby M, Fisher M, Martin M. Myocardial infarction, hyperkalaemia and ventricular tachycardia in a young male body-builder. *Int J Cardiol* 1994; **44**:171–174.
- 99 Yates K, O'Connor A, Horsley C. 'Herbal Ecstasy': a case series of adverse reactions. *NZ Med J* 2000; **113**:315–317.