Cardiovascular Adverse Effects of Doping in Sports

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In theory, sport is synonymous with health. However, in practice it is sometimes associated with various disorders, of which the most dangerous concern the cardiovascular system. Cardiovascular disorders are known to be the most common cause of sudden death during exercise. In younger athletes (below 45 years) this is due in the majority of cases to congenital heart diseases, while in older people atherosclerosis is the primary cause. There is, however, a non-negligible percentage of disorders of the cardiovascular system, even sudden cardiac death (SCD), that are attributable to the use of performance-enhancing drugs, either prohibited (doping) or legal. The users can be athletes, professional or amateur, or just people engaging in exercise in gyms or fitness and leisure centres, while both sexes and all age groups are involved. Seeking to improve their performance, according to the event in which they participate, most athletes use a combination of prohibited substances and methods, or of prohibited and non-prohibited drugs, so as to alleviate the complications and/or to avoid being detected by screening. The use of combinations or different dosing regimens, according to the sport, prevents us from detecting differences in the side effects between either the sexes or the types of training. Of course, the various endocrine complications in both sexes are well known, and involve mainly secondary sex characteristics. The most common and serious consequences of almost all illicit drugs in sport concern the cardiovascular system. These disorders, such as hypertension, cardiac arrhythmias, and acute myocardial infarction, may be manifested either directly, or as the result of long-term use. Frequent complications may also occur in other organs. Specifically, anabolic steroids have been implicated in liver cirrhosis and liver or kidney cancer, growth hormone in diabetes mellitus, erythropoietin in thromboembolic episodes, central nervous system stimulants in psychotic syndromes, and so on.

According to the International Olympic Committee, doping is defined as the presence of a prohibited substance or its metabolites or markers in an athlete’s bodily specimen, as well as evidence of the use or the attempt to use a prohibited substance or method in an attempt to increase athletic performance. Moreover, the presence even of a non-prohibited substance, provided that its use has not been permitted for therapeutic purposes by a responsible authority, is considered doping. It is significant, according to the current anti-doping code, that the athlete him or herself is responsible for any prohibited substance or its metabolites or markers found to be present in their samples. Table 1 shows a list of prohibited substances and methods according to the current Anti-Doping Regulations (World
Anti-Doping Agency, WADA 2012).9 Apart from the prohibited substances, however, cardiovascular disorders may be caused by other substances commonly used in sports, such as dietary supplements. Table 2 summarises the most significant cardiovascular disorders that can be caused by the use of prohibited substances.

### Prohibited substances and methods during competition and training – effects on the cardiovascular system

#### Androgens and anabolic steroids

The use of androgens and anabolic steroids (AAS) by athletes has been associated with a large number of cardiovascular disorders, either acute (such as arrhythmogenic SCD, thromboembolic episodes, or myocardial infarction), or chronic (such as hypertension, atheromatosis, or left ventricular hypertrophy and dysfunction).3,6 Research into the use of AAS has only been carried out on animals, since ethical and legal considerations prohibit their administration in athletes, even for research purposes. Existing studies of humans are either case reports, or studies of athletes caught using AAS, but at different doses and for different periods each time. In addition, many of them used combinations of different substances, prohibited or not, so that the results were not solely due to the AAS use. Experimental studies have demonstrated that AAS abuse leads to skeletal muscle hypertrophy and increased collagen accumulation10,11—changes that are similarly detected in the myocardial...
um. Studies in rats and mice have shown that AAS abuse leads to both myocardial hypertrophy and fibrosis, destruction of the mitochondria and other elements of the cardiomyocytes, disturbances of the microcirculation, and to a deterioration in systolic function and to diastolic dysfunction.\textsuperscript{12} Post-mortem studies of athletes who used AAS have found infiltration of eosinophils into myocardial cells, as well as destruction of myofibrils.\textsuperscript{4} Endothelial dysfunction was also observed.\textsuperscript{13}

In athletes who are mainly involved in bodybuilding, echocardiographic studies have derived conflicting results regarding the effects of AAS on left ventricular mass and function, mainly for the reasons mentioned above. Most studies compared the echocardiographic results between AAS users and nonusers or healthy controls. Dickerman et al.\textsuperscript{14} found significant left ventricular wall thickening in elite power athletes using AAS compared to non AAS-users. Indeed, in one case the wall thickness was 16 mm. However, none of them demonstrated diastolic dysfunction. Other studies reported similar results.\textsuperscript{15-17}

In contrast, a number of studies found no significant difference in left ventricular hypertrophy between AAS users and non-users.\textsuperscript{18-23} In most cases, the hypertrophy observed was concentric, as would be expected after long-term static exercise training, while only a few showed eccentric hypertrophy due to dilatation of the cardiac cavities.\textsuperscript{23} It is noteworthy that studies until early 2000 found no particular evidence for systolic and diastolic dysfunction in athletes using AAS. However, with the use of the latest echocardiographic techniques, such as tissue Doppler, some researchers detected left ventricular diastolic dysfunction in athletes who are AAS users.\textsuperscript{24,25} In a study of ours the use of pulsed tissue Doppler was helpful in the early detection of diastolic dysfunction caused by AAS abuse, which was not detectable using the classical estimation of transmitral flow. Moreover, the diastolic dysfunction was found to be correlated with the dosage and the duration of use.\textsuperscript{1,20} Apart from left ventricular diastolic dysfunction, D’Andrea et al, using Doppler myocardial imaging and strain rate imaging, also recorded early findings of deteriorated systolic function in drug users.\textsuperscript{27} It is likely that studies using the latest non-invasive diagnostic techniques will confirm the possibility that AAS lead to cardiomyopathy in athletes, mainly due to a direct toxic effect on the myocardium.\textsuperscript{28} There are reports of athletes with dilated cardiomyopathy and heart failure after AAS abuse.\textsuperscript{29,30}

Several studies have described cases of acute myocardial infarction and thromboembolic vascular episodes in athletes using AAS.\textsuperscript{31-33} The following mechanisms have been implicated in atherothrombosis of the coronary and other arteries in steroid users: atherogenesis, thrombosis, vasospasm, and direct myocardial damage.\textsuperscript{3} Another cause of atherothrombosis may be the increase in erythrocytosis caused by testosterone. A number of studies have demonstrated a significant disturbance of lipid metabolism in athletes who have used anabolic steroids.\textsuperscript{34} A review by Glazer\textsuperscript{35} reported a reduction in high-density lipoprotein cholesterol (HDL) of 39-70% and in HDL\textsubscript{2} of 71-89%, an increase in hepatic triacylglyceride lipase of 143-232%, an increase in low-density lipoprotein cholesterol (LDL) by 36%, and a reduction in apolipoprotein-A1 by 33-41%. A significant reduction in

**Table 2. Common cardiovascular complications caused by the most frequently used doping substances.**

<table>
<thead>
<tr>
<th>Substance</th>
<th>AMI</th>
<th>CAD</th>
<th>Cardiomyopathy</th>
<th>Arrhythmias</th>
<th>Hypertension</th>
<th>SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAS</td>
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<tr>
<td>Other anabolic agents (clenbuterol)</td>
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<td>hGH</td>
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<td>EPO</td>
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<td>Beta-2 agonists</td>
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<td>Diuretics</td>
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<td>Amphetamines</td>
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<td>Ephedrine</td>
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<td>Cocaine</td>
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<tr>
<td>Narcotics</td>
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<tr>
<td>Cannabinoids</td>
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</tbody>
</table>

\(\angle\) indicates an effect. AMI – acute myocardial infarction; CAD – coronary artery disease; SCD – sudden cardiac death; AAS – anabolic androgenic steroids; hGH – growth hormone; EPO – erythropoietin.
lipoprotein-alpha and an increase in homocysteine have also been described.\textsuperscript{36,37} The beneficial effect of AAS on platelet aggregation and the mechanism of thrombosis, mainly through the activation of prostaglandins and plasminogen, is well known from experimental studies.\textsuperscript{38} However, there are conflicting results regarding the effects of anabolic steroids on the mechanism of thrombosis in athletes\textsuperscript{39,40} In addition, there are only a few reports on the effect of anabolic steroids on vascular function in athletes. Sader et al\textsuperscript{41} measured carotid intima–media thickness and radial and brachial artery reactivity in bodybuilders using AAS. They found a non-significant increase in the thickness and diameter of the arteries in users compared to non-users, which was attributed mainly to fluid retention. A small degree of endothelial dysfunction was also reported by other investigators.\textsuperscript{42,43} Kasikcioglu et al\textsuperscript{44} found changes of aortic wall elasticity in athletes who used steroids. Moreover, Santora et al\textsuperscript{45} using an electron beam tomography system, found increased calcium deposition in the coronary arteries of bodybuilders using AAS. The authors hypothesised that this was due to a direct toxic or inflammatory effect of steroids on the vascular endothelium. There have been several cases of SCD in athletes using AAS.\textsuperscript{14,46-49} However, the frequency and the pathophysiological mechanism of SCD remain unknown. Some researchers have concluded that AAS have an arrhythmogenic action, while others believe that SCD is a secondary event, resulting from the cardiovascular side effects caused by their abuse.\textsuperscript{30,34,49,50} Cases of atrial fibrillation and ventricular tachycardia have also been described in athletes users.\textsuperscript{5,51,52} It has been suggested that the chronic administration of anabolic agents prolongs and increases the inhomogeneity of repolarisation, thus creating an arrhythmogenic substrate.\textsuperscript{5,50} These disturbances are more apparent in athletes with significant cardiac hypertrophy as an adaptation to long term exercise training (athlete’s heart) or to the use of anabolic substances.\textsuperscript{5} In an electrophysiological study by Stolt et al\textsuperscript{53} power athletes taking AAS were found to have increased QT dispersion and short QT intervals. The authors associated these changes with the manifestation of arrhythmias. In addition, in an experimental study Pereira-Junior et al found that the administration of nandrolone decanoate to rats led to a disturbance of cardiac autonomic nervous system function.\textsuperscript{54} We found analogous results in a study of athletes who used anabolic steroids, who presented a reduction in baroreflex sensitivity.\textsuperscript{55} Fineschi et al\textsuperscript{48} maintained that anabolic steroids lead to degenerative changes in endomycocardial sympathetic neurons, resulting in the appearance of malignant arrhythmias.\textsuperscript{46} This degenerative mechanism is referred to as catecholamine myotoxicity.

In experimental studies it has been found that the administration of AAS leads to hypertension.\textsuperscript{56-58} An increase in the secretion of 11-deoxycorticosterone, norepinephrine, renin, or aldosterone has been implicated as a possible mechanism, while others have noted an increase in cardiac output and peripheral resistances.\textsuperscript{59-61} However, clinical studies in athletes have led to conflicting results. Some observed a significant increase in both systolic and diastolic blood pressure, whereas others noted only the latter.\textsuperscript{16,62-64} Riebe et al\textsuperscript{64} attributed the increase in blood pressure in steroid-using athletes to an increase in plasma volume.\textsuperscript{64} In contrast, other authors found no significant increase in blood pressure at rest or during exercise in athletes who used steroids compared to non-users.\textsuperscript{23,24,65,66}

**Peptide hormones, similar substances, and analogues**

This category includes growth hormone, erythropoietin (EPO), corticotropin (ACTH), insulin-like growth factor-1 (IGF-1) and insulin.

Taking growth hormone as a doping substance leads to an increase in muscle mass and strength, especially when accompanied by strength training and/or the administration of other substances, such as anabolic steroids.\textsuperscript{67} However, it seems that hypertrophy of the muscle fibres is associated with an increase in the inelastic elements of the muscles and with fluid retention.\textsuperscript{58,69} This also affects the action of this hormone on the myocardium, where, in contrast to the view that it leads only to myocardial hypertrophy without affecting the functional capacity, it seems to lead to an increase in collagen, fibrosis, and cellular infiltration and necrosis.\textsuperscript{3,70} These alterations are associated with the manifestation of arrhythmias and the development of heart failure.\textsuperscript{71,72}

Sales of erythropoietin increased significantly, when it started to be used as a doping substance in sport. It replaced doping through blood transfusion and high altitude training, which aimed to increase haematocrit levels and thus to increase aerobic capacity. However, the use of this hormone, too, is associated with cardiovascular disorders, to a degree that depends mainly on the dosage.\textsuperscript{73} Clinical studies of both patients and athletes have determined that an
increase in haematocrit leads to an increase in blood viscosity and cardiac afterload, complications that predispose to hypertension, left ventricular dysfunction, and thromboembolic episodes. These disorders have also been demonstrated by experimental studies, where hypertension, cardiac hypertrophy and fibrosis, overactivity of the sympathetic and serotonergic systems, and SCD were seen following the administration of high doses of erythropoietin.

**Beta-2 agonists**

The use of β₂-agonists is permitted in sport only after their declaration for the treatment of asthma and exercise-induced bronchospasm. However, because of their known anabolic action in increasing muscle mass and strength, salbutamol and clenbuterol are mainly used as doping substances. The results of their use and their side effects appear to be dose-dependent. The stimulation they cause to the β₂ cardiac and peripheral receptors leads to a positive chronotropic and inotropic action, resulting in an increase in heart rate and the strength of cardiac systole. Vasodilation and redistribution of the blood in the coronary arteries are also observed. Acute myocardial infarction, arrhythmias, and SCD have been described in athletes who use these substances. Their administration is also accompanied by QT prolongation, probably because of electrolyte (mainly K⁺) and metabolic disorders.

**Diuretics and other masking agents**

Many athletes use masking agents, such as sulphonamides, probenecid, anti-oestrogens, thyroid hormones, human chorionic gonadotropin, and diuretics, to mask or modify the levels of AAS during doping control. In addition, diuretics are used for weight loss, with a view to changing participation category, such as in martial arts, gymnastics, and other events. The dehydration and possible electrolytic disorders resulting from their use can lead to arrhythmias and haemodynamic disorders, especially in athletes with genetic abnormalities of Na⁺ and K⁺ metabolism.

**Substances and methods prohibited only in competition – effects on the cardiovascular system**

**Stimulants of the central nervous system**

The most commonly used of these substances are amphetamines, cocaine, ephedrine, and pseudoephedrine. These substances have a sympathomimetic action and act by stimulating the secretion of dopamine, noradrenaline, and serotonin. Their main ergogenic effect is to reduce the feeling of fatigue.

**Amphetamines**

These are one of the oldest substances used in doping. Many cardiovascular disorders have been described, even SCD, from both their acute and chronic use. Specifically, they can cause coronary artery spasm, resulting in acute myocardial infarction, and or diffuse vasospasm. Their long-term use leads to arterial and pulmonary hypertension, stroke, and cardiomyopathy. Also common is the appearance of rhythm disturbances. Amphetamines are believed to increase levels of intracellular cyclic adenosine monophosphate and sympathetic nervous system tone. Thus, they favour the development of arrhythmias, especially in athletes with myocardial hypertrophy and heterogeneity of ventricular repolarisation.

**Cocaine**

Unfortunately, this is very commonly used in sport, not just because of its undoubted ergogenic effects, but also because of addiction. It is a particularly toxic substance for the cardiovascular and respiratory system, so its use can lead to serious complications. Among these, the most tragic is SCD, which may be due to coronary artery vasospasm, lethal arrhythmia, direct toxic action on the myocardium, or severe suppression of the respiratory centre. Ischaemia and/or acute myocardial infarction are common complications, both in individuals with normal coronary vessels and, to a greater extent, on a substrate of atherosclerosis, and are not always related to the cocaine dosage.

The main pathophysiological mechanism that leads to the appearance of ischaemia is the strong sympathomimetic and parasympatholytic effects of the drug, which are enhanced by the increased adenylyl cyclase activity. The consequence of this is an increase in oxygen demand, because of the tachycardia, and in blood pressure, and at the same time a reduction in oxygen supply because of the vasospasm, while also promoting the thrombogenic process. Also common is the manifestation of rhythm disorders, because of sudden vasospasm, or its local anaesthetic effect from obstruction of the Na⁺/K⁺ pump, or its toxic effect on the myocardium. Because of
this latter, direct effect, there is an increase in endothelial permeability in the pulmonary capillaries, which can result in pulmonary oedema.97 Finally, other complications that have been described are infective endocarditis, myocarditis and dilated cardiomyopathy (chemical cardiomyopathy), rupture of aortic aneurysms, arterial and pulmonary hypertension, and thromboembolic vascular episodes.3,90,91,99

Ephedrine alkaloids

These are usually found through the internet or on the sports black market under names like “ma-huang”, “herbal Ecstasy”, and so on. Very frequent cardiovascular complications have been described as a result of their use, such as arrhythmias, hypertension, acute myocardial infarction, stroke, myocarditis, dilated cardiomyopathy, and SCD.100-103 The pathophysiological mechanism of action is similar to that of the other sympathomimetic amines.104,105

Narcotic opiates

These substances, which include morphine, heroin, and codeine, have a negative ergogenic action, but are still used by athletes, either because of addiction or, in combination with other substances, to repress fear or pain from injuries. They affect the heart rate and blood pressure, but their main toxic effect is suppression of respiration.106

Cannabinoids

As with cocaine, marijuana and hashish are used by athletes, not so much for their ergogenic action, as because of addiction. Cases of acute myocardial infarction, arrhythmias, and SCD have been described among athletes who use them.107,108 The cardiovascular complications are mainly due to sympathomimetic action and to suppression of peripheral vasoreflexes. These pathophysiological mechanisms lead to increased demand and at the same time decreased supply of oxygen, as well as the presence of arrhythmias.3

Glucocorticoids

These are classified as doping substances and so their use in any form for therapeutic reasons must be declared. An indirect side effect that concerns the cardiovascular system is the disturbance of lipid metabolism, leading to an increase in total cholesterol, triglycerides, and LDL cholesterol.109 The main direct complication is arterial hypertension, which is attributable to fluid retention, an increase in peripheral vascular resistances, and an increase in myocardial contractility.110

Prohibited substances in particular sports – effects on the cardiovascular system

This category includes two substances that have a negative ergogenic action: alcohol and β-blockers. However, they are used in sport either, in the former case, because of addiction, or because they repress anxiety, mainly in the case of β-blockers, as a consequence of their sympatholytic action.

Alcohol

It is well-known that the moderate use of alcohol has a cardioprotective effect, especially as regards the process of atherothrombosis. This is mainly due to an increase in levels of HDL cholesterol and apolipoproteins A-I and A-II, and a decrease in levels of LDL cholesterol, as well as its favourable action on fibrinolytic activity.111,112 However, the long-term use of large quantities of alcohol leads to cardiovascular complications, such as arterial hypertension, dilated cardiomyopathy, stroke, arrhythmias, and coronary artery spasm, because of its sympathomimetic action.91,113-115

Beta-blockers

The most common cardiovascular complications are significant bradycardia and hypotension, as well as conduction disturbances.116

The use of prohibited methods in sport

The best-known methods are transfusion of blood or its factors, the use of artificial oxygen carriers, plasma expanders (e.g. albumin, dextran, etc.), and, the great threat of the future, gene doping. Cardiovascular side effects have been reported as a result of blood transfusion, because of the increased blood viscosity and the increase in cardiac afterload, including hypertension, myocardial infarction, thromboembolic episodes, and heart failure.78

Non-prohibited substances often used by athletes

These substances, such as dietary supplements, caffeine, nicotine, antidepressants, etc., nowadays do
not belong to the categories of prohibited substances. However, they are widely used by athletes and in large doses can lead to cardiovascular disorders.

The use of proteins, creatine, carnitine, vitamins, or electrolytes has not been described to be associated with cardiovascular complications, apart from haemosiderosis of the viscera after long-term excessive iron intake. Cases have also been reported of severe arrhythmias after using caesium and calcium. The consumption of soy products has been associated with cardiac hypertrophy. In addition, the excessive consumption of grapefruit may lead to QT prolongation, which can cause arrhythmias, especially after the simultaneous administration of drugs that prolongation, which can cause arrhythmias, especially after the simultaneous administration of drugs that can lead to the well-known cardiotoxic complications described above. An interesting study by Haller and Benowitz described 26 cases of severe cardiovascular side effects, such as SCD, arrhythmias, hypertensive episodes, and stroke, in users of dietary supplements. Similar findings have been reported by other authors.

Caffeine is an adenosine antagonist and prompts the secretion of catecholamines. In large doses it leads to tachycardia, arrhythmias, and peripheral vasoconstriction or vasodilation; rarer complications are hypertensive episodes, severe arrhythmias, and SCD. Finally, athletes use nicotine, either in the classical way of smoking because of addiction, or during competition in the form of gum (smokeless tobacco), because of its psychokinetic action. WADA has placed this substance under surveillance for 2012, with a view to prohibiting it. Nicotine increases adrenergic activity and leads to arrhythmias. It is also known that, apart from its vasoconstrictive action in both healthy and atherosclerotic coronary vessels, because of its sympathomimetic action it shows atherogenic and thrombogenic activity.

**Gene doping**

In clinical practice gene therapy has been associated with unexpected and lethal complications, which depend on the kind of therapy. Experimental studies have detected complications of the circulatory system, such as thrombotic episodes in primates, following gene therapy with erythropoietin. Concerning sport, we do not yet have any information about complications, as would be expected considering that officially there are no reports of the use of gene doping. However, the complications are expected to depend mainly on the type of method used.

**Conclusions**

Doping in sport is associated with serious health complications, of which the most common and especially dangerous involve the cardiovascular system. The prohibited substances most commonly used by athletes are AAS, erythropoietin, and central nervous system stimulants, while the most common non-prohibited substances are dietary supplements. Most systematic studies of the effect of these substances on the heart and the blood vessels were experimental; however, there are a large number of clinical observations and even more case reports. AAS have an atherogenic, vasoconstrictive, and thrombogenic action, as well as a direct toxic effect on the myocardium; central nervous system stimulants and dietary supplements act mainly via their sympathomimetic effect. The complications are either acute or chronic. Arrhythmias, acute myocardial infarction, cardiomyopathies, thromboembolic episodes, and sudden cardiac death have all been described.

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