Arrhythmogenic effects of illicit drugs in athletes

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Cardiac arrhythmias are among the most important causes of non-eligibility to sports activities, and may be due to different causes (cardiomyopathies, myocarditis, coronary abnormalities, valvular diseases, primary electrical disorders, abuse of illicit drugs).

The list of illicit drugs banned by the International Olympic Committee and yearly updated by the World Anti-Doping Agency includes the following classes: stimulants, narcotics, anabolic agents (androgenic steroids and others such as beta-2 stimulants), peptide hormones, mimetics and analogues, diuretics, agents with an antiestrogenic activity, masking agents.

Almost all illicit drugs may cause, through a direct or indirect arrhythmogenic effect, in the short, medium or long term, a wide range of cardiac arrhythmias (focal or reentry type, supraventricular and/or ventricular), lethal or not, even in healthy subjects with no previous history of cardiac diseases. Therefore, given the widespread abuse of illicit drugs among athletes, in the management of arrhythmic athletes the cardiologist should always take into consideration the possibility that the arrhythmias be due to the assumption of illicit drugs (sometimes more than one type), especially if no signs of cardiac diseases are present. On the other hand, in the presence of latent underlying arrhythmogenic heart disease including some inherited cardiomyopathies at risk of sudden cardiac death, illicit drugs could induce severe cardiac arrhythmic effects.

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When evaluating competitive athletes, a history or documentation of cardiac arrhythmias has become particularly important because arrhythmias may be the initial expression of an underlying cardiac disease or of primary electrical disorders, sometimes early manifestations of potentially life-threatening events[1-4].

Cardiac arrhythmias are among the most important causes of non-eligibility to sports activities, and some arrhythmogenic disease are 3 times more frequent among athletes than among sedentary subjects of the same age[3,5-8].

The current management of athletes with arrhythmias is further complicated by the widespread use of "illicit drugs" taken both by professional and non-professional young athletes.

It is preferable to use the term "illicit drugs" rather than "doping", in that they comprise both drugs taken as true "doping", with "ergogenic effects", or "performance enhancing drugs"[9], and "masking agents", i.e. drugs taken with the aim of masking the presence of other specific drugs in tests for doping control[10]. They are products that have the potential of impairing the excretion of prohibited substances or to conceal their presence in urine or other samples used in doping control. Masking agents include diuretics, epitestosterone (prohibited because its administration lowers the urinary testosterone/epitestosterone ratio, a marker of testosterone administration)[11], probenecid and plasma expanders. They are also referred to in "Pharmacological, chemical and physical manipulation" as "substances and methods, which alter, attempt to alter or may reasonably be expected to alter the integrity and validity of specimens collected in doping controls" (Table I).

Almost all illicit drugs, banned by the International Olympic Committee (IOC) and yearly updated (since 1999) by the World Anti-Doping Agency, may cause, through a direct or indirect arrhythmogenic effect, in the short, medium or long term, a wide range of cardiac arrhythmias (focal or reentry type, supraventricular and/or ventricular), lethal or not, even in healthy subjects with no previous history of cardiac diseases. In subjects with preexisting health problems, particularly a latent arrhythmogenic substrate or primary arrhyth-

Table I. Prohibited classes of substances and prohibited methods (International Olympic Committee, 2003, www.wada-ama.org).

I. *Prohibited classes of substances*

A) Stimulants
1) amfepramone, amiphenazole, amphetamine, bambuterol, bromantan, caffeine, carphedon, cathine, clobenzorex, cocaine, cropropamide, crotethamide, ephedrine, etamivan, ethylamphetamine, etilefrine, fencamfamin, fenetylline, fenfluramine, fenproporex, heptaminol, mefenorex, mephentermine, mesocarb, methamphetamine, methoxyphenamine, methylenedioxyamphetamine, methylenedioxymethamphetamine, methylephedrine, methylphenidate, nikethamide, norfenfluramine, parahydroxyamphetamine, pemoline, pentetrazol, phendimetrazine, phentermine, phenmetrazine, phenylpropanolamine, pholedrine, pipradrol, prolintane, propylhexedrine, pseudoephedrine, reproterol, selegilinem, strychnine
2) formeterol, salbutamol, salmeterol and terbutaline

B) Narcotics
buprenorphine, dextromoramide, diamorphine (heroin), hydrocodone, methadone, morphine (at concentrations > 1 μg/ml), pentazocine, pethidine

C) Anabolic agents
1) anabolic androgenic steroids:
androstenediol, androstenedione, bambuterol, bolasterone, boldenone, clenbuterol, clostebol, danazol, dehydrochlormethyltestosterone, dehydroepiandrosterone, dihydrotestosterone, drostanolone, fenoterol, fluoxymesterone, formebolone, formoterol, gestrinone, mesterolone, metandienone, metenolone, methandriol, methyltestosterone, mibolerone, nandrolone, 19-norandrostenediol, 19-norandrostenedione, norbolethone, norethandrolone, oxandrolone, oxymesterone, oxymetholone, reproterol, stanozolol, testosterone, trenbolone
2) other anabolic agents:
clenbuterol, formeterol, salbutamol (the anabolic nature of salbutamol above a concentration of 1000 ng/ml has been clearly described), salmeterol and terbutaline

D) Peptide hormones, mimetics and analogues*
1) chorionic gonadotropin (prohibited in males only)
2) pituitary and synthetic gonadotropins (prohibited in males only)
3) corticotropins (adenocorticotropin, tetracosactide)
4) growth hormone
5) insulin-like growth factor, and all the respective releasing factors and their analogues
6) erythropoietin
7) insulin (permitted only for the treatment of athletes with written certification of insulin-dependent diabetes, obtained from an endocrinologist or from a team of physicians).

E) Diuretics
acetazolamide, amiloride, bendroflumethiazide, bumetanide, canrenone, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, mannitol (prohibited by intravenous injection), mersalyl, spironolactone, triamterene

F) Agents with antiestrogenic activity
aromatase inhibitors, clomiphene, cyclofenil, tamoxifen (prohibited only in males)

G) Masking agents**
diuretics, epitestosterone***, probenecid, plasma expanders (e.g. hydroxyethyl starch)

II. *Prohibited methods*

A) Enhancement of oxygen transfer
1) blood doping. Blood doping is the administration of autologous, homologous or heterologous blood or red blood cell products of any origin, other than for legitimate medical treatment
2) the administration of products that enhance the uptake, transport or delivery of oxygen, e.g. modified hemoglobin products including but not limited to bovine and cross-linked hemoglobins, microencapsulated hemoglobin products, perfluorochemicals, and RSR13

B) Pharmacological, chemical and physical manipulation
Pharmacological, chemical and physical manipulation is the use of substances and methods, including masking agents (ref G), which alter, attempt to alter or may reasonably be expected to alter the integrity and validity of specimens collected in doping controls. These include, without limitation, catheterization, urine substitution and/or tampering, inhibition or renal excretion and alterations of testosterone and epitestosterone (ref G) measurements

C) Gene doping
Gene or cell doping is defined as the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance

* the presence of an abnormal concentration of an endogenous hormone in class D or of its diagnostic marker(s) in the urine of a competitor constitutes an offence unless it has been proven to be due to a physiological or pathological condition; ** these are products that have the potential of impairing the excretion of prohibited substances or to conceal their presence in the urine or in other samples used in doping control; *** a urinary concentration of epitestosterone > 200 ng/ml constitutes an antidoping violation unless there is evidence that it is due to a physiological condition.

mic disorders including some inherited cardiomyopathies at risk of sudden cardiac death, the illicit assumption of drugs could be the cause of arrhythmic destabilization leading to life-threatening arrhythmias, cardiac arrest and sudden cardiac death.

The IOC list of "Prohibited classes of substances" includes (www.wada-ama.org - The World Anti-Doping Code version 3.0, February 20, 2003) (Table I): a) stimulants, b) narcotics, c) anabolic agents (androgenic steroids and others such as beta-2 stimulants), d) peptide hormones, mimetics and analogues, e) diuretics, f) agents with antiestrogenic activity, g) masking agents. The IOC list of "Prohibited methods" includes a) enhancement of oxygen transfer (blood doping, oxygen carriers), b) pharmacological, chemical and physical manipulation, c) gene doping.

In the IOC list of illicit drugs there are also "classes of substances subjected to specific restrictions", such as:
• alcohol. Its use is prohibited by some International Sport Committees. A depressant action on the central nervous system, lack of concentration, gait alterations, the late occurrence of alcoholic cardiomyopathy and atrial fibrillation are well-known effects of alcohol;
• cannabinoids. They include marijuana and hashish. The IOC has established a threshold value for doping positivity. The active molecule is tetrahydrocannabinol which acts mostly as an antidepressant, but which may also slow physical activity to a variable extent. Cannabinoids show a remarkable arrhythmogenic effect, particularly supraventricular arrhythmias including atrial fibrillation;
• local anesthetics. Injectable local anesthetics are permitted with some limitations: a) bupivacaine, lidocaine, mepivacaine, procaine, and related substances, can be used but not cocaine (vasoconstrictor agents may be used in association with local anesthetics); b) only local or intra-articular injections may be administered; c) only when medically justified. Notification of administration may be necessary, if required by the Authority rules;
• glucocorticosteroids. The systemic use of glucocorticosteroids is prohibited when administered orally, rectally, or by intravenous or intramuscular injection. When medically necessary, local and intra-articular injections of glucocorticosteroids are permitted. Where the rules of the governing body so provide, notification of administration may be necessary;
• beta-blockers (acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, bunolol, cartelol, carvedilol, celiprolol, esmolol, labetalol, levobulonol, metipranolol, meto-prolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, timolol). Their use is subject to particular regulations. Where the rules of the governing body so provide, tests will be conducted to detect the presence of beta-blockers.

Illicit drugs and performance

According to Clarkson and Thompson[12], there are three leading classes of drugs used by athletes to increase physical performance: 1) substances which enhance physical performance (i.e. stimulants such as amphetamine, ephedrine, cocaine); 2) substances used to reduce heart rate and tremors (beta-blockers); 3) substances used to gain (anabolic steroids such as androgens, beta-2-agonists, growth hormone-GH) or to lose (diuretics) body weight.

The IOC list of prohibited classes of substances and prohibited methods is continuously updated, by including for instance the value of urinary concentrations above which a doping violation occurs. Some new substances such as norbolethone, an anabolic steroid never marketed[13] or the perfluorocarbons[14] and RSR13[15] used in blood doping have been added on the basis of the results of antidoping suggestions in competitive athletes. Some substances such as amineptine and bupropion have been removed from the list. In summary, at present the available information about the list of illicit drugs for antidoping and legislative decisions is considerable, but exhaustive notices on their cardiac side effects and particularly on their arrhythmogenic complications are still lacking.

The aim of the following review is to point out the arrhythmogenic effects of illicit drugs, in order to achieve a better comprehension of the problem from the speculative and clinical points of view, and to disseminate precise scientific information not only in the field of sports medicine, but, possibly, also among teams of athletes, who usually receive imprecise, generic messages on the toxicity and risks of the drugs used.

Cocaine

The relationship between cocaine use, sport and arrhythmogenic effects is well established. This drug, included in the "illicit drug" list as a stimulant, is usually taken for its euphoric effects rather than to improve physical performance. There is no scientific documentation about the efficacy of cocaine in improving physical activity, even though it is well known that it may alter fatigue perception through its euphoric effects. Furthermore, its use represents a serious social problem (millions of addicted in the United States, including many athletes).

Cocaine, an alkaloid derived from *Erythroxylon coca*, has an important acute action, especially if inhaled or smoked and has many chronic effects as well. Indeed, this alkaloid may cause different kinds of focal or reentry supraventricular and ventricular arrhythmias such as ectopic beats, atrial fibrillation, atrioventricular nodal reentry tachycardia, Wolff-Parkinson-White arrhythmias, non-sustained and sustained ventricular tachycardia and fibrillation. The association of the sympathomimetic effects of physical exertion with cocaine addiction may play an important role in the genesis of these arrhythmias[16-18].

Experimental studies on the effects of cocaine showed a prolongation of the PR, QRS, QT and QTc intervals, supraventricular and ventricular ectopic activity, ventricular tachycardia and fibrillation[19,20]. Multiple arrhythmogenic mechanisms have been identified following acute cocaine administration, namely: local anesthetic effect with block of the sodium and potassium channels; sympathomimetic effect with alpha and beta-receptor stimulation and consequent heart rate and excitability increase; intracellular calcium overload (afterdepolarization arrhythmias); increase in heart rate due to a vagolytic effect; arrhythmias due to ischemia/reperfusion.

The arrhythmias may also be secondary to the systemic effects of the drug such as hyperthermia, acidosis and stroke, which are favored by particular environmental conditions (high temperature, high humidity, pollution).

The ability of cocaine to cause myocardial infarction even in patients with a normal coronary angiography is well known (114 cases reported up to the year 2000). Myocardial infarction as well as various arrhythmias may occur even after the first administration of cocaine, regardless of the dosage. Typical are the cases of young athletes involved in physical activity soon after cocaine inhalation, in whom many types of arrhythmias have been observed (supraventricular tachycardia, atrial fibrillation, ventricular tachycardia and fibrillation, torsades de pointes due to secondary long QT syndrome, asystole), either in the setting of ischemia/reperfusion events or not. "Chaotic atrial arrhythmia", similar to that observed in severe respiratory insufficiency or acute myocarditis, is considered a typical toxic cocaine-related arrhythmia.

The long-term abuse of cocaine could result in myocarditis, dilated cardiomyopathy, hypertrophic cardiomyopathy, rupture of an aortic aneurysm, as well as an acceleration of the course of atherosclerosis. *Post-mortem* examinations of these patients have shown areas of myocardial necrosis with "contraction bands". In these subjects different arrhythmias due to the underlying diseases have been observed, with lethal events often during physical exertion.

Stimulants

Besides cocaine, this group (class A, Table I) encompasses many other drugs, in particular amphetamines (ephedrine, methylephedrine, pseudoephedrine, caffeine and related substances), widely used among competitive athletes for their well-known effects: performance enhancement, increased level of aggressiveness, better standing of strain perception[21]. At present, their use is much more widespread among non-competitive athletes than among competitive, because of their easy detection in urine sampling regardless of the route of administration.

Some cases of myocardial infarction and ventricular tachycardia were reported in amphetamine addicted subjects, even with a normal coronary angiography[22].

Stimulants may cause focal and reentry arrhythmias, ventricular and supraventricular ectopic beats, atrioventricular nodal reentry tachycardia, focal atrial tachycardia, atrial fibrillation, ventricular tachycardia and fibrillation.

Their assumption may prove particularly hazardous in athletes with the Wolff-Parkinson-White syndrome (even in the subgroups of Wolff-Parkinson-White patients previously considered at low risk) because of the increase in atrial and ventricular excitability and the shortening of the accessory pathway refractoriness, with possible consequent fast atrial fibrillation and ventricular fibrillation. If assumption of stimulants and other illicit substances (e.g. beta-2-agonists, cannabinoids, anabolic steroids) is suspected, transcatheter ablation of the accessory pathways could be anticipated as these athletes are considered "not reliable" as far as competitive activity is concerned.

In the long term, the abuse of stimulants may cause dilated cardiomyopathy and related arrhythmias. Moreover, many side effects such as insomnia, anxiety, aggressiveness, digestive disorders, and sexual dysfunction have been reported.

Anabolic steroids

Anabolic steroids are derived from modified testosterone to enhance their anabolic rather than their androgenic action. They represent the most widely used illicit drugs (in the year 2000 more than 1 million athletes in the United States), often taken by very young athletes[23,24]. They are taken to increase protein synthesis, the muscle mass, level of aggressiveness and rapid recovery after effort. Their administration is often associated with that of other substances, to mask identification in antidoping controls. Among anabolic steroids, the drugs most frequently taken (often orally, sometimes intramuscular) are: stanozolol, oxandrolone, testosterone, oxymetholone, oxymesterone, and nandrolone, which is probably the most widely used[25]. In table I (class C) of the IOC banned drugs, many other types of anabolic steroids, including some substances which have become available only very recently, are listed.

Various cardiac adverse events have been reported with the use of these drugs: cerebral thromboembolism due to intraventricular thrombi[26], myocardial infarction without coronary thrombus[10], sudden death due to hypertrophic cardiomyopathy and myocarditis during sports activity[27,28]; a particular, reversible form of hypertrophic cardiomyopathy has also been observed.

In 1994, an interesting case of a 31-year-old body builder was reported. After massive administration of several illicit drugs (steroids, amphetamines, furo-

semide, potassium and amyloride) he presented with hyperkalemic ventricular tachycardia and myocardial infarction[29]. Another 34-year-old body builder, who had been using various anabolic steroids for 4 years, developed hemiplegia and aphasia which manifested during physical activity[30].

Anabolic steroids produce several changes in lipid metabolism, with an increase in LDL and a decrease in HDL cholesterol levels[31,32], as well as increased platelet adhesion and prothrombotic modifications of the endothelium and of the coagulation factors.

Various arrhythmias may result from different cardiac abnormalities induced by anabolic steroids through different mechanisms. Arrhythmias often occur during physical activity and may be due to myocellular alterations. The arrhythmias most frequently reported during treatment with anabolic steroids are: atrial fibrillation[33], supraventricular and ventricular ectopic beats, sustained and non-sustained ventricular tachycardia, ventricular fibrillation. QT prolongation may also occur, particularly in genetically predisposed subjects.

Anabolic steroids are often administered along with masking agents such as diuretics, tamoxifen (to reduce gynecomastia) (class F, Table I), chorionic gonadotropin (which increases endogenous testosterone levels), thyroid hormones (to increase metabolic activity), GH for its well-known anabolic effects, together with recreational substances such as marijuana and alcohol. In sports based on muscular strength (such as body building) the dosage of anabolic steroids may sometimes be quite impressive (from 10 to 100 fold the therapeutic levels).

The administration of anabolic steroids may produce many side effects, with serious alterations of the liver function resulting in high levels of transaminases, hepatic tumors[32,34], gynecomastia, modifications of the structure of connective tissue with decreased collagen and tension on tendons[35], sterility, testicular hypotrophy, insulin resistance, acne, virilization in women and early calcification of the epiphyseal cartilages, the latter particularly serious among teenagers.

As documented for some stimulants (e.g., ephedrine and caffeine), pro-hormones and steroid hormones may be present, even though they are not clearly specified in the contents list, in some dietary supplements for athletes, who, therefore, are exposed to a possible positive doping control[36-39].

Beta-2-agonists

The commonly used beta-2-receptor agonists are: salbutamol, salmeterol, formoterol, terbutaline and clenbuterol. The IOC considers them as "anabolic agents" and "stimulants" (classes C and A, Table I), used to increase the muscle mass and physical strength. Inhalatory administration is allowed only in case of asthma (including asthma due to physical activity), for which the team doctors must provide the sports authorities with all the clinical documents required[10]. During the Sydney Olympics the high number (607) of athletes addicted to inhalatory beta-2-agonist drugs gave rise to suspicion; therefore, a method to distinguish oral (not allowed) from inhalatory (allowed if declared before) drug administration was used[40]. However, a controlled study did not demonstrate any improvement in the physical performance of athletes treated with inhalatory formoterol vs placebo[41]. At the Olympic Games, athletes who request permission to inhale a permitted beta-2-agonist, will be assessed by an independent medical panel[42].

Beta-2-agonists may induce ventricular and supraventricular ectopic beats, as well as focal and reentry arrhythmias, supraventricular and ventricular, especially in subjects with underlying cardiomyopathies and in case of concomitant administration with other drugs. The arrhythmogenic effect of these drugs is related both to their direct beta-2 stimulant action (particularly when inhaled) and, in the long term, to their anabolic action.

In our experience, the suspension of these drugs is associated with a return to normal of the patient's clinical conditions within a short time, as documented in some elite athletes.

Beta-blockers

Beta-blockers are classes of substances prohibited by the IOC in specific sports: rifle shooting, archery, diving, equestrian sports, motor sports, modern pentathlon and bob-sleigh. They are used when a high degree of concentration and steadiness is required, in order to minimize tremors, anxiety and emotional tachycardia. Of note, in all cases in which a great physical strength is required, these drugs are detrimental for their well-known action on cardiac function.

These drugs may obviously induce sinus bradycardia, atrioventricular blocks of various degrees, junctional and ventricular escape rhythms, bradycardia-dependent ventricular ectopic beats, especially in patients with underlying structural and electrical disorders. Evidence of their abuse may be obtained by urine sampling, with methods able to identify up to 20 different types of beta-blockers[43].

Diuretics

Diuretics are classes of heterogeneous substances prohibited by the IOC. Diuretics (class E, Table I) are often taken to mask the assumption of other drugs excreted in the urine (class G): the purpose is to attempt to dilute those drugs the cut-off urinary concentration of which is evaluated in tests for doping control (e.g.,

stimulants, narcotics and anabolic steroids such as nandrolone, methandienone metabolites, methyltestosterone, stanazolol). Probenecid (included in the masking agent class) is a typical drug used for this purpose. The topical (ophthalmic) use of a carbonic-anhydrase inhibitor, dorzolamide, was not associated with any illicit effect[43].

Diuretics are also used to lose weight temporarily in boxing and in other sports sorted by weight categories, as well as to get better shaped muscles in body building. To this end, intravenous injections of furosemide are often used by body builders before competitions, usually together with many other illicit drugs.

The administration of diuretics may cause arrhythmias due to hypokalemia and dehydration. This effect is further facilitated by the concomitant administration of other illicit drugs. Moreover, these arrhythmias may be particularly severe in case of underlying primary or "toxic" cardiac diseases. In those athletes with silent genetic mutations of the sodium and potassium channels, induction of torsades de pointes, due to electrolytic imbalance and the subsequent prolongation of the QT interval, may be particularly dangerous.

Peptide hormones, mimetics and analogues

The new techniques based on recombinant DNA have made it possible to synthesize very active substances, identical or almost identical to the equivalent endogenous molecules, such as erythropoietin (EPO)-like exogenous recombinant human EPO (rhEPO), GH or somatotropin-like exogenous recombinant GH (rGH), insulin-like growth factor (IGF-I) or somatomedin-like exogenous recombinant human IGF-I or mecasermin. Whereas the identification in urine analysis of some classes of illicit drugs (i.e., stimulants) may be easy, the discrimination of the recombinant substances is very demanding, these molecules being almost indistinguishable from their endogenous counterparts.

For this reason and for their powerful ergogenic effect (as "hematologic" and "anabolic doping"), at present these substances are the most commonly used by athletes.

Erythropoietin. It became available as a drug (rhEPO), synthesized from Chinese ovary cells since 1988, thanks to genetic engineering techniques based on recombinant DNA[44]. Its administration as medical therapy is quite limited, and it is mainly used in urologic, surgical and cardiosurgical fields. On the contrary, it is widely used as "hematologic doping"[45,46] in place of the former autologous or heterologous blood transfusion doping. Athletes often take EPO to gain a sensation of strength and stamina while engaged in physical activities such as cycling, skiing, marathon running and swimming, but also in competitive short duration performances. It is deemed that up to 3-7% of elite endurance athletes have used it.

EPO enhances oxygen transfer and tissue availability, increasing its arterial blood concentration, by raising the hemoglobin and red cell levels. In the bone marrow it stimulates erythroid precursors (but also regulates apoptosis), according to the physiologic inputs of oxygen requirements from the interstitial renal tubular cells.

The ergonomic effects rhEPO are usually achieved following injection of the drug every 2 or 3 days for 3-4 weeks, with concomitant iron supplements; once the steady state has been reached, the dosage is reduced so that its identification in antidoping controls could become difficult[47].

Recently, another synthetic derivative of EPO, "alpha-darbopoietin", has been introduced in clinical practice. It was shown to have a longer and powerful erythropoietic effect, probably due to its longer half-life with respect to EPO.

The long-term use of rhEPO and darbopoietin is characterized by many side effects. The increase in the total number of red cells leads to a rise in blood viscosity, which in athletes could be further exacerbated by natural perspiration during intense athletic performances. Besides, due to their actions on the endothelium and platelets, the thromboembolic risk could be increased in predisposed subjects, with cases of hypertension, myocardial infarction and stroke.

It is of interest that there are some differences in the regulatory action on erythropoiesis and apoptosis between rhEPO and natural EPO. This could be associated with the potential development of serious hematologic disorders such as acute leukemia, polycythemia and marrow aplasia[47].

Although hematologic doping is widespread among athletes, a reliable antidoping method has not yet been developed. At present, indirect indicators of doping, such as the hematocrit (normal value up to 50% in males, up to 47% in females), are commonly adopted by international authorities. Unfortunately, this method may lead to false positive (due to para-physiologic variants)[48-50] as well as false negative results, and for this reason it has been deemed unreliable. On the other hand, it is usually very difficult to discriminate endogenous from exogenous EPO; moreover, because the erythropoietic effects become more evident when the drug is no longer present in the blood[47], the time frame useful to establish any antidoping rule violation is quite limited. Other indirect methods to rule out illicit drug administration, based on different markers of altered erythropoiesis[49,50], have been proposed: erythrocyte and reticulocyte hematocrits, serum EPO, soluble transferrin factor, percentage of macrocytes. These methods, in combination with mathematical predictive models, can identify EPO even after a relatively long period following injection. Recently, the development of a blood test for drug testing methods has been proposed[44].

Other substances used as enhancers of oxygen transfer are "human and animal (bovine) synthetic hemoglobins" and "perfluorocarbons", which are used in oncology to increase the radiosensitivity of some tumors. The use of these substances has aroused great medical interest but, due to their multiple side effects, it is advisable to strongly discourage athletes from using them.

Arrhythmias occurring in athletes with "hematologic doping" (often subjects who are dehydrated and exposed to prolonged physical activity) are usually secondary to the circulatory effects induced by the increased erythroid mass, increased blood viscosity, and altered endothelial and platelet function with possible thromboembolic events and hypertension during effort[51], as well as to the concomitant administration of ergonomic (stimulants, anabolic steroids) and masking (diuretics) agents.

Growth hormone and insulin-like growth factor. The therapeutic use of GH and IGF-I is quite limited, being indicated in some congenital or acquired nutritional and endocrine disorders. They are instead widely used in the exogenous recombinant forms (rhGH and rhIGF-I) by athletes as anabolic agents, to increase the muscle mass, cardiac performance and stamina on the job[52-54], even though the real effect on muscle strength is still subject of debate[55-57].

The association with anabolic steroids enhances their effects and could negatively interfere with some antidoping tests[58]. To date, the identification of rhGH administration is impossible by means of the commonly used urine sampling tests. In view of their very short half-life, more sophisticated tests (such as specific hepatic metabolic activity markers) have been proposed[59-61].

Up to now no side effects related to GH abuse are clearly known, but a significant increase in mortality was reported among patients submitted to treatment for catabolic diseases[62]. With regard to athletes taking these drugs for a long time and at high dosages the following side effects are possible: systemic disorders such as myalgia, asthenia, headache, arthralgia, diabetes mellitus, thyroid disorders, acromegaly, metabolic-ionic alterations; hypertension and various types of cardiomyopathies (hypertrophic or dilated), similar to those observed in acromegaly. All these conditions may contribute, to a variable extent, to the development of different types (focal or reentry) of supraventricular and ventricular arrhythmias, which are often found in athletes.

Insulin. Its use as the mainstay of diabetes therapy is well known. In an athlete who is engaging in physical activity, the addition of insulin may provide anabolic ergogenic aid, especially if administered together with other illicit drugs. Nevertheless, it may be dangerous to handle since its use may cause hypoglycemia, mental derangement up to coma, lipodystrophy, insulin resistance and secondary arrhythmias, especially in case of underlying cardiac hypertrophy or metabolic-ionic disorders.

Corticotropin (adenocorticotropin, tetracosactide). Its real efficacy in improving physical performance is still debated. It provides a sensation of strength and stamina on the job, improving exercise duration. The side effects in case of long-lasting treatments are corticosteroid-like and include obesity, hyperglycemia, osteoporosis, immunodeficiency, hypertension, and metabolic disorders.

Arrhythmias may result mainly from cardiac hypertrophy, metabolic and ionic disorders.

Remarks

The assumption of illicit drugs (e.g. stimulants, including cocaine, beta-2-agonists, cannabinoids, anabolic agents) could be particularly dangerous in competitive athletes with previous arrhythmic manifestations including atrial fibrillation, flutter, atrioventricular nodal reentry tachycardia, or with an underlying arrhythmogenic substrate such as accessory atrioventricular pathways, primary arrhythmic disorders and latent structural heart diseases (hypertrophic or dilated cardiomyopathies, coronary artery disease, myocarditis).

Besides, athletes with latent inherited arrhythmogenic molecular cardiac diseases due to defects of the genes encoding the cytoskeleton, sarcomere, cell junction and ion channels, are most likely at high risk of severe arrhythmic events. For instance, subjects with "silent" mutations on the long QT syndrome genes may be particularly sensitive to illicit drugs (namely, cocaine, anabolic steroids, beta-2-agonists, diuretics) which, in combination with physical exercise, could produce a critical prolongation of the action potential duration that triggers the onset of ventricular tachycardia/fibrillation. Catecholaminergic polymorphic ventricular tachycardias (CPVT) due to cardiac ryanodine receptor gene (hRyR2) defects (CPVT type I) or to calsequestrin (CASQ2) gene defects (CPVT type II) or related to arrhythmogenic right ventricular dysplasia type II, are genetic arrhythmogenic diseases with characteristic "polymorphic ventricular tachycardia" during physical or emotional stress[63-65]. In athletes carrying these gene mutations, illicit drugs that could be particularly dangerous include: stimulants, cocaine, beta-2-agonists, cannabinoids, anabolic steroids, as well as variable combinations of these substances.

Moreover, it is worth noting that in athletes assuming illicit drugs the following manifestations are quite possible:

• atrial fibrillation and atrial flutter, related to the assumption of stimulants, including cocaine, cannabinoids, alcohol, beta-2-agonists, anabolic steroids, and the combination of these substances;

• effort-related arrhythmias (some forms of atrioventricular nodal reentry tachycardia, atrial fibrillation in the presence of preexcitation, the previously described CPVT, sustained ventricular tachycardia primary or secondary to arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, dilated cardiomyopathy, coronary artery disease, myocarditis), precipitated by the assumption of stimulants, cannabinoids, beta-2-agonists, anabolic agents, and various combinations of these drugs.

Finally, the prolonged assumption of several illicit drugs such as stimulants (including cocaine), narcotics and all types of anabolic agents may induce the development of some forms of hypertrophic or dilated cardiomyopathy, coronary artery disease, and myocarditis.

Conclusions

Most of the illicit drugs included in the IOC list taken to improve athletic performance or as masking agents may cause, through a direct or indirect arrhythmogenic effect, in the short, medium or long term, a wide spectrum of arrhythmias, even in healthy subjects with no previous history of cardiac diseases. Therefore, given the widespread abuse of illicit drugs among athletes, in the management of arrhythmic athletes the cardiologist should always take into consideration the possibility that the presenting arrhythmias could be due to the assumption of illicit drugs (sometimes more than one type), especially if no signs of cardiac structural diseases are present. On the other hand, in the presence of a latent underlying arrhythmogenic heart disease, including some inherited cardiomyopathies at risk of sudden cardiac death, illicit drugs could induce severe arrhythmic events.

With regard to the prevention of doping, good results could be reached both by means of thorough information campaigns among athletes (especially the youngest) about the various and dangerous side effects of the illicit drugs as well as through the development of newer antidoping measures.

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