Doping in sport and cardiovascular risk

Dopaje en el deporte y riesgo cardiovascular

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Introduction

Although the definition in the World Anti-Doping Code (hereafter Code)[1] describes 11 different actions and behaviours that can be considered doping, in practical medical terms, the most usual problem is handling drugs that might be on the list of prohibited substances and methods (hereafter List)[2]. The possession or the use or attempted use of any of these substances, their administration or attempted administration or, of course, trafficking or attempted trafficking, the presence of any of them or their metabolites or markers in a physiological sample from an athlete can caused serious problems for the athlete and also the professional.

Medical and deontological ethics and rules must guide our conduct, including the principle of 'non maleficence *(primum nil nocere)*.' This is the guiding light for healthcare professionals who should never act without weighing up the risk-benefit balance.

In the field of sport, and also in the medical profession, even for doctors working specifically in sports medicine, it is widely received that these prohibited substances can improve sporting performance and in turn represent a danger to athletes' health or even their lives, so that this 'non maleficence' principle prevents ethical doctors from handling these substances to enhance sports performance.

However, if we take a closer look at the definition of these substances in article 4.3 of the Code, we will see that there are three criteria for the World Anti-Doping Agency (WADA) to classify a substance as prohibited:

Scientific or medical evidence that the substance has the potential capacity to enhance sports performance.

Scientific or medical evidence that the substance represents a risk to the athlete's health.

That the WADA has determined that the use of the substance violates the 'spirit of sport'.

In the Code, the WADA defines 'spirit of sport' as: "The celebration of human spirit, body and mind. It is the essence of the Olympic movement and is reflected in sporting values," and then adds a list of these values, which are just as subjective as the definition itself. This means that this list might contain substances that do not enhance sporting performance and also substances that do not represent a health risk. This all gives the WADA licence to declare any performance-enhancing or dangerous drug as prohibited.

In countries with an advanced anti-doping system, as in Spain, this means that the anti-doping rules are applied to all offences as administrative rules (Organic Law 11/2021, of 28 December, to fight doping in sport) and in the case of a health risk, they are processed as crimes with a penal punishment (Organic Law 10/1995, of 23 November, from the Criminal Code, article 362, delinquents).

Regarding behaviour from the healthcare professionals, this lack of clarity in the causes of including substances and drugs on the list is causing an attempt to justify the use of prohibited substances by invoking the lack of evidence of a health risk and even talking about "protecting health" with its use.

It is thereby essential to have evidence of the real health risk incurred by the use of prohibited substances among healthy athletes. Evidence has been stacking up over the last ten years[3-7]. We can state that the most compromised physiological system when doing sport and where most of the severe pathologies and sudden death occur in sport is the cardiovascular system[8-18].

The main reason for this editorial is to provide sports doctors with objective data on the real risk of doping by using evidence of its effects on the cardiovascular system. Do to this, we would like to recall and

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recommend reading the publication in 2022 by Adami *et al.*[19] as the official position of the European Cardiology Society throughout its sport cardiology hub, on the cardiovascular effects of doping substances, and other frequently prescribed medicines and ergogenic aids.

In the publication, the authors update the official position of European Society of Cardiology's study group on Sports Cardiology, published in 2006[11]. This work gives a systematic critical review of the evidence on the cardiovascular effects of these substances (with 170 references). It includes a study of the pharmacological and physiopathological mechanisms in the cardiovascular system, their real impact on sports performance and their risk/benefit ratio.

We believe that any doctor working in the field of Sports Medicine should study this official position carefully.

Prohibited substances and cardiovascular risk

We are going to emphasise the cardiovascular risk and the main substances that cause it. This does not mean that there are no other dangerous substances on the list with other types of health risks, but these are the ones recognised by the position of the European Society of Cardiology.

Non-approved substances

We do not think it is necessary to insist on the danger of this type of substances, that have not been approved because studies have not continued as there was some evidence of risks that prevent its use on humans, that were directly discarded due to evidence of severe risks in clinical phases or that are still in clinical trials which have not finished yet. We do not think it is necessary to look at the cardiovascular risks and all the categories in these non-approved substances.

Metabolic modulators are this type of substances where minimum medical ethics immediately advise against their use. These are substances with unknown, potentially severe side effects as they interfere with central aspects of muscular metabolism and they modify the activation of the genetic transcription in a variety of loci, joining specific points of DNA. The list mentions AICAR, Stenabolic, PPAR-delta, Cardarine or Endurobol.

Anabolic-androgenic steroids (AAS)

The use of AAS has demonstrated a 30% increase in mortality, due to cardiovascular causes[8] and defines this increase in mortality due to the rise in atherogenesis, thrombosis and vasospasm. These factors lead to direct myocardial lesions, arterial hypertension, acute myocardial infarction, arrhythmia and sudden death[8,20]. There is now considerable evidence relating AAS consumption with coronary atherosclerosis and the appearance of cardiomyopathies[21-26].

On the other hand, we should consider the selective androgen receiver modulators (SARM) designed to isolate the androgenic effects of the anabolic effects that are caused by the AAS. These are substances considered to be experimental in humans, the list mentions Andarine, Enobosarm (Ostarine), Ligandrol, Testolone, Sarmbolone and Myostane, that are substances with an illegal origin. The quantities detected in recent entries and records in clandestine labs by security forces working with the CELAD reveal that they are being used in possibly massive quantities by athletes. After 20 years of research, they have not been approved due to potential severe effects such as carcinogenesis and cardiovascular alterations[27].

Clenbuterol appears on the list of these anabolic steroids although it seems advisable to study its effects among the beta-2-agonists.

Peptide hormones, growth factors, related and mimetic substances

In this section, the list includes erythropoietin recombinants (rHuEPO) (including Darbopoetin, CERA and similar) and agents that affect erythropoiesis, such as hypoxia-inducible factor activators, and cobalt, Daprodustat, Molidustat, Roxadustat, Vadadustat, Xenon and GATA inhibitors.

The rHuEPOs present many cardiovascular side effects with a potentially severe impact on the health of athletes that use them in a doping context: increase in viscosity of the blood[14-15], increased coagulation and platelet reactivity and risk of thrombosis[7,16].

In the case of other oxygen transport modulators, cobalt chloride is associated with developing dilated cardiomyopathies[3,28], while the mechanism of others can alter the saturation curve in O_2, which can cause hypoxaemia at rest and at sea level, with a high potential cardiovascular risk.

Regarding the use of the human growth hormone (hGH), it is well-known that patients with acromegaly frequently develop arterial hypertension, congestive heart failure and cardiomyopathies6 with concentric remodelling of the left ventricle[10], that might lead to fibrosis, inflammation and end up as myocardium necrosis[11].

Narcotics

Narcotics have a strong effect on the electric mechanisms of myocardium contraction. We know that methadone and Levacetylmethadol increase the time and the dispersion of the QT space on the electrocardiogram, with the consequent risk of polymorphic ventricular tachycardia[29]. Furthermore, reference is made to the appearance of stress cardiomyopathies similar to the Takotsubo (broken heart) syndrome and syndromes similar to Brugada syndrome[30].

Stimulants

There is a well-established relationship between cardiac arrhythmia, especially when a genetic base is known, and the use of stimulants[4]. These substances have profound effects on the neurophysiology of the central nervous system and on the cardiovascular system. They are described as aetiological factors or provoking congestive heart

failure, acute myocardium arrest, valvular fibrosis, fibrosis of the heart chambers, cardiomyopathies, pulmonary hypertension and brain arrest and haemorrhage[5,13,31,32], the anatomical and functional changes that stimulants such as amphetamines can cause have been demonstrated as substrates causing sudden death[33].

We cannot forget the mounting evidence of the negative impact of stimulants on thermoregulation, so when taken during sport in a warm, damp atmosphere, they can cause severe effects[34,35].

Beta-2-Agonists

The list comprises Arformoterol, Fenoterol, Formoterol, Higenamine, Indacaterol, Levosalbutamol, Olodaterol, Procaterol, Reproterol, Salbutamol, Salmeterol, Terbutaline, Tretoquinol, Tulobuterol and Vilanterol. All as specific substances.

Clenbuterol is on the list for "other anabolic steroids" and as a specific substance.

In high doses and when taken orally, Salbutamol would be a stimulant and improve anaerobic power and strength. Clenbuterol also stimulates lipolysis. At effective doses these drugs cause tachycardia, trembling, gastrointestinal disturbance, they can have a supraventricular and ventricular arrhythmongenic effect with myocardium ischemia[14,36] and acute heart failure[9,37].

Glucocorticoids

These are prohibited via any injection line, via mouth or nose or rectally. They are known to have a cardiovascular effect with arterial hypertension and dyslipidemia[12,38].

Other contributions

The Position document also compiles evidence of assessing the potential sporting improvements brought about by each of the substances being studied.

We would also like to highlight the interest of this publication due to other aspects such as the detailed description of the potential undesirable cardiovascular effects of many drugs frequently handled by the sports doctor for their patients, although not included on the lists, such as antiarrhythmics, beta-blockers (only prohibited in certain sports) platelet drugs, anticoagulants, benzodiazepines, antidepressants, antiepileptics and anti-inflammatories.

Finally, the review extends to the effects of many sports supplements that can be legally used in sport such as caffeine, creatinine, carbohydrates, Beta-alanine, bicarbonate of soda, nitrates, proteins and energy drinks; and also looks at unhealthy recreational substances and habits such as alcohol, tobacco and nicotine.

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