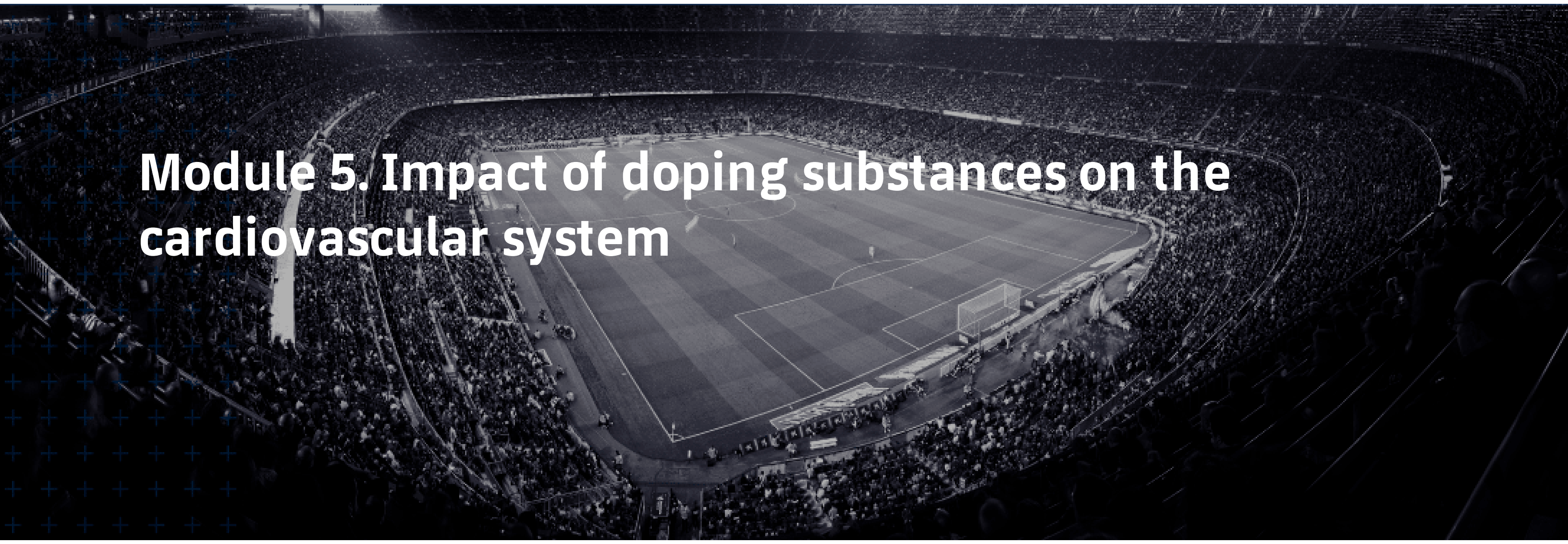

Module 5. Impact of doping substances on the cardiovascular system

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Next, in order to explain the impact of doping substances on the cardiovascular system, we will present part of the work of Adami et al. (2021)

Impact of doping substances on the cardiovascular system

Impact of doping substances on the cardiovascular system

“Doping is defined as the use of a substance or method that is potentially dangerous to an athlete's health and is capable of enhancing athletic performance (Kent, 2007). With the aim of leading a worldwide collaborative movement for doping-free sport, sports and governmental associations came together in 1999 to found the World Anti-Doping Agency (WADA). In 2004, the WADA code was introduced, the latest version of which was updated in 2023 and accepted by 700 sports organizations, including the International Olympic Committee (IOC), the International Paralympic Committee (IPC), the International Federations (IFs), national Olympic and Paralympic committees, as well as national and regional anti-doping associations. In addition, WADA annually updates the list of substances and methods prohibited in sports practice. However, the use of novel and unclassifiable substances and methods is currently a relevant problem. This relates to the time lag between the moment in which athletes start experimenting with such novel substances and the time at which authorities become aware of such substances and start monitoring them (La Gerche and Brosnan, 2017), which poses a problem in terms of safety, fairness, and regulation. A recently published systematic review (Gleaves et al., 2021) showed that the prevalence of doping substance use estimated by different studies is very disparate, ranging from 0% to 73%, with 5% being the most accepted and common prevalence. This systematic review also revealed that the use of doping substances impacts all levels of the sports field, from recreational athletes to elite athletes. This review also confirms that the use of banned substances and/or methods has progressively increased in recent years in recreational athletes, which is of particular concern given the lower health monitoring they undergo (Bojsen-Møller and Christiansen, 2010). A retrospective study in which all doping test samples from the Summer Olympic Games from 1968 to

2012 were included revealed that most of the positive tests for doping contained exogenous metabolites of anabolic-androgenic steroids (AAS) (Kolliari-Turner et al., 2021). Nevertheless, the WADA list is actually very extensive. On the other hand, it is important to distinguish between those substances that are considered prohibited at all times, i.e., before, after and at the time of competitions, from those that are only considered prohibited if consumed at the time of competition [see Table 1]" (Adami et al., 2022, https://goo.su/3a66p).

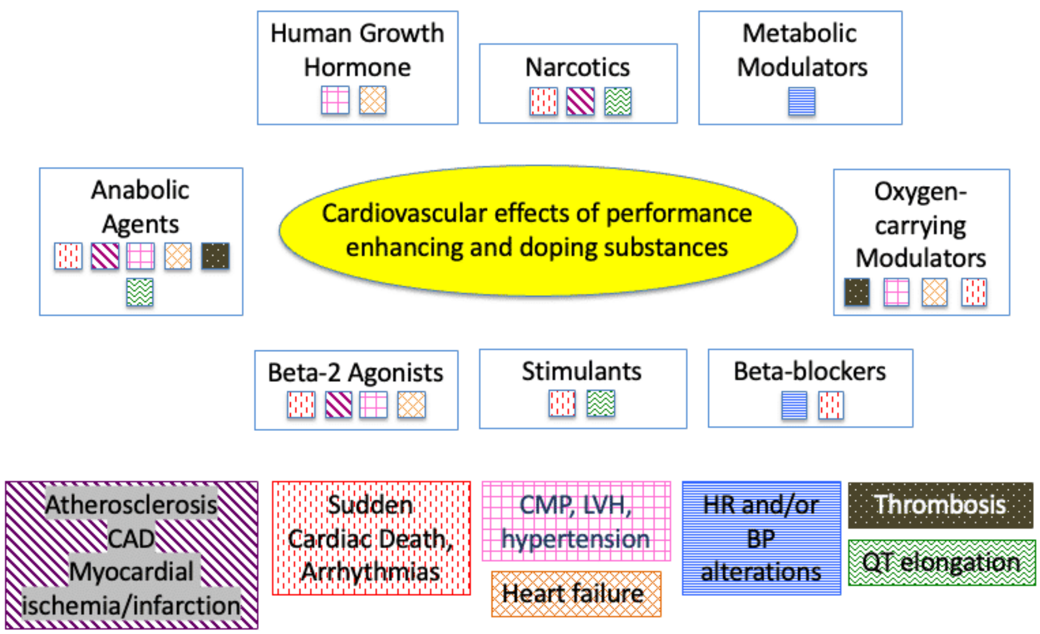
Table 1. List of prohibited substances (S) and prohibited methods (M)

Substances and methods prohibited at all times (during, after, and before competition) S0. Substances not approved S1. Anabolic agents S2. Peptide hormones, growth factors, and related substances S3. Beta-2 agonists S4. Hormone and metabolic modulators S5. Diuretics and masking agents M1 - M2 - M3. Prohibited methods
Substances and methods prohibited in competition S6. Stimulants S7. Narcotics S8. Cannabinoids S9. Glucocorticosteroids
Substances prohibited in certain sports disciplines P1 Beta-blockers

Source: own source based on Adami et al., 2022.

Prohibited substances and methods have multiple side effects at all levels of the body. In this chapter, we will focus on the negative impact on the cardiovascular system, which is especially important, given the vital risk that such effects can entail (Figure 1).

Figure 1. Cardiovascular effects of substances and methods associated with doping



Source: Adami et al., 2022, https://goo.su/3a66p.

The figure above summarizes the main cardiovascular effects of the different substances associated with doping. BP: Blood pressure; CAD: Coronary artery disease; CMP: Cardiomyopathy; and LVH: Left ventricular hypertrophy.

Oxygen-carrying modulators and dissociation curve modulators

These modulators are agents that can increase the availability of oxygen through the following:

1. The increase of oxygen content in the blood
2. Improvement in cardiac output
3. Improvement of peripheral oxygen extraction

Theoretically, such modulators improve performance in endurance sports; nonetheless, evidence on the positive impact on sports performance is scarce for several of these agents.

Blood doping

"It usually consists of the transfusion of autologous blood, with the aim of increasing red blood cells mass. They have been used for decades. The existing evidence is derived from double-blind studies, which include small population sizes. These studies support the concept that blood doping increases the oxygen-carrying capacity and, with it, athletic performance (Berglund and Hemmingson, 1987;

Brien and Simon, 1987). The most important studies related to this concept are specified below.

- Berglund et al. conducted a double-blind study in 6 cross-country skiers and observed that infusion of 1350 mL of autologous blood significantly reduced the 15 km race time by 6% at 3 and 14 days after infusion (Berglund and Hemmingson, 1987)..

- Brian et al., in a randomized, double-blind, placebo-controlled study in 6 recreational runners, but with high training volumes and high sports performance, found that, with an infusion of 400 mL of blood, the hematocrit increased significantly by 5% and the 10 km race time decreased by one minute with respect to the placebo group (saline infusion) (Brien and Simon, 1987)" (Adami et al., 2022, https://goo.su/3a66p).

Recombinant human erythropoietin (rhEPO)

"It is a substance that has been shown to induce a significant increase in red blood cell mass and hemoglobin concentration in a manner similar to blood doping, in addition to increasing oxygen consumption. However, we currently lack evidence for a significant effect of such a substance on sports performance (Heuberger et al., 2017a; Heuberger et al., 2017b).

- Birkeland et al., in a double-blind, placebo-controlled study in a population of 10 highly-trained cyclists, demonstrated that the administration of rhEPO for 4 weeks increased maximal oxygen uptake (VO2 max). This period was necessary to demonstrate a significant increase of 42.7 versus 50.8% in hematocrit and 63.6 versus 68.1 mL/min/kg in the erythropoietin (EPO) group with respect to placebo (Birkeland et al., 2000). Although this study did not include a direct measurement of athletic performance, the time to exhaustion in a training session was significantly longer in the EPO intake group from 12.8 to 14 minutes ($p<0.0001$), with respect to the control group from 13.1 to 13.3 minutes ($p=0.04$) (Birkeland et al., 2000).

- Other double-blind placebo-controlled studies, similar to the one mentioned above (Heuberger et al., 2017b; Wilkerson et al., 2005; Parisotto et al., 2000; Connes, et al., 2003), confirmed these results, demonstrating that rhEPO administration led to a significant increase in oxygen consumption. Nevertheless, in the study by Heuberger et al. (2017b), EPO administration achieved a 5% improvement in oxygen consumption, but this did not

Translate into a significant increase in athletic performance as assessed by Mont Ventoux race finish time" (Adami et al., 2022, https://goo.su/3a66p).

Although there is currently no scientific evidence of an impact of rhEPO on sports performance, the repeated confirmation that this substance significantly improves oxygen consumption has led—and is leading—athletes to use different formulations of rhEPO and its receptor agonists to achieve this effect. However, the increase in sports performance is not confirmed.

"The harmful cardiovascular effects of these substances have been demonstrated in a prospective study involving 3,000 healthy adults, in whom a doubled serum EPO value was independently associated with a 25% increased risk of heart failure at a 10-year follow-up" (Garimella et al., 2016 as cited in Adami et al., 2022, https://goo.su/3a66p).

Other substances that are grouped in this category are those that increase oxygen consumption by increasing the amount of oxygen that hemoglobin can transport to the different tissues. The following is a summary of the best-known substances that use this mechanism.

- **“Cobalt chloride:** A substance that would stimulate erythropoiesis and angiogenesis, presumably by activating hypoxia inducible factor-1 (HIF-1) signaling (Lippi et al., 1972). Although the cardiovascular effects of its use in the sports setting have not been studied prospectively, non-voluntary intake of such a substance has been associated with the development of dilated cardiomyopathy (Alexander, 1972; Ebert and Jelkmann, 2014).

- **RSR13** (right shifting reagent 13 or efaproxiral): It is a synthetic allosteric hemoglobin modifier. In in vivo studies, it has been shown to shift the hemoglobin-oxygen dissociation curve to the right and thereby increase oxygen dissociation in peripheral muscles. RSR13 has been shown to increase skeletal muscle oxygen consumption in a canine experimental model (Richardson et al., 1998). However, in humans, at sea level, the shift of the hemoglobin/oxygen curve to the right leads to an increase in hypoxemia at rest that would potentially increase during exercise (Suh et al., 2006). The cardiovascular effects that the use of such substances could have in the long term are currently unknown” (Adami et al., 2022, https://goo.su/3a66p).

In addition, methods and substances have been developed that seek to increase oxygen consumption by increasing cardiac output. These substances include **sildenafil,** a specific vasodilator of the pulmonary vasculature that seems to be frequently used by endurance athletes. The rationale behind this use derives from the fact that such a vasodilator has been shown to reduce pulmonary resistances in patients with pulmonary hypertension and, in fact, is a drug indicated for a subgroup of these patients. This led to the hypothesis that the same effect could occur in a healthy population.

Reduced pulmonary resistances would mean a lower afterload, i.e., less work for the right heart cardiac muscle, leading to an increase in the time during which that ventricle could respond to exercise-induced increased cardiac output requirements (La Gerche and Claessen, 2014). This is especially relevant, given that the right ventricle bears a disproportionate pressure and volume overload with respect to the left ventricle during sports practice (La Gerche and Heidbuchel, 2014). Many studies have evaluated the impact of these vasodilators on sports performance in healthy volunteers and athletes; one of the most important was conducted by Ghofrani and collaborators.

“This is a randomized, double-blind, placebo-controlled study in 14 healthy volunteers, where the impact of sildenafil on exercise capacity under normobaric hypoxia (10% 02) and at altitude (Mount Everest, 5,245 m above sea level) was evaluated, showing a significant increase" (Ghofrani et al., 2004 as cited in Adami et al., 2022, https://goo.su/3a66p).

Nevertheless, although the various studies using this type of substance have consistently shown an increase in hemodynamics and improvement in sports performance under hypoxic conditions, they have not shown such effect nor any positive effect under normoxic conditions (Faoro et al., 2009; Guidetti et al., 2008; Hsu, et al., 2005). In fact, these agents are not currently considered prohibited by the World Anti-Doping Agency (WADA). However, this agency maintains a continuous monitoring of the scientific evidence that is being developed in this regard, in order to evaluate a potential effect on sports performance (Adami et al., 2022).

Anabolic agents

The list of anabolic-androgenic steroids (AAS) included in the list of substances prohibited by WADA is extensive. Indeed, it is estimated that 60% of positive doping test cases are due to AAS. These are the oldest abused drugs and, therefore, we have more scientific evidence of their potential harmful effects on the cardiovascular system.

In relation to sports performance:

“AAS, combined with physical training, have been shown to significantly increase muscle mass, reduce fat percentage, and increase muscle strength (Bhasin et al., 1996; Forbes et al., 1992). These findings have been verified in a randomized, double-blind study that included 10 individuals and confirmed that the use of AAS for 12 weeks is able to significantly increase muscle strength compared to placebo (Giorgi et al., 2000)” (Adami et al., 2022, https://goo.su/3a66p).

A common misconception is that the use of AAS is limited to the field of strength athletes; nonetheless, its use is also common in endurance athletes to accelerate recovery after intense training. Thus, concomitant use of anabolic agents and EPO is common in both strength athletes and endurance athletes (Pope et al., 2013).

It is estimated that mortality among athletes who use AAS is 6 to 10 times higher than in athletes who do not use them. One out of three deaths derived from its use is associated with cardiovascular causes (Achar et al., 2010). The most common and important harmful cardiovascular effects associated with the use of AAS are the following:

1 Cardiomyopathy

2. Acute myocardial infarction
3. Dyslipidemia
4. Cardiac conduction disturbances
5. Alterations in coagulation (Pope et al., 2013; Hartgens et al., 2004; Darke et al., 2014; Baggish, et al., 2010; Thompson, et al., 1989).

Cardiomyopathy associated with the use of AAS has been first described by postmortem studies. The use of echocardiograms and MRIs has made it possible to describe the characteristics of such cardiomyopathy, including increased cardiac mass; increased left ventricular wall thickness, referred to as left ventricular hypertrophy; increased prevalence of myocardial fibrosis; and worsening left ventricular systolic and diastolic function (Darke et al., 2014; D'Andrea et al., 2006; Baggish, et al., 2010; Far, et al., 2011).

The pathogenesis of arrhythmic events associated with AAS use is not well established, but is considered multifactorial, both due to myocardial fibrosis and potential atherosclerotic plaques, which are commonly documented in individuals who consume them.

Traditionally, based on the Monganroth hypothesis, it was considered that the greater left ventricular thickness associated with sports practice would occur in strength athletes. Nonetheless, later studies did not confirm this hypothesis, and the thickness values were found to be higher in athletes with a high dynamic component. The use of AAS in strength athletes has promoted this mistaken idea of cardiac remodeling with an increase in left ventricular thickness associated with sport, when in fact the increase in left ventricular thickness is largely explained by the use of AAS and not by the training itself. This was confirmed by Luijckx et al. in a study on strength athletes in which they compared those who used AAS with those who did not, finding significant left ventricular hypertrophy only in the former (Luijckx et al., 2012; Baggish, et al., 2010).

SARMs (selective androgen receptor modulators, e.g., thymosin beta 4)

"They are a new class of abused drugs designed to dissociate the androgenic effect and the anabolic effect of AAS, making their detection more difficult. Given the short life of use of these substances, we have little evidence on the potential cardiovascular effects that these agents could have. The hypothesis is that both the effects on the increase in sports performance and the side effects would be less than those of AAS, but it is difficult to affirm this, given the scarce evidence currently available." (Adami et al., 2022, https://goo.su/3a66p).

Human growth hormone (HGH)

"It is an endogenous neurohormone that is associated with anabolic effects when used in supraphysiological doses. Its use is widespread among athletes; however, we have little evidence that this agent accelerates recovery and prevents tissue damage potentially associated with physical training (Pope et al., 2013). Likewise, we have little information regarding the harmful effects on the cardiovascular system that HGH could have." (Adami et al., 2022, https://goo.su/3a66p).

What has been confirmed is that patients with acromegaly, in whom there is excessive endogenous production of said hormone, the prevalence of hypertension, heart failure, and cardiomyopathy is significantly higher than in the general population (Pope et al., 2013).

Metabolic modulators

Meldonium (mildronate) is a drug licensed for clinical use in Eastern European countries; it is used as an antianginal. The mechanism of action derives from the modulation of L-carnitine metabolism; such agent reduces the availability of L-carnitine and thereby stimulates glucose metabolism and accelerates the process of L-carnitine regeneration, with a consequent increase in athletic performance, both from the physical and mental point of view (Dambrova et al., 2016). However, we have little evidence regarding its true efficacy on sports performance and the potential harmful effects that such a substance could entail (Adami et al., 2022).

“In the London 2012 Olympics, the prevalence of use was anecdotal, increasing exponentially in the 2015 European games, with a prevalence of 9% (Stuart et al., 2016). This led WADA to place this substance on the banned substance list in January 2016.” (Adami et al., 2022, https://goo.su/3a66p).

Beta-2 agonists

“Beta-2 agonists, such as salbutamol or clenbuterol, are commonly used drugs licensed for clinical use in allergic asthma, given their bronchodilator effect on the smooth muscle of the lung. In 2011, Pluim et al. conducted a meta-analysis of clinical trials comparing inhaled or systemic use of beta-2 agonists (salbutamol, albuterol, or terburaline) with placebo, and concluded that there was no evidence to confirm a positive effect of the use of such substances on maximal oxygen consumption or on sports performance, both in relation to the strength component and to the endurance component (Pluim et al., 2010). They did confirm an increase in anaerobic capacity and strength with high doses of oral salbutamol, although the evidence was weak (Pluim et al., 2010). High doses of beta-2 agonists have been associated with the following harmful cardiovascular effects: Tachycardia, ventricular extrasystoles, tremor, and hypokalemia (Sears, 2002).

Recently, clenbuterol has emerged as an abused drug in elite and recreational athletes, given its effect on the beta-3 receptor of adipocytes, which generates increased lipolysis and consequent weight and fat mass loss (Milano et al., 2018). The dose required to achieve such training-enhancing effects is 120-160 μg daily, which corresponds with 3-4 times more than what is usually prescribed in the clinical setting for the asthmatic population (Milano et al., 2018). It is not surprising, therefore, that such doses are associated with harmful effects on the cardiovascular system, including tachycardia, gastrointestinal problems, tremor, etc.; a case of cardiac arrest associated with the use of these substances has even been reported (Brett et al., 2014)." (Adami et al., 2022, https://goo.su/3a66p).

Narcotics

"WADA includes the following narcotics on the list of prohibited substances: Buprenorphine, dextromoramide, diamorphine (heroin), fentanyl, hydromorphine, methadone, morphine, oxycodone, oxymorphine, pentazocine, and pethidine. Narcotics are used in sports to reduce post-traumatic pain. Oxycodone is a high-potency opioid analgesic, and its use has increased progressively among young athletes (Friedman, 2006).

Narcotics can cause significant psychic problems, reducing the perception of pain and giving a dangerous false sense of well-being. Likewise, methadone and levomethadyl have been shown to cause

QT interval lengthening and, with it, the development of potentially lethal polymorphic ventricular tachycardia (torsade de pointes) (Fanoe et al., 2006).” (Adami et al., 2022, https://goo.su/3a66p).

Stimulants

The use of ergogenic substances has been extensively documented in athletes through anonymized questionnaires. These substances, such as energy drinks and food supplements, are usually prescribed by the athlete himself, with the aim of increasing his physical and mental performance.

Most energy drinks available on the market include high doses of caffeine associated with other molecules, with similar stimulating effects.

Data derived from retrospective postmortem studies of hospital emergency units have shown a significant relationship between high-dose caffeine abuse and lethal cardiac arrhythmias. This hypothesis has not yet been confirmed by prospective studies with large populations; nonetheless, the initial data should serve as a warning to limit its indiscriminate use.

Other commonly used stimulants are those prescribed as treatment for attention deficit hyperactivity disorder (ADHD), a condition whose diagnosis has increased exponentially in recent years. The usual treatment is with methylphenidate or derivatives. The prescription of such substances for the purpose of treating ADHD is strictly regulated by WADA, international sports federations, and national anti-doping agencies.

“The use of amphetamine derivatives is not recommended in individuals with a family or personal history of cardiac arrhythmias, especially in those with demonstrated predisposing genetics. The use of methylphenidate in athletes is accepted only if its use can be demonstrated for the previously mentioned clinical purpose.

In addition to the arrhythmogenic component of amphetamine-derived substances, they are associated with many other harmful cardiovascular effects.

Amphetamines could mask and delay fatigue by slowing the temperature rise associated with exercise, which could increase the risk of muscle overheating (Roelands et al., 2008).

The use of dopamine reuptake inhibitors has been shown to increase athletic performance, but also to cause hyperthermia, increasing the risk of exercise-associated heat injuries (Keisler and Hosey, 2005).

Compounds containing ephedrine could produce a similar effect. Given their sympathomimetic effect, they could reduce the body's ability to dissipate the temperature rise adequately (Morozova et al., 2016).” (Adami et al., 2022, https://goo.su/3a66p).

Beta-blockers

“Beta-blockers reduce heart rate and the tremor associated with anxiety, which is why they are considered prohibited substances in certain sports disciplines in which precision is especially relevant, such as archery or pistol shooting. On the contrary, in athletes of other disciplines, in which beta-blockers would be considered for prescription due to heart disease, their use is reduced, given their potential detrimental effect on the ability to increase heart rate in response to exercise demand and, consequently, the reduction in sports performance. This is especially relevant in endurance athletes who need to maintain high cardiac output for long periods of time (Van Bortel, 1992).

- In a small group of healthy non-athletes, the consumption of nebivolol (selective beta-1 beta-blocker) at a dose of 5mg daily was not associated with a significant reduction in peak oxygen consumption or peak power, compared to placebo, despite inducing a 14% reduction in peak heart rate (Van Bortel, 1992).

- In this same study, 100 mg of atenolol (selective beta-1 beta-blocker) induced a 25% reduction in peak heart rate and a significant 5% reduction in peak power and oxygen consumption, which led the authors to conclude that the lack of impact on sports performance of nebivolol compared to atenolol could derive from a lower impact on peak heart rate and a greater vasodilator effect..

- Chronic intake of propanolol (non-selective beta-blocker) at a dose of 240 mg daily in healthy non-athletic subjects has been shown to decrease maximum heart rate by 25% and oxygen consumption by 7.5% (Gullestad et al., 1996).

- Sotalol (non-selective beta-blocker) has shown a dose-dependent relationship with peak heart rate reduction from 4%, at doses of 160 mg daily, to 25%, at doses of 640 mg daily (Funck-Brentano et al., 1991).

- A similar effect has also been demonstrated with propanol, with a marked interindividual variability of the effect (Coltart and Shand, 1970)." (Adami et al., 2022, https://goo.su/3a66p).

The figure summarizes the main cardiovascular effects of the different substances associated with doping. BP: Blood pressure; CAD:

Coronary artery disease; CMP: Cardiomyopathy; and LVH: Left ventricular hypertrophy.

CONTINUE

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