

Review

The Cardiac Effects of Performance-Enhancing Medications: Caffeine vs. Anabolic Steroids

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Abstract: Several performance-enhancing or ergogenic drugs have been linked to both significant adverse cardiovascular effects and increased cardiovascular risk. Even with increased scrutiny on the governance of performance-enhancing drugs (PEDs) in professional sport and heightened awareness of the associated cardiovascular risk, there are some who are prepared to risk their use to gain competitive advantage. Caffeine is the most commonly consumed drug in the world and its ergogenic properties have been reported for decades. Thus, the removal of caffeine from the World Anti-Doping Agency (WADA) list of banned substances, in 2004, has naturally led to an exponential rise in its use amongst athletes. The response to caffeine is complex and influenced by both genetic and environmental factors. Whilst the evidence may be equivocal, the ability of an athlete to train longer or at a greater power output cannot be overlooked. Furthermore, its impact on the myocardium remains unanswered. In contrast, anabolic steroids are recognised PEDs that improve athletic performance, increase muscle growth and suppress fatigue. Their use, however, comes at a cost, afflicting the individual with several side effects, including those that are detrimental to the cardiovascular system. This review addresses the effects of the two commonest PEDs, one legal, the other prohibited, and their respective effects on the heart, as well as the long-term implications.

Keywords: sports cardiology; athlete; caffeine; anabolic steroids; heart disease; cardiac magnetic resonance imaging

1. Introduction

Caffeine (1,3,7-Trimethylxanthine) is a popular workplace substance that has been well-researched, with its ergogenic effects being known for centuries [1]. Caffeine has a wide range of acute benefits that includes an increase in alertness and concentration, accompanied by a reduction in fatigue and pain perception. As a result, its use has become highly prevalent amongst athletes, especially after 2004, when it was removed from the World Anti-Doping Agency (WADA) list of banned substances; it was, therefore unsurprising when a study reported that 74% of urine samples from athletes, between 2004 to 2008, demonstrated measurable levels [1]. Common physiological effects of caffeine on the body include an increase in heart rate, catecholamine levels, blood lactate, free fatty acids and glycerol. More significantly, its use has illustrated benefits in both endurance-based and high-intensity exercise, permitting the athlete to train longer and at a greater intensity. A recent meta-analysis yielded a positive relationship of caffeine on muscle strength, muscle endurance and anaerobic power [2]. As a result, it is recommended that ingestion of 3-9 mg/kg approximately 60 minutes prior to exercise may provide the extra competitive advantage for the athlete [1]. Nonetheless, the response to caffeine is multifaceted, influenced by both genetic and non-genetic predilections, with there being inter-subject variation in response to caffeine consumption, and this heterogeneous response makes it difficult to extrapolate the objective impact of caffeine as a vital ingredient to athletic prowess.

In contrast, anabolic steroids, synthetic derivatives of testosterone, have been abused by athletes since the 1950s for their ability to increase muscle mass and improve athletic performance. More significantly, they may shield the user from muscle fibre damage, through enhanced protein synthesis during recovery. Steroid abuse has dramatically increased over the past two decades in the general population who live in an increasingly image-obsessed era. Whilst anabolic steroids can play an important role in clinical treatment of endocrine disorders there are several established adverse outcomes, if misused, that includes an increased risk of cardiovascular disease, risk of tendon ruptures, hepatorenal disorders and psychiatric symptoms.

Given such a variability in effects of both caffeine and anabolic steroids, this review discusses the impact of the two commonest performance-enhancing drugs (PEDs) and its documented cardiac sequelae.

2. Materials and Methods

This review follows the guidelines set forth by PRISMA (preferred reporting items for systematic reviews and meta-analyses). We performed a comprehensive search on Pubmed, Scopus and EMBASE focusing on the effects of caffeine and/or anabolic steroids to exercise and its subsequent effects on the myocardium. Reviews, meta-analyses, prospective, retrospective, interventional and observational studies were included in our search. Key search terms included: 'caffeine', 'caffeinated', 'CAF', 'tea', 'energy drinks', 'anabolic steroids' in combination with 'exercise', 'athlete', 'myocardium', 'cardiac', and 'heart'.

3. Discussion

3.1. Caffeine as a Performance Enhancing Agent

In many sports, changes in performance of 1% may be the difference between first or second place [3]. Caffeine is a readily available performance enhancing aid that improves athletic ability across virtually all sporting disciplines. Historically, it was recommended to be banned in 1939, due to its ergogenic properties that may influence sporting accomplishments. Since its legalisation in 2004, it has become a major source for athletes, commonly being in the form of energy drinks, but may vary in the form of a gum, gel, pill or inhaler. Through fat mobilisation and thus sparing of the glycogen reserve, it diminishes the impact of fatigue, pain and effort that is associated with exercise, leading to the more significant motives of athletes for its consumption. A typical 250ml energy drink (ED) may contain up to 80mg of caffeine, similar to that in filtered coffee (90mg), and twice the amount of that in tea (30mg); additional substances that complement the influence of caffeine include ginseng, taurine and guarana [4-8].

Caffeine use may be classified as low, moderate or high, with ingestion of ~3mg/kg (~200mg for a 70kg individual; 1-2 small cups of coffee) being considered low, 5-6 mg/kg considered moderate and ~10-13 mg/kg viewed as high. It should be noted that the dose-response relationship between caffeine and athletic performance has yet to be established, with low dose caffeine appearing to exhibit the most ergogenic effect on athletes. For instance, caffeine containing drinks, with a dose equivalence to 3mg/kg, have shown an increased ability of football players in sprinting, jumping and the distance covered [9]. Further meta-analyses investigating the role of caffeine have demonstrated a significant increase in jump height, muscular endurance, aerobic endurance performance and muscle strength [8].

Like most substances, caffeine, when consumed in larger doses, may result in side effects that includes dehydration, seizures, migraines, insomnia, arrhythmias, gastrointestinal problems and psychological permutations [6,7,11].

3.1.1. *Caffeine Pharmacology and Cardiac Physiology*

Caffeine is rapidly absorbed by the body, with its concentration peaking between 40 to 80 minutes, and rising to ~15-20 $\mu\text{mol/L}$ with a low caffeine dose, ~40 $\mu\text{mol/L}$ with a moderate and ~60-70 $\mu\text{mol/L}$ with a high dose. It appears in the blood within 5-15 minutes of ingestion and has a long half-life (3-5 hours) [11]. For both female and male athletes, for a given dose of caffeine, it appears that the concentration of caffeine and its metabolites are the same [12, 13].

The effects of caffeine are exerted primarily through the blockade of adenosine receptors (subtypes A_1 and A_2), which are found throughout the myocardium and coronary circulation; they are also found in the brain, adipocytes, skeletal and smooth muscle. The result in the competitive blockade of these receptors leads to an increase in peripheral vascular resistance, sympathetic tone and increase in renin, subsequently amplifying the heart rate, cardiac contractility and blood pressure [14]. Secondary metabolic changes of caffeine include stimulating the secretion of epinephrine.

Whilst the concerns of caffeine on overall health has permeated through society, there are many epidemiological studies that have shown its benefit to overall mortality, and in particular cardiac disease [15]. Caffeine may, however, conversely attenuate the physiological response to exercise, such that there may be reduced coronary blood flow or response of the endothelial cell in mediating the vascular tone during exercise, which signifies a potential risk to an athlete with silent coronary disease. Other impacts of caffeine include a delayed return of the parasympathetic nervous system, and with a state of sustained sympathetic activity, this may confer an increased risk of life-threatening arrhythmias [12].

3.1.2. *Caffeine and Risk of Arrhythmia*

Whilst many studies have reported the arrhythmogenic effect of caffeine, it has not been replicated on large population studies. With the consumption of caffeine being ubiquitous in Western society, the widely held belief that caffeine may contribute to arrhythmia or the risk and development of coronary heart disease may not be evidence-based [14-19]. Intoxication of caffeine, however, is still reported, demonstrating its potential in provoking fatal arrhythmias [20]. Physiologically, through the blockade of calcium reuptake into the sarcoplasmic reticulum, and thus a rise in intracellular calcium, the potential of atrial arrhythmia, through enhanced automaticity of atrial pacemaker cells, exists; 3 cups of coffee (250mg) have shown to increase both epi- and norepinephrine [21]. More importantly, energy drinks often contain caffeine at a significantly higher concentration than either coffee or tea; the stimulant properties of other compounds in EDs, such as taurine, complicates matters further. Taurine, for instance, is suggested to increase calcium accumulation in the sarcoplasmic reticulum, favouring the excitation-contraction of skeletal muscles, but may also induce unfavourable arrhythmias [22].

It could be argued that the absence of risk may not relate to athletes or those who harbour an underlying abnormal cardiac substrate, especially as the amount of caffeine consumed through energy drinks may be invariably higher. For instance, there has been reports of EDs prolonging QTc and unmasking Brugada syndrome [21]. Another important impact of caffeine includes the augmentation of ryanodine receptors, that may further lead to an increase in calcium release within cardiac cells, affecting the heart's ability to contract and use oxygen, which may predispose to arrhythmias [23].

On the other hand, when attempting to explore the relationship between caffeine and arrhythmias in those with pre-existing cardiac disease, there failed to be a connection, suggesting the complex pharmacodynamics of caffeine [20].

3.1.3. *Genetics*

It is evident that genetic factors demonstrate a huge role on the individual response to the effects of caffeine [24-26]. Whilst its mechanisms may not be well defined, there are certain drivers of these individual differences; notable genes include CYP1A2, ADORA2A and catechol-O-methyltransferase (COMT) [27]. Of the most significance is CYP1A2, which is involved in the breakdown of caffeine and has two alleles (A & C), dichotomising into either fast or slow metabolisers respectively. The significance of this phenomenon is that those who are slow metabolisers, who consume moderate (3-4 cups) amounts of coffee have a greater risk of hypertension and myocardial infarction [1]. This is also reflected in athletes, with those who are fast metabolisers showing greater improvement in performance; this may be due a rapid accumulation of caffeine metabolites, and may reflect why timing of caffeine consumption becomes important [1].

In contrast, polymorphisms affecting ADORA2A could lead to an individual to experience greater sleep disturbance, impacting athletes that compete in the evening, or increased anxiety resulting in poor competition performance [3].

3.1.4. *Role in Sudden Cardiac Death*

Energy drinks has been associated with coronary vasospasm and ischaemia, arrhythmias, endothelial dysfunction and increased platelet aggregation [28]. Its use has been a particular concern amongst the younger athletes, where case reports of sudden cardiac death were in part attributed to the consumption of energy drinks. However, whilst no direct link between caffeine and its supposed harmful effects on the heart exist, further studies are required to establish its true safety, particularly in those with underlying electrical or structural cardiac abnormalities. Additional studies would be important in recognising the effects of strength and delivery of caffeine, and the effects of age and genetic expression on the individual's response to caffeine.

3.2. *Steroids as a Performance Enhancing Agent*

Anabolic steroids first gained popularity in the 1954 Olympics and given its potential to improve physical ability, appearance and performance, it has been banned for any sporting use since 1974. Regardless, it is continued to be misused by athletes in sports such as weightlifting, football, cycling and many others to improve both performance and in order to gain a competitive advantage; it is reported that up to 50% of positive doping cases account for anabolic steroid use [29]. The lifetime prevalence of anabolic steroids ranges from 1-5% in Western countries, and its use has increased four-fold, since 2016, from 0.1% to 0.4% of the population, affecting an extra 19,000 young people (aged 16-24 years old). With mounting evidence in developing several physical and psychological health disorders, its use has become more than a concern restricted to athletes but one of public health.

3.2.1. *Steroid Pharmacology and Cardiac Physiology*

Anabolic steroids upregulate and increase the number of androgen receptors, increasing the transcription of DNA in skeletal muscle required for muscle growth, thereby contributing to an increase in muscle size and strength. It also includes a direct effect on cardiac muscle metabolism, altering both electrical and structural features of the myocardium [30]. Supraphysiological doses of anabolic steroids induces toxicity of the cardiovascular system, with the proposed mechanisms including changes in the lipid profile, elevations in blood pressure, myocyte hypertrophy, disarray and apoptosis and a procoagulant state [31]. Thereby, contributing to disorders such coronary artery disease (CAD), hypertension, cardiomyopathy and thromboembolic disorders (Figure 1); the above

findings have been correlated with histopathological case reports [32, 33]. The progression of such events take time, but is often argued to be non-reversible, resulting in those to require cardiac devices or listed for transplantation.

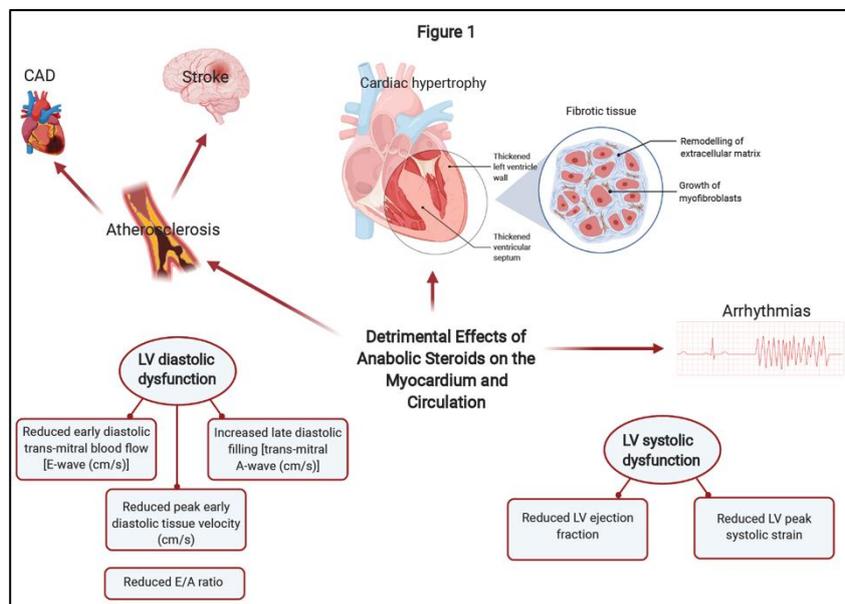


Figure 1. Impaired LV relaxation is a cardinal feature of the adverse cardiac effects of anabolic steroids. With long term abuse, there is evidence of reduced systolic strain and systolic dysfunction with resultant cardiomyopathies. Other sequelae of anabolic steroid abuse include circulatory dysfunction and arrhythmias. (Created with BioRender.com)

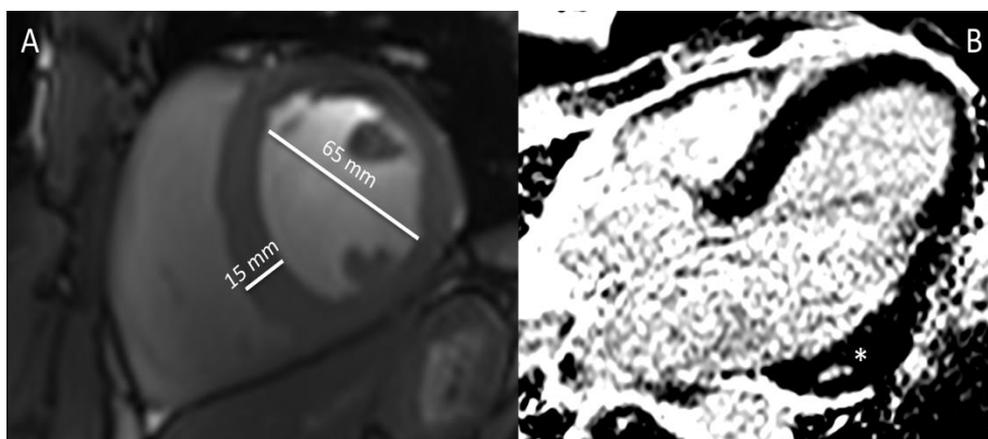


Figure 2. A and B. Cardiac magnetic resonance (CMR) images of a 38-year old bodybuilder with anabolic steroid use – A. Cine steady-state free precession (SSFP) in mid-ventricular short-axis view at end-diastole showing hypertrophied interventricular septum (15 mm) and enlarged left ventricle (62 mm) with decreased systolic function (ejection fraction = 44%, not shown), B. Late gadolinium enhancement (LGE) image in 3-chamber view showing midventricular area of fibrosis (non-ischemic) in the basal infero-lateral segment of the left ventricle (asterisk).

Significant adverse adaptations include an increase in wall thickness, and left ventricular cavity size; there has been observable difference in left ventricular posterior wall and septal wall thickness [34]. Such changes are commonly accompanied with deleterious effects on the myocardium (Figure

2). For instance, it has been noted that anabolic steroid abusers demonstrate a reduction in peak strain and strain rates of the left posterior and septal walls [35]. Diastolic function also appears to be affected, whereby a reduction in early and late diastolic filling velocity ratios is expected; a reduction in myocardial relaxation through increased collagen cross-linking and fibrosis may explain such a phenomenon in anabolic steroid use [36]. Other ramifications include an increase in ventricular rigidity, as its use may reduce myocardial compliance through an apoptogenic effect on the cardiac myocytes [37]. More importantly, the effects of anabolic steroids are not limited to the left ventricle and several studies have suggested a global impact. For instance, there is an increase in right ventricular strain, and left atrial dysfunction [38]. As a result, anabolic steroids have led to the emergence of acquired cardiac disease in younger and middle-aged athletes.

Other important manifestations of anabolic steroid abuse include myocardial infarction and heart failure, secondary to premature atherosclerosis; infarcts may even occur without significant coronary vessel disease [39]. Animal models have illustrated increased androgen-induced vascular calcification, which could be secondary to steroid induced cell damage resulting in loss of tissue elasticity and thus fibrosis. A landmark study among experienced male weightlifters reported that long-term anabolic steroid use was associated with myocardial dysfunction and accelerated coronary atherosclerosis [36]. These forms of anabolic steroid-associated adverse cardiovascular phenotypes may represent a previously underrecognized public-health problem.

3.2.2. *Anabolic Steroids and Risk of Arrhythmia*

Several studies have illustrated the harmful cardiac autonomic effects of anabolic steroids. For instance, there may be QRS-wave delay, sinus tachycardia, supraventricular and ventricular arrhythmias. Testosterone, in particular, has been associated with rhythmic disturbances, possibly through the potentiation of potassium channels involved in ventricular repolarisation [30].

3.2.3. *Role in Sudden Cardiac Death*

Anabolic steroids have the potential of increasing the risk of sudden cardiac death through multiple mechanisms; it is, unfortunately, unclear to the exact nature of these events, especially since those who misuse often use a combination of drugs. Structurally, several modalities of dysfunction that may predispose to sudden cardiac death have been proposed that includes cardiac hypertrophy, ventricular dilatation, myocardial fibrosis and cardiomyopathy. There have been several case reports of young athletes that have developed rapidly progressive (dilated) cardiomyopathy [31]. Ventricular arrhythmias are another possibility, where it has been suggested that anabolic steroids inhibit the re-uptake of catecholamines, and with a combination of exercise, stimulating the nervous system that may increase the likelihood of fatal arrhythmias.

Given its role in endothelial dysfunction, anabolic steroid use can lead to fatal thrombotic complications that includes ischaemic stroke or pulmonary embolism. Physiologically, it is secondary to its capability to amplify platelet generation and aggregation, and the promotion of thromboxane A2 and thrombin, inducing a state of hypercoagulability.

4. Limitations

Even though certain physiological mechanisms have been argued to be the benefits or drawbacks of both caffeine and anabolic steroids, these are still viewed as hypotheses and associations and, remain incomplete as explanations without larger randomised controlled trials. To what extent caffeine may be regarded as a drug to the athlete is difficult. There are several preparations, majority of which are in combinations, and there is lack of consistency on both performance and cardiac outcomes. Furthermore, it should be noted that the documented adverse effects of anabolic steroids have failed to be replicated in a few studies. For instance, not all anabolic steroid users experience left ventricular hypertrophy and/or endothelial dysfunction.

5. Conclusions

There is a large growing body of evidence that describes the impact of both caffeine and anabolic steroid use on the cardiovascular health of both the athlete and non-athlete. Whilst caffeine may not necessarily give an athlete the essential edge, its use may not disadvantage them either, especially since the majority have consumed such a supplement prior their sporting event. In contrast, anabolic steroids have documented improvement in athletic proficiency. However, it does not negate the several adverse cardiovascular effects that is associated with its use. With the continued use of both caffeine and anabolic steroids, regular assessment, that includes evaluating the electrical activity and morphology of the myocardium, using non-invasive imaging and functional methods would be important in identifying those who are at an increased risk of cardiovascular disease or an acute cardiac event.

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