Performance-enhancing drugs, supplements and the athlete's heart

Andrew Pipe

Minto Prevention & Rehabilitation Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

Address for correspondence:
Prof Andrew Pipe
Minto Prevention & Rehabilitation Centre
University of Ottawa Heart Institute
Ottawa
Ontario
K1Y 4W7
Canada

Email:
apipe@ottawaheart.ca

ABSTRACT

The use of performance-enhancing drugs is an unfortunate reality of contemporary sport. It would be a mistake to believe that this is a phenomenon found only in elite sport. Athletes at all levels and young adults may be tempted to accentuate performance or physique with prohibited drugs or products marketed as supplements. No defined populations of users ingesting known quantities of known substances are generally available for study. Many of these products have been associated with adverse health effects; cardiac structure and function are known to be affected by many of the products commonly abused. Changes to the lipoprotein profile, propensity for coagulation, coronary circulation, and ventricular function may accompany the use of many performance-enhancing compounds and methods. Anabolic steroids, other peptide hormones, stimulants, erythropoietin and blood doping, have all been associated with significant cardiovascular consequences. So-called nutritional supplements aggressively marketed to the athletically inclined, are available over the Internet and typically totally unregulated in the country of their origin. Clinicians should be aware of the problems that such drug use can engender, and be sensitive to the possibilities of such abuse in caring for athletes and young patients, particularly in those presenting with unusual or unanticipated cardiovascular signs and symptoms.

SAHeart 2011; 8:164-170

INTRODUCTION

The use of performance-enhancing drugs is an unfortunate reality of sport.[1,2] Since 2004, responsibility for the development, application and oversight of international anti-doping activities has been vested in the World Anti-Doping Agency (WADA) headquartered in Montreal, Canada and supported by the international sport community principally through the International Olympic Committee (IOC), international sport organisations (ISOs), and international governments. Responsibility for the implementation of testing and adjudication procedures in sport rests with International Sport Organisations (ISOs), National Sport Federations (NSFs) and National Anti-Doping Organisations (NADOs).[3] The development of WADA, and more specifically the adoption of the WADA Code, has meant that there is now consistency between and among sport organisations at virtually every level in the approach taken to address the doping issue e.g. harmonised testing standards, review processes and sanctions.[4] In North America, professional sport organisations have been slow to adopt the approaches that are found more consistently throughout the rest of the world.

It is a committee of WADA, the "List Committee", that ultimately determines what substances and methods are prohibited in sport. A substance can be considered for inclusion if it meets two of three criteria: it enhances performance; it is harmful to health; and/or its use contravenes the "spirit of sport". The prohibited list (The List) is reviewed annually and comments and contributions from the sport community regarding any proposed changes are welcomed and encouraged. At the same time it is recognised that the legitimate health needs of many athletes may frequently require the use of otherwise prohibited medications. The WADA Code provides for the administration of such medications following special application and a review of a particular case by a suitably qualified panel of clinicians.

The use of many prohibited drugs is not restricted to the elite; such drug-taking behaviour can be seen at virtually every level of sport.[5-7] It is equally important to recognise that the use of prohibited substances is not limited to those involved in competitive activities; many young adults use a variety of drugs and other substances in attempts to enhance their physique or in the pursuit of mood-altering experiences. The use of so-called nutritional

supplements has spawned an array of other problems for sport authorities and clinicians. Typically the product of a US-based, multi-billion-dollar industry, supplements have until recently escaped any meaningful forms of regulation.[8] Thus, their quality, ingredients, manufacture, labelling and marketing were subject to minimal oversight – with significant consequences for health and safety.[9]

It is difficult to quantify the degree to which doping practices are common. It is typical that approximately 1% of all doping-control tests are found to contain evidence of a prohibited substance or suggest the use of a prohibited method.

Three important caveats must be understood: the true incidence of the use of prohibited drugs in sport is difficult to define because it is illicit, concealed behaviour; it is particularly difficult to develop clear evidence of the adverse effects of drugs or compounds whose use is surreptitious – the ability to develop significant clinical experience in defined populations is lacking; and finally, it is naive in the extreme to believe that a recitation of the side effects of drugs or doping practices, real or potential, will have significant impact in deterring the use of these drugs by individuals who are part of sub-cultures where such drug-taking behaviour is the norm or encouraged. It is important that we understand the consequences of such drug-taking behaviour; it is equally important that we develop sensitive, realistic and thoughtful approaches to deter it.[10]

DOPING AND THE HEART

Many of the substances and methods prohibited in sport have the potential to cause significant health consequences. Cardiovascular clinicians should be aware of the nature of the adverse cardiac consequences that can befall those who are exposed to the hazards implicit in the use of certain drugs or other products that have been commonly used by athletes in attempts to accentuate athletic performance. Physicians must be aware that it is commonly the case that many products sold to athletes (frequently on the black market – often via the Internet) differ markedly in composition and quality further impeding our understanding of the complications associated with these substances. The picture becomes muddier when it is realised that many athletes use combinations of products thereby increasing the likelihood of unanticipated interactions and effects. Many authors have described the array of complications and pathologies that can follow the use of certain drugs or so-called "supplements".[8,11]

ANABOLIC-ANDROGENIC STEROIDS

Anabolic-androgenic steroids (AAS), synthetic derivatives of testosterone, were initially products of the German chemical industry and introduced in the late 1930s to address conditions that resulted from a deficiency of this male hormone.[12] Ultimately researchers identified that these compounds accentuated anabolic processes and enhanced muscle size, strength and power.[12] It is speculated that they found application in military settings because of their ability to augment physical performance and aggressiveness.[13] The use of such hormones increased as perceptions grew that they were capable of enhancing libido and accentuating sport performance.[14] In the post-war years their use spread to the European weight-lifting community and eventually to North America and sport communities in which strength, power and size were important. Soon US, Russian and East German athletes were using these substances either independently or under the supervision of sport authorities – but always surreptitiously.[15,16] The IOC prohibited their use in 1974; the first testing for these drugs during Olympic competition took place in Montreal in 1976. In 1988 the Canadian sprinter, Ben Johnson, tested positive for the presence of the AAS stanozolol after winning the 100m final at the 1988 Seoul Olympic Games. In recent years these drugs have been used extensively by those in power sports but also by athletes in a variety of sporting disciplines and those who seek only to enhance their strength and appearance. Their pharmacology is well understood; their effects are protean; they are among the most commonly abused drugs in sport; and "designer" modifications are often synthesised in black market laboratories.[17] They may be commonly purchased in weight training facilities and other black market settings. They are often used in combination according to regimens in which "stacking" (the use of two or more steroids) and "cycling" (in which doses are adjusted in the course of a multi-week cycle) are commonplace. It has been estimated that more than 1 million Americans use AAS; young athletes, collegiate competitors, body builders, police officers and firefighters have been noted to be among those who ingest or inject these products.[18] In 1996 a national survey revealed high levels of steroid use and needle-sharing behaviours among 11- to 18-year-old Canadians.[19] Clinicians must be aware, therefore, of the ubiquitous presence of these drugs in many communities…and of the likelihood of seeing the undesirable consequences of their use.

CARDIOVASCULAR CONSEQUENCES OF AAS USE

Our ability to understand the cardiovascular consequences of AAS use is limited by the fact that there are no defined populations of users who have been carefully followed and evaluated. Our perception that the use of these drugs is harmful is fuelled by the numerous case reports of cardiovascular problems occurring in association with AAS usage. There are now numerous reports of atrial fibrillation, QT dispersion, myocardial infarction, cardio-

myopathy, heart failure and other cardiovascular issues in the literature.[13,20-25] It has been noted that the incidence of such events is likely under reported.[26]

The cardiovascular effects of anabolic steroids may be mediated by their effect on lipids; their ability to damage myocardial tissue; their ability to accentuate thrombosis; and their negative effects on endothelial function.[27] AAS use may also contribute to the development of hypertension; a finding, however, that is inconsistent.[28,29]

AAS use is known to cause a distortion of normal lipoprotein levels – increasing triglycerides, elevating LDL (by 11% to 100%), and lowering HDL (by 39% to 70%).[30,31] Notwithstanding the creation of an atherogenic lipid profile, it must be acknowledged that there is no direct evidence that AAS will cause atherosclerosis.[32] It has been speculated that AAS create an atherogenic profile by increasing hepatic triglyceride lipase activity (HTGL) which catabolises HDL.[32] Lipid levels are known to return to normal within months of cessation of AAS use. The risk of cardiac disease has been estimated to be three-fold in users of AAS.[13,27]

Damage to myocardial cells is initiated by disruption of myocardial mitochondria and the stimulation of intrafibrillar collagen dysplasia resulting in the development of scar tissue. The development of hypertension can contribute to ventricular hypertrophy and changes to ventricular function.[33] Animal studies have demonstrated that AAS influences cardiac structure and function.[25,34] The association between AAS and ventricular dysfunction has been frequently noted.[8] More recently, echocardiographic investigations have revealed the relationship between long-term AAS use and both systolic and diastolic ventricular dysfunction.[34-37] The effects of AAS use may still be evident several years after their discontinuation.[38] AAS use has also been noted to adversely affect right ventricular diastolic function.[39] It has been speculated that AAS could contribute directly to myocardial cell damage with resulting cell death and fibrosis establishing lesions that might serve to stimulate ventricular arrhythmias and sudden death.[27]

Multiple cases of thromboembolic disease have been reported among AAS users.[40] Yet, to date there is no direct evidence that AAS are thrombogenic in humans; studies of haemostasis in steroid users are rare. Nevertheless, it has been concluded that the use of AAS confers an enhanced pro-thrombotic state.[40]

Arterial structure and function are adversely affected by the use of AAS.[41] Disruption of normal nitric oxide activity is speculated to impair endothelial function.[13,27] Vascular distensibility has been shown to be lower in AAS users, providing further evidence of altered vascular function.[42]

Sudden cardiac death has been frequently reported among AAS users.[22,43-45] Yet there is no clear epidemiological data on which to conclude that there is a cause-effect relationship; the picture is complicated by poor follow-up of those who have presented with arrhythmias; the concomitant use of a variety of other drugs; and an inability to control for those who may have an inherited susceptibility to arrhythmogenic disease. There is evidence that AAS use in association with resistance training can lead to an increased risk of malignant arrhythmia.[46] Some have speculated that the use of AAS increases the risk of life-threatening arrhythmia; the underlying mechanisms remain to be elucidated.[40] Superimposed upon a distorted and potentially atherogenic lipoprotein profile (a recognised by-product of AAS use), the dramatic, intermittent elevations in blood pressure reported in weightlifters and body builders may also play a role in the development of the cerebrovascular accidents reported among such athletes.[47-49]

For many years it has been recognised that the abuse of growth hormone (hGH) poses significant challenge to sport authorities and the health of athletes.[50-52] Acromegaly, with its known relationship to premature cardiovascular disease, is a well-recognised complication of an abundance of this hormone; considerations are now being given to its impact on other aspects of cardiovascular health. Hypertension, dyslipidaemia and cardiomyopathy have been identified as potential areas of concern.[53] Detection of hGh poses a challenge to anti-doping authorities.[54]

In summary, there is concern grounded in clinical experience that the use of AAS contributes to an enhanced risk of cardiac disease and associated complications. Cardiologists should be sensitive to the possibility of AAS use when seeing young, athletic or muscular patients with pronounced dyslipidaemia, ventricular dysfunction, premature coronary artery disease and other cardiac presentations in the absence of common contributing factors. Careful questioning and a non-judgmental manner may reveal a history of AAS use in some of these patients.

STIMULANTS

The use of stimulants in sport is more than a hundred years old; the earliest deaths associated with doping involved stimulant abuse in six day bicycle races. In the 1960s the death of cyclists using amphetamines in the Tour de France spawned the developments, in 1968, of the IOC Medical Committee. These powerful stimulants have been used by unscrupulous athletes and their handlers

for many years; their ability to enhance certain sport performances has been understood for decades.[55,56] Testing for amphetamines first occurred at the 1968 Mexico City Olympic Games. Stimulant use continues in sport.

Stimulants are commonly used in nearly all societies and are found in a variety of foodstuffs and beverages e.g. caffeine. Others are available as over-the-counter medications and used to treat a variety of common minor respiratory illnesses e.g. pseudoephedrine, phenylpropanolamine. All have been used by athletes in an attempt to accentuate performance and enhance arousal while reducing the perception of fatigue; their use may also be intended to enhance the intensity of training. It is difficult to prohibit substances which are used commonly in daily life or treat common illness. The use of stimulants continues to challenge sport authorities and poses specific hazards to athletes and would-be athletes alike.[57]

Caffeine, once prohibited is now permitted in sport – in part because it is ergogenic at doses compatible with the incidental use of caffeinated beverages and the ingestion of chocolate, while degrading performance at higher doses (a fact that is lost on many athletes). The use of caffeine combined with ephedrine was common in weight-loss products and has been shown to have significant effect on blood pressure.[58,59] The combination of these products has also been shown to enhance performance in a variety of exercise settings.[60,61] Ephedrine is a prohibited substance in sport.

Pseudoephedrine was removed from the prohibited list (because of its presence the globe over in cough and cold medications) but has since been re-introduced with much higher detection thresholds as a consequence of evidence of its use at very high doses in certain sports in certain nations. Notably, however, this drug is now being removed from many markets because of its use as a cheap precursor for use in the manufacture of other illicit drugs.

Most cardiologists in urban areas will, sadly, be familiar with the vasospastic effects of cocaine on the coronary vasculature.[62] The use of this stimulant has receded from sport following a number of untimely and unseemly deaths associated with its use by high profile athletes.[62-64] Cocaine is still a prohibited drug in sport; it is most commonly detected as a consequence of its use as a "social drug of abuse" in non-sporting situations.

In South Africa there is understandable concern regarding an epidemic of methamphetamine use in the community.[65] While not typically considered as a performance-enhancer, methamphetamine or "tik", as it is commonly known in South Africa, has been recognised as a cause of damaged cardiac structure and function.[66-68] Its use may coincide with the administration of other performance enhancing substances in settings where social drug use is common; adolescent use of this drug in South Africa and elsewhere is burgeoning and disconcerting.

SUPPLEMENTS

Athletes are highly disposed to purchase and consume nutritional supplements; a large majority of Canadian athletes at the 1996 and 2000 Olympic Games were using a supplement of some kind (69% and 74% respectively).[69] Since 1994 the US Supplement industry has, until recently, been largely unregulated. The result has been that athletes (and would-be athletes) have been exposed to a variety of "supplements" whose nature, manufacture and marketing are unregulated.[70] As a consequence there have been frequent examples of athletes purchasing or being provided with nutritional products containing prohibited substances or other hazardous ingredients.[9,71-73]

The popularity of nutritional supplements within the athlete community meant that for many years these largely unregulated products frequently contained quantities of ephedra alkaloids, sympathomimetics that were touted to enhance performance, minimise the development of fatigue, and facilitate weight loss.[74] Use of ephedra resulted in a significant number of deaths in the sport and exercising community because of its propensity, in susceptible individuals, to cause coronary artery spasm leading to heart attacks and death.[9,75-81] Other significant side-effects are associated with the use of ephedra and ephedra-like substances: high blood pressure, tachycardia, tremor, and restlessness are commonly associated with these products; left ventricular dysfunction has also been described following their use.[82] At one point ephedra accounted for 0.82% of all herbal product sales in the USA, but was implicated in 64% of adverse reactions.[83] The use of products containing ephedra may be suspected in young, otherwise healthy individuals who present with angina, with evidence of coronary artery spasm or unexplained cerebrovascular symptoms.[84]

Athletes are frequent consumers of a variety of products, many of which may have the potential to produce cardiovascular side-effects. In recent years, following the regulation of the use of ephedrine, other "ephedra-like" agents are now found in supplement products the most common of which is bitter orange or citrus aurantium. This compound contains synephrine, a sympathomimetic agent with a structural similarity to ephedra alkaloids; it will inhibit the cytochrome P-450 system. Its safety profile is therefore open to question.[3,81]

It is impossible to comment on the safety or suitability of the wide variety of products offered to athletes as supplements and available over the internet.[85] To many athletes and their advisors, nutrition is virtually a religion not a scientific discipline, and supplements have particular appeal.

BLOOD DOPING AND ERYTHROPOIETIN

It has been known for years that accentuation of the red cell mass would enhance performance; infusion of blood was noted to increase running time to exhaustion by 23%![86,87] At the 1984 Los Angeles Olympic Games, US cyclists won gold medals after autologous and heterologous transfusions – controversy erupted in the aftermath. Blood doping was now a concern in sport; but the picture was to grow more complicated.

Erythropoietin, the natural stimulus for the production of red blood cells, is normally produced in the kidneys and exerts its influence on the bone marrow. The development of a synthetic product, rHuEPO, is a boon for patients with significant haematological, renal, or oncologic disorders. Sadly, its ability to increase the production of red blood cells, with a resulting increase in aerobic capacity, has spawned widespread use of this product, and its successors, in a variety of sport cultures.[88] Disastrous results for the health of athletes and the integrity of sport have followed.[89-91]

An increase in the red blood cell count invariably leads to an increase in blood viscosity and therefore may predispose to augmented clotting, which in turn may lead to the development of a variety of thrombotic complications including stroke, myocardial infarction and venous thromboembolism.[92] The abuse of rHuEPO products in sport settings, where dehydration is commonplace, may potentiate the likelihood of such untoward events.[93] A significant number of deaths were reported in cycling following the commercial availability of rHuEPO in the late 1980s. The deaths have been imputed to the use of this hormonal product and its thrombogenic potential.[89] More insidious is the development of "red cell aplasia"; a life-threatening complication associated with the use of rHuEPO, and the result of the development of antibodies to erythropoietin with a resulting arrest of red cell production.[94] Concerns are now emerging regarding the relationship between the use of rHuEPO and the development of malignant tumours which themselves may be dependent upon the availability of blood supply.[95]

The use of rHuEPO was preceded, as noted, by "blood doping", a process in which the blood of an athlete (an autologous transfusion), or of others (a homologous transfusion), was infused so as to increase the red cell mass. Not surprisingly such administration was fraught with problems, including transfusion reactions.[86,96] The practice of blood doping declined, it is assumed, with the availability of rHuEPO. Sadly, now that technologies are available which make possible the detection of rHuEPO – and longer-acting agents have become available, it is believed that the re-administration of previously withdrawn red blood cells is increasing. We may have come full circle. These practices have typically been more pronounced in "aerobic" sport, where endurance activity predominates.

CONCLUSION

Experience in sport leads one, at times, to believe that athletes are capable of the unimaginable in their quest for optimal performance. Considerations of doping and the associated health consequences expose the less attractive dimensions of sporting activities that, seen in another light, reflect some of the most celebrated aspects of human character. Sport is enthralling and empowering because it illuminates the human capacity to strive and excel; sport can be depressing or disillusioning when other, less admirable human qualities are revealed. Attempts to enhance sport performance artificially, pharmacologically, ultimately erode the sport experience for all. Clinicians should be aware of the cardiac signs and symptoms that might alert us to the use of performance-enhancing drugs, while serving as community exponents of sport that is more human – the result of training and dedication – not the product of a steroid biochemist.

REFERENCES

1. Noakes TD. Tainted glory – doping and athletic performance. NEJM. 2004; 351(9):847-9.
2. Pipe A. Doping and its impact on the healthy athlete. In: Fourcroy JL, editor. Pharmacology, doping and sports – a scientific guide for athletes, coaches, physicians, scientists and administrators. London and New York: Routledge 2009. p.177-98.
3. Bowers LD. Abuse of performance-enhancing drugs in sport. Ther Drug Monit. 2002 Feb;24(1):178-81.
4. WADA. World Anti-Doping Code. Montreal: World Anti-Doping Agency.
5. Green GA, Uryasz FD, Petr TA, et al. NCAA study of substance use and abuse habits of college student-athletes. Clin J Sport Med. 2001 Jan;11(1):51-6.
6. Pipe A, Hebert PC. Doping, sport and the community. CMAJ. 2008 Aug 12;179(4):303,5.
7. Laos C, Metzl JD. Performance-enhancing drug use in young athletes. Adolesc Med Clin. 2006 Oct;17(3):719-31; abstract xii.
8. Dhar R, Stout CW, Link MS, et al. Cardiovascular toxicities of performance-enhancing substances in sports. Mayo Clinic proceedings. 2005 Oct;80(10): 1307-15.
9. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med. 2000 Dec 21;343(25):1833-8.
10. Pipe A. The adverse effects of elite competition on health and well-being. Can J Appl Physiol. 2001;26 Suppl:S192-201.
11. Deligiannis A, Bjornstad H, Carre F, et al. ESC Study group of sports cardiology position paper on adverse cardiovascular effects of doping in athletes. Eur J Cardiovasc Prev Rehabil. 2006;13:687-94.
12. Hoberman JM, Yesalis CE. The history of synthetic testosterone. Sci Am. 1995 Feb;272(2):76-81.
13. Sullivan ML, Martinez CM, Gennis P, et al. The cardiac toxicity of anabolic steroids. Prog Cardiovasc Dis. 1998 Jul-Aug;41(1):1-15.
14. Freeman ER, Bloom DA, McGuire EJ. A brief history of testosterone. J Urol. 2001 Feb;165(2):371-3.
15. Hoberman JM. Mortal Engines. The science of performance and the dehmanisation of sport. New York: The Free Press; 1992.
16. Franke WW, Berendonk B. Hormonal doping and androgenisation of athletes: a secret programme of the German Democratic Republic government. Clin Chem. 1997 Jul;43(7):1262-79.
17. Kicman AT. Pharmacology of anabolic steroids. Br J Pharmacol. 2008 Jun; 154(3):502-21.
18. Evans NA. Current concepts in anabolic-androgenic steroids. Am J Sports Med. 2004 Mar;32(2):534-42.
19. Melia P, Pipe A, Greenberg L. The use of anabolic-androgenic steroids by Canadian students. Clin J Sport Med. 1996 Jan;6(1):9-14.
20. Menkis AH, Daniel JK, McKenzie FN, et al. Cardiac transplantation after myocardial infarction in a 24-year-old body builder using anabolic steroids. Clin J Sport Med. 1991;1(2):138-40.
21. McCarthy K, Tang AT, Dalrymple-Hay MJ, et al. Ventricular thrombosis and systemic embolism in body builders: etiology and management. Ann Thorac Surg. 2000 Aug;70(2):658-60.
22. Fineschi V, Baroldi G, Monciotti F, et al. Anabolic steroid abuse and cardiac sudden death: a pathologic study. Arch Pathol Lab Med. 2001 Feb;125(2):253-5.
23. Thiblin I, Lindquist O, Rajs J. Cause and manner of death among users of anabolic androgenic steroids. J Forensic Sci. 2000 Jan;45(1):16-23.
24. Kierzkowska B, Stanczyk J, Kasprzak JD. Myocardial infarction in a 17-year-old body builder using clenbuterol. Circ J. 2005 Sep;69(9):1144-6.
25. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. 2004. 2004;Sports Med(34):8.
26. Pipe A. Reports of steroid use needed. CMAJ. 1995 Feb 15;152(4):469.
27. Melchert RB, Welder AA. Cardiovascular effects of androgenic-anabolic steroids. Med Sci Sports Exerc. 1995 Sep;27(9):1252-62.
28. Kuipers H, Wijnen JA, Hartgens F, Willems SM. Influence of anabolic steroids on body composition, blood pressure, lipid profile and liver functions in body builders. Int J Sports Med. 1991 Aug;12(4):413-8.
29. Hartgens F, Cheriex EC, Kuipers H. Prospective echocardiographic assessment of androgenic-anabolic steroids effects on cardiac structure and function in strength athletes. Int J Sports Med. 2003;24:344-51.
30. Thompson PD, Cullinane EM, Sady SP, et al. Contrasting effects of testosterone and stanozolol on serum lipoprotein levels. JAMA. 1989 Feb 24;261(8):1165-8.
31. Hartgens F, Rietjens G, Keizer HA, et al. Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein(a). British Journal of Sports Medicine. 2004; 38:253-9.
32. Glazer G. Atherogenic effects of anabolic steroids on serum lipid levels. A literature review. Arch Intern Med. 1991 Oct;151(10):1925-33.
33. Kutscher EC, Lund BC, Perry PJ. Anabolic steroids: a review for the clinician. Sports Med. 2002;32(5):285-96.
34. Hassan NA, Salem MF, Sayed MAEL. Doping and effects of anabolic androgenic steroids on the heart: histological, ultrastructural, and echocardiographic assessment in strength athletes. Human & Experimental Toxicology. 2009;28:273-83.
35. D'Andrea A, Caso P, Salerno G, et al. Left ventricular early myocardial dysfunction after chronic misuse of anabolic androgenic steroids: a Doppler myocardial and strain imaging analysis. British Journal of Sports Medicine. 2007 Mar;41(3):149-55.
36. Krieg A, Scharag J, Albers T, et al. Cardiac tissue doppler in steroid users. Int J Sports Med. 2007;28(638-643).
37. Climstein M, O'Shea P, Adams KJ et al. The effects of anabolic-androgenic steroids upon resting and peak exercise left ventricular heart wall motion kinetics in male strength and power athletes. Journal of Science and Medicine in Sport. 2003; 6(4):387-97.
38. Urhausen A, Albers T, Kindermann W. Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? Heart. 2004;90(496-501).
39. Kasikcioglu E, Oflaz H, Umman B, et al. Androgenic anabolic steroids also impair right ventricular function. Int J Cardiol. 2008;134(1):123-5.
40. Vanberg P, Atar D. Androgenic anabolic steroid abuse and the cardiovascular system. In: Theime DaH, P., editor. Doping in Sports, Handbook of Experimental Pharmacology 195. Berlin Heidelberg: Springer-Verlag; 2010. p. 411-57.
41. Sader MA, Griffiths KA, McCredie RJ, Handelsman DJ, Celermajer DS. Androgenic anabolic steroids and arterial structure and function in male body builders. J Am Coll Cardiol. 2001 Jan;37(1):224-30.
42. Kasikcioglu E, Oflaz H, Arslan A, et al. Aortic elastic properties in athletes using anabolic-androgenic steroids. Int J Cardiol. 2007 Jan 2;114(1):132-4.
43. Dickerman RD, Schaller F, Prather I, et al. Sudden cardiac death in a 20-year-old body builder using anabolic steroids. Cardiology. 1995;86(2):172-3.
44. Kennedy MC, Lawrence C. Anabolic steroid abuse and cardiac death. Med J Aust. 1993 Mar 1;158(5):346-8.
45. Luke JL, Farb A, Virmani R, Sample RH. Sudden cardiac death during exercise in a weight lifter using anabolic androgenic steroids: pathological and toxicological findings. J Forensic Sci. 1990 Nov;35(6):1441-7.
46. Stolt A, Karila T, Viitasalo M, et al. QT interval and QT dispersion in endurance athletes and in power athletes using large doses of anabolic steroids. Am J Cardiol. 1999 Aug 1;84(3):364-6, A9.
47. MacDougall JD, McKelvie RS, Moroz DE, et al. Factors affecting blood pressure during heavy weight lifting and static contractions. J Appl Physiol. 1992 Oct; 73(4):1590-7.
48. MacDougall JD, Tuxen D, Sale DG, et al. Arterial blood pressure response to heavy resistance exercise. J Appl Physiol. 1985 Mar;58(3):785-90.
49. Alaraj AM, Chamoun RB, Dahdaleh NS, et al. Spontaneous subdural haematoma in anabolic steroids dependent weight lifters: reports of two cases and review of literature. Acta Neurochir (Wien). 2005 Jan;147(1):85-7; discussion 7-8.

50. Velloso CP. Regulation of muscle mass by growth hormone and IGF-I. Br J Pharmacol. 2008 Jun;154(3):557-68.
51. Holt RI, Sonksen PH. Growth hormone, IGF-I and insulin and their abuse in sport. Br J Pharmacol. 2008 Jun;154(3):542-56.
52. Ehrnborg C, Rosen T. Physiological and pharmacological basis for the ergogenic effects of growth hormone in elite sports. Asian J Androl. 2008;10(3):373-83.
53. Saugy M, Robinson N, Saudan C, et al. Human growth hormone doping in sport. British Journal of Sports Medicine. 2006 Jul;40 Suppl 1:i35-9.
54. McHugh CM, Park RT, Sonksen PH, et al. Challenges in detecting the abuse of growth hormone in sport. Clin Chem. 2005 Sep;51(9):1587-93.
55. Laties VG, Weiss B. The amphetamine margin in sports. Fed Proc. 1981;40(12): 2689-92.
56. Lippi G, Franchini M, Guidi GC. Switch off the light on cycling, switch off the light on doping. British Journal of Sports Medicine. 2007;Nov 5 [e-pub ahead of print].
57. Avois L, Robinson N, Saudan C, et al. Central nervous system stimulants and sport practice. British Journal of Sports Medicine. 2006 Jul;40 Suppl 1:i16-20.
58. Vukovich MD, Schoorman R, Heilman C, et al. Caffeine-herbal ephedra combination increases resting energy expenditure, heart rate and blood pressure. Clin Exp Pharmacol Physiol. 2005 Jan-Feb;32(1-2):47-53.
59. Haller CA, Jacob P, 3rd, Benowitz NL. Pharmacology of ephedra alkaloids and caffeine after single-dose dietary supplement use. Clin Pharmacol Ther. 2002 Jun;71(6):421-32.
60. Bell DG, McLellan TM, Sabiston CM. Effect of ingesting caffeine and ephedrine on 10 km run performance. Med Sci Sports Exerc. 2002 Feb;34(2):344-9.
61. Magkos F, Kavouras SA. Caffeine and ephedrine: physiological, metabolic and performance-enhancing effects. Sports Med. 2004;34(13):871-89.
62. Aforso L, Mohammad T, Thatai D. Crack whips the heart: a review of the cardiotoxicity of cocaine. Am J Cardiol. 2007;100(6):1040-3.
63. Cregler LL, Mark H. Medical complications of cocaine abuse. N Engl J Med. 1986 Dec 4;315(23):1495-500.
64. Weider AA, Melchert RB. Cardiotoxic effects of cocaine and anabolic-androgenic steroids in the athlete. J Pharmacol Toxicol Methods. 1993;29(2):61-8.
65. Pluddemann A, Flisher AJ, McKetin R, et al. Methamphetamine use, aggressive behavior and other mental health issues among high-school students in Cape Town, South Africa. Drug and Alcohol Dependence. 2010;109:14-9.
66. Kaye S, McKetin R, Duflou J, et al. Methamphetamine and cardiovascular pathology: a review of the evidence. Addiction. 2007;102:1204-11.
67. Turdi S, Schamber RM, Roe N, et al. Acute methamphetamine exposure inhibits cardiac contractile function. Toxicol Lett. 2009;189(152-158).
68. Islam MN, Jesmine K, Molh AKS, et al. Histopathological studies of cardiac lesions after long-term administration of methamphetamine in high dosage – Part II. Legal Medicine. 2009;11:S147-S50.
69. Huang SH, Johnson K, Pipe AL. The use of dietary supplements and medications by Canadian athletes at the Atlanta and Sydney Olympic Games. Clin J Sport Med. 2006 Jan;16(1):27-33.
70. Pipe A, Ayotte C. Nutritional supplements and doping. Clin J Sport Med. 2002 Jul;12(4):245-9.
71. Catlin DH, Leder BZ, Ahrens B, et al. Trace contamination of over-the-counter androstenedione and positive urine test results for a nandrolone metabolite. JAMA. 2000 Nov 22-29;284(20):2618-21.
72. Palmer ME, Haller C, McKinney PE, et al. Adverse events associated with dietary supplements: an observational study. Lancet. 2003 Jan 11;361(9352):101-6.
73. Maughan RJ. Contamination of dietary supplements and positive drug tests in sport. J Sports Sci. 2005 Sep;23(9):883-9.
74. Gruber AJ, Pope HG, Jr. Ephedrine use among 36 female weight lifters. Am J Addict. 1998;7(4):256-61.
75. Centers for Disease Control and Prevention (CDC). Adverse events associated with ephedrine containing products - Texas, December 1993 - September, 1995. MMWR Morb Mortal Wkly Rep. 1996;45(37):689-93.
76. Cupp MJ. Herbal remedies: adverse effects and drug interactions. Am Fam Phys. 1999;59(5):1239-45.
77. Izzo A, Ernst E. Interactions between herbal medications and prescribed drugs: a systematic review. Drugs. 2001;61(15):2163-75.
78. Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance. A meta-analysis. JAMA. 2003;289(537-1545).
79. Pittler MH, Schmidt K, Ernst E. Adverse events of herbal food supplements for body weight reduction: systematic review. Obes Rev. 2005;6(2):93-111.
80. Samenuk D, Link MS, Homoud MK, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. Mayo Clinic proceedings. 2002 Jan;77(1):12-6.
81. Andraws R, Chawla P, Brown DL. Cardiovascular effects of ephedra alkaloids: a comprehensive review. Prog Cardiovasc Dis. 2005 Jan-Feb;47(4):217-25.
82. Peters CM, O'Neill JO, Young JB, et al. Is there an association between ephedra and heart failure? A case series. Journal of Cardiac Failure. 2005;11(1):9-11.
83. Bent S, Tiedt TN, Odden MC, et al. The relative safety of ephedra compared with other herbal products. Annals of internal medicine. 2003 Mar 18;138(6):468-71.
84. Foxford RJ, Sahlas DJ, Wingfield KA. Vasospasm-induced stroke in a varsity athlete secondary to ephedrine ingestion. Clin J Sport Med. 2003 May;13(3):183-5.
85. Morris CA, Avorn J. Internet marketing of herbal products. JAMA. 2003 Sep 17;290(11):1505-9.
86. Shaskey DJ, Green GA. Sports haematology. Sports Med. 2000 Jan;29(1):27-38.
87. Ekblom B, Goldbarg AN, Gullbring B. Response to exercise after blood loss and reinfusion. J Appl Physiol. 1972 Aug;33(2):175-80.
88. Birkeland K, Stray-Gundersen J, Hemmersbach P, et al. Effect of rhEPO administration on serum levels of sTfR and cycling performance. Med Sci Sports Exerc. 1999;32(7):1238-43.
89. Eichner ER. Better dead than second. J Lab Clin Med. 1992;120:359-60.
90. Fotheringham W. Inquiry into Belgian cyclists' deaths raises new fears over EPO. The Guardian. 2004 February 16.
91. Voet W. Breaking the chain: drugs & cycling; the true story. London: Yellow Jersey (Random House); 2001.
92. Lage J, Panizo C, Masdeu J, Rocha E. Cyclist's doping associated with cerebral sinus thrombosis. Neurology. 2002;58:665.
93. Lippi G, Franchini M, Salvagno GL, et al. Biochemistry, physiology, and complications of blood doping: facts and speculation. Crit Rev Clin Lab Sci. 2006; 43(4):349-91.
94. Bennett C, Luminari S, Nissenson AR, et al. Pure red-call aplasia and epoietin therapy. N Engl J Med. 2004;351:1403-8.
95. Yasuda J, Fujita Y, Matsuo T, et al. Erythropoietin regulates tumour growth of human malignancies. Carcinogenesis. 2003;24:1021-9.
96. Scheen A. Pharma-clinics. Doping with erythropoietin or the misuse of therapeutic advances. (Fr). Rev Med Liege. 1998;53(8):499-502.