SIDE EFFECTS OF TESTOSTERONE AND OTHER ANABOLIC STEROIDS ON THE HEART AND VASCULAR SYSTEM

A systematic collection of published scientific literature on “doping and exercise in sports” 2000-2015

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SUMMARY

Since the 1970s anabolic androgenic steroids (AAS) have been abused at ever increasing rates in competitive athletics, in recreational sports and in bodybuilding. Anabolic androgenic steroids may have not only the desired effect, but also adverse side effects, resulting from the combination of different AASs in extremely high doses with other drugs and from duration of administration over periods ranging from months to many years – usually seen with abuse in sports. Due to the secret nature of this drug abuse type, doses and duration are mostly unknown and properly controlled clinical trials do not exist. Hence the scientific assessment of the sequelae of AASs abuse relies on case reports and on a few retrospective investigations. Proper diagnosis is further hindered by the reluctance of the doped patient to admit the consumption of AASs and being ignorant about their possible serious side effects. Abuse is not, or only reluctantly admitted to physicians, who must be aware of the multitude of serious side effects of AAS when confronted athletes with unclear symptoms.

Since AAS abuse is not or only reluctantly admitted physicians should be aware of the multitude of serious side effects when confronted with unclear symptoms. Whilst attaining accurate data on the prevalence of their use has limitations, studies suggest the illicit use of doping agents by athletes and non-athletes may be 1-5 percent in the population and greater than 50 percent in some groups; with the prevalence being higher in males. The use of doping substances and methods is, however, extensive not only among elite athletes, but also among amateur and recreational athletes. Many types of drugs are used by athletes to enhance performance, to reduce anxiety, to increase muscle mass, to reduce weight or to mask the use of other drugs during testing. Among biomedical side-effects of doping, the cardiovascular ones are the most deleterious. Myocardial infarction, hyperlipidemia, hypertension, thrombosis, arrhythmogenesis, heart failure and sudden cardiac death have been noted following drug abuse.

A caveat is warranted when drawing conclusions from animal studies to human beings. There are a reasonable number of studies reporting potential adverse cardiovascular effects, while studies indicating an absence of adverse effects are not reported. Supplying information, whatever its validity, is not equivalent, however, to creating and sustaining needed, useable knowledge to enable health-promoting awareness, perceptions, expectations, judgments, decisions, which are implemented or not, and necessary learning, which is integrated into daily adapting and functioning in a range of roles, networks, contexts, situations, and environments – each with their own conditions and “demands.”

Is side effects of anabolic steroids an overstated problem?

Historically, the side effects of AAS use have probably been overstated. Serious health problems are rare, and the more common adverse effects are benign and reversible. The incidence of complications associated with the nonmedical use of AAS as performance-enhancing drugs is unclear because the denominator of drug use in athletes is not well defined. However, data from larger observational studies suggest that the majority (88-96 %) of AAS users experience at least one minor subjective side effect, including acne (40-54%), testicular atrophy (40-51 %), gynecomastia (10-34 %), cutaneous striae (34 %), and injection site pain (36 %). Prospective clinical studies report a good safety profile for pharmacologic and suprapharmacologic doses of AAS when used in the short term. With the exception of a few reversible laboratory abnormalities – decreased HDL, elevated hemoglobin, and raised liver enzymes – high doses of AAS administered for periods of up to 20 weeks rarely demonstrate any significant systemic toxicity.

The side effects reported in at least 40 percent of the male subjects include increased sexual drive, increased body hair and an increase in aggressive behavior. Furthermore,
sleeplessness, increased irritability, decreased libido, increased appetite, enhanced transpiration, increased feeling of well-being, depressive mood states, loss of head hair and the occurrence of gynaecomastia are also reported.

**Female misuse**

Data relating to female athletes are very scanty. In one study it was interviewed females who all reported lowering of the voice brought on by AAS use. Furthermore, nine of ten females admitted increased growth of facial hair, enlargement of the clitoris and an increase in aggressiveness and appetite. Other side effects reported were acne (50 %), fluid retention (40 %) and alteration of libido (50 %).

**Impurities in illicit samples of anabolic steroids**

There are few data on the purity of illicit amples of AASs as a result of the lack of regulation. Consequently, there are no assurances that the chronic AAS abuser knows the dose or type of AAS. The difficulty determining doses used by AAS abusers limits the ability of studies to elucidate the effect of AAS abuse. Frequently, illicit samples of AASs do not contain declared ingredients or concentrations of ingredients. Analysis of 70 products confiscated from illegal sources demonstrated 17 (35 %) of the 48 steroidal compounds did not contain labeled ingredients as measured by liquid chromatography-tandem mass-spectrometry, gas chromatography mass-spectrometry with nitrogen-phosphorus detection, gel-electrophoresis, and immunological tests. Visual inspection does not distinguish original products from counterfeits.

**Physiological effects on the heart of testosterone and its analogues**

Some of the effects of testosterone on the heart and the cardiovascular system are still a matter of debate, but some influences of testosterone on cardiac function and morphology have been established. This is primarily in regard to a nonphysiologic situation of testosterone misuse when the side-effects include left ventricular hypertrophy with systolic and diastolic dysfunction. However, in patients with heart failure and reduced left ventricular ejection fraction, testosterone supplementation significantly improves exercise capacity in both men and women, without affecting left ventricular systolic function. In addition, in male patients with heart failure, neither total, free nor bioavailable testosterone levels correlate with the left ventricular ejection fraction. Lower testosterone levels are associated with increased all-cause and cardiovascular mortality as well as vascular mortality defined as death from cardiac arrest, heart failure and atherosclerosis.

Most of the adverse effects following the use of AASs result from the enhancement of normal physiologic response to testosterone by either direct receptor agonist activity or suppression of steroid biosynthesis is. In general, toxic effects associated with AAS abuse involve the following:

- anabolic side effects
- enhanced androgenic effects
- estrogenic side effects
- antiandrogenic effects from the suppression of the hypothalamus-pituitary-adrenal/gonadal axes
- hepatotoxicity
- neuropsychiatric effects

Most medical data on the toxic effects of AAS abuse involve case reports rather than epidemiologic studies. Pathologic abnormalities from AAS abuse are, however, well
documented in the cardiovascular system. Animal studies suggest that AAS can cause dysplasia of collagen fibrils and decreased tensile strength, and potentially the use of these drugs could cause disruption of connective tissue.

Cardiac muscle cells have receptors for androgens, and both testosterone and dihydrotestosterone produce a hypertrophic response by acting directly on cardiac muscle cells, increasing amino acid incorporation into protein.

**Explanatory models for adverse effects of anabolic steroids**

The cardiovascular system may be affected via at least four different pathways. Although hypothetical, they provide interesting models to explain AAS-induced adverse effects on this system:

- **The atherogenesis model.** The atherogenesis model is based on the association between AAS and HTGL, an enzyme that regulates serum lipids and lipoproteins. AAS administration enhances HTGL activity that decreases regression of atherosclerotic plaques by suppression of serum HDL-cholesterol and elevation of LDL-cholesterol.

- **The thrombosis model.** The thrombosis model is characterised by influence on the haemostatic system, with the strongest effects of AAS on platelet aggregation that results in enhanced blood-clot formation, including an increased cardiovascular risk.

- **The coronary artery vasospasm model.** Since no evidence of atherosclerosis or thrombosis of the coronary arteries was involved in several reports of sudden cardiac death, nitric oxide has been suggested to play a role in the third model, the coronary artery vasospasm model. Nitric oxide acts as an endothelial-derived relaxing factor in smooth muscles of arteries. AAS may inhibit nitric oxide properties and may induce vasospasm, although the authors suggested that other models may be involved in conjunction with the vasospasm theory. The latter is supported by recent findings in animal studies. It was demonstrated that AAS may impair capillary supply of the heart as a result of an increase in myocardial muscle mass and a relative decrease in capillary density, which may provoke compression of coronary vessels that could trigger myocardial infarction.

- **The direct injury model.** The fourth hypothesis is the direct injury model. AAS is hypothesised to induce direct myocardial cell injury, leading to myocardial cell death and replacement of dead cells by scar tissue within the myocardium. Development of fibrotic areas predisposes to arrhythmias, which exposes the individual to an increased risk of fatal events. Postmortem pathological findings in previous AAS users included focal, regional, interstitial and disseminated fibrosis of the myocardium, although the impact of myocardial fibrosis is still unclear.

- **Other models.** Several other hypotheses have been postulated, especially those affecting red blood cells and volume. It has been suggested that cardiac arrest may be mediated catecholamine myotoxicity associated with ventricular fibrillation due to myocardial necrosis and degenerative changes within the intramyocardic sympathetic neurons. All mechanisms proposed for explaining cardiovascular disease due to AAS use have interesting points; however, future research is needed to clarify the relevance of each theory.
Anabolic steroids’ negative impact on the cardiovascular system

The most common cardiovascular consequences of AAS include atherosclerosis (secondary to changes in cholesterol metabolism and platelet function), hypertension, cardiac hypertrophy, impaired cardiac function, and sudden death. AAS use causes metabolic derangements that increase the risk for atherosclerosis and thrombus formation. Studies using animal models and various steroid regimens have demonstrated changes in serum cholesterol levels with decreased high-density lipoprotein and increased low-density lipoprotein, both promoting atherosclerotic and peripheral vascular disease. Cholesterol alterations vary among different AASs; alkylated agents (e.g. stanozolol) cause greater changes than testosterone.

In other studies it was concluded that potential adverse effects of AAS on the cardiovascular system include atherogenesis, thrombosis, vasospasm, myocarditis, concentric left ventricular hypertrophy, myocardial fibrosis, hypertrophic cardiomyopathy with ventricular dysrhythmias, and direct myocardial injury. However, the contribution of AAS use to these potential adverse cardiovascular effects remains unclear. Chronic AAS use enhances hepatic triglyceride lipase activity, resulting in reduction of high-density lipoproteins and elevation of low-density lipoproteins. Although these changes are reversible within several months of cessation of AAS use, chronic AAS use theoretically increases the risk of cardiac disease. Potentially, the chronic abuse of AAS enhances coagulability and thrombosis, but the clinical importance of this potential adverse effect also remains unclear. Studies of chronic AAS abuse in weight lifters suggest that some anabolic-androgenic steroid using weight lifters have accelerated activation of their hemostatic system as evidenced by increased generation of both thrombin and plasmin. A study of AAS-positive steroid using weight lifters indicated that these individuals had a higher percentage of abnormally high plasma thrombin-antithrombin complexes along with elevated plasma concentrations of prothrombin fragment 1, antithrombin II, and protein S, when compared with non-AAS using controls. Additionally, the plasma concentrations of tissue plasminogen activator and its inhibit or were lower in AAS users than in controls. Clinical studies on body builders suggest that chronic AAS use impairs vascular reactivity independent of the smooth muscle hypertrophy and vascular stiffness associated with bodybuilding. Anabolic-androgenic steroids decrease the production of cyclic guanosine monophosphate (cGMP) by inhibiting guanylyltransferase. As a result, AAS potentially inhibit the ability of nitric oxide store lax smooth muscles in the coronary arteries resulting in coronary artery vasospasm and potentially sensitizing AAS users to sudden death. Case reports associate the chronic use of anabolic steroids with sudden death and contraction band necrosis in the myocardium. In these cases, no other cause of death was apparent, but the role of chronic, high-dose anabolic steroid use in these deaths remains unclear. Athletes with certain genetic mutations and structural abnormalities may be particularly vulnerable to the use of anabolic steroids including athletes with accessory AV pathways, latent structural heart diseases (dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia type II, myocarditis, segmental arrhythmogenic ventricular cardiomyopathy, and coronary artery anomalies), latent Brugada syndrome, mutations of the long QT syndrome genes, and other genetic mutations of ion channels (cardiac cation channel gene defects and calsequestrin gene defects). Pathologic evidence of some of these abnormalities may not appear on postmortem examination. The use of diuretics to mask the use of anabolic steroids may predispose these athletes to serious ventricular dysrhythmias from hypokalemia and dehydration.

Individual case reports or small case series have described a variety of cardiovascular effects, including cardiomyopathy, myocardial infarction, cerebrovascular accidents, conduction abnormalities, and coagulation abnormalities, in known or suspected AAS users. More recently, larger controlled studies, using a variety of methodologies, have supported these findings. In a recent postmortem pathologic study, comparing 87 deceased men testing
positive for AAS with 173 control men, AAS users exhibited significantly greater cardiac mass even after adjusting for body mass, age, and history of trauma. Another pathologic study found ventricular hypertrophy, associated with fibrosis and myocytolysis, after cardiac death in 4 AAS users. Recent conduction studies have demonstrated decreased cardiac electrical stability, abnormal tonic cardiac autonomic regulation, and ventricular repolarization abnormalities in AAS users; the last finding has also been demonstrated in rats that received AAS. Perhaps most importantly, numerous recent controlled studies (using echocardiography or cardiac magnetic resonance imaging to compare AAS users with non-AAS-using athletes and/or nonathletes) have demonstrated cardiomyopathy in AAS users, characterized by decreased ventricular ejection fractions and reduced diastolic tissue velocities. One study also found decreased aortic elasticity in AAS users. These changes may be profound but may be at least partially reversible after AAS abstinence. However, loss of tissue elasticity appears likely due at least in part to increased fibrotic content resulting from direct AAS-induced cellular injury and hence may be irreversible.

**Increased left-ventricular mass**

Increased left-ventricular mass is probably the most important cardiovascular risk factor for morbidity and mortality. Apart from obvious differences in cardiac size, the changes in left-ventricular mass in response to age and hypertrophic stimuli are very different in men and women. Whereas left-ventricular mass increases with age in apparently healthy women, it remains constant in men. Under increased cardiac loading conditions, such as hypertension or aortic stenosis, this disparity between sexes is even more striking. Findings are especially pronounced in people aged 50 years or older, in whom reproductive hormone concentrations have fallen. Whether the differences in left-ventricular mass changes are related to endogenous sex-hormone concentrations has never been shown. Androgens have anabolic effects on cardiac cells, and estrogens have anti-proliferative properties.

The use of anabolic androgenic steroids (AAS) has been associated with hypertrophy of the left cardiac ventricle (LVH) as diagnosed by echocardiography. Case reports suggest that AAS-related LVH may lead to sudden death. Analysis of the logarithm of heart mass by multivariate statistics implies a strong correlations between body mass and heart mass, height and heart mass, and age and heart mass. After controlling for these factors in a forensic material, a significantly higher heart mass was found among the AAS-positive males. The findings suggest that use of AAS may lead to cardiac hypertrophy with a direct cardiotropic effect.

Given the putative effects of steroid hormones (and AAS in particular) on LV growth, it might be expected exposure to exogenously administered steroid hormones to be associated with an exaggerated LV hypertrophic response to any other hypertrophic stimulus. Exercise is just such a potent cardiac hypertrophic stimulus. Meanwhile, athletes are increasingly exposing themselves to supra-physiological doses of AAS. These are known to increase skeletal muscle mass and strength – effects which form the basis for their administration to enhance athletic performance. A variety of AAS are often taken simultaneously (so called “stacking”), and in doses which result in 10-100 fold increases in androgen concentrations. Administration regimens usually involve a 6-12 week cycle and are often administered in a “pyramidal” fashion, with doses tapering from low to high to low. Abused substances include testosterone, its 17-beta esters, and those based on modified steroid rings (including 17-alpha derivatives). The largest group to make such use of AAS are the very group whose LVH response to exercise is likely to be the greatest – the strength or resistance training (RT) athletes.
Right ventricular myocardial dysfunction after use of anabolic steroids

Chronic anabolic steroid use thus suppresses left ventricular functions. However, there is little information regarding the chronic effects of anabolic steroids on right ventricular function which also plays a key role in global cardiac function but at least one study shows that androgenic anabolic steroids-using bodybuilders exhibited depressed diastolic functions of both ventricles.

Increased risk for ischemia

When left ventricular diastolic dysfunction occurs, emptying of the left atrium is impaired as well. Following impaired left ventricular diastolic relaxation, there is increased atrial contribution to the mitral flow in the left ventricular diastolic flow, thus leading to atrial overstretched and enlargement. The left atrium diameter is known to be correlated with cardiovascular events and is a risk factor for AF. In one study, the left atrial diameters of the AAS user and nonuser groups were similar. The presence of LV hypertrophy is an indicator of increased myocardial demand for oxygen and hence decreases coronary reserve. When coronary blood flow is fixed or reduced, there is a supply-demand mismatch, resulting in increased risk for ischemia. In such a scenario, a decrease in blood flow can be catastrophic to the already increased demand of the myocardial cells. Patients with LV pathological hypertrophy are at increased risk for ischemia.

Heart failure due to anabolic-androgenic steroids

It has been concluded that anabolic-androgenic steroid-induced advanced heart failure is generally not a reversible condition. If diagnosed in the early stages some recovery of ventricular function is possible, but the long-term prognosis is uncertain. Likely, a substantial proportion of patients will eventually require LVADs or cardiac transplantation.

Cardiac arrhythmias and abnormal electrocardiography

Apart from important peripheral mechanisms, additional cardiac effects of testosterone most likely include the influence on electrophysiology and arhythmogenesis. Higher levels of endogenous testosterone are associated with shorter QT and QTc interval and consequently a reduced arhythmogenesis. Physiologic testosterone supplementation has been shown to reduce QT dispersion in patients with congestive heart failure. In contrast, supraphysiologic doses of testosterone and other anabolic androgen steroids may facilitate ventricular arrhythmias by increasing QTc interval and dispersion and by predisposing to reentry mechanism. Androgen misuse has been also associated with episodes of atrial fibrillation. Nevertheless, the possibility of a protective effect of testosterone against atrial fibrillation has been contradicted by both a meta-analysis which included middle-aged and older men and by animal research associating testosterone supplementation with higher occurrence of atrial fibrillation.

Altered autonomic system regulation

Probably adverse effects of AAS on the cardiovascular system are also due to direct toxicity on myocardial structure with increased collagen deposition, fibrosis, and altered microcirculation with intimal hyperplasia of the intramural coronary arteries resulting in chronic ischemic damage. Vascular endothelial cells may be directly affected by AAS, which may result in vasospasm. As the cause of these alterations, AAS may directly affect the atrium, causing heterogeneity in the atrial conduction. It has been speculated that long-term illicit use of supraphysiologic doses of AAS might directly affect atrial conduction time (inter-AMED). The last possible mechanism to increase AEMD may be sympathetic activation. It
has been shown that chronic consumption of supraphysiologic doses of AAS induces cardiac autonomic imbalance by reduction in parasympathetic cardiac modulation and increase in sympathetic cardiac modulation. Experimental studies showed that greater sympathetic activation leads to myocardial injury. Increased sympathetic activity may also trigger atrial arrhythmias. Therefore, altered autonomic system regulation occurring secondary to the chronic consumption of supraphysiologic doses of AAS may be the other reason underlying the delayed interatrial electromechanical coupling intervals.

Arterial hypertension

The literature regarding the blood pressure response to AAS use is equivocal. In addition, there is currently little data available on the rate pressure product (RPP) response to anabolic androgenic steroids (AAS) use. Findings indicate that the AAS group exhibits significant increases in standard cardiovascular measurements compared with the control bodybuilders, and provides a contraindication to AAS use especially in borderline hypertensives.

Although not shown in all studies, an association between elevated blood pressure and AAS abuse has been reported. Enhanced reactivity of the vasculature to norepinephrine, increased plasma renin activity, stimulation of aldosterone production by testosterone, and sodium retention by the kidneys are suggested mechanisms for high blood pressure following AAS use in athletes. Blood pressure response to androgen use typically shows a dose-response relation. The effects of AAS abuse on blood pressure may persist for long periods; some studies have shown persistent elevations for 5 to 12 months after discontinuing steroids.

Vascular effects of anabolic steroids

Regarding the vascular mechanisms of testosterone and its effects on blood vessels, a body of evidence suggests that one of testosterone’s beneficial cardiovascular effects is the vasodilation of systemic, coronary and pulmonary vessels. Mechanisms available from experimental studies have been proposed to explain testosterone induced vasodilation. Testosterone may influence the tonus of vascular smooth muscle cells by modulating the activity of several ion channels such as the voltage-sensitive potassium ion channels, non-ATP-sensitive potassium ion channels, calcium-activated potassium ion channels and L-type calcium ion channels. Whether the effect on only one type of channel is dominant or a concomitant effect on several types of channels produces vasodilation remains to be elucidated. In heart failure, the chief beneficial cardiovascular mechanism of testosterone seems to be primarily vascular and peripheral since peripheral vasodilation produces a reduced cardiac afterload and increased cardiac output. In addition, coronary vasodilation improves myocardial oxygenation which is important in heart failure patients with ischemic etiopathogenesis.

Cardiac structure and functioning

The harmful cardiovascular effects of indiscriminate use of AAS to the cardiac structure and functioning can include increased cardiac tissue collagen, imbalance of vasomotor tone, reduction in the number of capillaries, and pathological cardiac hypertrophy in animal and human models. In addition, supraphysiological doses of AAS have already demonstrated that they may inhibit angiogenesis induced by physical training.
The exact mediators of myocardial hypertrophy are diverse and vary from mechanical stimuli to circulating humoral factors released by the heart and peripheral organs. Exercise-induced cardiac hypertrophy is thought to be due to increases in the pre-load (diastolic filling) on the heart, while the exact mechanisms for anabolic steroid-induced myocardial hypertrophy are at present unknown. Studies have shown that circulating cytokines such as TNF-alpha may play a role in cardiac remodeling and that anabolic steroids strongly stimulate leukocyte TNF-alpha production.

Fibrillar fibrosing

Fibrillar collagens, types I and III, are the major structural proteins of the myocardial collagen matrix, exerting an important influence on ventricular compliance. Exposure to supraphysiological doses of AAS can lead to tissue necrosis and diastolic dysfunction, resulting in structural changes similar to those seen in the earlier stages of heart failure. There are several mechanisms that appear to be related to cardiac hypertrophy and collagen accumulation. AAS can induce such hypertrophy through nuclear receptors, acting directly on RNA and increasing the protein synthesis and acting as well on specific enzymes, on ions flow and the structural matrix in the myocardium. Increased circulating pro-inflammatory cytokines such as TNF-alpha and increased cAMP concentration have been documented, which contributes to the positive inotropic response through the calcium in the cytosol of the myocardial cell.

Sudden death after using anabolic steroids

Autopsies, histology, immunohistochemistry, biochemistry and toxicology have been performed in many cases of sudden deaths during sports of athletes using anabolic steroids. Pathological changes often consisted of various degrees of interstitial and perivascular fibrosis as well as fibroadipous metaplasia and perineural fibrosis within the myocardium of the left ventricle. Within the limits of the number of investigated cases, the results appear to confirm former observations on this topic and suggest anabolic androgenic steroid's potential causative role in the pathogenesis of sudden cardiac deaths in chronic users.

Long-term effects on the heart of anabolic steroids

Several years after chronic misuse of AAS, power athletes show a subclinical impairment of both systolic and diastolic myocardial function, strongly associated with mean dosage and duration of AAS use. The combined use of DMI and SRI may therefore be useful for the early identification of patients with more diffused cardiac involvement, and eventually for investigation of the reversibility of such myocardial effects after discontinuation of the drug.

Dyslipidemia

AS have been associated with negative alterations in lipid profiles. Changes reported include a decrease in high-density lipoprotein (HDL), an elevation in low-density lipoprotein (LDL) and reduced apolipoprotein levels, possibly through up-regulation of hepatic triglyceride lipase. The changes in lipid profiles indicate an increase in atherosclerotic risk. Increases in homocysteine, a naturally occurring amino-acid thought to have a role in vaso-control, and C-reactive proteins (CRP), an acute-phase protein that rises in response to inflammation, have been implicated as risk factors for CV disease. It has been demonstrated a significant increase in CRP in AS users. It is noted a significant elevation in homocysteine in AS users as well as those who had abstained from AS use for 3 months, indicating a possible effect of AS on vitamin B absorption. Previous studies have also suggested a possible link between
AS use and thrombotic risk through alterations in hemoglobin levels [136]. A meta-analysis including 19 studies and comprising 272 hypogonadal men showed that substitution therapy with intramuscularly administered testosterone results in a decrease in plasma HDL cholesterol levels. The same results were also demonstrated in a meta-analysis including 51 studies on men with low or low-to-normal plasma testosterone levels who received testosterone in different doses as therapy.

**Increased risk of diabetes**

Anabolic steroids decrease glucose tolerance and increase insulin resistance, which lead to hyperinsulinism and secondary diabetes mellitus with type II symptoms.
GENERAL ASPECTS OF SIDE EFFECTS OF ANABOLIC STEROIDS

Anabolic androgenic steroids (AAS) may have not only the desired effect, but also adverse side effects, resulting from the combination of different AASs in extremely high doses with other drugs and from duration of administration over periods ranging from months to many years. Due to the secret nature of this drug abuse type, doses and duration are mostly unknown and properly controlled clinical trials do not exist. Hence the scientific assessment of the sequelae of AASs abuse relies on case reports and on a few retrospective investigations, making a review of the field in the age of evidence-based medicine extremely difficult and frustrating. Proper diagnosis is further hindered by the reluctance of the doped patient to admit the consumption of AASs and being ignorant about their possible serious side effects [001].

Since the 1970s anabolic androgenic steroids have been abused at ever increasing rates in competitive athletics, in recreational sports and in bodybuilding. Exceedingly high doses are often consumed over long periods, in particular by bodybuilders, causing acute or chronic adverse side effects frequently complicated by additional polypharmacy. Among the most striking AAS side effects are increases in haematocrit and coagulation causing thromboembolism, intracardiac thrombosis and stroke as well as other cardiac disturbances including arrhythmias, cardiomyopathies and possibly sudden death. Since AAS abuse is not or only reluctantly admitted physicians should be aware of the multitude of serious side effects when confronted with unclear symptoms [002].

The use of doping agents are evident within competitive sport in senior and junior age groups, where they are taken by non-elite as well as elite participants. They are also taken in non-sporting contexts by individuals seeking to “improve” their physique through an increase in muscle and/or decrease in fat mass. Whilst attaining accurate data on the prevalence of their use has limitations, studies suggest the illicit use of doping agents by athletes and non-athletes may be 1-5 percent in the population and greater than 50 percent in some groups; with the prevalence being higher in males [003].

The use of doping substances and methods is, however, extensive not only among elite athletes, but also among amateur and recreational athletes. Many types of drugs are used by athletes to enhance performance, to reduce anxiety, to increase muscle mass, to reduce weight or to mask the use of other drugs during testing. However, the abuse of doping substances and methods has been associated with the occurrence of numerous health side-effects. The adverse effects depend on the type of the consumed drug, as well as the amount and duration of intake and the sensitivity of the body, since there is a large inter-individual variability in responses to a drug. Usually the doses used in sports are much higher than those used for therapeutic purposes and the use of several drugs in combination is frequent, leading to higher risk of side-effects. Among biomedical side-effects of doping, the cardiovascular ones are the most deleterious. Myocardial infarction, hyperlipidemia, hypertension, thrombosis, arrhythmogenesis, heart failure and sudden cardiac death have been noted following drug abuse [004].

Many different bodily function are targeted

To date, the data available in the literature point to possible adverse effects of AAS use on the cardiovascular system. Dyslipidemia, increased blood pressure, oxidative stress, myocardial remodeling, and even myocardial infarction and deaths are likely to occur as a result of AAS use. However, because of ethical and methodological limitations, the studies are very limited, especially in the aspect of sample size, which makes it difficult to generalize the data. A caveat is warranted when drawing conclusions from animal studies to human
beings. There are a reasonable number of studies reporting potential adverse cardiovascular effects, while studies indicating an absence of adverse effects are not reported. The adverse effects reviewed may be used as a resource in anti-doping educational programs. Supplying information, whatever its validity, is not equivalent, however, to creating and sustaining needed, usable knowledge to enable health-promoting awareness, perceptions, expectations, judgments, decisions, which are implemented or not, and necessary learning, which is integrated into daily adapting and functioning in a range of roles, networks, contexts, situations, and environments – each with their own conditions and “demands” [005].

Doping is observed early on, even in childhood. Many substances are used and they are increasingly available: all bodily functions are targeted: cerebral, metabolic, cardiovascular, respiratory, haematological and, in the near future, genetic. Detection of doping is difficult and unpredictable in a legislative environment which is gradually improving. The different modes of action of the doping substances often target the cardiovascular system, especially with regards to their potential complications: hypertension, arrhythmias, thrombosis, coronary artery and peripheral artery diseases and also cardiomyopathies. Every cardiologist should therefore be aware of the problem, even outside the context of sport, as it may impact on daily cardiological practice [006].

**Effects on the heart**

The effects of testosterone on the heart and the cardiovascular system are still a matter of debate. Some influences of testosterone on cardiac function and morphology have been established. This is primarily in regard to a nonphysiologic situation of testosterone misuse when the side-effects include left ventricular hypertrophy with systolic and diastolic dysfunction. However, in patients with heart failure and reduced left ventricular ejection fraction, testosterone supplementation significantly improves exercise capacity in both men and women, without affecting left ventricular systolic function. In addition, in male patients with heart failure, neither total, free nor bioavailable testosterone levels correlate with the left ventricular ejection fraction. Although some disagreement exists, clinical evidence suggests that men with coronary disease have lower levels of endogenous testosterone. The most likely explanation is that low testosterone is associated with diabetic and metabolic derangements such as hypertension, insulin resistance dyslipidemia and obesity. However, one of the most intriguing questions is whether low testosterone is one of the ethiopathogenic mechanisms of coronary disease; is it just comorbidity or perhaps a consequence of generalized atherosclerotic vascular disease? Moreover, an inverse association between the degree of hypogonadism and the severity of coronary disease exists. Lower testosterone levels are associated with increased all-cause and cardiovascular mortality as well as vascular mortality defined as death from cardiac arrest, heart failure and atherosclerosis [007].

This is an area of controversy as the risk of significant major side effects may have been overstated in the healthy population using anabolic steroids. However, as studies in this area are notoriously difficult, and there is no reporting of side effects to a central body, whilst one cannot predict universal harm from using anabolic steroids the potential risks should be monitored [008].

Most of the adverse effects following the use of AASs result from the enhancement of normal physiologic response to testosterone by either direct receptor agonist activity or suppression of steroid biosynthesis is. In general, toxic effects associated with AAS abuse involve the following:
- anabolic side effects
- enhanced androgenic effects
- estrogenic side effects
- antiandrogenic effects from the suppression of the hypothalamus-pituitary-adrenal/gonadal axes
- hepatotoxicity
- neuropsychiatric effects

Methodological issues limit the determination of the toxic effects of illicit AAS use including the extraordinary doses and types of AAS used by athletes compared with medical use, reporting bias of self-reports, the paucity of well-documented pathologic findings, and the lack of well-defined postmortem markers of AAS use. Most medical data on the toxic effects of AAS abuse involve case reports rather than epidemiologic studies. Pathologic abnormalities from AAS abuse are best-documented in the cardiovascular system, reproductive system, liver, and serum lipids. Animal studies suggest that AAS can cause dysplasia of collagen fibrils and decreased tensile strength, and potentially the use of these drugs could cause disruption of connective tissue [009].

**Cardiac muscle cells have receptors for androgens**

Left ventricular hypertrophy (LVH) has been reported in androgen abusers. Several groups have shown that athletes using AAS have reduced end diastolic dimension, a thicker posterior wall and interventricular septum, and a larger left ventricular mass than athletes not using AAS. Cardiac muscle cells have receptors for androgens, and both testosterone and dihydrotestosterone produce a hypertrophic response by acting directly on cardiac muscle cells, increasing amino acid incorporation into protein. The problem is that LVH may persist after discontinuation of AAS [010].

**Is side effects of anabolic steroids an overstated problem?**

Historically, the side effects of AAS use have probably been overstated. Serious health problems are rare, and the more common adverse effects are benign and reversible. The incidence of complications associated with the nonmedical use of AAS as performance-enhancing drugs is unclear because the denominator of drug use in athletes is not well defined. However, data from larger observational studies suggest that the majority (88-96 %) of AAS users experience at least one minor subjective side effect, including acne (40%-54%), testicular atrophy (40-51 %), gynecomastia (10-34 %), cutaneous striae (34 %), and injection site pain (36 %). Recent prospective clinical studies report a good safety profile for pharmacologic and suprapharmacologic doses of AAS when used in the short term. With the exception of a few reversible laboratory abnormalities – decreased HDL, elevated hemoglobin, and raised liver enzymes – high doses of AAS administered for periods of up to 20 weeks failed to demonstrate any significant systemic toxicity [011].

**Self-reported adverse effects**

To date, only a few reports investigating the self-reported adverse effects in athletes using AAS have been published. These reports employing questionnaires showed clearly that the majority of athletes experienced undesired health effects not only when on AAS, but also after drug withdrawal. These data are very valuable since they indicate the extent of self-reported untoward effects when using high doses of AAS in stacking regimens reflecting real-life AAS abuse. The side effects reported in at least 40 percent of the male subjects in these studies included increased sexual drive, occurrence of acne, increased body hair and an
increase in aggressive behavior. Furthermore, many other side effects affecting several body systems were mentioned by the steroid users. These include fluid retention, elevated blood pressure (BP), sleeplessness, increased irritability, decreased libido, increased appetite, enhanced transpiration, increased feeling of well-being, depressive mood states, loss of head hair and the occurrence of gynaecomastia [012].

Female misuse

Data relating to female athletes are very scanty. In one study it was interviewed ten females who all reported lowering of the voice brought on by AAS use. Furthermore, nine of ten females admitted increased growth of facial hair, enlargement of the clitoris and an increase in aggressiveness and appetite. In another study nine of ten interviewed female athletes had experienced side effects due to steroid use. The side effects reported were acne (50 %), fluid retention (40 %) and alteration of libido (50 %). Other side effects were only mentioned by <20 percent of the women. Of great concern is that athletes are not aware of many side effects during steroid administration, since several unwanted health effects may be detected only after thorough medical examination, including blood analysis [012].

Different effects of different anabolic steroids

All synthetic AAS are derived from testosterone. They have a carbon skeleton with 4 fused rings; most have 19 carbons. Modifications include hydroxylation at the C10 position to increase receptor binding affinity (e.g. nandrolone) esterification to slow release into circulation (e.g. testosterone cypionate), or alkylation at the C17 position to permit moral delivery by reducing first-pass metabolism in the liver (e.g. oxymetholone). AAS can be converted to highly-androgenic or estrogenic metabolites. For testosterone, dihydrotestosterone is the principle androgenic product; estradiol is the major estrogenic metabolite. Non-aromatizable AAS (e.g. drostanolone) have fewer estrogenic side-effects such as gynecomastia. Non-reducible AAS (e.g. oxandrolone) have fewer androgenic side-effects such as acne, baldness, and prostatic hypertrophy because they have lower binding affinity for the androgen receptor. For athletes subject to drug testing, a key drawback of synthetic AAS is that their use is easily detected, since their metabolites are not normally present. An extended precompetition wash-out period is necessary to avoid a positive test. This varies with the route of administration and the half-life of the individual AAS. However, long-acting AAS such as nandrolone can be detected for at least 6 months. By contrast, the urinary metabolites of exogenous and endogenous testosterone are virtually identical. Many athletes take long-acting testosterone esters such as testosterone propionate. Although esterification prolongs the half-life in circulation, the active steroid is still testosterone [013].

Toxicokinetics

Most of the data on the kinetics of testosterone and AASs is derived from the pharmacokinetics of these compounds in animals or in hypogonadal males receiving therapeutic doses of AASs. There are few data on the toxicokinetics of AASs in individuals abusing AAS at doses up to 10-100 times the therapeutic dose. Despite the rapid absorption of testosterone, the systemic bioavailability of oral testosterone is low as a result of extensive first-pass hepatic metabolism. Structural modifications of testosterone produce synthetic testosterone derivatives (anabolic-androgenic steroids), which increase bioavailability and prolong the duration of action. Alkylation of the 17-alpha position of testosterone produces oral AAS, whereas esterification of the 17-beta position results in injectable AAS (e.g. lipid-soluble cypionate or enanthate). The duration of action of these esters depends on the rate of absorption from the site of administration as determined by the
chain length of the acid moiety and the formulation. Hydrolysis of these esters in vivo prolongs the duration of action compared with testosterone. Anabolic-androgenic steroids can diffuse across the skin and mucous membranes, allowing other delivery modes including transdermal patches, nasal sprays, and buccal tablets. Following oral administration of 120 mg testosterone undecanoate, volunteer studies indicate that plasma concentrations of testosterone are detectable for about 1-6 h after administration using gas chromatography–tandem mass spectrometry. There are dramatic individual variations (i.e. 10-fold) in the peak total plasma testosterone concentrations. In a study of 61 eugonadal men receiving long-acting gonadotropin-releasing hormone agonist to suppress endogenous testosterone secretion, the mean nadir testosterone concentrations ranged from 2.53 to 23.7 ng/mL following weekly injections of testosterone enanthate doses of 25-600 mg for 20 weeks [009].

Anabolic-androgenic steroids are bound in the plasma to sex-hormone-binding globulins. Although testosterone is highly protein bound (i.e. 98 %) in plasma, the binding of AAS to sex-hormone-binding globulins is highly variable based on done animal studies. The metabolism of endogenous testosterone involves the conversion to the estrogenic compound, estradiol, via steroid aromatase and the androgenic compound, 5alpha-dihydrotestosterone, via 5alpha–steroid-reductase. Comparatively, the biotransformation of AASs is quite complex. The initial and rate-limiting step in testosterone metabolism is reduction of the C4-C5 double bond on the A-ring with 5alpha-reductase and 5beta-reductase. Hydroxylation of testosterone by CYP450 isozymes results in the formation of a variety of minor urinary metabolites of testosterone. Single-dose human excretion studies indicate that 6-beta-hydroxylation is also a minor pathway for the biotransformation of boldenone (17beta-hydroxyandrosta-1,4-dien-3-one) and 17alpha-methyl-testosterone. However, 6beta-hydroxylation of the B-ring is the major metabolic pathway for 4-chloro-1,2-dehydro-17alpha-methyltestosterone, methandienone, and fluoxymesterone because the presence of a C1-C2 double bond in the former 2steroids and the C9 alpha-fluorine atom in the latter compound blocks A-ring reduction. Metabolic changes (e.g. 12-hydroxylation) of AASs at the C-ring are minor. D-ring metabolism by the enzymatic oxidation of 17beta-hydroxysteroid-dehydrogenase to form the corresponding 17-ketosteroid is a major metabolic pathway for testosterone and all AASs with secondary 17beta-hydroxy groups (e.g. boldenone, clostebol, drostanolone, mesterolone, methenolone, nandrolone, norclostebol, and stanolone). The main urinary metabolites of testosterone are androsterone (3alpha-hydroxy-5alpha-androstan-17-one), etiocholanolone (3alpha-hydroxy-5beta-androstan-17-one), epiandrosterone (3beta-hydroxy-5alpha-androstan-17-one), 5alpha-androstane-3alpha, 17beta-diol, and 5beta-androstane-3alpha,17beta-diol [009].

In individuals without AAS use, only small amounts (i.e. about 1 %) of endogenous testosterone appear unchanged in the urine. Phase II conjugation reactions couple AASs and associated metabolites with glucuronic acid or sulfate before excretion in the urine. The vast majority (i.e. about 90 %) of the absorbed dose of testosterone appears in the urine as glucuronide or sulfate conjugates. In a study of 8 hypogonadal males, the terminal elimination half-lives of 500 mg and 1000 mg intramuscular doses of testosterone undecanoate were 18.3 and 2.3 days and 23.7 and 2.7 days, respectively. The mean residence times were 21.7 and 1.1 days and 23.0 and 0.8 days, respectively. Not all anabolic steroids undergo phase II reactions. Unconjugated AASs in human urine include oxandrolone, fluoxymesterone, 4-chloro-1,2-dehydro-17alpha-methyltestosterone, and formebolone, along with metabolites of oxandrolone, methandienone, and stanozolol. There is very limited (i.e. about 5 %) enterohepatic recirculation of testosterone. Anabolic-androgenic steroids readily cross the placenta [009].

**Impurities in illicit samples of anabolic steroids**

There are few data on the purity of illicit amphi of AASs as a result of the lack of regulation.
Consequently, there are no assurances that the chronic AAS abuser knows the dose or type of AAS. The difficulty determining doses used by AAS abusers limits the ability of studies to elucidate the effect of AAS abuse. Frequently, illicit samples of AASs do not contain declared ingredients or concentrations of ingredients. Analysis of 70 products confiscated from illegal sources demonstrated 17 (35%) of the 48 steroidal compounds did not contain labeled ingredients as measured by liquid chromatography-tandem mass-spectrometry, gas chromatography mass-spectrometry with nitrogen-phosphorus detection, gel-electrophoresis, and immunological tests. Visual inspection did not distinguish original products from counterfeits [009].

**Explanatory models for adverse effects of anabolic steroids**

The cardiovascular system may be affected via at least four different pathways. Although hypothetical, they provide interesting models to explain AAS-induced adverse effects on this system [012]:

- **The atherogenesis model.** The atherogenesis model is based on the association between AAS and HTGL, an enzyme that regulates serum lipids and lipoproteins. AAS administration enhances HTGL activity that decreases regression of atherosclerotic plaques by suppression of serum HDL-cholesterol and elevation of LDL-cholesterol.

- **The thrombosis model.** The thrombosis model is characterised by influence on the haemostatic system, with the strongest effects of AAS on platelet aggregation that results in enhanced blood-clot formation, including an increased cardiovascular risk.

- **The coronary artery vasospasm model.** Since no evidence of atherosclerosis or thrombosis of the coronary arteries was involved in several reports of sudden cardiac death, nitric oxide has been suggested to play a role in the third model, the coronary artery vasospasm model. Nitric oxide acts as an endothelial-derived relaxing factor in smooth muscles of arteries. AAS may inhibit nitric oxide properties and may induce vasospasm, although the authors suggested that other models may be involved in conjunction with the vasospasm theory. The latter is supported by recent findings in animal studies. It was demonstrated that AAS may impair capillary supply of the heart as a result of an increase in myocardial muscle mass and a relative decrease in capillary density, which may provoke compression of coronary vessels that could trigger myocardial infarction.

- **The direct injury model.** The fourth hypothesis is the direct injury model. AAS is hypothesised to induce direct myocardial cell injury, leading to myocardial cell death and replacement of dead cells by scar tissue within the myocardium. Development of fibrotic areas predisposes to arrhythmias, which exposes the individual to an increased risk of fatal events. Postmortem pathological findings in previous AAS users included focal, regional, interstitial and disseminated fibrosis of the myocardium, although the impact of myocardial fibrosis is still unclear.

- **Other models.** Several other hypotheses have been postulated, especially those affecting red blood cells and volume. It has been suggested that cardiac arrest may be mediated catecholamine myotoxicity associated with ventricular fibrillation due to myocardial necrosis and degenerative changes within the intramyocardic sympathetic neurons. All mechanisms proposed for explaining cardiovascular disease due to AAS use have interesting points; however, future research is needed to clarify the relevance of each theory.
MORTALITY RATE AFTER USE OF ANABOLIC STEROIDS

An increased mortality rate

The side effects of AS are dependent on dose and their metabolism. Misuse of AS is claimed to have serious side effects. The mortality in 62 male weightlifters placed 1st-5th in weight series 82.5-125 Kg in Finland was compared with the mortality of population controls. The mortality during the 12-year follow-up was 12.9 percent for the weightlifters compared to 3.1 percent in the control population; thus, the risk of death among the weightlifters was 4.6 times higher [009].

Swedish data

One study aimed to investigate whether previous AAS-use affects mental health, present sociodemographic data, sport activity and substance abuse in a retrospective 30-year follow-up study of former elite athletes. During 2004, a questionnaire including structured questions concerning sociodemographic variables, previous and past sport activity, lifetime prevalence of seeking professional help for mental-health problems and previous and past substance use was sent to 996 Swedish male-elite power sport athletes on the top 10 national ranking lists during any of the years 1960-1979 in wrestling, Olympic lifting, powerlifting and the throwing events in track and field answered a questionnaire. At least 20 percent of the former athletes admitted previous AAS-use. A reminder to fill in the questionnaire was sent to those athletes who had not answered, and finally 683 (69 %) subjects had answered the questionnaire including the specific questions in the questionnaire concerning whether they had ever used AAS, and if so, when in relation to their sport career. Regarding their past sport activity, the former AAS-users were significantly older when they started training in the sport discipline within which they reached their highest ranking and they spent more hours per week training during their sport active years compared with non-AAS-users. There was no difference in mean age between the groups when they discontinued elite power sports. Compared with non-AAS-users, former AAS-users had significantly more often sought professional help for depression (13 % vs 5 %), anxiety (13% vs 6 %), melancholy (13 % vs 4 %), concentration deficit (4 % vs 1 %) and worry for mental health (8 % vs 3 %). The two groups did not differ regarding frequency of present alcohol consumption. Concerning tobacco use, the former AAS-users were less often present tobacco users compared with the non-AAS-users. Regarding previous tobacco use, the two groups did not differ. The former AAS-users showed higher lifetime prevalence of illicit drug use compared with the non-AAS-users but AAS-users had more often been offered AAS compared with the non-AAS-users (87 % vs 20). All the former AAS-users (n=143) reported having used AAS during their active sports career. The percentage of AAS-users in specific sport disciplines were: powerlifting (57 %), Olympic lifting (47 %), track and field (28 %) and wrestling (6 %). Forty-two percent (n=60) had administrated AAS by tablets, 3 percent (n=5), by injections and 55 percent (n=78) by both tablets and injections. The main reasons for using AAS were: to achieve better sport results (81 %), to train harder (56 %), a suspicion that their competitors used AAS (45 %) and faster recovery (43 %). There were no significant differences between former high and low AAS-users concerning sociodemographic variables and present and past sport activity. Furthermore, there were no differences in past and present substance use (tobacco, alcohol and illicit drugs). However, the former high AAS-users significantly more often combined AAS with the use of illicit drugs and with the use of alcohol compared with the former low AAS-users. The AAS-users also differed in former sport activity pattern compared to non AAS-users. It was concluded that a relationship exists between use of AAS and mental-health problems. Thus, the results from this study of former male-elite athletes in sport disciplines, where increased muscle strength has a marked influence on performance, showed that at least 20% admitted AAS-use during their active sport career. The study indicates that the former AAS-users had a higher frequency of lifetime prevalence of seeking
professional expertise for several mental problems. Furthermore, former AAS-users more often had used illicit drugs. Former AAS-users were significantly older when they started training in their sport discipline in which they had been most successful and they also spent more hours per week training. Furthermore, if the former AAS-using athletes used AAS for a longer time than 2 years, they had more often sought professional expertise for anxiety, irritation and anger and they had also more often a combined use of alcohol and illicit drugs together with AAS. These high-consumers of AAS reported having experienced more side effects of AAS, compared with those athletes having used AAS no longer than 2 years. A former use of AAS does not seem to have a negative long-term effect on either present substance abuse and present sport activity or on whether they presently lived in a relationship or not. The present results can be compared with previous results regarding lifetime prevalence of AAS-use among elite athletes active in the 60s and 70s. For example, in 1972, it was estimated that one-third of the Swedish-elite track and field athletes used AAS. The present study is, however, based on a larger number of athletes and in four power sports. In the same year's Olympic Games, 68 percent of the participants in the track and field events reported prior steroid abuse. The former elite athletes admitting AAS-use were significantly younger compared with the non-users. This age difference might explain why the former AAS-users are, to a higher degree, in their present employment. However, this difference disappeared when the old-age pensioners, that is, above 65 years of age, were excluded from the analysis [014].

Changes in the electrocardiogram QT interval are associated with high doses of AAS use and an increasing predisposition to arrhythmias and acute myocardial infarction. Increased vascular tone, blood pressure, platelet aggregation, and producing atherothrombotic phenomena are other causes attributed to AAS use. The use of AAS has been associated with sudden death among young bodybuilders with no history of cardiovascular diseases. In an interesting study, the mortality of 62 male power lifters between 1977 and 1982 was compared with the mortality of a control population. The data showed 13 percent mortality among power lifters and only 3 percent in the control population. In this same study, the authors report 62 deaths in power lifters and 34 controls in a population of 1,094 people. The misuse of AAS resulted in greater mortality 4.6. The causes of death were mainly acute myocardial infarction but also included suicide, liver disease, and lymphoma. In autopsies performed with 34 Swedish AAS users, chronic cardiac abnormalities such as cardiac hypertrophy, fibrosis, and atheromatous changes were found, although AAS were believed to contribute to the death of only two users. In another study, based on necropsies of AAS users, it was found that cardiac hypertrophy exceeded the physiological adaptations that reasonably explained the sudden death. Several cardiac structural alterations, such as left ventricular hypertrophy, ischemia, and autonomic dysfunction have been found in individuals using AAS who died suddenly [015].

Non-therapeutic use of anabolic androgenic steroids (AAS) has been associated with various adverse effects; one of the most serious being direct cardiovascular effects with unknown long-term consequences. Therefore, large studies of the association between AAS and cardiovascular outcomes are warranted. It was investigated cardiovascular morbidity and mortality in individuals who tested positive for AAS. Between 2002 and 2009, a total of 2013 men were enrolled in a cohort on the date of their first AAS test. Mortality and morbidity after cohort entry was retrieved from national registries. Of the 2013 individuals, 409 (20 %) tested positive for AAS. These men had twice the cardiovascular morbidity and mortality rate as those with negative tests (adjusted hazard ratio (aHR) 2.0; 95 % confidence interval (CI) 1.2 to 3.3). Compared to the Swedish population, all tested men had an increased risk of premature death from all causes (standardized mortality ratio for AAS-positive: 19.3, 95 % CI 12.4 to 30.0; for AAS-negative: 8.3, 95 % CI 6.1 to 11.0). Thus, non-therapeutic exposure to AAS appears to be an independent risk factor for cardiovascular morbidity and premature death [016].
**Increased mortality in former users of anabolic steroids**

The aim of the present study was to investigate mortality, including causes of death, in former Swedish male elite athletes, active 1960-1979, in wrestling, powerlifting, Olympic lifting, and the throwing events in track and field when the suspicion of former AAS use was high. Results indicate that, during the age period of 20-50 years, there was an excess mortality of around 45 percent. However, when analyzing the total study period, the mortality was not increased. Mortality from suicide was increased 2-4 times among the former athletes during the period of 30-50 years of age compared with the general population of men. Mortality rate from malignancy was lower among the athletes. As the use of AAS was marked between 1960 and 1979 and was not doping-listed until 1975, it seems probable that the effect of AAS use might play a part in the observed increased mortality and suicide rate. The otherwise healthy lifestyle among the athletes might explain the low malignancy rates [017].

**Finnish data**

One article focused on anabolic steroid adverse effects on the cardiovascular system and mental health issues as well as the possible increase in the incidence of neoplasms in anabolic steroid users. On the basis of findings in the literature, the authors consider these three issues as the most significant concerning morbidity and mortality among anabolic steroid users. A Finnish study has shown an increased incidence of premature mortality among power lifters. The study, concerning a 12-year follow-up study of 62 male-elite Finnish powerlifters, where there was a high suspicion of AAS-use, reported a 4.6 times higher death rate compared with the general population. The main causes of death were myocardial infarctions and suicides [018].

**A national population-based cohort study**

Non-therapeutic use of anabolic androgenic steroids (AAS) has been associated with various adverse effects; one of the most serious being direct cardiovascular effects with unknown long-term consequences. Therefore, large studies of the association between AAS and cardiovascular outcomes are warranted. It was investigated cardiovascular morbidity and mortality in individuals who tested positive for AAS. Between 2002 and 2009, a total of 2013 men were enrolled in a cohort on the date of their first AAS test. Mortality and morbidity after cohort entry was retrieved from national registries. Of the 2013 individuals, 409 (20 %) tested positive for AAS. These men had twice the cardiovascular morbidity and mortality rate as those with negative tests (adjusted hazard ratio (aHR) 2.0; 95 % confidence interval (CI) 1.2 to3.3). Compared to the Swedish population, all tested men had an increased risk of premature death from all causes (standardized mortality ratio for AAS-positive: 19.3, 95 % CI 12.4 to 30.0; for AAS-negative: 8.3, 95 % CI 6.1 to 11.0). It was concluded that non-therapeutic exposure to AAS appears to be an independent risk factor for cardiovascular morbidity and premature death [016].

The health risks associated with long-term therapeutic doses of testosterone and chronic supraphysiologic doses of AAS are unknown. With chronic AAS use, doses tend to increase and cycles become longer and more frequent, until some athletes take the drugs almost continuously. The most severe consequences of long-term AAS use may be on the cardiovascular system. Pathological AAS-induced left ventricular hypertrophy, impaired diastolic filling, and arrhythmia may lead to an increased risk of myocardial infarction and sudden death. The risk of mortality among chronic AAS users is reported to be 4.6 times higher than non-AAS users. Although AASs have been proposed as etiologic factors for some cancers, case reports linking these drugs with hepatic tumors, renal carcinoma, and
testicular tumors are rare. There are no reports linking AAS with prostate cancer, and androgen treatment in older men does not induce significant increases in prostate-specific antigen [018].

Tour de France (1947-2012)

In the context of recent concerns regarding performance enhancing techniques and potential negative health effects of high-level physical activity, data on the long-term outcomes and causes of death in elite endurance cyclists are of particular interest. Characteristics and vital status of all French participants in the Tour de France were collected for the 1947-2012 period. Causes of death were obtained from 1968. Overall and disease-specific mortalities were compared with the French male population using overall and specific standardized mortality ratios (SMRs) with their 95 percent confidence intervals (CIs). Among the 786 French cyclists who participated at least once between 1947 and 2012, 208 (26 %) died by 1 September 2012. Neoplasms and cardiovascular diseases accounted for 61 percent of deaths. It was observed a 41 percent lower mortality in French cyclists (SMR: 0.59, 95 % confidence interval 0.51 to 0.68), which did not change over time. It was observed for main mortality causes: for neoplasms (SMR: 0.56; 95 % confidence interval 0.42 to 0.72) and for cardiovascular death (SMR: 0.67; 95 % confidence interval 0.50 to 0.88), except mortality related to external causes (SMR: 1.06, 95 % confidence interval 0.71 to 1.53). It was observed a substantially and significantly lower mortality in participants in the Tour de France, compared with the general male population. However, the results do not allow us to assess in detail the balance between positive effects of high-level sports activity and selection of healthy elite athletes, versus any potential deleterious effects of excessive physical exercise or alleged doping [019].
ANABOLIC STEROIDS’ IMPACT ON THE CARDIOVASCULAR SYSTEM

Overview

The most common cardiovascular consequences of AAS include atherosclerosis (secondary to changes in cholesterol metabolism and platelet function), hypertension, cardiac hypertrophy, impaired cardiac function, and sudden death. AAS use causes metabolic derangements that increase the risk for atherosclerosis and thrombus formation. Studies using animal models and various steroid regimens have demonstrated changes in serum cholesterol levels with decreased high-density lipoprotein and increased low-density lipoprotein, both promoting atherosclerotic and peripheral vascular disease. Cholesterol alterations vary among different AASs; alkylated agents (e.g. stanozolol) cause greater changes than testosterone [020].

In another study it was concluded that potential adverse effects of AAS on the cardiovascular system include atherogenesis, thrombosis, vasospasm, myocarditis, concentric left ventricular hypertrophy, myocardial fibrosis, hypertrophic cardiomyopathy with ventricular dysrhythmias, and direct myocardial injury. However, the contribution of AAS use to these potential adverse cardiovascular effects remains unclear. Chronic AAS use enhances hepatic triglyceride lipase activity, resulting in reduction of high-density lipoproteins and elevation of low-density lipoproteins. Although these changes are reversible within several months of cessation of AAS use, chronic AAS use theoretically increases the risk of cardiac disease. Potentially, the chronic abuse of AAS enhances coagulability and thrombosis, but the clinical importance of this potential adverse effect also remains unclear. Studies of chronic AAS abuse in weight lifters suggest that some anabolic-androgenic steroid using weight lifters have accelerated activation of their hemostatic system as evidenced by increased generation of both thrombin and plasmin. A study of AAS-positive steroid using weight lifters indicated that these individuals had a higher percentage of abnormally high plasma thrombin-antithrombin complexes along with elevated plasma concentrations of prothrombin fragment 1, antithrombin II, and protein S, when compared with non-AAS using controls. Additionally, the plasma concentrations of tissue plasminogen activator and its inhibit or were lower in AAS users than in controls. Clinical studies on body builders suggest that chronic AAS use impairs vascular reactivity independent of the smooth muscle hypertrophy and vascular stiffness associated with bodybuilding. Anabolic-androgenic steroids decrease the production of cyclic guanosine monophosphate (cGMP) by inhibiting guanylyltransferase. As a result, AAS potently inhibit the ability of nitric oxide store lax smooth muscles in the coronary arteries resulting in coronary artery vasospasm and potentially sensitizing AAS users to sudden death. Case reports associate the chronic use of anabolic steroids with sudden death and contraction band necrosis in the myocardium. In these cases, no other cause of death was apparent, but the role of chronic, high-dose anabolic steroid use in these deaths remains unclear. Athletes with certain genetic mutations and structural abnormalities may be particularly vulnerable to the use of anabolic steroids including athletes with accessory AV pathways, latent structural heart diseases (dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia type II, myocarditis, segmental arrhythmogenic ventricular cardiomyopathy, and coronary artery anomalies), latent Brugada syndrome, mutations of the long QT syndrome genes, and other genetic mutations of ion channels (cardia cryanodine receptor gene defects and calsequestrin gene defects). Pathologic evidence of some of these abnormalities may not appear on postmortem examination. The use of diuretics to mask the use of anabolic steroids may predispose these athletes to serious ventricular dysrhythmias from hypokalemia and dehydration [009].

For decades, individual case reports or small case series have described a variety of cardiovascular effects, including cardiomyopathy, myocardial infarction, cerebrovascular accidents, conduction abnormalities, and coagulation abnormalities, in known or suspected
AAS users. More recently, larger controlled studies, using a variety of methodologies, have supported these findings. In a recent postmortem pathologic study, comparing 87 deceased men testing positive for AAS with 173 control men, AAS users exhibited significantly greater cardiac mass even after adjusting for body mass, age, and history of trauma. Another pathologic study found ventricular hypertrophy, associated with fibrosis and myocytolysis, after cardiac death in 4 AAS users. Recent conduction studies have demonstrated decreased cardiac electrical stability, abnormal tonic cardiac autonomic regulation, and ventricular repolarization abnormalities in AAS users; the last finding has also been demonstrated in rats that received AAS. Perhaps most importantly, numerous recent controlled studies (using echocardiography or cardiac magnetic resonance imaging) to compare AAS users with non-AAS-using athletes and/or nonathletes) have demonstrated cardiomyopathy in AAS users, characterized by decreased ventricular ejection fractions and reduced diastolic tissue velocities. One study also found decreased aortic elasticity in AAS users. These changes may be profound but may be at least partially reversible after AAS abstinence. However, loss of tissue elasticity appears likely due at least in part to increased fibrotic content resulting from direct AAS-induced cellular injury and hence may be irreversible [021].

Cardiologic adverse effects also of other doping substances

Cardiovascular effects of doping drugs are numerous, with different mechanisms: vasoconstriction of amphetamines, erythropoietin and cocaine; sodium water retention of anabolic steroids and corticosteroids; elevation in blood viscosity of erythropoietin, perfluorocarbon emulsion, recombinant hemoglobin and anabolic steroids; sympathetic nervous system activation of amphetamines, beta-agonists and clenbuterol; lipids profile disorder of anabolic steroids. Physical activity consequences, particularly bradycardia and dehydration, are worsening. Thrombosis and arrhythmogenic effects, with possibility of sudden death, are the severe immediate events. Hypertension and coronary diseases are medium-term effects; acute myocardial infarction is frequent. Heart failure can be secondary to cardiac muscle direct fibrosis, like with anabolic steroids. These cardiovascular effects are serious and it is necessary to early detect the doping drugs use in sportsmen; all prescribing physician should be aware of existing drugs and their clinical events [022].

Ephedrine is a potent sympathomimetic agent that can lead to cardiomyopathy similar to that seen with catecholamine excess. Adverse cardiovascular events attributed to anabolic steroid and ephedra use, such as arrhythmias, myocardial infarction, cardiomyopathy, and sudden death, are rarely reported. Bodybuilders have used gamma-hydroxybutyrate, a potent secretagogue of growth hormone, to promote muscle development. Although dilated cardiomyopathy is a known complication of excess growth hormone levels, it has not been associated with use of gamma-hydroxybutyrate. A healthy 40-year-old man was admitted to our hospital for new-onset congestive heart failure and severe acute hepatitis that developed several months after he began using anabolic-androgenic steroids, ephedra, and gamma-hydroxybutyrate supplements. Analysis with an objective causality assessment scale revealed a probable adverse drug reaction between the patient’s use of anabolic steroids, ephedra, and gamma-hydroxybutyrate and the development of his cardiomyopathy and acute liver injury [023].

Serious cardiovascular adverse effects from use of dietary supplements

Athletes commonly use drugs and dietary supplements to improve athletic performance or to assist with weight loss. Some of these substances are obtainable by prescription or by illegal means; others are marketed as supplements, vitamins, or minerals. Nutritional supplements are protected from Food and Drug Administration regulation by the 1994 US Dietary
Supplement Health and Education Act, and manufacturers are not required to demonstrate proof of efficacy or safety. Furthermore, the Food and Drug Administration lacks a regulatory body to evaluate such products for purity. Existing scientific data, which consist of case reports and clinical observations, describe, including sudden death. Although mounting evidence led to the recent ban of ephedra (ma huang), other performance-enhancing substances continue to be used frequently at all levels, from elementary school children to professional athletes. Thus, although the potential for cardiovascular injury is great, few appropriately designed studies have been conducted to assess the benefits and risks of using performance-enhancing substances. It was performed an exhaustive OVID MEDLINE search to identify all existing scientific data, review articles, case reports, and clinical observations that address this subject. In a review, it was examined the current evidence regarding cardiovascular risk for persons using anabolic-androgenic steroids including 2 synthetic substances, tetrahydrogestrinone and androstenedione (andro), stimulants such as ephedra, and nonsteroidal agents such as recombinant human erythropoietin, human growth hormone, creatine, and beta-hydroxy-beta-methylbutyrate [024].

**Cofactors for adverse events**

*Changes in lipid metabolism*

AAS use also increases platelet reactivity without an associated thrombocytosis; this has been proposed as an etiology for some of the myocardial infarctions, strokes, and peripheral vascular disease events reported in otherwise healthy individuals. AAS use also increases serum C-reactive protein (CRP), reflecting an inflammatory state that may contribute to atheroma formation and peripheral vascular disease. Conversely, changes in lipid metabolism may be protective from atheroma formation because of a reduction in lipoprotein A. Many studies show that AASs cause abnormal cholesterol profiles, increased CRP, and increased platelet reactivity. It is difficult to quantify the change in risk, but one study estimates AASs triple the cardiovascular risk [020].

In addition to their direct effects on cardiac tissue, AAS cause dyslipidemia, characterized by decreased high-density lipoprotein cholesterol (HDL-C) and increased low-density lipoprotein cholesterol (LDL-C) – an established risk profile for atherosclerotic disease. This effect is particularly associated with orally administered 17alpha-alkylated AAS. One imaging study of 14 professional weightlifters with long-term AAS exposure found coronary-artery calcium scores much higher than expected for men of comparable age. Atherosclerotic coronary disease may contribute to many of the cases of myocardial or cerebral infarction reported in young men with known or suspected AAS use [021].

*Metabolic syndrome*

Obesity is one of the constellations of factors that make up the definition of the metabolic syndrome. Metabolic syndrome is also associated with insulin resistance, dyslipidemia, hypertriglyceridemia, and type 2 diabetes mellitus. The presence of obesity and metabolic syndrome in men and women is also associated with increased risk of cardiovascular disease and hypertension. In men, obesity and metabolic syndrome are associated with reductions in testosterone levels. In women, obesity and metabolic syndrome are associated with increases in androgen levels. In men, reductions in androgen levels are associated with inflammation, and androgen supplements reduce inflammation. In women, increases in androgens are associated with increases in inflammatory cytokines, and reducing androgens reduces inflammation [025].
Other contributing factors

One review evaluated the documented cardiovascular functioning among anabolic-androgenic steroid (AAS) users. AAS users manifest a reduction in HDL cholesterol, increased inflammatory markers, and oxidative stress. Adverse cardiovascular effects have thus been reported with the use of AAS, such as dyslipidemia, high blood pressure, cardiovascular remodeling, and deaths from heart attacks and cerebral vascular accident. Strong evidence associating AAS use with blood pressure at hypertensive levels, as well as hypertrophy and cardiac dysfunction has also been reported. Both epidemiological and autopsy studies attest the relationship between AAS use and early mortality. There are a reasonable number of studies reporting potential adverse cardiovascular effects, while studies indicating an absence of adverse effects are not reported [026].

Conflicting data

Scientific data on the cardiac and metabolic complications of AAS abuse are divergent and often conflicting. A total of 49 studies describing 1,467 athletes were reviewed to investigate the cardiovascular effects of the abuse of AAS. Although studies were typically small and retrospective, some associated AAS abuse with unfavorable effects. Otherwise healthy young athletes abusing AAS may show elevated levels of low-density lipoprotein and low levels of high-density lipoprotein. Although data are conflicting, AAS have also been linked with elevated systolic and diastolic blood pressure and with left ventricular hypertrophy that may persist after AAS cessation. Finally, in small case studies, AAS abuse has been linked with acute myocardial infarction and fatal ventricular arrhythmias. In conclusion, recognition of these adverse effects may improve the education of athletes and increase vigilance when evaluating young athletes with cardiovascular abnormalities [027].

In athletes who are mainly involved in bodybuilding, echocardiographic studies have derived conflicting results regarding the effects of AAS on left ventricular mass and function. Most studies compared the echocardiographic results between AAS users and nonusers or healthy controls. It has been found significant left ventricular wall thickening in elite power athletes using AAS compared to non-AAS users. Indeed, in one case the wall thickness was 16 mm. However, none of them demonstrated diastolic dysfunction. In contrast, a number of studies found no significant difference in left ventricular hypertrophy between AAS users and non-users. In most cases, the hypertrophy observed was concentric, as would be expected after long-term static exercise training, while only a few showed eccentric hypertrophy due to dilatation of the cardiac cavities. It is noteworthy that studies until early 2000 found no particular evidence for systolic and diastolic dysfunction in athletes using AAS. However, with the use of the latest echocardiographic techniques, such as tissue Doppler, some researchers detected left ventricular diastolic dysfunction in athletes who are AAS users. In a study of ours, the use of pulsed tissue Doppler was helpful in the early detection of diastolic dysfunction caused by AAS abuse, which was not detectable using the classical estimation of transmitral flow. Moreover, the diastolic dysfunction was found to be correlated with the dosage and the duration of use. Apart from left ventricular diastolic dysfunction, it was found using Doppler myocardial imaging and strain rate imaging, also recorded early findings of deteriorated systolic function in drug users. It is likely that studies using the latest non-invasive diagnostic techniques will confirm the possibility that AAS lead to cardiomyopathy in athletes, mainly due to a direct toxic effect on the myocardium. There are reports of athletes with dilated cardiomyopathy and heart failure after AAS abuse [028].

In recent years the abuse of AAS has been associated with the occurrence of serious cardiovascular events in healthy young athletes, including the development of cardiomyopathy, atrial fibrillation, QT dispersion, cerebrovascular accident, myocardial
infarction, disturbances of the haemostatic system, ventricular thrombosis and systemic embolism, and acute heart failure. Moreover, several reports associated AAS abuse with cardiac sudden death. Although these reports must be interpreted with caution, they teach us to look thoroughly at the different mechanisms in which AAS abuse may affect the cardiovascular system. However, again, it should be remembered that in case reports the most dramatic side effects are often described and that they do not prove a causal relationship between AAS abuse and the disease condition or cardiac death [012].
TESTOSTERONE SUPPLEMENTATION IN (OLDER) HYPOGONADAL MEN

Recent evidence suggests that low, rather than high, testosterone (T) is associated with increased male morbidity and mortality. It was reviewed relationships between hypogonadism, metabolic syndrome (MetS) and cardiovascular (CV) disease (CVD), along with erectile dysfunction (ED), a common condition in the three diseases. Although several experimental data indicate that T exerts a protective effect on vascular function, epidemiological studies do not support a link between hypogonadism and CVD and three meta-analyses found no significant effect of testosterone replacement therapy (TRT) on CV events. Low T is associated with increased risk of CV death in community-dwelling men, and in men with ED. It is possible that both low T and CVD are associated with another, still unknown (or not assessed) factor, thus explaining the association, in the absence of any causal relationship. A meta-analysis on the effect of TRT in MetS-associated hypogonadism demonstrated positive effects of T on some of the components of MetS. Large-scale interventional studies with TRT are therefore advisable [029].

Cardiovascular risk in older men on testosterone

Ageing is accompanied by a reduction in circulating testosterone and progressive accumulation of medical morbidities. There is an intense debate whether low testosterone contributes to ill-health as opposed to being a biomarker for its presence. Prescriptions for testosterone are rising on a background of concern over potential adverse effects. One review examines evidence relating androgens to cardiovascular risk in older men. Observational studies show lower risk of cardiovascular events in older men with higher testosterone, and lower mortality from ischaemic heart disease in men with higher concentrations of its more potent androgenic metabolite dihydrotestosterone. However, randomized controlled trials of testosterone supplementation have been underpowered for the outcome of cardiovascular events. Recent meta-analyses have reached contrasting conclusions regarding cardiovascular adverse events associated with testosterone therapy. Retrospective studies of prescription databases have produced controversial and conflicting results. Thus, additional randomized controlled trials are required to clarify the role of testosterone supplementation in older men in the absence of pituitary or gonadal disease. Pending such studies, testosterone therapy should be considered in androgen-deficient men, with evaluation of potential benefits and risks [030].

Testosterone deficiency

Testosterone deficiency is highly prevalent in men with cardiovascular disease (CVD) and is associated with an increased mortality. Low testosterone also has an adverse effect on several cardiovascular risk factors, which include insulin resistance, diabetes, dyslipidaemia, central adiposity and endothelial dysfunction. Male gender is a well-recognised risk factor for premature CVD and mortality. The question of whether or not testosterone deficiency is a contributory factor to atherogenesis or merely a biomarker of ill health arises. Animal studies and experiments on isolated cells indicate that many of the mechanisms intimate to the atherosclerotic process are beneficially modulated by testosterone. Epidemiological studies have shown that men with endogenous testosterone levels in the mid-upper normal range have reduced cardiovascular events and mortality compared to those with low or lower range, and with high range testosterone. Testosterone replacement in men diagnosed with hypogonadism where mid-normal range levels are achieved have shown a beneficial effect on several cardiovascular risk factors, cardiac ischaemia, functional exercise capacity and improved mortality. Yet studies where patients were either undertreated or given high-dose testosterone have been associated with an increased risk of cardiovascular-related events.
Clinical monitoring and titration of testosterone dose is therefore of paramount importance [031].

Interestingly, if androgen levels are too low, cardiac risk may increase. Androgen-deprivation therapy (ADT) is a widely used treatment for prostate cancer, and several studies have reported an association between ADT and an increased risk of myocardial infarction and cardiovascular mortality. Antiandrogens (e.g. flutamide, bicalutamide) block the binding of androgen to its receptor, and they are often coupled with gonadotropin-releasing hormone (GnRH) agonists (e.g. leuprolide, goserelin, triptorelin). In one population-based Medicare study, the use of a GnRH agonist in men with prostate cancer for at least 1 to 4 months was associated with an increased risk of incident coronary heart disease (adjusted hazard ratio, HR, 1.16), myocardial infarction (adjusted HR), and sudden cardiac death or life-threatening ventricular arrhythmia (adjusted HR 1.16). Another population based study noted that the use of ADT was associated with a 20 percent higher risk of cardiovascular morbidity (HR 1.20) during 5 years of follow-up. In addition, androgen deficiency has been associated with cardiovascular risk factors by causing increased serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. There is also an association between low androgen levels and an adverse metabolic profile (insulin resistance, metabolic syndrome, and diabetes) [032].

**Independence of the level of heart dysfunction**

In addition to vasodilation, testosterone effects such as increased skeletal muscle strength and peak oxygen consumption, increased baroreflex sensitivity and higher hemoglobin levels all help to improve quality of life and functional capacity of patients with heart failure. A direct influence of testosterone on muscle strength may be explained by a stimulation of change of skeletal muscle composition toward type I muscle fibers which are, compared to type II fibers, associated with enhanced physical capability and strength. Vice versa, exercise induces an increase in endogenous testosterone levels, which in heart failure patients seems to be particularly associated with interval training exercise. Altogether, available research suggests that the beneficial effects of either endogenous testosterone levels or its supplementation on exercise capacity and quality of life are completely independent of the level of heart dysfunction and its impact on the clinical severity of heart failure [007].

**Testosterone supplementation**

Recent reports have significantly halted the enthusiasm regarding androgen-boosting; suggesting that testosterone supplementation (TS) increases cardiovascular (CV) events. In order to overcome some of the limitations of the current evidence, it was performed an updated systematic review and meta-analysis of all placebo-controlled randomized clinical trials (RCTs) on the effect of TS on CV-related problems. Out of 2747 retrieved articles, 75 were analyzed, including 3016 and 2448 patients in TS and placebo groups, respectively, and a mean duration of 34 weeks. The analyses, performed on the largest number of studies collected so far, indicate that TS is not related to any increase in CV risk, even when composite or single adverse events were considered. In RCTs performed in subjects with metabolic derangements a protective effect of TS on CV risk was observed. The present systematic review and meta-analysis does not support a causal role between TS and adverse CV events. The results are in agreement with a large body of literature from the last 20 years supporting TS of hypogonadal men as a valuable strategy in improving a patient's metabolic profile, reducing body fat and increasing lean muscle mass, which would ultimately reduce the risk of heart disease [033].
Experimental

The increasing prevalence of obesity adds another dimension to the pathophysiology of testosterone (TEST) deficiency (TD) and potentially impairs the therapeutic efficacy of classical TEST replacement therapy. It was investigated the therapeutic effects of selective androgen receptor modulation with trenbolone (TREN) in a model of TD with the metabolic syndrome (MetS). Male Wistar rats (n=50) were fed either a control standard rat chow (CTRL) or a high-fat/high-sucrose (HF/HS) diet. After 8 weeks of feeding, rats underwent sham surgery or an orchiectomy (ORX). Alzet miniosmotic pumps containing either vehicle, 2-mg/kg·d TEST or 2-mg/kg·d TREN were implanted in HF/HS+ORX rats. Body composition, fat distribution, lipid profile, and insulin sensitivity were assessed. Infarct size was quantified to assess myocardial damage after in vivo ischaemia reperfusion, before cardiac and prostate histology was performed. The HF/HS+ORX animals had increased sc and visceral adiposity; circulating triglycerides, cholesterol, and insulin; and myocardial damage, with low circulating TEST compared with CTRLs. Both TEST and TREN protected HF/HS+ORX animals against sc fat accumulation, hypercholesterolaemia, and myocardial damage. However, only TREN protected against visceral fat accumulation, hypertriglyceridaemia, and hyperinsulinaemia and reduced myocardial damage relative to CTRLs. TEST caused widespread cardiac fibrosis and prostate hyperplasia, which were less pronounced with TREN. We propose that TEST replacement therapy may have contraindications for males with TD and obesity-related MetS. TREN treatment may be more effective in restoring androgen status and reducing cardiovascular risk in males with TD and MetS [034].
SPECIFIED CARDIAC PATHOLOGY AFTER USE OF ANABOLIC STEROIDS

Myocardial hypertrophy

*Increased left-ventricular mass*

Increased left-ventricular mass is an important cardiovascular risk factor for morbidity and mortality. Apart from obvious differences in cardiac size, the changes in left-ventricular mass in response to age and hypertrophic stimuli are very different in men and women. Whereas left-ventricular mass increases with age in apparently healthy women, it remains constant in men. Under increased cardiac loading conditions, such as hypertension or aortic stenosis, this disparity between sexes is even more striking. Findings are especially pronounced in people aged 50 years or older, in whom reproductive hormone concentrations have fallen. Whether the differences in left-ventricular mass changes are related to endogenous sex-hormone concentrations has never been shown. Androgens have anabolic effects on cardiac cells, and estrogens have anti-proliferative properties [035].

The use of anabolic androgenic steroids (AASs) has been associated with hypertrophy of the left cardiac ventricle (LVH) as diagnosed by echocardiography. Case reports suggest that AAS-related LVH may lead to sudden death. It was performed an investigation of the gross cardiac pathological findings in deceased male AAS users in order to further elucidate the proposed role of AAS in cardiac hypertrophy. Eighty-seven deceased males who tested positive for AAS at autopsy and 173 age-adjusted control deceased males without suspected AAS use were studied for cardiac hypertrophy. The AAS-positive subjects had been examined at any of the six departments of forensic medicine in Sweden during the period from 1989 to 2009. Data were assessed employing multivariate analyses controlling for body weight, height, age, bleeding after trauma, and the impact of weight training. The analysis of the logarithm of heart mass by multivariate statistics implied that strong correlations existed between body mass and heart mass, height and heart mass, age and heart mass, and trauma (bleeding) and heart mass. After controlling for these factors, a significantly higher heart mass was found among the AAS-positive males. The findings suggest that use of AAS may lead to cardiac hypertrophy with a direct cardiotropic effect [036].

Out of the numerous and partly serious side effects of anabolic steroids, thus the cardiovascular ones maybe most important. An increase in left ventricular muscle mass is well documented, and some researchers have even reported concentric hypertrophy. By contrast, resistance training without AAS intake does not lead to increased ventricular wall thickness. AAS do not affect the systolic function of the left ventricle, whereas diastolic function might be impaired. Different ultrastructural myocardial alterations have been documented in animal studies. In addition, AAS can induce arterial hypertension. Blood clotting and fibrinolysis are negatively affected, and several case studies of thrombi exist in young strength athletes. Changes in the concentration of blood lipoproteins, particularly a reduction in vessel-protective HDL cholesterol, can lead to early atherosclerosis. Many case reports exist about cardiac deaths in seemingly healthy subjects-most often body builders and other strength athletes. In fatal and nonfatal myocardial infarctions patent coronary arteries were proven frequently. Besides the prothrombotic effects of AAS, an impaired endothelial function and vasospasms are discussed hypothetically as pathomechanisms. Also, cardiomyopathies can occur due to AAS abuse. On the basis of the described possible cardiovascular side effects, it can be concluded that in cases of sudden cardiac deaths in young athletes, a misuse of AS should be excluded [037].

Given these putative effects of steroid hormones (and AAS in particular) on LV growth, it might be expected exposure to exogenously administered steroid hormones to be associated with an exaggerated LV hypertrophic response to any other hypertrophic stimulus. Exercise
is just such a potent cardiac hypertrophic stimulus. Meanwhile, athletes are increasingly exposing themselves to supra-physiological doses of AAS. These are known to increase skeletal muscle mass and strength – effects which form the basis for their administration to enhance athletic performance. A variety of AAS are often taken simultaneously (so called “stacking”), and in doses which result in 10-100 fold increases in androgen concentrations. Administration regimens usually involve a 6-12 week cycle and are often administered in a “pyramidal” fashion, with doses tapering from low to high to low. Abused substances include testosterone, its 17-beta esters, and those based on modified steroid rings (including 17-alpha derivatives). The largest group to make such use of AAS are the very group whose LVH response to exercise is likely to be the greatest – the strength or resistance training (RT) athletes. One study from 1995 suggested that two thirds of elite US powerlifters have self-reported use of AAS to enhance performance; even “dope testing” may be underestimating the true extent of such use. What evidence is there that AAS administration enhances the LV hypertrophic response to resistance exercise? Male bodybuilders and powerlifters currently using AAS or ex-users who had abstained from AAS exposure for over 12 months (U and ExU, n=17 and 15, respectively) were compared to 15 weightlifters who denied current or past use of AAS (WL). Left ventricular wall thickness and cavity dimensions were assessed using echocardiography, and muscle mass (LVMM) calculated using the Devereux equation. Absolute LVMM measures were significantly greater for U than ExU or WL, with differences between ExU and WL only reaching significance after adjustment for body surface area or fat-free mass. These results suggest that AAS use increases the LV hypertrophic response to exercise, an effect which might last for well over a year [038].

Such data must nonetheless be treated with caution. It is known, for example, that the magnitude and pattern of hypertrophy is dependent on the nature, duration, and intensity of exercise undertaken. Thus, strength trained athletes (such as weightlifters, powerlifters, bodybuilders, and throwers) develop a greater increase in wall thickness, a more concentric pattern of LV growth, and a lesser increase in LV chamber internal dimensions in comparison to those undergoing predominantly aerobic/endurance exercise. In the study under discussion, training patterns will have varied. One might suspect that subjects taking AAS were also the most motivated to train (whether by initial predisposition, or psychological impact of the steroid use itself). However, this does not seem to be the case as the authors report that the magnitude of training did not differ between U, ExU, and WL groups. Even so, more subtle differences in training pattern may have existed between bodybuilders, powerlifters, and weightlifters. Although all groups lift exceptionally heavy weights, the total load and training pattern are likely to differ. Other factors may also have been of influence. Diet (including the use of supplements) may have differed between groups, as might the use of other agents. Abusers of AAS frequently also self administer other drugs including stimulants, antioestrogens, human chorionic gonadotrophin (hCG), and human growth hormone (hGH). It is unclear to what extent these and other drugs might have driven LV growth, and whether the ExU group were still taking any of these. Neither can mechanistic inferences be drawn from the data: the putative effects of AAS on LV growth may have been mediated directly, or through secondary phenotypes such as alterations in circulating volume or blood pressure. Certainly, resting systolic blood pressure is higher in the U v ExU group, a difference which persists as a trend for exercising blood pressure. The use of such drugs (as well as differences in patterns of training) may also have influenced fat-free mass and body surface area. The adjustment for such anthropometric measures may have contributed to the significance of the comparison between ExU and WL [038].

If AAS use is associated with an exaggerated LV hypertrophic response to training, what are the likely health implications? They may be profound. In terms of non-cardiac morbidity, AAS use is associated with hypogonadism, testicular atrophy, impaired spermatogenesis, baldness, acne, gynaecomastia, and psychiatric disturbance. Such drugs also have toxic effects on metabolic profile and hepatic structure and function, as well as potentially promoting neoplastic growth. Indeed, Parsinnen reported the 12 year mortality to be 13 per
1000 among 62 male powerlifters suspected of AAS use, compared to 3.1 percent in a control population. LVH is thus an independent risk factor for cardiovascular mortality and (through whatever mechanism) one might anticipate an excess cardiovascular mortality among AAS users in whom LVH occurs. In addition, the recognised association of AAS use with hypertension and dyslipidaemia (raised low density lipoprotein and reduced high density lipoprotein cholesterol, and raised triglycerides), as well as influences on coagulation and platelet aggregation, might increase such risk. While it is debatable whether ASS use is indeed associated with an increased risk of premature cardiovascular death, 38 percent of the deaths in Parssinen's powerlifting group were attributed to "myocardial infarction", while several case reports have attributed myocardial infarction in athletes to ASS abuse. In some cases, infarction has occurred without evident coronary thrombosis or atherosclerosis, leading to the hypothesis that ASS may induce coronary vasospasm in susceptible individuals. Similarly there are several case reports of increased thromboembolic risk [038].

Power athletes abuse anabolic androgenic steroids (AASs) and growth hormone (GH) to gain their muscular mass and strength. We wanted to determine how massive, self-administered doses of AASs with or without GH affect the left ventricular (LV) dimensions in power athletes. These substances are assumed to increase LVmass mainly by thickening the ventricular walls. Anecdotal evidence suggests a higher risk of cardiovascular events in AAS abusers. We were interested to see if LV dimensions and function in AAS abusers would indicate this increased risk. Twenty healthy male power athletes using massive doses of AAS without (n=16) or with (n=4) GH volunteered for the study. The controls were 15 sedentary male non-users of hormones. LV mass, geometry and filling were studied using standard echocardiographic methods. It was found a significant association between LVmass and AAS dose. In contrast to the controls, LV mass (274 g in the athletes, 167 g in the controls) among the AAS abusers did not correlate with body weight or height. Concomitant use of AAS and GH further increased LV mass and associated with concentric remodelling of LV. Multiple regression analysis indicated that the mean AAS dose accounted for 29 percent, age for 14 percent and systolic blood pressure for 17 percent of the variance in LV mass. It was concluded that AAS abuse associates dose-dependently with myocardial hypertrophy and that concomitant use of GH associates with concentric remodelling of the LV. The findings suggest that AASs and GH have a direct effect on the myocardium [039].

Experimental
The harmful cardiovascular effects of indiscriminate use of AAS to the cardiac structure and functioning can include increased cardiac tissue collagen, imbalance of vasomotor tone, reduction in the number of capillaries, and pathological cardiac hypertrophy in animal and human models. In addition, supraphysiological doses of AAS have already demonstrated that they may inhibit angiogenesis induced by physical training. In a study involving 152 men (between 18 and 40 years of age), non-athletes (n=52), strength-endurance athletes (n=52), and athletes (n=52) who admitted using AAS, showed ventricular volumes and ventricular wall thickness statistically higher than in non-users, and lower ejection fraction in both ventricles. An increase in cardiac collagen can induce electrophysiological changes in the myocardium with abnormal propagation of the excitation wave favoring tachycardia, which may explain the repeated occurrence of sudden death in users of AAS. But this possibility is raised based on a case report of a user 31 years of age. On the other hand, another study reports other factors occurring after massive doses of AAS for several years, namely, a case of ventricular fibrillation during exercise, one heart failure, and arterial thrombus in the lower left leg. Interestingly, all these patients had increased cardiac hypertrophy and fibrosis in the myocardium. It is certain that the character of case reports makes these inconsistent data. The development of experimental models is useful in helping us better understand the deleterious effects of SEA on cardiovascular tissue, but must consider the obvious limitations of extrapolating data to humans. So that our knowledge of this adverse effect is dependent on cases recorded and documented in the scientific literature. Owing to this limitation, it was investigated the effect of administration of nandrolone decanoate in rats for 10 weeks,
associated with swim training. They found a 10 percent increase in cardiac hypertrophy in rats treated with nandrolone decanoate and 17 percent who had been administered this drug associated with physical training, which were significantly higher than that found in mice not treated with the drug. Despite the limitations of data with an animal model, it was demonstrated by echocardiography that 17 bodybuilders and power-lifters and AAS users manifested cardiac hypertrophy. The most interesting aspect of the study was that 15 of the subjects who did not use AAS for at least 12 months still showed a slight concentric ventricular hypertrophy compared with those who remained on the drug [026].

Right ventricular myocardial dysfunction after use of anabolic steroids

Chronic anabolic steroid use suppresses left ventricular functions. However, there is no information regarding the chronic effects of anabolic steroids on right ventricular function which also plays a key role in global cardiac function. The main objective of one study was to investigate the effects of androgenic anabolic steroids usage among athletes on remodeling the right part of the heart. Androgenic-anabolic steroids-using bodybuilders had smaller diastolic velocities of both ventricles than drug-free bodybuilders and sedentary counterparts. This study shows that androgenic anabolic steroids-using bodybuilders exhibited depressed diastolic functions of both ventricles [040].

Increased risk for ischemia

There may be several mechanisms involved in increasing inter-AEMDs in chronic consumption of supraphysiologic doses of AAS. There are several studies that indicate impairment of LV diastolic function, which is known to play a role in the pathogenesis of AF, which was also found to be impaired in AAS using athletes. When left ventricular diastolic dysfunction occurs, emptying of the left atrium is impaired as well. Following impaired left ventricular diastolic relaxation, there is increased atrial contribution to the mitral flow in the left ventricular diastolic flow, thus leading to atrial overstretching and enlargement. The left atrium diameter is known to be correlated with cardiovascular events and is a risk factor for AF. In one study, the left atrial diameters of the AAS user and nonuser groups were similar. However, the presence of left ventricular diastolic dysfunction in AAS user athletes is a controversial issue. It was investigated the diastolic functions by using the tissue TDI method as well because the conventional Doppler method is load dependent and TDI constitutes a good index of LV relaxation properties. In previous studies, the E/E\(_m\) and E\(_{nv}/A\_m\) were demonstrated to be significantly correlated with the left ventricle end-diastolic pressure and diastolic dysfunctions. It was now found that E/E\(_m\) ratio was significantly higher in AAS users than in nonusers. In addition, the E\(_{nv}/A\_m\) ratio was significantly lower in AAS users than in nonusers. Also it was found that IVRT prolonged in AAS using group, indicating the impartment of diastolic function. The other possible mechanism for increasing inter-AEMD and intra-AEMD in AAS using athletes is LV pathological hypertrophy. LV pathological hypertrophy induced by AAS appears to be generated by a direct action on cardiac androgen receptors, whose effects are directly proportional to the doses, time, and duration of drug administration. LV wall thickness and LV mass index were enlarged in AAS using athletes compared to nonusers. The presence of LV hypertrophy is an indicator of increased myocardial demand for oxygen and hence decreases coronary reserve. When coronary blood flow is fixed or reduced, there is a supply-demand mismatch, resulting in increased risk for ischemia. In such a scenario, a decrease in blood flow can be catastrophic to the already increased demand of the myocardial cells. Patients with LV pathological hypertrophy are at increased risk for ischemia, probably causing prolongation of inter- and intra-AEMD [041].

Echocardiography

The introduction of echocardiography was important for investigating the physiological
responses of the heart to exercise and training. Echocardiography has also been applied for evaluation of AAS on heart structure and function. Eight cross-sectional studies observed differences in one or more echocardiographic variables between AAS users and non-using strength athletes, whereas five studies did not register any difference. Compared with non-users, steroid users have been demonstrated to show larger left ventricular mass and/or left ventricular index, and larger posterior wall and interventricular septum thicknesses. The majority of studies seem to show that the left ventricular cavity during diastole and systole is not subject to alterations under the use of steroids. Six prospective echocardiographic studies have been published and only one study reported steroid-induced changes in echocardiographic variables. It was observed significant changes of left ventricular mass, interventricular septum thickness and left ventricular end-diastolic diameter, but the left ventricular posterior wall thickness remained unaffected by AAS. However, the researchers did not pay attention to an increase in work load of the AAS users during the study period. Therefore, these results must be interpreted with caution, especially since all other studies unanimously reported no changes in any echocardiographic variable measured during AAS administration. Although a nonblinded design was applied in all studies except one, these results indicate that changes in heart structure and function are not to be expected when an athlete takes AAS for periods of up to 4 months. The effects of prolonged AAS abuse and/or the use of many successive AAS courses remains unknown. Nevertheless, animal studies clearly have shown that short-term use of androgens and anabolic agents may exert strong hazardous effects on cardiac structure and function and, therefore, it has been proposed that echocardiography might be not sensitive enough to detect early and small changes due to AAS administration [012].

Long-term intensive training is associated with distinctive cardiac adaptations which are known as athlete's heart. The aim of one study was to determine whether the use of anabolic androgenic steroids (AAS) could affect echocardiographic parameters of left ventricular (LV) morphology and function in elite strength and endurance athletes. A total of 20 elite strength athletes (10 AAS users and 10 non-users) were compared to 12 steroid-free endurance athletes. All the subjects underwent comprehensive standard echocardiography and tissue Doppler imaging. After being indexed for body surface area, both left atrium (LA) and LV end-diastolic diameter (LVEDD) were significantly higher in the endurance than strength athletes, regardless of AAS use. A significant correlation was found between LA diameter and LVEDD in the steroid-free endurance athletes, showing that 75 percent of LA size variability depends on variability of LVEDD. No significant differences in ejection fraction and cardiac output were observed among the groups, although mildly reduced LV ejection fraction was seen only in the AAS users. The AAS-using strength athletes had higher A-peak velocity when compared to steroid-free athletes, regardless of training type. Both AAS-using and AAS-free strength athletes had lower e' peak velocity and higher E/e' ratio than endurance athletes. It was concluded that there is no evidence that LV ejection fraction in elite athletes is altered by either type of training or AAS misuse. Long-term endurance training is associated with preferable effects on LV diastolic function compared to strength training, particularly when the latter is combined with AAS abuse [042].

Despite the limitations of data with an animal model, it was demonstrated by echocardiography that 17 bodybuilders and power-lifters and AAS users manifested cardiac hypertrophy. The most interesting aspect of this study was that 15 of the subjects who did not use AAS for at least 12 months still showed a slight concentric ventricular hypertrophy compared with those who remained on the drug. Several studies have demonstrated changes in the cardiac functioning aspects of AAS users, especially on diastolic functioning. Diastolic dysfunction has been strongly associated with collagen deposition. Fibrillar collagens, types I and III, are the major structural proteins of the myocardial collagen matrix exerting an important influence on ventricular compliance. Exposure to supraphysiological doses of AAS can lead to tissue necrosis and diastolic dysfunction, resulting in structural changes similar to those seen in the earlier stages of heart failure. There are several
mechanisms that appear to be related to cardiac hypertrophy and collagen accumulation. AAS can induce such hypertrophy through nuclear receptors, acting directly on RNA and increasing the protein synthesis and acting as well on specific enzymes, on ions flow and the structural matrix in the myocardium. Increased circulating pro-inflammatory cytokines such as TNF-alpha and increased cAMP concentration have been documented, which contributes to the positive inotropic response through the calcium in the cytosol of the myocardial cell. However, the exact mediators of such effects are diverse and not fully elucidated [043].

**Echocardiographic measures in weightlifters**

Particularly in athletes it is important to consider differences of fat-free body mass when comparing echocardiographic measures. The left ventricular muscle mass and wall thicknesses values of ex-users relative to fat-free body mass were similar to those of users. The weightlifters group, however, showed significantly lower values. This suggests not only a disproportionate increase in left ventricular muscle mass with AAS, but also residual left ventricular hypertrophy more than one year after discontinuing AAS intake. Increases in left ventricular muscle mass with AAS are well documented in strength athletes (with case reports of typical hypertrophic cardiomyopathy) as well as in animals, where an increased protein synthesis has been shown. Androgen receptors are known to be present in human myocardial tissue. Intracellular oedema and mitochondrial swelling in myocytes could also play a role in hypertrophy. In case reports, reversibility of significantly increased left ventricular muscle mass has been described after discontinuation of AAS. Other studies suggest that, relative to body dimensions, AAS have a long lasting disproportionately hypertrophic effect on the myocardium, as former users still show an increase in left ventricular muscle mass four to six weeks or nine months after discontinuing these agents. The results suggest that this effect is maintained for an even longer time. The extent to which increased left ventricular muscle mass caused by AAS abuse represents a long term risk for cardiac complications is controversial. The correlation between left ventricular muscle mass and cardiovascular mortality that is suggested by epidemiological evidence may be transferable to athletes only with caution. An increased left ventricular muscle mass of up to 170 g/m² can be found in healthy highly endurance trained athletes. Left ventricular wall thicknesses of 13–16 mm have been described in individual athletes with large body dimensions involved in combined strength-endurance sports, such as rowing. In contrast to those athlete’s hearts, clinical hypertrophic cardiomyopathy – even with endurance training – is always associated with a rather small internal left ventricular diameter of less than 48-50 mm. The higher ratio of wall thickness to internal diameter in ex-users and users underlines the assumption that there is a slight degree of concentric left ventricular hypertrophy in AAS users, even more than one year after discontinuing the intake of these agents. Today, most investigators agree that strength training without AAS intake does not induce concentric left ventricular hypertrophy. Previous echocardiographic data in athletes taking AAS are less conclusive. Some investigators describe significant wall thickening compared with steroid-free strength athletes, with regression after eight weeks off treatment or no change after nine weeks. Other studies, however, report only non-significant differences or no differences between strength athletes using or not using AAS. Ex-users lie between the non-users (weightlifters) and users with respect to left ventricular muscle mass, wall thicknesses, and hypertrophic index values. This could suggest that the hypertrophic effect of AAS decreases over the years. In the study, left ventricular systolic function in the users was still within the normal range, in agreement with other investigators' findings. An impairment of systolic left ventricular function in animals has been shown with AAS. Impairment of diastolic left ventricular function with AAS use is not unequivocal. These discrepancies might be explained by different methods used to assess the diastolic function as well as by variations in the dose of AAS. In the present study there was a higher maximum late transmitral flow velocity and at least a tendency towards a lower E/Amax ratio in ex-users and users compared with weightlifters, which might suggest a relaxation disturbance. Fibrosis of the myocardium, as described in the case of anabolic abuse, could be responsible for this. The greater age of ex-users should be considered, because diastolic function is known to decline with age;
however, the differences found were greater than could be expected from a difference in age of 10 years and persisted after correction for age. The E/Amax ratio on Doppler echocardiography depends on many other factors, especially preload and afterload conditions, and this makes it difficult to draw definitive conclusions about diastolic left ventricular function from conventional transmitral echocardiography [044].

**Left ventricular hypertrophy independently predicts cardiovascular mortality**

Anabolic steroid abuse in athletes has been associated with a wide range of adverse conditions, including hypogonadism, testicular atrophy, impaired spermatogenesis, gynaecomastia, and psychiatric disturbance. But what effect does steroid abuse have on the cardiovascular system? Left ventricular hypertrophy (LVH) independently predicts cardiovascular mortality and morbidity across diverse disease states. While cardiac diastolic or contractile failure might result directly from structural change within the ventricle (such as altered capillary density or matrix deposition), the association of LVH with cardiovascular disease is more likely dependent upon the increased activity of shared physiological pathways driving both processes. The nature of these underlying mechanisms remains poorly understood. In this regard, escalating attention has focused on the potential role of steroid hormones on LV growth responses. Whether of local or systemic origin, endogenous steroid hormones appear to drive LV growth. Systemic glucocorticoid excess is associated with significant hypertrophy. This action is more likely to be direct, rather than mediated through an elevated pressor burden, with aldosterone having similar effects. Local myocardial renin-angiotensin systems (RAS) play a role in regulating LV growth, and at least part of the hypertrophic responses to steroid hormones may be mediated through upregulation of local RAS expression. Anabolic/androgenic steroids are likely to share such influences on the LV hypertrophic response through actions on the androgen receptor (AR), a transcriptional regulator. Indeed, ARs are almost ubiquitously expressed, being found not only in skeletal muscle cells, but also on cardiac myocytes. Several lines of evidence also implicate endogenous androgenic pathways in the development of cardiac hypertrophy, including the demonstration of raised 5alpha reductase, aromatase, and AR expression in hypertrophic hearts of both humans and mice [045].

**Movement of the left ventricular wall**

Previous investigations reported alterations in myocardial fibres and systolic function associated with anabolic-androgenic steroid consumption by athletes. Advances in biomedical technology have allowed further investigation in assessing the possible effects of anabolic-androgenic steroids on gross left ventricular kinetics. Twenty-three male strength and power athletes with a past and current history of anabolic-androgenic steroid consumption (x 46 days, range 28 days to 70 days), were compared to 23 controls. Testing consisted of resting and immediate post-exercise transthoracic left ventricular wall cardiokymograms. Statistical results identified no difference over time between groups or condition. Cardiokymographic waveform analysis found 33 percent of all (n=184) waveforms to be abnormal (Type II, n=56 or Type III, n=4). There were 14 treatment subjects (61 %) who demonstrated an abnormal waveform as compared to 9 controls (39 %). A significant difference in the overall proportions of waveform types was identified where the treatment group exhibited 41 percent abnormal waveforms, compared to 24 percent by controls. Additionally, two athletes (1 treatment, 1 control) demonstrated abnormal left ventricular wall motions (Type III) analogous to impaired left ventricular performance. The results indicated: highly strength trained athletes with no history of anabolic-androgenic steroid usage exhibited an unexpected high incidence of Type II waveforms (28 % pre/24 % post); and a comparable group of strength trained athletes using anabolic-androgenic steroids exhibited a significantly higher percentage of abnormal waveforms as compared to controls (35 % pre/37 % post). Based on these results, high intensity strength training with and without anabolic-
androgenic steroid supplementation induced alterations in the left ventricular wall motion [046].

**Decreased ventricular compliance in rats**

Testosterone analogs have been used as performance enhancers by athletes for more than 40 yr. It was asked whether the anabolic steroid 17 alpha-methyl-4-androstene-17-ol-3-one (17 alpha-MT) would affect intrinsic contractile function of the heart. Male Sprague-Dawley rats, 125-150 g, were treated with 17 alpha-MT either parenterally or orally for up to 8 wk. Intrinsic contractile function of the hearts was assessed utilizing both the isolated working heart and isovolumic perfused heart preparations. Isolated working hearts from 17 alpha-MT-treated rats had a 45 percent decrease in heart work attributable largely to a similarly decreased stroke volume. Isovolumic perfused hearts from treated animals had elevated left ventricular systolic and diastolic pressures at similar intraventricular volumes compared to controls. Rates of ventricular pressure development (+dP/dT) or relaxation (-dP/dT) were unchanged as a result of the treatment. However, static elastance was reduced in potassium-arrested hearts from the 17 alpha-MT treatment (63 % increase in intraventricular pressure), consistent with a limitation being imposed on stroke volume by a decreased myocardial compliance. Hydroxyproline content of the hearts was not altered by 17 alpha-MT treatment suggesting that increased stiffness was not a consequence of collagen proliferation. Treatment of the steroid rats with beta-amino propionitrile, a compound that inhibits lysyl oxidase, restored the left ventricular volume-pressure relationship (elastance curve) to that of control hearts. Thus, chronic treatment with anabolic steroids appears to reduce left ventricular compliance, possibly related to an enhanced activity of lysyl oxidase, and results in increased crosslink formation between collagen strands in the extracellular matrix [047].

**Functional effects of left ventricular increased muscle thickness**

**Significantly lower ejection fraction**

Anabolic-androgenic steroids abuse has been shown to affect the cardiomyocyte survival and heart function in cell cultures, animal models and humans. A recent study reported that both diastolic and systolic functional parameters are impaired in AAS abuser athletes comparing with nonabuser athletes. In this study, echocardiography in AAS abusers showed a significantly lower ejection fraction (50 % vs 59 %) and longitudinal strain compared to AAS non-abusers. A similar trend was observed in diastolic functional parameters. The mechanisms of high-dose AAS-associated heart dysfunction are still not thoroughly investigated. However, some studies showed deleterious molecular and cellular effects of high-dose AAS administration on myocardium which overlap early injury pathways of heart failure. It is known that in hypertrophic myocardium, hypertrophy can be linked with any of the heart failure signaling pathways, resulting in heart failure. It has also been shown that AAS indirectly mediates the processes that precede mitochondrial damage, apoptosis and sarcomere disruption. It has also been reported that high-dose AAS treatment in small animal models is associated with interstitial collagen deposition and fibrosis. Fibrosis is assumed to occur initially as an adaptation in myocardial hypertrophy to preserve the function of the ventricles and, thereafter, as a repair mechanism to compensate apoptotic myocardial cell loss [048].

An echocardiographic study of 47 strength-training individuals (46 male subjects), 28 of whom were regular AAS users, revealed a lower systolic function in AAS users versus nonusers, ejection fractions 58 versus 63 percent, respectively. In addition, there was evidence of reduced diastolic function by tissue Doppler measurement in the AAS users (i.e. their hearts were weaker and stiffer). Another study of 12 long-term AAS users noted that compared with controls, they were noted to have significant systolic cardiac dysfunction as measured by lower left ventricular ejection fraction (50 % vs 59 %). An Italian Doppler
imaging study also showed reduced systolic function but in a regional distribution [010].

**Impaired left ventricular strain**

Bioprical data have shown that in athletes under the pharmacological effects of AAS, a focal increase in myocardial collagen content might occur as a repair mechanism against myocardial damage. To investigate the potential underlying left ventricular myocardial dysfunction after chronic misuse of AAS in athletes by use of Doppler myocardial imaging (DMI) and strain rate imaging (SRI). Standard Doppler echocardiography, DMI, SRI and ECG treadmill test were undertaken by 45 bodybuilders, including 20 athletes misusing AAS for at least 5 years (users), by 25 anabolic-free bodybuilders (non-users) and by 25 age-matched healthy sedentary controls, all men. The mean number of weeks of AAS use per year was 31 in users, compared with 9 years in non-users, and the mean weekly dosage of AAS was 525 mg. The groups were matched for age. Systolic blood pressure was higher in athletes (145 vs 130 mm Hg) than in controls. Left ventricular mass index did not significantly differ between the two groups of athletes. In particular, both users and non-users showed increased wall thickness and relative wall thickness compared with controls, whereas left ventricular ejection fraction, left ventricular end-diastolic diameter and transmitral Doppler indexes were comparable for the three groups. Colour DMI analysis showed significantly lower myocardial early: myocardial atrial diastolic wave ratios in users at the level of the basal interventricular septum (IVS) and left ventricular lateral wall, in comparison with both non-users and controls. In addition, in users, peak systolic left ventricular strain rate and strain were both reduced in the middle IVS and in the left ventricular lateral free wall. By stepwise forward multivariate analyses, the sum of the left ventricular wall thickness, the number of weeks of AAS use per year and the weekly dosage of AAS were the only independent determinants of middle IVS strain rate. In addition, impaired left ventricular strain in users was associated with a reduced performance during physical effort. Several years after chronic misuse of AAS, power athletes show a subclinical impairment of both systolic and diastolic myocardial function, strongly associated with mean dosage and duration of AAS use. The combined use of DMI and SRI may therefore be useful for the early identification of patients with more diffused cardiac involvement, and eventually for investigation of the reversibility of such myocardial effects after discontinuation of the drug [049].

**Negative alterations in diastolic function**

An increase in LV mass is an independent risk factor for CV disease. AS use has been associated with an increase in LV mass, but there is conflicting data. There are some data in AS users that suggest a reduction in systolic cardiac function although this is not a consistent finding between studies. A reduction in diastolic function has been observed more frequently and it has been suggested that a reduction in myocardial relaxation/elastance is associated with AS use [050].

Anabolic steroids cause a variety of side effects, among them a slight concentric left ventricular hypertrophy. The objective of the present study was to clarify if they also induce alterations in left ventricular function. Fourteen male body builders with substantial intake of anabolic steroids (users) were examined by standard echocardiography and cardiac tissue Doppler imaging. They were compared to 11 steroid-free strength athletes (non-users) and 15 sedentary control subjects. Users showed an increased left ventricular muscle mass index. The ratio of peak transmirtal blood flow velocities during early diastolic filling and atrial contraction did not differ between groups. In contrast an analogous tissue Doppler parameter, the ratio of myocardial velocities during early and late ventricular filling in the basal septum, was significantly lower in users when compared to non-users or controls. The velocity gradient during myocardial E-wave in the posterior wall showed significantly lower values in users as compared to controls. There were no differences in systolic function. Summarizing strength athletes abusing anabolic steroids show negative alterations in diastolic function [051].
Echocardiographic studies of AAS users demonstrate an increase in septal and left ventricular posterior wall thickness. This hypertrophy is greater in weight-trained individuals using AASs than in weight-trained individuals provided placebo or not using AASs and persists for years among former AAS users. Cardiac wall hypertrophy may not occur after short-term ASA use. AAS use impairs measures of diastolic function (e.g., isovolumetric relaxation time and altered tissue Doppler imaging of the left ventricle) that reflect impaired relaxation and altered filling during diastole. Possible etiologies for impaired diastolic function include increased collagen content or areas of focal necrosis, seen at autopsy of AAS users. Cardiovascular performance also can be assessed by way of formal exercise testing; although AASs may increase bulk and strength, they do not improve endurance. Despite having similar aerobic and weight-training schedules as control subjects, AAS users had a significantly decreased maximum oxygen consumption ($V_{O_{2}}$max; an index of metabolic and cardiovascular endurance ability). Impaired diastolic function could contribute to decreased $V_{O_{2}}$max [020].

The effects of anabolic androgenic steroids (AASs) on left ventricular (LV) diastolic function in strength-trained athletes are controversial. The main objective of this study was to evaluate the effects of regular AAS administration in bodybuilders using pulsed tissue Doppler imaging (TDI) to evaluate LV relaxation properties. Fifteen male bodybuilders with a history of intensive, long-term strength training and 16 age-matched sedentary controls were recruited. Six of the bodybuilders reported regular use of AASs, and 9 were drug free. To assess LV diastolic function, each subject underwent standard Doppler echocardiography and pulsed TDI. Drug-using bodybuilders exhibited altered LV diastolic filling characterized by a smaller contribution of passive filling to LV filling compared with their drug-free counterparts. TDI measurements indicated that drug-using bodybuilders had smaller peak $E(m)$ than drug-free bodybuilders and sedentary controls, except at the level of the anterior wall, at which peak $E(m)$ was significantly smaller than in drug-free bodybuilders only. The $E/E(m)$ ratio, an index of LV filling pressures, was not affected by strength training or by AAS use. Drug-using bodybuilders exhibited larger LV end-diastolic diameters, volumes, and masses than their drug-free counterparts. However, no difference was found in LV wall thickness between the groups. In conclusion, drug-using bodybuilders showed a decrease in the contribution in LV passive filling to LV filling associated with a decrease in LV relaxation properties. Because no wall thickening was obtained in drug-using bodybuilders, the decrease in LV relaxation properties might have been due to an alteration in the active properties of the myocardium, but that has yet to be confirmed [052].

**Effects of resistance training on left ventricular thickness**

Resistance training (RT) is a popular method of conditioning to enhance sport performance as well as an effective form of exercise to attenuate the age-mediated decline in muscle strength and mass. Although the benefits of RT on skeletal muscle morphology and function are well established, its effect on left ventricular (LV) morphology remains equivocal. Some investigations have found that RT is associated with an obligatory increase in LV wall thickness and mass with minimal alteration in LV internal cavity dimension, an effect called concentric hypertrophy. However, others report that short- (<5 years) to long-term (>18 years) RT does not alter LV morphology, arguing that concentric hypertrophy is not an obligatory adaptation secondary to this form of exertion. This disparity between studies on whether RT consistently results in cardiac hypertrophy could be caused by: (i) acute cardiopulmonary mechanisms that minimise the increase in transmural pressure (i.e., ventricular pressure minus intrathoracic pressure) and LV wall stress during exercise; (ii) the underlying use of anabolic steroids by the athletes; or (iii) the specific type of RT performed. It was proposed that when LV geometry is altered after RT, the pattern is usually concentric hypertrophy in Olympic weightlifters. However, the pattern of eccentric hypertrophy
(increased LV mass secondary to an increase in diastolic internal cavity dimension and wall thickness) is not uncommon in bodybuilders. Of particular interest, nearly 40 percent of all RT athletes have normal LV geometry, and these athletes are typically powerlifters. RT athletes who use anabolic steroids have been shown to have significantly higher LV mass compared with drug-free sport-matched athletes. One brief review will sort out some of the factors that may affect the acute and chronic outcome of RT on LV morphology. In addition, a conceptual framework is offered to help explain why cardiac hypertrophy is not always found in RT athletes [053].

Experimental

Abuse of anabolic androgenic steroids is linked to a variety of cardiovascular complications. The aim of our study was to investigate the possible cardiovascular effects of nandrolone decanoate on young rabbits using echocardiography, histology and monitoring of telomerase activity, oxidative stress and biochemical markers. Fourteen rabbits were divided into three administration groups and the control group. Doses of 4 mg/kg and 10 mg/kg of nandrolone decanoate, given intramuscularly and subcutaneously, two days per week for six months were applied. A 4-months wash-out period followed. Focal fibrosis and inflammatory infiltrations of cardiac tissue were observed in the high dose groups. Thiobarbituric acid-reactive species (TBARS) levels were significantly increased in the high dose groups, while catalase activity decreased. Myocardial Performance Index (MPI) is the main echocardiographic index primarily affected by nandrolone administration in rabbits. Despite the preserved systolic performance, histological lesions observed associated with distorted MPI values, point to diastolic impairment of the thickened myocardium due to nandrolone treatment. Oxidative stress accumulates and telomerase activity in cardiac tissue rises. Subcutaneous administration seems to be more deleterious to the cardiovascular system, as oxidative stress, telomerase activity and biochemical markers do not appear to return into normal values in the wash-out period [054].

The aim of one study was the investigation of effects of the metenolone enanthate (ME) that is used among athletes as doping and muscle amplifier, on hearts of male and female rats that are in puberty using morphometrical methods. A total of 36 rats which were divided into three separate groups (Experiment, ME; vehicle, PO; control, C) each consisting of 6 male and 6 female rats were used. 0.5mg/kg metenolone enanthate was applied intraperitoneally into experiment subjects 5 times a week over a period of 4 weeks. At the end of experiment, rats were euthanized and their hearts were cut at the level of musculus papillaris after the fixation in formalin. Hearts were taken out and embedded in paraffin wax. Photos were taken at cut surfaces, and thickness, diameters and surface area levels were measured. Left ventriculus mass (LVM) and left ventriculus mass index (LVMI) were calculated. In the study LVM and LVMI were found to be significantly higher in the ME group in females whereas left ventricular lumen diameter (LVLD) were found to be significantly lower. Thus left ventricular hypertrophy development was observed. LVM and LVMI were found to be similar in ME and C groups among male rats and the highest level of these data were found in the group. LVM and LVMI were higher among females. In conclusion, it has been shown that the adverse effects of ME on heart were developing starting from puberty and resulting with the enlargement of the heart and left ventricular hypertrophy and especially among females this condition was more evident. It has also been discussed that the continuous use of drugs may further enhance this condition [055].

Non-therapeutic use of androgenic anabolic steroids are administered in supraphysiological doses to enhance the development of muscle mass and strength and to reduce the recovery time after strenuous training bouts. These doses are however associated with pathologic changes in numerous physiological systems. Studies using rats have shown that supraphysiological doses of anabolic steroids cause pathophysiological myocardial hypertrophy in this model. In the mouse it has been associated with inadequate
vascularisation of the hypertrophied myocardium, and in isolated rat ventricular myocytes it has been linked to increased apoptosis. When combined with exercise, anabolic steroid use has been shown to change exercise-induced physiological cardiac hypertrophy to pathophysiological cardiac hypertrophy. In one study using the exercising rat, the anabolic steroid-induced changes in myocardial hypertrophy were associated with changes in the ratio of the left ventricular wall thickness to internal radius. These changes are thought to lead to detrimental increases in LV wall stress and to act as one of the stimuli for abnormal heart growth and development. It was hypothesized that AAS use increases myocardial susceptibility to ischaemia-reperfusion injury. Rats were trained (swimming) with or without intramuscular injection of nandrolone laurate (0.375 mg/kg). Untrained rats with or without nandrolone served as controls. Hearts were mounted on the Langendorff perfusion apparatus and mechanical function was measured before and after 20-min normothermic global ischaemia. Myocardial tissue samples were collected for determination of tissue cyclic nucleotide and TNFalpha concentrations. Anabolic steroids significantly decreased the rate pressure product (RPP) of the exercise-trained rat heart. Reperfusion RPP was lower in both the sedentary, and the exercise-trained, steroid-treated hearts than in their concurrent vehicle-treated controls. Myocardial TNFalpha and cAMP concentrations were elevated in the steroid-treated hearts when compared with their untreated counterparts. It was concluded that supraphysiological doses of anabolic steroids, whether taken during exercise training or under sedentary conditions increase myocardial susceptibility to ischaemia/reperfusion injury in our model. This increased susceptibility may be related to steroid-induced increases in the pre-ischaemic myocardial cAMP concentrations and/or increases in both pre-ischaemic and reperfusion TNFalpha concentrations [056].

**Electrical remodelling and increasing myocytes nuclei diameter**

The role of AAS abuse in myocardial hypertrophy has been shown in animal and human studies. In a recent investigation on rats treated with high-dose nandrolone for 8 weeks, electrical remodelling and increasing myocytes nuclei diameter in the AAS group suggested early stages of myocardial hypertrophy. Significant increase in left ventricular mass index, ranging from 7 to 24 percent, has been shown in studies on rats treated with low-dose and high-dose AAS for 8-10 weeks. Another study on the AAS treatment for 3 weeks in mice subjected to aerobic training and sedentary mice showed that high-dose AAS treatment in sedentary mice results in increased ventricular mass index by 25 percent. Also, many case reports of sudden cardiac death in athletes who abused AAS have shown clinically important left ventricular hypertrophy. Association between AAS abuse and echocardiographical detected myocardial hypertrophy has been shown in a study on athletes who chronically abused AAS (median 24 months). In this study, hypertrophic index (interventricular septum plus posterior wall thickness divided by the internal diameter) was significantly higher in AAS (ex-)abusers compared with nonuser athletes. Moreover, the extent of AAS abuse was linearly correlated with mean left ventricular wall thickness. It has been shown that long-term AAS abuse increases peripheral vascular resistance, blood pressure, and myocardial sympathetic nerve activity, which can explain mechanical stress-induced myocardial hypertrophy in AAS abusers. Moreover, androgen receptors which are responsible for AAS-induced hypertrophic effects on skeletal muscles are also present in myocytes and result in increased protein anabolism within myocardial cells and interstitium [057].

**Attenuated beta-adrenoceptor-mediated cardiac contractile responses**

Androgenic steroids administered in doses at pharmacological levels to sedentary animals have been shown to result in a reduced beta-adrenoceptor-mediated increase in systolic cardiac performance when assessed in vivo. Whether the attenuated adrenergic response occurs as a consequence of alterations in either cardiac loads, heart rate, modifications in left ventricular (LV) geometry, or a decrease in myocardial contractile performance has not been determined. In this study the effect of chronic administration (over 3 months) of an androgenic steroid (nandrolone decanoate, 5 mg./kg biweekly) on the response of load-insensitive indices of myocardial contractile function [the slope of the LV systolic stress-strain
relationship (LV-E(n)(max), where E(n)(max) is systolic myocardial elastance) to an adrenergic-inotropic stimulus was examined ex vivo in paced rat hearts. Systolic cardiac performance was assessed at 300 beats/min in isolated constant flow perfused heart preparations both before and during $10^{-8.5}$ mol/L isoproterenol (ISO) infusion (approximate concentration of ISO eliciting 50% maximal inotropic response to ISO). Steroid administration resulted in left-shifted LV systolic and diastolic pressure-volume (P-V) relationships. The left-shifted P-V relationships were attributed, in part, to increased slopes of these relationships. However, the steroid-mediated increment in the slope of the systolic P-V relationship (systolic chamber elastance, E(max)) was not associated with a similar change in LV E(n)(max) as determined in the absence of ISO. Isoproterenol infusion resulted in an increase in both E(max) and E(n)(max) in the control rats, without altering systolic performance in the steroid treated rats. Consequently, in the presence of ISO, the steroid treated rats exhibited a similar E(max), but a reduction in E(n)(max) compared to the control rats. In conclusion, these results would suggest that chronic high dose androgenic steroid administration produces a decrease in myocardial contractile reserve to beta-adrenoceptor stimulation [058].

**Heart failure due to anabolic-androgenic steroids**

Chronic heart failure (CHF) involves derangements in multiple neurohormonal axes leading to a procatabolic state and wasting syndrome associated with significant mortality. Catabolic abnormalities include excess catecholamines and glucocorticoids. Anabolic defects include deficiencies of sex steroids, insulin resistance, and growth hormone (GH) resistance. These abnormalities are also correlated with increased morbidity and mortality in CHF. Anabolic axes have been augmented in pilot studies in CHF with testosterone, GH, insulin-like growth factor-1, and GH secretagogues. Results have been varied although some treatments have been associated with improved surrogate endpoints. One review article explores the current understanding of metabolic derangements in CHF and highlights potential neuroendocrine treatment strategies [059].

A 36 year old competitive bodybuilder presented with increasing dyspnoea on exertion over a six week period. He gave a 10 year history of use of anabolic steroids, growth hormone, ephedrine, and thyroxine. Echocardiography demonstrated severe left ventricular hypertrophy and systolic dysfunction. Serum ferritin was normal and there was no serological evidence of viral infection or connective tissue disease. Angiography revealed normal coronary arteries and cardiac magnetic resonance imaging (CMR) was performed to further investigate the cause of the cardiomyopathy. The left ventricle, shown here in end diastole (panel A) was noted to be severely hypertrophied (myocardial mass 465 g; normal range 85–181 g), dilated (end diastolic volume 319 ml; normal range 102–235 mL), and systolic function was severely impaired (ejection fraction 20%). Imaging post administration of gadolinium-DTPA was negative for late enhancement (panel B), excluding both myocardial infarction and macroscopic evidence of myocardial fibrosis. Initial treatment has been commenced with a diuretic, angiotensin converting enzyme inhibitor, β blocker, and anticoagulation. Growth hormone excess has been associated with left ventricular hypertrophy while anabolic steroids have been associated both with myocardial hypertrophy, focal myocardial fibrosis, and premature myocardial infarction. Thyroxine may cause high output cardiac failure. CMR is the non-invasive investigation of choice in unexplained heart failure. This case illustrates that severe heart failure can occur in patients taking these performance enhancing drugs without CMR evidence of either myocardial infarction or myocardial fibrosis [060].

The objective of one study was to analyse the outcome of patients with advanced heart failure due to abuse of anabolic-androgenic steroids. A retrospective chart review of
patients admitted or referred for advanced heart failure, due to anabolic-androgenic steroid abuse, in the period 2009-2013 was performed. In 6 of 9 patients (median age: 31, all males) referred in the study period, some potential for recovery of left ventricular (LV) function was seen, with a maximal improvement in LV ejection fraction reached within 6 months of treatment with angiotensin-converting enzyme inhibitors and beta-blockers. The remaining 3 patients required implantation of a LV assist device (LVAD) and were listed for heart transplantation. No recovery of LV function in the patients treated with assist device was seen. It was concluded that anabolic-androgenic steroid-induced advanced heart failure is generally not a reversible condition. If diagnosed in the early stages some recovery of ventricular function is possible, but the long-term prognosis is uncertain. Likely, a substantial proportion of patients will eventually require LVADs or cardiac transplantation [061].

**Acute cardiac failure**

Though doping has become increasingly ostracized in the context of professional sports, an enormous number of unrecorded cases must be assumed in semi-professional competitive sports as well as in popular sports. This holds especially true for those forms of sports which are done in order to obtain a well-proportioned, athletic, healthy looking body. One case report describes a formerly healthy young man who had to be urgently admitted to an intensive care unit due to severe myocardial pump failure. As anamnestic information was insufficient and inadequate, the taking of anabolic steroids in high doses was proven, as their metabolites could be detected by urine analysis. Until now, myocardial contractile dysfunction has persisted for more than twelve months after the initial admission. Though other diagnoses which might have led to this impaired myocardial contractile performance have been excluded, cardiomyopathy associated with the taking of anabolic steroids must be assumed. Even in non-professional and public sports, a widespread abuse of doping substances exists. Hence, cardiomyopathy associated with the misuse of anabolic steroids has to be considered especially in young, formerly healthy patients [062].

**Treatment**

Chronic heart failure is associated with maladaptive and prolonged neurohormonal and pro-inflammatory cytokine activation causing a metabolic shift favouring catabolism, vasodilator incapacity, and loss of skeletal muscle bulk and function. In men, androgens are important determinants of anabolic function and physical strength and also possess anti-inflammatory and vasodilatory properties. It was conducted a randomized, double-blind, placebo-controlled parallel trial of testosterone replacement therapy (5 mg Androderm) at physiological doses in 76 men (mean age 64 years) with heart failure (ejection fraction 33 %) over a maximum follow-up period of 12 months. The primary endpoint was functional capacity as assessed by the incremental shuttle walk test (ISWT). At baseline, 18 (24 %) had serum testosterone below the normal range and bioavailable testosterone correlated with distance walked on the initial ISWT. Exercise capacity significantly improved with testosterone therapy compared with placebo over the full study period (mean change +25 m) corresponding to a 15 percent improvement from baseline. Symptoms improved by at least one functional class on testosterone in 13 (35 %) versus 3 (8 %) on placebo. No significant changes were found in handgrip strength, skeletal muscle bulk by cross-sectional computed tomography, or in tumour necrosis factor levels. Testosterone therapy was safe with no excess of adverse events although the patch preparation was not well tolerated by the study patients. It was concluded that testosterone replacement therapy improves functional capacity and symptoms in men with moderately severe heart failure [063].
Dilated cardiomyopathy

Case report

Athletes use androgenic-anabolic steroids but it may lead to dilated cardiomyopathy. It was report a case of a 41-year-old bodybuilder with severe systolic dysfunction and Class IV heart failure despite maximal medical therapy. He used anabolic steroids and insulin growth factor, and did not have any other risk factors for cardiomyopathy. It was briefly reviewed the literature and summarize other reported cases with similar scenarios. In most of them cardiomyopathy was at least partially reversible after discontinuation of anabolics. Abuse of anabolic steroids may be an uncommon cause of cardiomyopathy in young and otherwise healthy individuals [064].

Atherosclorosis

Coronary artery calcifications

The authors measured coronary artery calcification as a means of examining the impact of anabolic steroids on the development of atherosclerotic disease in body builders using anabolic steroids over an extended period of time. Fourteen male professional body builders with no history of cardiovascular disease were evaluated for coronary artery calcium, serum lipids, left ventricular function, and exercise-induced myocardial ischemia. Seven subjects had coronary artery calcium, with a much higher than expected mean score of 98. Six of the 7 calcium scores were >90th percentile. Mean total cholesterol was 192 mg/dL, while mean high-density lipoprotein was 23 mg/dL and the mean ratio of total cholesterol to high-density lipoprotein was 8.3. Left ventricular ejection fraction ranged between 49 percent and 68 percent, with a mean of 59 percent. No subject had evidence of myocardial ischemia. This small group of professional body builders with a long history of steroid abuse had high levels of coronary artery calcium for age. The authors conclude that in this small pilot study there is an association between early coronary artery calcium and long-term steroid abuse. Large-scale studies are warranted to further explore this association [065].

Myocardial infarction

Sudden cardiac deaths secondary to myocardial infarction and related to AAS use in previously healthy athletes have been reported; however, it must be pointed out that these effects are reported in individual case reports and no large, randomized study has been conducted to verify these results. Exposure to AAS alters endothelial cell growth with a strong antiproliferative effect, induces apoptosis, and modifies intracellular levels of calcium. These observed endothelial alterations may be considered events that predispose to serious damage at the cell vasculature level. Androgens impair arterial vasomotor response and consequently increase collagen and other fibrous proteins in arterial vascular tissue and they impair flow-mediated, endothelium-dependent vasodilation. This effect may improve after the discontinuation of agents. Moreover, experimental studies have shown that androgens potentiate platelet aggregation in vitro and in vivo. Androgens may exert their effect on platelets through an effect on the prostaglandin system and lead to increasing platelet prostacycline (prostaglandin I2, an inhibitor of platelet aggregation) and increasing fibrinogen levels. They also increase human platelet thromboxane A2 receptor density and their aggregation responses. The above-mentioned physiological changes may predispose individuals to be at higher risk for myocardial infarction. It also has been shown that aortic distensibility decreases in athletes who use AAS. This went against previously reported increases in aortic distensibility in athletes in comparison with age-matched sedentary
volunteers. Aortic stiffness by increasing ventricular load predisposes to the development of LVH, progressing to left ventricular dysfunction and cardiac failure, and creating an unfavorable oxygen supply/demand ratio. It also causes a reduction in aortic pressure during diastole, which decreases the coronary perfusion pressure and contributes to myocardial ischemia even in the absence of coronary artery atherosclerotic narrowing [010].

Case reports

The potential cardiotoxicity of anabolic steroids is not well known. The authors report the case of a young man who was a top class body builder and who developed severe ischaemic cardiomyopathy presenting with an inferior wall myocardial infarction. The clinical history revealed prolonged and intensive usage of two types of anabolic steroids to be the only risk factor. This cardiotoxicity may be related to several physiopathological mechanisms: accelerated atherogenesis by lipid changes, increased platelet aggregation, coronary spasm or a direct toxic effect on the myocytes. The apparent scarcity of the reported clinical details in the literature is probably an underestimation of the consequences of this usage [066].

Anabolic-androgenic steroids are associated with numerous side effects, including acute myocardial infarction. It was reported a case of myocardial infarction in a young 31-year-old bodybuilder. Because of the serious cardiovascular complications of anabolic steroids, physicians should be aware of their abuse and consequences [067].

A few case reports suggest that the use of androgenic anabolic steroids may be associated with myocardial infarction. It was reported a case of a 27-year-old male bodybuilder with acute myocardial infarction due to occlusion of the proximal left anterior descending coronary artery. He was treated with primary angioplasty with stent implantation and intra-aortic balloon support, but still developed a large myocardial infarction as determined by both echocardiography and myocardial perfusion tomography. The patient had been using androgenic anabolic steroids regularly for ten years. There was no family history of heart disease or lipid disorder. The actual frequency of myocardial infarction and even sudden death among users of anabolic steroids is presumably underreported in the medical literature. A causal relationship is not established, but a pathogenic role is plausible. Use of androgenic anabolic steroids has been associated with platelet hyperactivity, effects on vasoreactivity and changes in lipid levels. It is important for clinicians to be aware of this association and to counsel patients carefully about this and other side effects that may occur with these agents [068].

Thromboembolic disease

Cardiac thrombosis

Increased thrombogenicity and acute embolism are well-recognized complications of chronic anabolic steroid abuse. The following cases highlight such dangers in steroid-enhanced bodybuilders who developed intracardiac thrombosis that subsequently embolized. Systemic anticoagulation and surgical thrombectomy constituted the mainstay treatment. This represents the first report of such devastating cardiovascular complications after anabolic steroid abuse and their management [069].

Chronic abuse of anabolic steroids is widespread. Hypertrophy of skeletal and heart muscle is a well-known effect of chronic anabolic steroid abuse. Structural alterations of blood vessels are new side effects. It was reported a case of a 32-year-old bodybuilder after long-term use of anabolic steroids who died of cardiac arrest. Coronary angiography and autopsy findings showed especially a hypertrophic heart, structural changes of coronary arteries,
intracoronary thrombosis and myocardial infarction, ventricular thrombosis and systemic embolism [070].

**Cerebral venous thrombosis**

There are only a few reports of patients developing cerebral venous sinus thrombosis (CVST) after androgen therapy. It was presented a young man who developed cortical venous thrombosis after using androgens to increase muscle mass. He was hospitalised for paraesthesia and dyspraxia in the left hand followed by a generalised tonic-clonic seizure. At admission, he was drowsy, not fully orientated, had sensory inattention, pronation drift and a positive extensor response, all on the left side. The patient had been using anabolic steroids (dianabol 20 mg/day) for the last month for bodybuilding. CT angiography showed a right cortical venous thrombosis. Anticoagulation therapy was started with intravenous heparin for 11 days and oral anticoagulation (warfarin) thereafter. A control CT angiography 4 months later showed resolution of the thrombosis. He recovered fully [071].

**Cerebral or sinus thrombosis**

Cerebral venous sinus thrombosis is an infrequent disease with a variety of causes. Pregnancy, puerperium, contraceptive pills and intracranial infections are the most common causes. The patient may present with headache, focal neurological deficits and seizures. The clinical outcome is highly variable and treatment with heparin is advised. In a case report patient is a 22 year old male who presented with headache, repeated vomiting and papilledema. He was a bodybuilder doing exercise since 5 years ago, who had used nandrolone decanoate 25 milligrams intramuscularly during the previous 5 months. Brain MRI and MRV showed superior sagital and transverse sinus thrombosis and extensive investigations did not reveal any known cause. It was suggested that androgen was the predisposing factor in our patient. Androgens may increase coagulation factors or platelet activity and cause arterial or venous thrombosis. As athletes may hide using androgens it should be considered as a predisposing factor for thrombotic events in such patients [072].

**Thrombosis**

It was presented a case of a 19-year-old male athlete with protein C deficiency who developed proximal deep venous thrombosis and pulmonary embolism while abusing anabolic-androgenic steroids. Anabolic-androgenic steroids have been reported to have anticoagulatory and profibrinolytic effects in patients with protein C deficiency. Despite these antithrombotic effects, the patient developed repeated venous thromboembolism during treatment with low-molecular-weight heparin. The net effect of anabolic-androgenic steroids on the haemostatic system may change from antithrombotic to prothrombotic in male abusers of anabolic steroids with protein C deficiency [073].

**Pulmonary embolism**

It was presented case of a 56-year-old man with deep vein thrombosis (DVT) and pulmonary embolism (PE). He had been given intramuscular injections of testosterone and the anabolic-androgenic steroid nandrolone, due to a muscle injury, a total of three times prior to manifestation of the symptoms. An ultrasonographic examination of the right leg revealed a DVT and computed tomography of the pulmonary arteries showed PE. The thromboembolic episodes in this previously healthy patient were in all probability associated with intramuscular injections of testosterone and nandrolone, to which there is a clear correlation in time [074].
Cardiac arrhythmias and abnormal electrocardiography

Cardiac arrhythmias are among the most important causes of non-eligibility to sports activities, and may be due to different causes (cardiomyopathies, myocarditis, coronary abnormalities, valvular diseases, primary electrical disorders, abuse of illicit drugs). The list of illicit drugs banned by the International Olympic Committee and yearly updated by the World Anti-Doping Agency includes the following classes: stimulants, narcotics, anabolic agents (androgenic steroids and others such as beta-2 stimulants), peptide hormones, mimetics and analogues, diuretics, agents with an antiestrogenic activity, masking agents. Almost all illicit drugs may cause, through a direct or indirect arrhythmogenic effect, in the short, medium or long term, a wide range of cardiac arrhythmias (focal or reentry type, supraventricular and/or ventricular), lethal or not, even in healthy subjects with no previous history of cardiac diseases. Therefore, given the widespread abuse of illicit drugs among athletes, in the management of arrhythmic athletes the cardiologist should always take into consideration the possibility that the arrhythmias be due to the assumption of illicit drugs (sometimes more than one type), especially if no signs of cardiac diseases are present. On the other hand, in the presence of latent underlying arrhythmogenic heart disease including some inherited cardiomyopathies at risk of sudden cardiac death, illicit drugs could induce severe cardiac arrhythmic effects [075].

Apart from important peripheral mechanisms, additional cardiac effects of testosterone most likely include the influence on electrophysiology and arrhythmogenesis. Higher levels of endogenous testosterone are associated with shorter QT and QTc interval and consequently a reduced arrhythmogenesis. Physiologic testosterone supplementation has been shown to reduce QT dispersion in patients with congestive heart failure. In contrast, supraphysiologic doses of testosterone and other anabolic androgen steroids may facilitate ventricular arrhythmias by increasing QTc interval and dispersion and by predisposing to reentry mechanism. Androgen misuse has been also associated with episodes of atrial fibrillation. Nevertheless, the possibility of a protective effect of testosterone against atrial fibrillation has been contradicted by both a meta-analysis which included middle-aged and older men and by animal research associating testosterone supplementation with higher occurrence of atrial fibrillation [076].

Sudden cardiac arrhythmia resulting from inflammatory process and myocardial fibrosis has been suggested to be the cause of death in athletes using AAS. AAS cause the deepest and most prolonged depression of stimulation threshold in the heart muscles. Long-term use may be responsible for an alteration in the electrophysiology of the myocardium that may predispose to reentry mechanism. It also has been shown that QTc interval and dispersion are increased in individuals who abuse androgens, suggesting the presence of ventricular repolarization abnormalities that could increase the risk of cardiac arrhythmias and sudden cardiac death. Atrial fibrillation secondary to high-dose steroids was reported in two cases of athletes who were using AAS and had no other known cause of atrial fibrillation [010].

Cardiac arrhythmias are associated with AAS abuse. Most commonly, atrial fibrillation but also ventricular tachycardia and ventricular fibrillation has been described secondary to AAS abuse in human case reports. In a study on rats treated with high-dose nandrolone for 10 weeks, heart rate variability measurements revealed a reduction in parasympathetic activity compared with the vehicle-treated group. Sympathetic indices were also higher in the AAS-treated group. It was also shown that AAS-treated animals show prolonged action potentials as a result of reduced density of transient potassium outward current in the left ventricle [077].

The current management of athletes with cardiac arrhythmias has become complicated by the widespread use of illicit drugs, which can be arrhythmogenic. The World Anti-Doping Agency annually updates a list of prohibited substances and methods banned by the
International Olympic Committee that includes different classes of substances namely, anabolic androgenic steroids, hormones and related substances, beta2-agonists, diuretics, stimulants, narcotics, cannabinoids, glucocorticosteroids, alcohol, beta-blockers and others. Almost all illicit drugs may cause, through a direct or indirect arrhythmogenic effect, a wide range of cardiac arrhythmias (focal or reentry type, supraventricular and/or ventricular) that can even be lethal and which are frequently sport activity related. A large use of illicit drugs has been documented in competitive athletes, but the arrhythmogenic effect of specific substances is not precisely known. Precipitation of cardiac arrhythmias, particularly in the presence of a latent electrophysiologic substrate including some inherited cardiomyopathies, at risk of sudden death or due to long-term consumption of the substances, should raise the suspicion that illicit drugs may be a possible cause and lead cardiologists to investigate carefully this relationship and appropriately prevent the clinical consequences [078].

**Increased atrial electromechanical delay**

It was investigated the effect of long-term supraphysiologic doses of anabolic androgenic steroids (AAS) on atrial electromechanical delay (AEMD) in male bodybuilders. It was clearly demonstrated that long-term consumption of supraphysiologic doses of AAS is associated with higher values of inter- and intra-AEMD in healthy young bodybuilders. Self-administration of high doses of anabolic androgenic steroids (AAS) is a widespread practice among athletes to increase lean body mass and muscular strength. Long-term illicit use of supraphysiologic doses of AAS may cause several adverse cardiovascular effects. Recent studies have found pathological left ventricular (LV) hypertrophy, diastolic dysfunction, and subclinical LV systolic impairment in long-term AAS users. In addition, ventricular and atrial arrhythmic events were described secondary to the intake of AAS. Atrial fibrillation (AF) is the most frequently observed arrhythmia in bodybuilders who are using AAS. Moreover, various case reports of AF among AAS users suggest a causal link between AAS use and AF in power athletes. However, the mechanisms underlying such predispositions to AF are poorly understood and also it is not clear that AAS using athletes are more prone to atrial rhythm disturbances than non-AAS users. The prolongation of intra-atrial and interatrial conduction times and the inhomogeneous propagation of sinus impulses are typical electrophysiological features of the atrium which is prone to fibrillate. Moreover, atrial electromechanical delay (AEMD) as measured by tissue Doppler imaging (TDI) has been shown to detect atrial impairment in paroxysmal AF. Another important point is that AEMD may also predict the development of new-onset AF. Since AF is a reentrant arrhythmia, it is logical that the triggering factor generally is a critically timed atrial activation that may give rise to reentry in a vulnerable structure. Atrial and ventricular structural alteration, increased atrial stretch, autonomic imbalance, atrial interstitial fibrosis, inflammation, and ischemia may act in this respect as an internal or external factor by modulating atrial refractoriness through both atria and modifying intra-atrial conduction. Because these factors are effected by long-term use of supraphysiologic doses of AAS, there might be an association between AAS use and AEMD [041].

Previous studies reported that long-term illicit use of supraphysiologic doses of AAS was associated with reduced LV diastolic functions (impaired relaxation and reduced compliance of LV), increased LV mass, LV/atrial hypertrophy, subclinical systolic impairment, increased myocardial stiffness and myocardial fibrosis, and altered cardiac autonomic system regulation. Furthermore, it has been reported that myocardial infarction, cardiomyopathy, sudden death, cardiovascular morbidity, and mortality have significantly increased in long-term AAS using bodybuilders more than nonusers. In addition, arrhythmic events were described secondary to the long-term intake of AAS. Although AF is the most frequently observed arrhythmia, ventricular arrhythmias were also described. However, it is not clear that AAS using bodybuilders are more prone to rhythm disturbances compared with nonusers. The prolongation of intra- and inter-AEMD and the inhomogeneous propagation of
sinus impulses are well-known electrophysiologic characteristics of the atria which is prone to fibrillation. The evaluation of AEMD by using TDI has been studied in patients with rheumatic mitral stenosis, paroxysmal AF, acute sleep deprivation, and type I diabetes mellitus. Also, it has been found that atrial electromechanical interval is a predictor of AF emerging after coronary artery bypass grafting and demonstrated that the preoperative administration of amiodarone to patients having longer atrial electromechanical interval has decreased the postoperative atrial fibrillation incidence. Furthermore, it was shown that prolonged PA-TDI interval (indicator of AEMD) predicted the development of new-onset AF in one study, which included 249 patients. In addition, prolonged AEMD in patients with paroxysmal AF was reported with TDI and pulsed-wave Doppler echocardiographic studies. In the present study, we found that inter- and intra-atrial AEMD were prolonged in AAS users compared with both nonusers [041].

Altered autonomic system regulation

Probably adverse effects of AAS on the cardiovascular system are also due to direct toxicity on myocardial structure with increased collagen deposition, fibrosis, and altered microcirculation with intimal hyperplasia of the intramural coronary arteries resulting in chronic ischemic damage. Vascular endothelial cells may be directly affected by AAS, which may result in vasospasm. As the cause of these alterations, AAS may directly affect the atrium, causing heterogeneity in the atrial conduction. It was speculated that long-term illicit use of supraphysiologic doses of AAS might directly affect atrial conduction time (inter-AMED). The last possible mechanism to increase AEMD may be sympathetic activation. It has been shown that chronic consumption of supraphysiologic doses of AAS induces cardiac autonomic imbalance by reduction in parasympathetic cardiac modulation and increase in sympathetic cardiac modulation. Experimental studies showed that greater sympathetic activation leads to myocardial injury. Increased sympathetic activity may also trigger atrial arrhythmias. Therefore, altered autonomic system regulation occurring secondary to the chronic consumption of supraphysiologic doses of AAS may be the other reason underlying the delayed interatrial electromechanical coupling intervals [041].

Data now exist regarding the effects of chronic high-dose anabolic-androgenic steroid administration on tonic cardiac autonomic control. The aim of one study was to evaluate, by power spectral analysis of heart rate variability (HRV), the effects of chronic treatment with supraphysiologic doses of nandrolone decanoate (DECA) on tonic cardiac autonomic regulation in sedentary rats. Male Wistar rats were treated weekly with 10 mg/kg of DECA (n=7) or vehicle (CONTROL, n=7) for 10 weeks. At the 8th week of treatment, electrocardiogram was recorded in the conscious state, for time- and frequency-domain HRV analysis. Parasympathetic indexes were reduced in DECA group: high-frequency power, RMSSD, and pNN5. The sympathetic index LF/HF tended to be higher in DECA group. In conclusion, chronic treatment with DECA, in rats, impairs tonic cardiac autonomic regulation, which may provide a key mechanism for anabolic steroid-induced arrhythmia and sudden cardiac death [079].

One study aimed to evaluate if androgenic-anabolic steroids (AAS) abuse may induce cardiac autonomic dysfunction in recreational trained subjects. Twenty-two men were volunteered for the study. The AAS group (n=11) utilized AAS at mean dosage of 410 ± 78.6 mg/week. All of them were submitted to submaximal exercise testing using an Astrand-Rhyming protocol. Electrocardiogram (ECG) and respired gas analysis were monitored at rest, during, and post-effort. Mean values of VO2, VCO2, and VE were higher in AAS group only at rest. The heart rate variability indexes were calculated from ECG using MATLAB-based algorithms. At rest, AAS group showed lower values of the standard deviation of R-R intervals, the proportion of adjacent R-R intervals differing by more than 50 ms (pNN50), the root mean square of successive differences (RMSSD), and the total, the low-frequency (LF)
and the high-frequency (HF) spectral power, as compared to Control group. After submaximal exercise testing, pNN50, RMSSD, and HF were lower, and the LF/HF ratio was higher in AAS group when compared to control group. Thus, the use of supraphysiological doses of AAS seems to induce dysfunction in tonic cardiac autonomic regulation in recreational trained subjects [080].

**QT-interval**

The association between physiologic levels of sex hormones and QT-interval duration in humans was evaluated using data from 727 men enrolled in the Third National Health and Nutrition Examination Survey and 2,942 men and 1,885 postmenopausal women enrolled in the Multi-Ethnic Study of Atherosclerosis. Testosterone, estradiol, and sex hormone-binding globulin levels were measured in serum and free testosterone was calculated from those values. QT interval was measured using a standard 12-lead electrocardiogram. In men from the Third National Health and Nutrition Survey, the multivariate adjusted differences in average QT-interval duration comparing the highest quartiles with the lowest quartiles of total testosterone and free testosterone were -8.5 ms (95 % confidence interval: -15.5 to -1.4) and -8.0 ms (95 % confidence interval -13.2, -2.8), respectively. The corresponding differences were -1.8 ms and -4.7 ms, respectively. Estradiol levels were not associated with QT-interval duration in men, but there was a marginally significant positive association in postmenopausal women. The findings suggest that testosterone levels may explain differences in QT-interval duration between men and women and could be a contributor to population variability in QT-interval duration among men [081].

Androgenic anabolic steroid (AAS) abuse is associated with changes in cardiac electrophysiology. Recently heart rate corrected QT interval (QTc) has been suggested as a method of screening for AAS use in athletes despite conflicting reports. This study aimed to further investigate the effect of AAS on QTc in a cohort of long-term AAS users in whom the affects may be more pronounced. Using a cross-sectional cohort design with AAS using resistance trained athletes (AS n = 15) and a group of non-AAS using resistance trained, age matched controls (C n = 15). AS had a long history of AAS use (18 ± 2 years) and AS and C both had >19 years of resistance training. Participants underwent a resting electrocardiogram (ECG), from which, the QTc interval was calculated using the Bazett formula. The main outcome measure was significant differences in mean corrected QTc between groups. A secondary outcome was to calculate a QTc that best differentiated between C and AS. Results indicated that QTc was shorter in AS than in C (382.0 ± 21.01 ms versus 409 ± 18.77 ms for AS and C respectively). Chi squared analyses revealed a greater incidence of QTc < 380 ms in AS versus C, specificity 93 % sensitivity 60 %). In conclusion these results supports previous findings that AAS use causes a reduction in QTc, however, the specificity and sensitivity in our sample is lower than reported previously and precludes use as a screening tool [082].

**Increased QT dispersion and short QT intervals**

In an electrophysiological study power athletes taking AAS were found to have increased QT dispersion and short QT intervals. The authors associated these changes with the manifestation of arrhythmias. In addition, in an experimental study it was found that the administration of nandrolone decanoate to rats led to a disturbance of cardiac autonomic nervous system function. It was also found analogous results in a study of athletes who used anabolic steroids, who presented a reduction in baroreflex sensitivity and maintained that anabolic steroids lead to degenerative changes in endomyocardial sympathetic neurons, resulting in the appearance of malignant arrhythmias. This degenerative mechanism is referred to as catecholamine myotoxicity [083].
Effect on Tp-E Interval, Tp-E/Qt Ratio, and Tp-E/Qtc ratio in male bodybuilders

The chronic consumption of androgenic anabolic steroids has shown to cause atrial arrhythmias. Several studies have suggested that the interval from the peak to the end of the electrocardiographic T wave (Tp-e) may correspond to the transmural dispersion of repolarization and that increased Tp-e interval and Tp-e/QT ratio are associated with malignant ventricular arrhythmias. The aim of on study was to evaluate repolarization dispersion measured from the 12-lead surface electrocardiogram (including Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio) in bodybuilders who are using anabolic androgenic steroids (AAS). It was selected a population of 33 competitive bodybuilders, including 15 actively using AAS for ≥ 2 years (users) and 18 who had never used AAS (nonusers), all men. QT, cQT, QTd, cQTd, JT, and cJT were significantly increased in AAS users bodybuilders compared to the nonusers. Tp-e interval, Tp-e/QT ratio, and Tp-e/cQT ratio were also significantly higher in AAS user group compared to the nonuser group. QRS duration was not different between the groups. There were negative correlation between Em and Tp-e, Tp-e/QT ratio, Tp-e/cQT ration. There were also negative correlation between Sm and Tp-e, Tp-e/QT ratio, Tp-e/cQT ration. In conclusion, it was presented a strong evidence suggesting that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTC ratio were increased in AAS users, which suggest that there might be a link between AAS use and ventricular arrhythmias and sudden death [084].

Experimental

Increased risk of ventricular arrhythmias in the rat

It was examined the influence of chronic administration of nandrolone decanoate with low-intensity endurance swimming exercise on susceptibility to lethal ventricular arrhythmias in rat. The animal groups included the control group, exercise group (EX), nandrolone group (Nan), vehicle group (Arach), trained vehicle group (Arach + Ex) and trained nandrolone group (Nan + Ex) that treated for 8 weeks. Then, arrhythmia induction was performed by intravenous infusion of aconitine and electrocardiogram recorded. Then, malondialdehyde (MDA), hydroxyproline (HYP) and glutathione peroxidase of heart tissue were measured. Chronic administration of nandrolone with low-intensity endurance swimming exercise had no significant effect on blood pressure, heart rate and basal ECG parameters except RR interval that showed increase. Low-intensity exercise could prevent the incremental effect of nandrolone on MDA and HYP significantly. It also increased the heart hypertrophy index and reduced the abating effect of nandrolone on animal weighting. Nandrolone along with exercise significantly increased the duration of VF and reduced the VF latency. The findings suggest that chronic co-administration of nandrolone with low-intensity endurance swimming exercise to some extent facilitates the occurrence of ventricular fibrillation in rat. Complementary studies are needed to elucidate the involved mechanisms of this abnormality [085].

Anabolic steroids used to improve muscular strength and performance in athletics. Its long-term consumption may induce cardiovascular adverse effects. It was assessed the risk of ventricular arrhythmias in rats which subjected to chronic nandrolone plus high-intensity endurance exercise. Animals were grouped as; control (CTL), exercise (Ex): 8 weeks under exercise, vehicle group (Arach): received arachis oil, and Nan group: received nandrolone decanoate 5mg/kg twice a week for 8 weeks, Arach+Ex group, and Nan+Ex. Finally, under anesthesia, arrhythmia was induced by infusion of 1.5 microg/0.1mL/min of aconitine IV and ventricular arrhythmias were recorded for 15min. Then, animals' hearts were excised and tissue samples were taken. Nandrolone plus exercise had no significant effect on blood pressure but decreased the heart rate and increased the RR and JT intervals of electrocardiogram. Nandrolone-exercise significantly increased the ventricular fibrillation (VF) frequency and also significantly decreased the VF latency. Combination of exercise and nandrolone could not recover the decreasing effects of nandrolone on animals weight gain.
but, it enhanced the heart hypertrophy index. In addition, nandrolone increased the level of hydroxyproline (HYP) and malondialdehyde (MDA) but had no significant effect on glutathione peroxidase of heart. Exercise only prevented the effect of nandrolone on HYP. Nandrolone plus severe exercise increases the risk of VF that cannot be explained only by the changes in redox system. The intensification of cardiac hypertrophy and prolongation of JT interval may be a part of involved mechanisms [086].

The objectives of one study were to investigate the time-course and the cellular, ionic and molecular processes underlying ventricular repolarization in rats chronically treated with AAS. Male Wistar rats were treated weekly for 8 weeks with 10 mg/kg of nandrolone decanoate (n=21) or vehicle (n=20). ECG was recorded weekly. Action potential and transient outward potassium current (I_{to}) were recorded in rat hearts. Expression of KChIP2, Kv1.4, Kv4.2, and Kv4.3 was assessed by real-time PCR. Hematoxylin/eosin and Picrosirius red staining were used for histological analysis. QTc was greater in the DECA group. After nandrolone treatment the left, but not right, ventricle showed a longer AP duration than did the control. I_{to} current densities were 48 percent lower in the left but not in the right ventricle after nandrolone. In the right ventricle the I_{to} inactivation time-course was slower than in the control group. After nandrolone treatment the left ventricle showed lower KChIP2 (approximately 26 %), Kv1.4 (approximately 23 %) and 4.3 (approximately 70 %) expression while the Kv 4.2 increased in 4 (approximately 250 %) and diminished in 3 (approximately 30 %) animals of this group. In the right ventricle the expression of I(to) subunits was similar between the treatment and control groups. Nandrolone-treated hearts had 25 percent fewer nuclei and greater nuclei diameters in both ventricles. The results strongly suggest that supraphysiological doses of AAS induce morphological remodeling in both ventricles. However, the electrical remodeling was mainly observed in the left ventricle [088].

Heart rate

Maximal heart rate

Previous study showed that muscle sympathetic nerve activity (MSNA) was augmented in anabolic steroids users (AASU). In one study, it was tested the hypothesis that the heart rate (HR) responses after maximal exercise testing would be reduced in AASU. Ten male AASU and 10 AAS nonusers (AASNU) were studied. Cardiopulmonary exercise was performed to assess the functional capacity and heart rate recovery. MSNA was recorded directly from the peroneal nerve by microneurography technique. Peak oxygen consumption (VO\textsubscript{2}) was lower in AASU compared to AASNU (44 ± 2 vs 53 ± 2 mL/kg/min). HR recovery (HRR) at first and second minute was lower in AASU than AASNU (21 vs 27 bpm, and 37 vs 45 bpm, respectively). MSNA was higher in AASU than AASNU (29 vs 20 bursts/min). Further analysis showed a correlation between HRR and MSNA, HRR at first minute and peak VO\textsubscript{2} and HRR at second minute and peak VO\textsubscript{2}. The exacerbated sympathetic outflow associated with a lower parasympathetic activation after maximal exercise, which impairs heart rate recovery, strengthens the idea of autonomic imbalance in AASU [089].

Heart rate recovery

Previous study showed that muscle sympathetic nerve activity (MSNA) was augmented in anabolic steroids users (AASU). In the present study, we tested the hypothesis that the heart rate (HR) responses after maximal exercise testing would be reduced in AASU. Ten male AASU and 10 AAS nonusers (AASNU) were studied. Cardiopulmonary exercise was performed to assess the functional capacity and heart rate recovery. MSNA was recorded directly from the peroneal nerve by microneurography technique. Peak oxygen consumption (VO\textsubscript{2}) was significantly lower in AASU compared to AASNU. HR recovery (HRR) at first and
second minute was significantly lower in AASU than AASNU. MSNA was higher in AASU than AASNU. Further analysis showed a correlation between HRR and MSNA, HRR at first minute and peak VO\textsubscript{2} and HRR at second minute and peak VO\textsubscript{2}. The exacerbated sympathetic outflow associated with a lower parasympathetic activation after maximal exercise, which impairs heart rate recovery, strengthens the idea of autonomic imbalance in AASU [090].

Reflex control in heart rate
The aim of one study was to analyze the cardiovascular effects of chronic stanozolol administration in male rats. The rats were randomly assigned to one of three groups: control (n=12), chronic treatment with low dose of stanozolol (LD, n=18, 5 mg/kg/week) and; treatment with high dose of stanozolol (HD, n=28, 20 mg/kg/week). Mean arterial pressure (MAP) was higher in both HD and LD than control. The LD group showed an increase in cardiac output, whereas in the HD group total peripheral resistance increased. Acute sympathetic blockade caused a similar decrease in MAP in all groups. In conscious rats, the baroreflex index for bradycardia and tachycardia responses changed only in the LD group. Cardiac hypertrophy was observed in both treated groups. In conclusion, hypertension with differential hemodynamic changes and alterations in the reflex control in heart rate is seen at different stanozolol doses, which may be important variables in the cardiovascular effects of anabolic steroids [091].

Arterial hypertension
The literature regarding the blood pressure response to AAS use is equivocal. In addition, there is currently little data available on the rate pressure product (RPP) response to anabolic androgenic steroids (AAS) use. The experimental aim of this study was to investigate the effects of AAS administration in combination with resistance training on blood pressure and rate pressure product in male amateur bodybuilders and compare the results with a morphologically matched, resistance trained control group. Subjects were divided into two groups (n=16 AAS users; n=16 controls). Systolic and Diastolic Blood Pressure, RPP, Resting Heart Rate and Body Composition measurements were obtained before (Pre), during (During) and 6-8 weeks following (Post) the AAS cycle in the AAS users with similar time intervals for the control group. No significant cardiovascular or morphological changes in the control group were found throughout the study. Significant increases in both diastolic and mean arterial blood pressures were found from Pre to Post cycle in the AAS group. RPP also increased significantly from pre to post AAS cycle. All cardiovascular parameters returned to normal baseline measurements between 6 and 8 weeks post cycle. No blood pressure measurements throughout the study were consistent with clinically defined hypertension. The findings indicate that the AAS group exhibited significant increases in standard cardiovascular measurements compared with the control bodybuilders, and provides a contraindication to AAS use especially in borderline hypertensives [092].

In a study conducted to evaluate the effects of the use and discontinuation of AAS on the cardiovascular system, both AAS users (140 ± 10 mmHg) and former users (130 ± 5 mmHg) had higher blood pressure than a control group of non-using weight lifters (125 ± 10 mmHg). Five of the 16 users, 2 of the 15 former users, and 1 of the 15 non-users in this study manifested blood pressure values at rest consistent with hypertension (values equal or greater than 140/90 mmHg) and higher blood pressure response in response to a physical exercise protocol. This phenomenon occurred despite the users having an average age of only 31 ± 5 years. In another study, the blood pressure of 16 subjects who performed an AAS cycle was significantly higher after 8 weeks than controls, and end values were compatible with hypertension. The blood pressure values returned to normal 8 weeks later, closing the cycle. The difference between these two studies related to blood pressure
returning to normal after discontinuation of the AAS treatment is the use for a short time in this second study. The transitory aspect of the blood pressure increase was corroborated. However, these data are insufficient to determine whether the extended use of AAS can cause irreversible blood pressure increases. The return of blood pressure values to initial conditions after treatment discontinuation still requires additional generalizable data, particularly related to the sample size, time of use, and dose of AAS [093].

Significant research attention has focused on the impact of AAS use on cardiovascular (CV) disease risk factors namely blood pressure, lipid profile, left ventricular (LV) mass, cardiac function and arterial function. Elevated systemic arterial blood pressure is associated with an increased CV disease risk. Compared to healthy controls, AAS users have increased resting and exercise systolic blood pressure. Conversely, other studies have not observed increased blood pressure in AAS users. Differences in the training level of the participants along with age could be responsible for the differences seen in these studies [094].

Although not shown in all studies, an association between elevated blood pressure and AAS abuse has been reported. Enhanced reactivity of the vasculature to norepinephrine, increased plasma renin activity, stimulation of aldosterone production by testosterone, and sodium retention by the kidneys are suggested mechanisms for high blood pressure following AAS use in athletes. Blood pressure response to androgen use typically shows a dose-response relation. The effects of AAS abuse on blood pressure may persist for long periods; some studies have shown persistent elevations for 5 to 12 months after discontinuing steroids [010].

In experimental studies it has been found that the administration of AAS leads to hypertension. An increase in the secretion of 11-deoxycorticosterone, norepinephrine, renin, or aldosterone has been implicated as a possible mechanism, while others have noted an increase in cardiac output and peripheral resistances. However, clinical studies in athletes have led to conflicting results. Some observed a significant increase in both systolic and diastolic blood pressure, whereas others noted only the latter. It has been attributed the increase in blood pressure in steroid-using athletes to an increase in plasma volume. In contrast, other authors found no significant increase in blood pressure at rest or during exercise in athletes who used steroids compared to non-users [083].

Systemic hypertension is a side effect of medical steroid administration and may require antihypertensive therapy; therefore, high-dose ASA use also should result in systemic hypertension. This is found in some reports, but not consistently. AAS-induced hypertension may be related to vascular endothelial response, increased responsiveness to catecholamines, and increased renin production. The magnitude and incidence of hypertension likely are related to dosage and to the specific AAS [020].

In a study conducted to evaluate the effects of the use and discontinuation of AAS on the cardiovascular system, both AAS users (140 ± 10 mmHg) and former users (130 ± 5 mmHg) had higher blood pressure than a control group of non-using weight lifters (125 ± 10 mmHg). Five of the 16 users, 2 of the 15 former users, and 1 of the 15 non-users in this study manifested blood pressure values at rest consistent with hypertension (values equal or greater than 140/90 mmHg) and higher blood pressure response in response to a physical exercise protocol. This phenomenon occurred despite the users having an average age of only 31 ± 5 years. In another study, the blood pressure of 16 subjects who performed an AAS cycle was significantly higher after 8 weeks than controls, and end values were compatible with hypertension. The blood pressure values returned to normal 8 weeks later, closing the cycle. The difference between these two studies related to blood pressure returning to normal after discontinuation of the AAS treatment is the use for a short time in this second study. However, these data are insufficient to determine whether the extended
use of AAS can cause irreversible blood pressure increases. The return of blood pressure values to initial conditions after treatment discontinuation still requires additional generalizable data – particularly related to the sample size, time of use, and dose of AAS [015].

Several studies investigating different AAS regimens showed no alteration in blood pressure (BP) in healthy strength athletes. However, in other investigations, an elevation of systolic or diastolic BP has been observed as a result of the administration of high doses of AAS. An elevation of BP may be present within 4 weeks of taking steroids. The most pronounced increase of diastolic pressure found an increase from 74 to 86 mmHg due to 10 weeks of self-administration of high-dose AAS. Increments of systolic BP of about 10 and 12 mmHg in normotensive strength athletes due to AAS have been reported. After drug cessation the BP seems to return to pre-steroid levels within several weeks. However, a prospective study could not confirm elevations of BP in athletes, even in those self-administering supratherapeutic doses of AAS for periods of up to 16 weeks. The available literature is thus not conclusive with respect to the effects of AAS on BP. It is suggested that elevations of systolic and/or diastolic BP may occur in some individuals; however, the effect does not seem to be consistent. Androgens seem to affect BP more than anabolic agents, although the exact mechanism remains to be established. However, if elevations of BP occur they seem to be small and transient, indicating that the impact on health status of the athlete may be limited [010].

**Vascular effects of anabolic steroids**

Regarding the vascular mechanisms of testosterone and its effects on blood vessels, a body of evidence suggests that one of testosterone’s beneficial cardiovascular effects is the vasodilation of systemic, coronary and pulmonary vessels. Mechanisms available from experimental studies have been proposed to explain testosterone induced vasodilation. Testosterone may influence the tonus of vascular smooth muscle cells by modulating the activity of several ion channels such as the voltage-sensitive potassium ion channels, non-ATP-sensitive potassium ion channels, calcium-activated potassium ion channels and L-type calcium ion channels. Whether the effect on only one type of channel is dominant or a concomitant effect on several types of channels produces vasodilation remains to be elucidated. In heart failure, the chief beneficial cardiovascular mechanism of testosterone seems to be primarily vascular and peripheral since peripheral vasodilation produces a reduced cardiac afterload and increased cardiac output. In addition, coronary vasodilation improves myocardial oxygenation which is important in heart failure patients with ischemic etiopathogenesis. However, the association of serum testosterone levels with clinical severity of heart failure seems to be present only in non-obese heart failure patients. In obese patients with heart failure, a lack of such association and comparably lower testosterone levels may suggest altered hormonal and hemodynamic mechanisms which could contribute to the obesity paradox and a better prognosis of such patients [007].

**Androgenic anabolic steroids and arterial structure and function**

The physiologic and pharmacologic effects of androgens on arterial structure and function are poorly characterized. Several lines of evidence implicate a pro-atherogenic effect. Epidemiologic studies demonstrate that cardiovascular disease is more prevalent and severe in adult men than in women at all ages. It has previously been observed that androgens may promote monocyte adhesion to endothelial cells and macrophage lipid loading. Regarding vascular function, androgens are associated with impaired arterial reactivity in genetic females taking high-dose androgenic steroids, and endothelial function is enhanced in androgen-deprived older men. In contrast, certain observations are consistent with an anti-
ischemic effect of androgens. Testosterone is an acute coronary vasodilator. Furthermore, although men have greater cardiovascular risk than women, men with low androgen levels have a higher risk of cardiovascular events. The vascular effect of androgens is important in assessing the potential influence of illicit androgenic anabolic steroid (AAS) use on arterial structure and function in healthy young athletes. One study examined arterial and cardiac structure and function in bodybuilders using androgenic anabolic steroids (AAS), compared to non-steroid-using bodybuilder controls. Adverse cardiovascular events have been reported in bodybuilders taking anabolic steroids. The cardiovascular effects of AAS, however, have not been investigated in detail. It was recruited 20 male bodybuilders (aged 35 ± 3 years), 10 actively using AAS and 10 who denied ever using steroids. Serum lipid and hormone levels, carotid intima-media thickness (IMT), arterial reactivity, and left ventricular (LV) dimensions were measured. Vessel diameter was measured by ultrasound at rest, during reactive hyperemia (an endothelium-dependent response, leading to flow-mediated dilation, FMD), and after sublingual nitroglycerin (GTN, an endothelium-independent dilator). Arterial reactivity was also measured in 10 age-matched non-bodybuilding sedentary controls. Use of AAS was associated with significant decreases in high density lipoprotein cholesterol, sex hormone binding globulin, testosterone and gonadotrophin levels, and significant increases in LV mass and self-reported physical strength. Carotid IMT arterial FMD and GTN responses were similar in both bodybuilding groups. The GTN responses were significantly lower and carotid IMT significantly higher in both bodybuilding groups, however, compared with the non-bodybuilding sedentary controls. It was concluded that although high-level bodybuilding is associated with impaired vascular reactivity and increased arterial thickening, the use of AAS per se is not associated with significant abnormalities of arterial structure or function [095].

**Vascular reactivity**

The use of supraphysiological doses of anabolic androgenic steroids can have serious side effects. One article reported the case of a young man who suffered potentially life-threatening arterial thromboses following the use of these drugs [096].

Anabolic androgenic steroids are used by some bodybuilders to enhance performance. While the cardiovascular implications of supraphysiological androgen levels requires further clarification, use is associated with sudden death, left ventricular hypertrophy, thromboembolism and cerebro-vascular events. To further understand the effect of androgenic anabolic steroid abuse on vascular function, this study assessed vascular stiffness (pulse-wave analysis) and cardiovascular risk factors in 28 male, bodybuilding subjects, of whom ten were actively receiving anabolic agents (group A; 26 years) and eight had undergone a 3-month "wash-out" period (group B; 32 years). The remaining ten bodybuilding subjects (group C; 24 years) denied any past use of anabolic steroids or other performance enhancing drugs. Comparisons were made with ten sedentary male controls (group D, 29 years). Endothelial independent dilatation in response to glycerol trinitrate was significantly impaired in the group currently using anabolic steroids (group A) compared with the other three groups, whereas no significant differences in endothelial-dependent dilatation were detected between the groups. Previous studies described a decline in vascular reactivity occurring in bodybuilding subjects which is independent of anabolic steroid use and may result from smooth muscle hypertrophy with increased vascular stiffness. This study revealed impaired vascular reactivity associated with anabolic agents and that improvement in vascular function may occur following their discontinuation [097].

**Impaired vasodilatation**

Although endogeneous testosterone has been shown to exert vasodilatory effects, AAS use in hypogonadal men has been shown to result in paradoxical pro-atherogenic
vasoconstrictive effects. It was shown that testosterone therapy in hypogonadal men is
correlated with impaired vasodilation, independently from lipid profile measures.
Supraphysiological doses of AAS have also shown to exert similar effects on vasoreactivity
in human and animal studies. In a study on male bodybuilders who abused AAS for 3-4
years, vasodilatation was significantly lower than that of ex-abusers and controls. AAS abuse
in body builders independently of the other factors impaired endothelium-independent
vasodilator pathways. It was also shown that a 3-month period of abstinence results in a
degree of improvement in vascular function. Moreover, longterm therapy with
supraphysiological doses of AAS in female-to-male transsexuals has shown to result in
decreased vasodilation independent of the effects of age, lipid profile and vessel size. The
mechanisms through which AAS induces deleterious effects on vasodilatation are not
sufficiently investigated. However, endothelial injury as a result of lipid profile alterati-
on of atherosclerosis could explain the impairment in endothelium-dependent
pathway through decreased NO production [048].

Arterial thrombosis

The use of supraphysiological doses of anabolic androgenic steroids can have serious side
effects. One article reports the case of a young man who suffered potentially life-threatening
arterial thromboses following the use of these drugs [096].

Coronary thrombus

A 23 year old male body builder presented with a recent onset of central chest pain. He was
a smoker with cholesterol concentration of 7.1 mmol/L on admission. He had been taking
anabolic steroids (methandrostenolone 20 mg daily) for three months. Anteroseptal T wave
inversion on a 12 lead ECG along with elevated troponin T prompted early coronary
angiography. This revealed multiple filling defects in the mid left anterior descending (LAD)
artery consistent with the presence of thrombus (below left). His LAD filled by collaterals from
the right coronary artery. The rest of his coronary arteries were smooth and unobstructed.
Repeat angiography was performed 48 hours later after treatment with abciximab, aspirin,
and low molecular weight heparin and revealed complete dissolution of all thrombus.
Intravascular ultrasound (IVUS) examination performed at this time revealed a segment of
eccentric atheroma at the site of the previous filling defects (below right); the echogenicity
was uniform with no focal echo lucent regions. The remainder of the LAD was normal at
IVUS examination. The patient made an uneventful recovery and was discharged well to
follow up. There have been several case reports of acute myocardial infarction in young male
athletes using anabolic steroids. The mechanism is unclear but may involve the adverse
effects on thrombosis and lipid profile. Some reports suggest thrombosis in “normal”
coronary arteries, but underlying atheroma cannot be excluded without IVUS. This case
supports the concept that both atheroma and the thrombogenic effects of anabolic steroids
may be necessary for vessel occlusion [098].

Vascular effects in the brain

Lacunar infarction is traditionally ascribed to lipohyalinosis or microatheroma. It was reported
a case of 40-year-old man, without traditional risk factors for ischemic stroke, who presented
to the Emergency Department with recurrent episodes of transient right-sided weakness and
paresthesia. Lacunar infarction was confirmed on diffusion-weighted MRI and blood tests
showed a marked polycythemia. Quantitative magnetic resonance perfusion imaging
demonstrated dramatically abnormal perfusion throughout both cerebral hemispheres, and
transcranial Doppler revealed reduced cerebral artery velocities, both consistent with the
proposed mechanism of hyperviscosity. His symptoms settled with treatment of the
polycythemia and workup did not find another cause of ischemic stroke. It was proposed that
hyperviscosity secondary to steroid-induced polycythemia caused ischemia in this case and
not lipohyalinosis or microatheroma, to which lacunar disease is commonly attributed [099].
It was reported a case of a 37-year-old man presented with acute stroke and hepatorenal impairment which were associated with anabolic-androgenic steroids (AAS) abuse over 2 years. Despite the absence of apparent symptoms and signs of congestive heart failure at presentation, an AAS-induced dilated cardiomyopathy with multiple thrombi in the left ventricle was attributed to be the underlying cause of his condition. Awareness of the complications of AAS led to the prompt treatment of the initially unrecognised dilated cardiomyopathy, and improved the liver and kidney functions. However, the patient was exposed to a second severe ischaemic event, which led to his death. This unique and complex presentation of AAS complications opens for better recognition and treatment of their potentially fatal effects [100].

**Endothelial cells**

The aim of one study was to investigate the effects in vitro induced by androgenic anabolic steroids (AAS) (testosterone, nandrolone, androstenedione, norandrostenedione, and norandrostenediol) used illicitly in sport competitions, on the proliferation ability, apoptosis and the intracellular calcium concentration ([Ca$^{2+}$]) in human umbilical vein endothelial cells (HUVECs), selected as a prototype of a biological target system whose structure and function can be affected by steroids. For this purpose, it was evaluated the proliferation inhibition by cytotoxic assay expressed as the concentration of drug inducing a 50 percent decrease in growth (IC$_{50}$). The IC$_{50}$ was reached for testosterone at 100 microM, androstenedione at 375 microM, nandrolone at 9 microM, norandrostenedione at 500 microM. The IC$_{50}$ value for norandrostenediol was not reached until a concentration of 6000 microM. The apoptotic effect was evaluated by flow cytometry at IC$_{50}$ for each drug. It was observed that testosterone induced 31 percent of apoptotic cells, norandrostenedione 25 percent, androstenedione 15 percent and nandrolone 18 percent. It was analyzed the effects of these drugs on [Ca$^{2+}$] both in the immediate and long-term continuous presence of each compound. The data show a statistically significant increase of [Ca$^{2+}$] in the acute condition and in long-term treated cultures, suggesting that androgen steroids modulate intracellular levels of calcium independent of incubation time or compound identity. As a whole, the study demonstrates that AAS might alter endothelial homeostasis, predisposing to the early endothelial cell activation that is responsible for vascular complications observed frequently in AAS users [101].

**Atherothrombotic markers and endothelial dysfunction**

The use of androgenic anabolic steroids (AAS) may be associated with changes in atherothrombotic markers and endothelial function. The purpose of one study was to compare atherothrombotic markers and endothelial function of AAS users and non-users. Ten athletes who were users of AAS (confirmed by urine analysis) and 12 non-user athletes were evaluated. Body weight, blood pressure, exercise load (hours/week), complete blood count (CBC), platelets, fibrinogen, lipids, high-sensitivity C-reactive protein (hs-CRP), follicle-stimulating hormone, testosterone and estradiol were measured. Endothelium-dependent and independent functions were assessed by brachial artery ultrasound. AAS users had significantly higher body mass and blood pressure. Platelet count was higher whereas HDL-cholesterol was lower in AAS users compared with non-users. Levels of hs-CRP were higher in AAS users. Follicle-stimulating hormone was suppressed in all users and not suppressed in non-users. Compared with non-users, flow-mediated dilation was significantly reduced in AAS users, whereas endothelium-independent function was similar in both groups. Additionally, flow-mediated dilation was positively associated with levels of HDL-cholesterol. AAS users present important changes in blood lipids as well as in inflammatory markers, which are compatible with increased cardiovascular risk. Furthermore, this profile is accompanied by a reduction in the endothelial function [102].
Flow-mediated, endothelium-dependent vasodilatation

Self-administration of anabolic-androgenic steroids to increase muscular strength and lean body mass has been used widely among athletes. Flow mediated dilatation (FMD) determined by ultrasound of the brachial artery is accepted as both an in vivo index of endothelial function and an indicator for future atherosclerosis. FMD was calculated in 20 male non-smoking body builders in different phases of their training cycle and in six male non-smoking control athletes. Ultrasound studies of the brachial artery were performed according to the protocol of Celermajer et al. Of the entire training cycle, work-out phase was training phase without actual intake of anabolic-androgenic steroids over 8 weeks; build-up phase included actual intake of anabolic-androgenic steroids; and competition phase consisted of 8 weeks post intake of anabolic-androgenic steroids. Baseline characteristics did not differ between body builder groups except for a higher weight in competition phase body builders. Hormonal analysis revealed suppressed luteinizing hormone and follicle stimulating hormone levels in build-up phase body builders. The lipid profiles showed a marked reduction of HDL-C in build-up phase body builders. FMD was reduced in body builders of all phases when compared to control athletes. The differences in FMD persisted after adjustment for vessel size. The data indicate that intake of anabolic-androgenic steroids is associated with both an atherogenic blood lipid profile and endothelial dysfunction and thus may pose an increased risk of atherosclerosis [103].

Increased intima-media thickness

AS use has also been associated with reduced endothelial function in conduit arteries. It was noted a reduced flow-mediated dilation in AS users as well as a reduced vasodilator response to glyceryl-trinitrate [050].

It has been measured carotid intima-media thickness and radial and brachial artery reactivity in bodybuilders using AAS. It was found a non-significant increase in the thickness and diameter of the arteries in users compared to non-users, which was attributed mainly to fluid retention. A small degree of endothelial dysfunction was also reported by other investigators. It was also found changes of aortic wall elasticity in athletes who used steroids. Moreover, using an electron beam tomography system, it was found increased calcium deposition in the coronary arteries of bodybuilders using AAS. The authors hypothesised that this was due to a direct toxic or inflammatory effect of steroids on the vascular endothelium [083].

Aortic elasticity

The use of anabolic-androgenic steroids (AAS) has been linked to acute cardiovascular events in athletes. The purpose of the present study was to investigate the aortic elastic properties in athletes who had been self-administering AAS compared with a group of athletes not using these drugs. Fourteen male bodybuilders using AAS and 27 male wrestlers (non-users) volunteered to the study. All subjects were placed in a mild recumbent position and the ascending aorta was recorded in the two-dimensional guided M-mode tracings. The aortic distensibility was found to be reduced in user athletes. The results of this study indicate that aortic stiffness is increasing in athletes using AAS [104].

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Aortic distensibility was found to be reduced in user athletes (2.1 ± 1.1 vs 3.8 ± 1.4 cm²/dyn 10⁶; 9.3 ± 3.7 vs 5.9 ± 2.5, respectively). The results of this study indicate that aortic stiffness is increasing in athletes using AAS [104].

Experimental: Aortic adaptations to exercise
In one study it was investigated the interaction between exercise-induced mitochondrial adaptation of large vessels and the effects of chronic anabolic androgenic steroids (AASs). Four groups of Sprague-Dawley rats were studied: (i) sedentary, (ii) sedentary + nandrolone-treated, (iii) aerobic exercise trained, and (iv) trained + nandrolone-treated. Aerobic training increased the levels of aortic endothelial nitric oxide synthase (eNOS) and heme oxygenase-1 (HO-1) in accordance with improved acetylcholine-induced vascular relaxation. These beneficial effects were associated with induction of mitochondrial complexes I and V, increased mitochondrial DNA copy number, and greater expression of transcription factors involved in mitochondrial biogenesis/fusion. It was also observed enhanced mitochondrial autophagy pathway activity, including increased conversion of LC3-I to LC3-II and greater expression of beclin1 and autophagy-related protein-7 (ATG7). The levels of thiobarbituric acid-reactive substances and protein carbonyls remained unchanged, whereas significant increases in catalase and mitochondrial manganese superoxide dismutase (MnSOD) levels were observed in the aortas of trained animals, when compared with sedentary controls. Nandrolone increased oxidative stress biomarkers and inhibited exercise-induced increases of eNOS, HO-1, catalase, and MnSOD expression. In addition, it also attenuated elevated peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha) and mitofusin-2 expression, and further up-regulated LC3II conversion, beclin1, ATG7, and dynamin-related protein-1 expression. These results demonstrate that nandrolone attenuates aortic adaptations to exercise by regulating mitochondrial dynamic remodelling, including down-regulation of mitochondrial biogenesis and intensive autophagy [105].

Stroke
Anabolic-androgenic steroids are synthetic substances derived from testosterone that are employed for their trophic effect on muscle tissue, among other uses. Their consumption can give trigger a series of adverse side effects on the body, including the suppression of the hypothalamus-pituitary-gonadal axis as well as liver, psychiatric and cardiovascular disorders. The most common effects are altered fat profiles and blood pressure values, cardiac remodelling, arrhythmias or myocardial infarcts. It was reported a case of a young male, with a background of anabolic-androgenic steroids abuse, who visited because of an acute neurological focus in the right hemisphere related with an ischaemic stroke. The etiological study, including cardiac monitoring, echocardiograph and imaging studies (magnetic resonance and arteriography) and lab findings (thrombophilia, serology, autoimmunity, tumor markers) showed no alterations. Thus, the association between consumption of anabolic-androgenic steroids and cardiovascular pathologies is known, but its relation with cerebrovascular disease has not received so much attention from researchers [106].

Popliteal-artery entrapment syndrome
The popliteal-artery entrapment syndrome is a potentially serious but rare cause of ischemia of the legs. It occurs predominantly in young persons and is due to an abnormal anatomical relation between the popliteal artery and the tendinous insertion of the gastrocnemius muscle. Usually, symptoms arise when there is occlusion of the functional artery during contraction of the calf muscle; arterial thrombosis is a rare cause. Abuse of anabolic steroids has increased in frequency during the past decade and is associated with a documented risk of acute coronary-artery and peripheral-artery thrombosis. It was described the occurrence of thrombotic occlusion of the popliteal artery in an athlete with the popliteal-artery entrapment
syndrome who abused anabolic steroids. It was speculated that the abuse of anabolic steroids, as a result of their prothrombotic action and promotion of muscle hypertrophy, may have led to the popliteal-artery entrapment syndrome in this patient. Athletes and the medical community should be aware of this potential complication of the use of anabolic steroids [107].

Other vascular effects

Reported severe adverse effects of anabolic-androgenic steroid use include cerebral venous sinus thrombosis, ischemic cerebral stroke, and cardiovascular events in the absence of risk factors. Two cases of limb-threatening arterial thrombosis were reported with the use of danazol (Danocrine®), an antigonadotropin steroid-like compound with weak anabolic properties [108].
CARDIAC MORPHOLOGY ALTERATIONS DUE TO ANABOLIC STEROIDS

Cardiac structure and functioning

The harmful cardiovascular effects of indiscriminate use of AAS to the cardiac structure and functioning can include increased cardiac tissue collagen, imbalance of vasomotor tone, reduction in the number of capillaries, and pathological cardiac hypertrophy in animal and human models. In addition, supraphysiological doses of AAS have already demonstrated that they may inhibit angiogenesis induced by physical training. In a study involving 152 men (between 18 and 40 years of age), non-athletes (n=52), strength-endurance athletes (n=52), and athletes (n=52) who admitted using AAS, showed ventricular volumes and ventricular wall thickness statistically higher than in non-users, and lower ejection fraction in both ventricles. An increase in cardiac collagen can induce electrophysiological changes in the myocardium with abnormal propagation of the excitation wave favoring tachycardia, which may explain the repeated occurrence of sudden death in users of AAS. But this possibility is raised based on a case report of a user 31 years of age. On the other hand, another study reports other factors occurring after massive doses of AAS for several years, namely, a case of ventricular fibrillation during exercise, one heart failure, and arterial thrombus in the lower left leg. Interestingly, all these patients had increased cardiac hypertrophy and fibrosis in the myocardium. It is certain that the character of case reports makes these inconsistent data. The development of experimental models is useful in helping us better understand the deleterious effects of SEA on cardiovascular tissue, but must consider the obvious limitations of extrapolating data to humans. So that our knowledge of this adverse effect is dependent on cases recorded and documented in the scientific literature. Owing to this limitation, it was also investigated the effect of administration of nandrolone decanoate in rats for 10 weeks, associated with swim training. They found a 10 percent increase in cardiac hypertrophy in rats treated with nandrolone decanoate and 17 percent who had been administered this drug associated with physical training, which were significantly higher than that found in mice not treated with the drug [109].

TNF-alpha

The exact mediators of myocardial hypertrophy are diverse and vary from mechanical stimuli to circulating humoral factors released by the heart and peripheral organs. Exercise-induced cardiac hypertrophy is thought to be due to increases in the pre-load (diastolic filling) on the heart, while the exact mechanisms for anabolic steroid-induced myocardial hypertrophy are at present unknown. Recent studies have shown that circulating cytokines such as TNF-alpha may play a role in cardiac remodeling and that anabolic steroids strongly stimulate leukocyte TNF-alpha production. The question of whether a link exists between anabolic steroid use, serum and myocardial TNF-alpha concentrations and myocardial hypertrophy remains to be established. Exercise training in rats has been shown to improve myocardial resistance to ischaemia-reperfusion injury. In addition, exercise-induced physiological cardiac hypertrophy alters the heart’s susceptibility to ischaemia and reperfusion and renders it more resistant to ischaemia-reperfusion injury in in vivo rat hearts. These changes were associated with an increased energy charge and decreased lipid peroxidation during ischaemia and reperfusion in the hearts from these animals. What, however, remains unclear is whether anabolic steroid-induced hypertrophy alters the susceptibility of the heart to ischaemia-reperfusion injury. In addition, should these hearts be more susceptible to ischaemia-reperfusion injury, the mechanisms that contribute to this phenomenon need to be elucidated. TNF-alpha has been implicated in ischaemia/reperfusion injury. Mice devoid of myocardial TNF-alpha (knockouts) have been shown to be more resistant to ischaemia-reperfusion injury than their wild-type counterparts and treatment of rat hearts with anti-murine TNF-alpha antibody before ischaemia also improved reperfusion function of these hearts. Besides cytokines, elevations in cytosolic cAMP concentrations during ischaemia
would be expected to increase cytosolic calcium concentrations and exacerbate ischaemia-
reperfusion injury in this model of ischaemia and reperfusion. Interestingly, the basal
myocardial cAMP concentrations are elevated by anabolic androgenic steroids in isolated rat
atrial muscle and contribute to the positive inotropic response observed with steroid
treatment. These recent findings suggest that anabolic steroids could also potentially
promote calcium overload during ischaemia in the anabolic steroid-treated heart. The final
question remains whether chronic anabolic steroid treatment alters ventricular myocardial
cAMP concentrations, and if so, what the effects of this alteration are on susceptibility to
ischaemia-reperfusion injury. Several studies have also suggested that there is a correlation
between myocardial cAMP and cGMP concentrations and that the ratio between these cyclic
nucleotides during ischaemia may be important in determining the severity of
ischaemia/reperfusion injury. The effects of anabolic steroids on NO-cGMP pathway activity,
as assessed by measuring myocardial cGMP concentrations, also remain unknown [110].

Experimental
Anabolic androgenic steroids lead to cardiac complications and have been shown to exhibit
proapoptotic effects in cardiac cells; however, the mechanism involved in those effects is
unclear. The aim of one study was to assess whether apoptosis and the activation of
caspase-3 (Casp-3) induced by testosterone in high concentrations involves increments in
tumor necrosis factor-alpha (TNF-alpha) concentrations and angiotensin-converting enzyme
(ACE) activity in cardiomyocytes (H9c2) cell cultures. Cardiomyocytes were treated with
testosterone (5 × 10⁻⁶ mol/L), doxorubicin (9.2 × 10⁻⁶ mol/L), testosterone + etanercept (Eta;
6.67 × 10⁻⁵ mol/L), testosterone + losartan (Los; 10⁻⁷ mol/L), and testosterone + AC-DEVD-
CHO (10⁻⁵ mol/L; Casp-3 inhibitor). Apoptosis was determined by flow cytometry and by the
proteolytic activity of Casp-3. It was demonstrated that incubation of H9c2 cells for 48 h with
testosterone causes the apoptotic death of 60-70 percent of the cells and co-
treatments with Eta, Los, or AC-DEVD-CHO reduced this effect. Testosterone also induces apoptosis
(concentration dependent) and increases the proteolytic activity of Casp-3, which were
reduced by co-treatments. TNF-alpha and ACE activities were elevated by testosterone
treatment, while co-treatment with Los and Eta reduced these effects. It was concluded that
an interaction between testosterone, angiotensin II, and TNF-alpha induced apoptosis and
Casp-3 activity in cultured cardiomyocytes, which contributed to the reduced viability of these
cells induced by testosterone in toxic concentrations [111].

Cardiopulmonary reflex and cardiac cytokines

One study evaluated the effects of nandrolone associated with resistance training (RT) on
cardiac cytokines, angiotensin-converting enzyme activity (ACEA), and the sensitivity of the
Bezold-Jarisch reflex (BJR). Male Wistar rats were divided into 3 groups: CONT (received
vehicle, no training); EXERC (RT: after one week of water adaptation, rats were exercised by
jumping into water twice a week for 4 weeks), and ND+EXERC (received nandrolone
decanoate 10 mg/kg, twice/week, i.m, associated with RT). The BJR was analysed by
measuring bradycardic and hypotensive responses elicited by serotonin administration.
Myocyte hypertrophy and matrix collagen deposition were determined by morphometric
analysis of H&E and picrosirius red-stained samples, respectively. TNF-alpha and ACEA
were also studied. RT promoted physiological myocyte hypertrophy but did not cause
changes in the other parameters. The association of ND with RT increased myocyte
hypertrophy, deposition of matrix type I collagen, TNF-alpha and ACEA; decreased IL-10,
and impairment in the BJR were observed in ND+EXERC compared with CONT and
EXERC. ND is associated with alterations in cardiac structure and function as a result of the
development of pathological cardiac hypertrophy (cardiac cytokine imbalance, elevation of
ACEA) and cardiac injury, even when combined with resistance training [112].
Anabolic androgenic steroids (AAS) are used by some athletes to enhance performance despite the health risk they may pose in some persons. This work was carried out to evaluate the possible structural and functional alterations in the heart using two-dimensional, M-mode, tissue Doppler imaging (TDI) and strain rate imaging (SRI) in athletes using supraphysiological doses of AAS. Additionally, the histological and ultrastructural changes in cardiac muscles of adult albino rats after injection of sustanon, as an example of AAS, were studied. Fifteen male bodybuilders using anabolic steroids constituted group 1, five male bodybuilders who are not using anabolic steroids constituted group 2, and five nonathletic males constituted negative control group (group 3). They were investigated by two-dimensional, M-mode, TDI and SRI. Moreover, a study was performed on 30 adult albino rats. They were divided into two groups. Group I (Control group) (n=10) was subdivided into negative control, subgroup 1a (n=5), and subgroup 1b (n=5), which received 0.8 ml olive oil intramuscularly once a week for 8 weeks. Group II (Experimental group) (n=20) received sustanon 10 mg/kg intramuscularly once a week for 8 weeks. The heart specimens were prepared for light microscopy and transmission electron microscopy. Echocardiographic results showed that bodybuilders who use steroids have smaller left ventricular dimension with thicker walls, impaired diastolic function, as well as higher peak systolic strain rate in steroid-using bodybuilders as compared to the other two groups. Light microscopy examination of cardiac muscle fibers showed focal areas of degeneration with loss of striations and vacuolation in the experimental group. Ultrastructural examination showed disturbance of the banding pattern of the cardiac muscle fiber with disintegration, loss of striations, dehiscent intercalated disc, and interrupted Z-bands. Administration of supraphysiological doses of AAS caused severe deleterious effects in the myocardium both in athletes and in experimental animals. The SRI shows promise in the early detection of systolic dysfunction in those athletes who use steroids [113].

Infiltration of eosinophils into myocardial cells

Experimental studies have demonstrated that AAS abuse leads to skeletal muscle hypertrophy and increased collagen accumulation; changes that are similarly detected in the myocardium. Studies in rats and mice have shown that AAS abuse leads to both myocardial hypertrophy and fibrosis, destruction of the mitochondria and other elements of the cardiomyocytes, disturbances of the microcirculation, and to a deterioration in systolic function and to diastolic dysfunction. Post-mortem studies of athletes who used AAS have found infiltration of eosinophils into myocardial cells, as well as destruction of myofibrils. Endothelial dysfunction was also observed [083].

Cardiac fibrosing

Several studies have demonstrated changes in the cardiac functioning aspects of AAS users, especially on diastolic functioning. Diastolic dysfunction has been strongly associated with collagen deposition. Fibrillar collagens, types I and III, are the major structural proteins of the myocardial collagen matrix, exerting an important influence on ventricular compliance. Exposure to supraphysiological doses of AAS can lead to tissue necrosis and diastolic dysfunction, resulting in structural changes similar to those seen in the earlier stages of heart failure. There are several mechanisms that appear to be related to cardiac hypertrophy and collagen accumulation. AAS can induce such hypertrophy through nuclear receptors, acting directly on RNA and increasing the protein synthesis and acting as well on specific enzymes, on ions flow and the structural matrix in the myocardium. Increased circulating pro-inflammatory cytokines such as TNF-alpha and increased cAMP concentration have been documented, which contributes to the positive inotropic response through the calcium in the cytosol of the myocardial cell. However, the exact mediators of such effects are diverse and
not fully elucidated [015].

A 2005 study reported two cases of sudden cardiac death in young male athletes related to AAS abuse. Both cases involved healthy individuals without any history of coronary artery disease (CAD) and with no evidence of significant abnormality in arterial microscopic examination. Autopsy of both hearts showed focal myocardial fibrosis suggestive of prior myocardial injury. In a study of a sudden unexpected death in a female fitness athlete using steroids and ephedrine, the only pathological finding was a few small foci of granulation tissue, which was interpreted as evidence of earlier myocardial necrosis. Sudden cardiac arrhythmia resulting from inflammatory process and myocardial fibrosis was suggested to be the cause of death in these cases. Other researchers have reported sudden cardiac deaths related to steroids that also showed myocardial fibrosis in the absence of CAD [010].

A study recently published describes the potentially beneficial cellular effects of testosterone against cardiac fibrosis. In a rat model, it was observed that testosterone inhibited cardiac fibroblast migration and proliferation in addition to myofibroblast differentiation induced by transforming growth factor-beta1. Moreover, the authors suggested that modulated cell signaling and response of cardiac fibroblasts through a decreased production of collagen after stimulation by transforming growth factor-beta1 and angiotensin II is the mechanism by which testosterone may attenuate cardiac fibrosis and progression of heart failure [007].

One study explores another possible cardiac mechanism of testosterone – a modulatory role in cardiac fibrosis. The authors reported no change in baseline cardiac fibroblast proliferative and migration potential, but described an androgen receptor-mediated antiproliferative, anti-collagen and anti-fibrotic effect of physiological testosterone levels in the myocardium unaffected by a pathological process. Although they recognized that the cardiac fibroblasts were from normal hearts, the authors' conclusion was that testosterone decreased the production of collagen after transforming growth factor-beta1 and angiotensin II stimulation which can attenuate the genesis of cardiac fibrosis under pathological conditions. However, this sounds rather speculative because in pathological conditions, testosterone effects could be quite the opposite. Cardiac remodeling is characterized by removal of destroyed necrotic tissue, formation of scar tissue, compensatory myocyte hypertrophy and enlargement of the affected cardiac chamber. An important study has investigated the impact of sex hormones on cardiac remodeling after myocardial infarction in a mouse model and showed that testosterone worsened cardiac dysfunction and remodeling in both sexes. Testosterone was linked to decreased ejection fraction, increased left ventricular dimension and increased myocyte size. A detrimental chronic effect on postinfarction healing and aggravation of cardiac dysfunction was observed through the association of testosterone with occurrence of cardiac rupture and lethal outcome. In male mice, both castration and estrogen supplementation reduced the occurrence of most of those adverse testosterone effects [007].

The mechanisms of a profound impact of sex hormones on cardiac fibrosis and remodeling in both healthy and diseased hearts must be further explored. Such mechanisms are only a part of cardiac effects which act in concert with peripheral mechanisms and are exceptionally important for a growing population of patients with heart failure. There is a possibility that normal testosterone levels within a physiological range have beneficial biological effects only in relatively healthy individuals from the cardiovascular point of view. Conversely, in aged or diseased hearts, like those after myocardial infarction or in obesity, when the pathological cascade of myocardial remodeling has already started, higher testosterone may have a detrimental effect. Certainly we should more clearly delineate the conditions in which higher testosterone is useful from the conditions where it may have adverse effects [007].

Experimental
Cardiac aldosterone might be involved in nandrolone decanoate (ND) deleterious effects on the heart. Therefore, it was investigated the involvement of cardiac aldosterone, by the
pharmacological block of AT1 or mineralocorticoid receptors, on cardiac hypertrophy and fibrosis. Male Wistar rats were randomized into 8 groups (n=14/group). Nandrolone (10 mg/kg/week), was administered during 10 weeks of swimming training (5 times/wk). Losartan (20 mg/kg/day) and spironolactone (10mg/kg/day) were administered in drinking water. Cardiac hypertrophy was increased 10 percent by using nandrolone and 17 percent by nandrolone plus training. In both groups, there was a significant increase in the collagen volumetric fraction (CVF) and cardiac collagen type III expression. The nandrolone treatment increased: LV-ACE activity, AT1 receptor expression, aldosterone synthase (CYP11B2) and 11-beta hydroxysteroid dehydrogenase 2 (11betaHSD2) gene expression and inflammatory markers, TGFbeta and osteopontin. Both losartan and spironolactone inhibited the increase of CVF and collagen type III. In addition, both treatments inhibited the increase in LV-ACE activity, CYP11B2, 11betaHSD2, TGFbeta and osteopontin induce by the nandrolone treatment. The results suggest that these effects may be associated to TGFbeta and osteopontin. Thus, it was conclude that the cardiac aldosterone has an important role on the deleterious effects on the heart induced by nandrolone [114].

Effects of methyltestosterone on collagen strands in vitro
Testosterone analogs have been used as performance enhancers by athletes for more than 40 years. It was asked whether the anabolic steroid 17 alpha-methyl-4-androstene-17-ol-3-one (17 alpha-MT) would affect intrinsic contractile function of the heart. Male Sprague-Dawley rats, 125-150 g, were treated with 17 alpha-MT either parenterally or orally for up to 8 wk. Intrinsic contractile function of the hearts was assessed utilizing both the isolated working heart and isovolumic perfused heart preparations. Isolated working hearts from 17 alpha-MT-treated rats had a 45 percent decrease in heart work attributable largely to a similarly decreased stroke volume. Isovolumic perfused hearts from treated animals had elevated left ventricular systolic and diastolic pressures at similar interventricular volumes compared to controls. Rates of ventricular pressure development (+dP/dT) or relaxation (-dP/dT) were unchanged as a result of the treatment. However, static elastance was reduced in potassium-arrested hearts from the 17 alpha-MT treatment (63 % increase in interventricular pressure), consistent with a limitation being imposed on stroke volume by a decreased myocardial compliance. Hydroxyproline content of the hearts was not altered by 17 alpha-MT treatment suggesting that increased stiffness was not a consequence of collagen proliferation. Treatment of the steroid rats with beta-aminopropionitrile, a compound that inhibits lysyl oxidase, restored the left ventricular volume-pressure relationship (elastance curve) to that of control hearts. Thus, chronic treatment with anabolic steroids appears to reduce left ventricular compliance, possibly related to an enhanced activity of lysyl oxidase, and results in increased crosslink formation between collagen strands in the extracellular matrix [115].

Experimental

Impaired exercise-induced growth of the cardiac capillary bed
Concomitant application of anabolic-androgenic steroids and physical exercise can induce cardiac hypertrophy. These experiments investigate the still unknown response of the cardiac myocytes and capillaries to the combined influence of various anabolic steroids and muscular exercise. Female SPF-NMRI mice were divided into the following groups: a) sedentary control, b) exercise (treadmill running); c) sedentary receiving Dianabol; d) exercise + Dianabol; e) exercise + Oral-Turinabol. After 3 and 6 weeks the left ventricular papillary muscles were studied morphometrically. Evaluated variables: minimal myocyte diameter, number of capillaries around a single myocyte, capillary density and intercapillary distance. Only the anabolic steroids + exercise groups showed a mild myocyte hypertrophy. In contrast, only exercise alone caused a significant increase of the capillary density after both experimental periods; e.g. capillary density after 6 weeks. Moreover, unlike all other regimens, only exercise alone shortened the intercapillary distance. Finally, exercise without
drugs induced the greatest increase in the number of capillaries around a single myocyte. It was concluded that anabolic steroids combined with exercise: 1) induce mild hypertrophy of the cardiac myocytes, 2) impair the cardiac microvascular adaptation to physical conditioning. The microvascular impairment may cause a detrimental alteration of the myocardial oxygen supply, especially during muscular exercise [116].

**Hypertrophy of cardiomyocytes**

To investigate the effects of exercise training and anabolic androgenic steroids (AAS) on hemodynamics, glycogen content, angiogenesis, apoptosis and histology of cardiac muscle. Forty rats were divided into 4 groups; control, steroid, exercise-trained and exercise-trained plus steroid groups. The exercise-trained and trained plus steroid groups, after one week of water adaptation, were exercised by jumping into water for 5 weeks. The steroid and trained plus steroid groups received nandrolone decanoate, for 5 weeks. Systolic blood pressure and heart rate (HR) were monitored weekly. Heart weight/body weight ratio (HW/BW ratio) was determined. Serum testosterone, vascular endothelial growth factor (VEGF), cardiac caspase-3 activity and glycogen content were measured. Compared with control, the steroid group had significantly higher blood pressure, HR, sympathetic nerve activity, testosterone level, HW/BW and cardiac caspase-3 activity. Histological examination revealed apoptotic changes and hypertrophy of cardiomyocytes. In exercise-trained group, cardiac glycogen, VEGF and testosterone levels were significantly higher while HR was significantly lower than control. HW/BW was more than control confirmed by hypertrophy of cardiomyocytes with angiogenesis on histological examination. Trained plus steroid group, had no change in HR, with higher blood pressure and HW/BW than control, cardiac glycogen and serum VEGF were higher than control but lower than exercise-trained group. Histological examination showed hypertrophy of cardiomyocytes with mild angiogenesis rather than apoptosis. Thus, when exercise is augmented with AAS, exercise-associated cardiac benefits may not be fully gained with potential cardiac risk from AAS if used alone or combined with exercise [117].
SUDDEN DEATH AFTER USING ANABOLIC STEROIDS

Overviews

Several classes of recreational and prescription drugs have additional effects on the heart and vasculature, which may significantly contribute to morbidity and mortality in chronic users. The study presented herein focuses on pathological changes involving the heart possibly due to anabolic androgenic steroid use. The role these hormones may play in their occurrence of sudden cardiac death is also investigated. 98 medico-legal cases including 6 anabolic androgenic steroid users were retrospectively reviewed. Autopsies, histology, immunohistochemistry, biochemistry and toxicology were performed in all cases. Pathological changes consisted of various degrees of interstitial and perivascular fibrosis as well as fibroadipous metaplasia and perineural fibrosis within the myocardium of the left ventricle. Within the limits of the small number of investigated cases, the results appear to confirm former observations on this topic and suggest anabolic androgenic steroid's potential causative role in the pathogenesis of sudden cardiac deaths in chronic users [118].

Cardiovascular disorders are known to be the most common cause of sudden death during exercise. In younger athletes (below 45 years) this is due in the majority of cases to congenital heart diseases, while in older people atherosclerosis is the primary cause. There is, however, a non-negligible percentage of disorders of the cardiovascular system, even sudden cardiac death (SCD), that are attributable to the use of performance-enhancing drugs, either prohibited (doping) or legal. The users can be athletes, professional or amateur, or just people engaging in exercise in gyms or fitness and leisure centres, while both sexes and all age groups are involved. Seeking to improve their performance, according to the event in which they participate, most athletes use a combination of prohibited substances and methods, or of prohibited and non-prohibited drugs, so as to alleviate the complications and/or to avoid being detected by screening. The most common and serious consequences of almost all illicit drugs in sport concern the cardiovascular system. These disorders, such as hypertension, cardiac arrhythmias, and acute myocardial infarction, may be manifested either directly, or as the result of long-term use. Frequent complications may also occur in other organs. Specifically, anabolic steroids have been implicated in liver cirrhosis and liver or kidney cancer, growth hormone in diabetes mellitus, erythropoietin in thromboembolic episodes, central nervous system stimulants in psychotic syndromes, and so on. Apart from the prohibited substances, however, cardiovascular disorders may be caused by other substances commonly used in sports, such as dietary supplements [083].

Anabolic androgenic steroids (AASs) represent a large group of synthetic derivatives of testosterone, produced to maximize anabolic effects and minimize the androgenic ones. AAS can be administered orally, parenterally by intramuscular injection and transdermally. Androgens act by binding to the nuclear androgen receptor (AR) in the cytoplasm and then translocate into the nucleus. This binding results in sequential conformational changes of the receptor affecting the interaction between receptor and protein, and receptor and DNA. Skeletal muscle can be considered as the main target tissue for the anabolic effects of AAS, which are mediated by ARs which after exposure to AASs are up-regulated and their number increases with body building. Therefore, AASs determine an increase in muscle size as a consequence of a dose-dependent hypertrophy resulting in an increase of the cross-sectional areas of both type I and type II muscle fibers and myonuclear domains. Moreover, it has been reported that AASs can increase tolerance to exercise by making the muscles more capable to overload therefore shielding them from muscle fiber damage and improving the level of protein synthesis during recovery. Despite some therapeutic use of AASs, there is also wide abuse among athletes especially bodybuilders in order to improve their performances and to increase muscle growth and lean body mass, taking into account the significant anabolic effects of these drugs. The prolonged misuse and abuse of AASs can determine several adverse effects, some of which may be even fatal especially on the
cardiovascular system because they may increase the risk of sudden cardiac death (SCD), myocardial infarction, altered serum lipoproteins, and cardiac hypertrophy. The aim of one review was to focus on deaths related to AAS abuse, trying to evaluate the autopic, histopathological and toxicological findings in order to investigate the pathophysiological mechanism that underlines this type of death, which is still obscure in several aspects. The review of the literature allowed us to identify 19 fatal cases between 1990 and 2012, in which the autopsy excluded in all cases, extracardiac causes of death [118].

There have been several cases described of sudden death, SCD, in athletes using AAS. However, the frequency and the pathophysiological mechanism of SCD remain unknown. Some researchers have concluded that AAS have an arrhythmogenic action, while others believe that SCD is a secondary event, resulting from the cardiovascular side effects caused by their abuse. Cases of atrial fibrillation and ventricular tachycardia have also been described in athletes users. It has been suggested that the chronic administration of anabolic agents prolongs and increases the inhomogeneity of repolarisation, thus creating an arrhythmogenic substrate. These disturbances are more apparent in athletes with significant cardiac hypertrophy as an adaptation to long term exercise training (“athlete’s heart”) or to the use of anabolic substances [083].

**Forensic cases**

Sudden death is the most frightening consequence of AAS use. The etiology of these events likely is multifactorial, with AAS use contributing to the observed pathology. There are case reports of myocardial infarctions, stroke, and peripheral vascular obstruction from thrombus that likely are related to the changes in platelet function, inflammation, and cholesterol metabolism discussed above. Autopsies of 34 users of AASs found chronic cardiac changes consisting of cardiac hypertrophy, myocardial fibrosis, and coronary artery atheromatous changes in 12 victims, although these were believed to contribute to the deaths of only 2 victims. Many sudden death events among AAS users have been due to ischemia secondary to coronary artery disease; however, there is a report of ventricular tachycardia during exercise testing of an AAS user who had myocardial fibrosis on biopsy. Other case reports of sudden death demonstrate diffuse, patchy fibrotic changes in the myocardium of AAS users without coronary artery atherosclerosis. The presence of scar or infiltrative processes is commonly believed to be a cause for arrhythmia. The exact cause of sudden death in AAS users is unclear but likely is due to ischemia or arrhythmia [020].

Anabolic-androgenic steroids (AASs) are frequently misused. To determine causes of death, characteristics, toxicology, and pathology of AAS positive cases, all cases (n=24) presenting to the New South Wales Department of Forensic Medicine (1995-2012) were retrieved. All were male, and the mean age was 32 years. Deaths were mainly due to accidental drug toxicity (63 %), then suicide (17 %) and homicide (13 %). Abnormal testosterone/epitestosterone ratios were reported in 63 percent, followed by metabolites of nandrolone (58 %), stanozolol (33 %), and methandienone (21 %). In 23 of 24 cases, substances other than steroids were detected, most commonly psychostimulants (67 %). In nearly half, testicular atrophy was noted, as was testicular fibrosis and arrested spermatogenesis. Left ventricular hypertrophy was noted in 30 percent, and moderate to severe narrowing of the coronary arteries in 26 percent. To summarize, the typical case was a male polydrug user aged in their thirties, with death due to drug toxicity. Extensive cardiovascular disease was particularly notable [119].

Among 15,000 forensic post-mortem examinations performed on the coroner's order over a 24-year period (1981-2004) in the area of Lyon, France (population: 2,000,000), 2250 cases of unexpected cardiac sudden death were identified retrospectively according to WHO
criteria. Of these, 108 occurred during recreational sport and 12 occurred in athletes. In the latter category, a history of anabolic steroid abuse was found in 6 cases, whereas pre-existing ordinary cardiac lesions were observed in the 6 remaining cases. To shed light on the possible role of anabolic steroids in the induction of cardiac lesions, an experimental study was conducted in rabbits that were treated orally with norethandrolone 8mg/kg/day for 60 days, and sacrificed at day 90. The histopathological examination of the heart from treated animals showed coronary thrombosis associated with left ventricle hypertrophy in 3 cases, and lesions analogous to toxic or adrenergic myocarditis in all other treated animals. These findings were very similar to those observed after cardiac sudden death in the 6 athletes with a history of anabolic steroid abuse. In addition, elevated caspase-3 activity in the heart of treated rabbits as compared to controls suggests that apoptosis is involved in the induction of norethandrolone-induced cardiac lesions. These results confirm the cardiotoxic potential of anabolic steroid abuse [120].

Sudden death among athletes is very rare (1:50,000-1:100,000 annually) but it is still 2-4 times more frequent than in the age-matched control population and attracts significant media attention. It was proposed a mechanism underlying sudden cardiac death in athletes that does not relate to myocardial ischemia but is based on repolarization abnormalities due to potassium channel downregulation and can also be best explained by the concurrent presence of several factors such as cardiac hypertrophy (athlete’s heart), and/or hypertrophic cardiomyopathy, increased sympathetic tone, genetic defects, drugs, doping agents, food, or dietary ingredients. These factors together can increase the repolarization inhomogeneity of the heart (“substrate”) and an otherwise harmless extrasystole (“trigger”) occurring with a very unfortunate timing may sometimes induce life-threatening arrhythmias. The effective and possible prevention of sudden cardiac death requires the development of novel cost effective cardiac electrophysiological screening methods. Athletes identified by these tests as individuals at higher pro-arrhythmic risk should then be subjected to more costly genetic tests in order to uncover possible underlying genetic causes for alterations in ionic channel structure and/or function [121].

In a postmortem series of 34 AAS abusers aged 20-45 years (comprising 12 homicides, 11 suicides, 12 “accidental” deaths, and two of indeterminate cause), 12 of the deceased showed cardiac pathology. Findings included hypertrophy (7 cases), myocardial or endocardial fibrosis (5), cardiac steatosis (1), myocardial coagulation necrosis (2), and coronary atheroma (4). Cardiac changes were adjudged to have contributed to death by poisoning in two cases. However mediated, such a morbid burden is likely to rise with time [122].

**During surgery**

It was reported two cases of sudden cardiac death (SCD) involving previously healthy bodybuilders who were chronic androgenic-anabolic steroids users. In both instances, autopsies, histology of the organs, and toxicologic screening were performed. The findings support an emerging consensus that the effects of vigorous weight training, combined with anabolic steroid use and increased androgen sensitivity, may predispose these young men to myocardial injury and even SCD [123].

It is estimated that 80 percent of weight lifters and body-builders take anabolic-androgenic steroids. Their long-term use is associated with a variety of pathological conditions and premature death. Anabolic-androgenic steroid abuse may lead to changes in the presentation and progression of some conditions. It remains unclear whether anabolic steroids should be given to patients with a history of abuse of these drugs who are to
undergo surgery. It was reported on a fatal outcome following surgery in a 48-year-old weight lifter [124].

Case reports

Several case reports associate the chronic use of AAS with serious cardiovascular complications including acute myocardial infarction, cardiac arrest, and hypertrophic cardiomyopathy without significant cardiac valvula or coronary artery disease. Case reports associate chronic AAS abuse with myocardial infarctions in young men with and without evidence of coronary artery occlusion; the presence of coronary artery disease in these athletes occurs despite the lack of known risk factors for coronary artery disease. The development of an acute myocardial infarction was associated with high-dose AAS abuse (e.g. 6 weeks daily, years intermittently) by a 44-year-old recreational bodybuilder with diffuse coronary artery disease and multiple myocardial risk factors including polycythemia, smoking, and family history of early coronary artery disease. Left ventricular hypertrophy is a common structural abnormality in bodybuilders with AAS abuse. A study of 21 bodybuilders with reported AAS abuse suggests that concentric hypertrophy of the left ventricular wall and impaired diastolic function are common complications of steroid abuse. Echocardiographic studies of these athletes demonstrated increased left ventricular posterior wall thickness and end-diastolic volumes as well as decreased ratios of ventricular end-diastolic diameter to body mass. A case report of 2 previously healthy bodybuilders associated sudden cardiac death with chronic AAS abuse. There was evidence of focal myocardial necrosis without clinically significant coronary artery disease, but the role of chronic AAS abuse in the cardiac arrest remains unclear. Ventricular dysrhythmias are not commonly associated with chronic AAS abuse. Several case reports associate persistent atrial fibrillation with chronic AAS use. A 22-year-old man developed generalized weakness, diaphoresis, anxiety, and dyspnea. The electrocardiogram revealed rapid atrial fibrillation and the echocardiogram indicated an early cardiomyopathy. He had gynecomastia, and he admitted to the recent injection of anabolic steroids. Although there is no direct evidence that AASs are thrombogenic in humans, case reports suggest a possible causal relationship between AAS use and thrombogenic events (e.g. massive pulmonary embolus, cerebral thrombosis, cardiomyopathy with congestive heart failure, biventricular thrombi, and hepatorenal dysfunction). Studies on the association between chronic AAS use and hypertension or left ventricular hypertrophy are inconsistent [125].

Anabolic androgenic steroids (AAS) are the main class of doping agents and their consumption produces adverse effects involving several organs and systems. Three cases of sudden cardiac death (SCD) and one of death due to congestive heart failure of previously healthy athletes who were AAS users are herein reported. Concentric cardiac hypertrophy with focal fibrosis (one case), dilated cardiomyopathy with patchy myocyte death (two cases) and eosinophilic myocarditis (one case) were observed and most probably relate to the final event. Molecular investigation for viral genomes was positive in one case (Ebstein virus). The data confirm previous findings, showing that the most typical cardiac abnormality in AAS abusers is left ventricular hypertrophy, associated with fibrosis and myocytolysis. An exceptional cardiovascular substrate was represented by the case with drug induced eosinophilic myocarditis. These features are at risk of ventricular arrhythmias as well as congestive heart failure. The cause-effect relationship between AAS abuse and cardiac death can be established only by a rigorous methodology with the use of standardized protocols, including precise morphological studies of all target organs to search for chronic toxic effects. Laboratory investigations should focus on AAS searching on a wide range of biological matrices to demonstrate type, magnitude and time of exposure [126].

Sudden cardiac death related to sports in young patients can have many causes. Hypertrophic cardiomyopathy, congenital coronary abnormalities, and myocarditis make up
about half of the causes of sudden cardiac death after sports. Screening for all athletes is important to prevent such episodes. This involves yearly examinations including clinical examinations, stress echocardiograms, echocardiography, and laboratory investigations. Also, behavioral follow up should be addressed, as cocaine administration and doping can both lead to cardiac problems and sudden cardiac death after sports. It was presented a case of a 17-year-old boy who collapsed after an ice hockey competition as a result of an acute myocardial infarction, which was first represented by ventricular fibrillation. It was also reviewed the main causes of sudden cardiac death in such young athletes and the main investigations that have to be performed to reach the proper diagnosis and etiology of the condition [127].

Doping – the abuse of anabolic-androgenic steroids in particular – is widespread in amateur and recreational sports and does not solely represent a problem of professional sports. Excessive overdose of anabolic steroids is well documented in bodybuilding or powerlifting leading to significant side effects. Cardiovascular damages are most relevant next to adverse endocrine effects. Clinical cases as well as forensic investigations of fatalities or steroid consumption in connection with trafficking of doping agents provide only anecdotal evidence of correlations between side effects and substance abuse. Analytical verification and self-declarations of steroid users have repeatedly confirmed the presumption of weekly dosages between 300 and 2000 mg, extra to the fact that co-administration of therapeutics to treat side-effects represent a routine procedure. Beside the most frequent use of medications used to treat erectile dysfunction or estrogenic side-effects, a substantial number of antihypertensive drugs of various classes, i.e. beta-blockers, diuretics, angiotensin II receptor antagonists, calcium channel blockers, as well as ACE inhibitors were recently confiscated in relevant doping cases. The presumptive correlation between misuse of anabolic steroids and self-treatment of cardiovascular side effects was explicitly confirmed by detailed user statements. Two representative fatalities of bodybuilders were introduced to outline characteristic, often lethal side effects of excessive steroid abuse. Moreover, illustrative autopsy findings of steroid acne, thrombotic occlusion of Ramus interventricularis anterior and signs of cardiac infarctions are presented. A potential steroid abuse should be carefully considered in cases of medical consultations of patients exhibiting apparent constitutional modifications and corresponding adverse effects. Moreover, common self-medications – as frequently applied by steroid consumers – should be taken into therapeutic considerations [128].

It was reported two cases of sudden cardiac death (SCD) involving previously healthy bodybuilders who were chronic androgenic-anabolic steroids users. In both instances, autopsies, histology of the organs, and toxicologic screening were performed. The findings support an emerging consensus that the effects of vigorous weight training, combined with anabolic steroid use and increased androgen sensitivity, may predispose these young men to myocardial injury and even SCD [129].

Androgenic anabolic steroids (AAS) used for improving physical performance have been considered responsible for acute myocardial infarction and sudden cardiac death. Two young, healthy, male bodybuilders using AAS was investigated after “sudden death” regarding pathologic cardiac findings associated with AAS ingestion. The autopsy revealed normal coronary arteries. In one case, it was documented a typical infarct with a histologic age of 2 weeks. A segmentation of myocardial cells at the intercalated disc level was observed in the noninfarcted region. This segmentation was the only anomaly detected in the second case. No other pathologic findings in the heart or other organs were found. Urine in both subjects contained the metabolites of nortestosterone and stanozolol. It was concluded that a myocardial infarct without vascular lesions is rare. Its association with AAS use, bodybuilding, or both lacks any evidence of a cause-effect relationship. The histologic findings in the 2 cases and in the few others reported in medical literature are nonspecific and do not prove the cardiac toxicity of AAS. A better understanding of AAS action on the
neurogenic control of the cardiac function in relation to regional myocardial contraction and vascular regulation is required [130].

Chronic abuse of anabolic steroids is widespread. Hypertrophy of skeletal and heart muscle is a well-known effect of chronic anabolic steroid abuse. Structural alterations of blood vessels are new side effects. It was reported a case of a 32-year-old bodybuilder after long-term use of anabolic steroids who died of cardiac arrest. Coronary angiography and autopsy findings showed especially a hypertrophic heart, structural changes of coronary arteries, intracoronary thrombosis and myocardial infarction, ventricular thrombosis and systemic embolism [131].

Concentric left ventricular myocardial hypertrophy is a common pathologic finding following the chronic use of AAS. A 21-year-old, previously healthy weight lifter collapsed during a benchpress workout, and paramedics found him in ventricular fibrillation. For the preceding several months, he used parenteral AASs (nandrolone, 19-nortestosterone). Postmortem findings included marked cardiac hypertrophy, regional myocardial fibrosis, and focal myocardial necrosis along with hepatosplenomegaly and renal hypertrophy. There was no evidence of recent myocardial inflammation. Other autopsies of AAS abusers have not demonstrated cardiac hypertrophy, but histologic examination of cardiac tissue also detected focal myocardial necrosis. The postmortem examination of 2 cases of sudden death in 2 previously healthy chronic AAS abusers (i.e. bodybuilders) demonstrated also focal myocardial necrosis (contraction band necrosis) without evidence of significant coronary artery disease or myocardial hypertrophy. Other pathologic changes associated with cardiac arrest in previously healthy athletes following AAS use (e.g. oxymesterone) include hypertrophic cardiomyopathy, acute cellular ecrosis, interstitial fibrosis, and myocarditis. Typically, there is no evidence of coronary thrombosis in these cases of sudden death. However, evidence of recent (i.e. 2 weeks) myocardial infarction may occur in these cases without evidence of coronary artery disease [132].
LONG-TERM EFFECTS ON THE HEART OF ANABOLIC STEROIDS

Anabolic androgenic steroids (AAS) are sometimes used by power athletes to improve performance by increasing muscle mass and strength. Recent bioptical data have shown that in athletes under the pharmacological effects of AAS, a focal increase in myocardial collagen content might occur as a repair mechanism against myocardial damage. To investigate the potential underlying left ventricular myocardial dysfunction after chronic misuse of AAS in athletes by use of Doppler myocardial imaging (DMI) and strain rate imaging (SRI). Standard Doppler echocardiography, DMI, SRI and ECG treadmill test were undertaken by 45 bodybuilders, including 20 athletes misusing AAS for at least 5 years (users), by 25 anabolic-free bodybuilders (non-users) and by 25 age-matched healthy sedentary controls, all men. The mean number of weeks of AAS use per year was 31 in users, compared with 9 years in non-users, and the mean weekly dosage of AAS was 525 mg. The groups were matched for age. Systolic blood pressure was higher in athletes than in controls. Left ventricular mass index did not significantly differ between the two groups of athletes. In particular, both users and non-users showed increased wall thickness and relative wall thickness compared with controls, whereas left ventricular ejection fraction, left ventricular end-diastolic diameter and transmitral Doppler indexes were comparable for the three groups. Colour DMI analysis showed significantly lower myocardial early: myocardial atrial diastolic wave ratios in users at the level of the basal interventricular septum (IVS) and left ventricular lateral wall (p<0.01), in comparison with both non-users and controls. In addition, in users, peak systolic left ventricular strain rate and strain were both reduced in the middle IVS and in the left ventricular lateral free wall. By stepwise forward multivariate analyses, the sum of the left ventricular wall thickness the number of weeks of AAS use per year and the weekly dosage of AAS were the only independent determinants of middle IVS strain rate. In addition, impaired left ventricular strain in users was associated with a reduced performance during physical effort. Several years after chronic misuse of AAS, power athletes show a subclinical impairment of both systolic and diastolic myocardial function, strongly associated with mean dosage and duration of AAS use. The combined use of DMI and SRI may therefore be useful for the early identification of patients with more diffused cardiac involvement, and eventually for investigation of the reversibility of such myocardial effects after discontinuation of the drug [133].

Conflicting results

Anabolic androgenic steroids (AAS) abuse for improving physical appearance and performance in body builders is common and has been considered responsible for serious cardiovascular effects. Due to disagreement about cardiovascular side effects of these drugs in published articles, this case control study was designed to evaluate the echocardiographic findings in body builder athletes who are current and chronic abusers of these drugs. Body builder athletes with continuous practice for the preceding two years and were training at least twice weekly were selected and divided into AAS abuser and non-user and compared with age and BMI matched non athletic healthy volunteers (15 cases in each group). There was no significant difference in left ventricular size or function either systolic or diastolic in comparison to cases and control groups. The only difference was in diastolic size of septum and free wall but observed differences were only significant between first (athletic with AAS abuser) and third group (non-athletic and nonuser). The difference between the above-mentioned indexes was not significant between two groups of athletes. Observed differences in diastolic size of septum and free wall is in favor of that long term abuse of anabolic steroid results in accentuation of physiologic hypertrophy due to long term sport most probably due to higher rate pressure product. Furthermore long term abuse and supra-pharmacologic doses do not have significant effect in size and left ventricular function [134].
Experimental

*Progressive myocardial mass reduction*

One study focused on the short term effects of repeated low level administration of turinabol and methanabol on cardiac function in young rabbits (4 months). The experimental scheme consisted of two oral administration periods, lasting 1 month each, interrupted by 1 month wash-out period. Serial echocardiographic evaluation at the end of all three experimental periods was performed in all animals. Oxidative stress markers have also been monitored at the end of each administration period. Treated animals originally showed significantly increased myocardial mass and systolic cardiac output, which normalized at the end of the wash out period. Re-administration led to increased cardiac output, at the cost though of a progressive myocardial mass reduction. A dose-dependent trend towards impaired longitudinal systolic, diastolic and global myocardial function was also observed. The adverse effects were more pronounced in the methanabol group. For both anabolic steroids studied, the low dose had no significant effects on oxidative stress markers monitored, while the high dose created a hostile oxidative environment. In conclusion, anabolic administration has been found to create a possible deleterious long term effect on the growth of the immature heart and should be strongly discouraged especially in young human subjects [135].
DYSLIPIDEMIA

AS have been associated with negative alterations in lipid profiles. Changes reported include a decrease in high-density lipoprotein (HDL), an elevation in low-density lipoprotein (LDL) and reduced apolipoprotein levels, possibly through up-regulation of hepatic triglyceride lipase. The changes in lipid profiles indicate an increase in atherosclerotic risk. Increases in homocysteine, a naturally occurring amino-acid thought to have a role in vaso-control, and C-reactive proteins (CRP), an acute-phase protein that rises in response to inflammation, have been implicated as risk factors for CV disease. It has been demonstrated a significant increase in CRP in AS users. It was noted a significant elevation in homocysteine in AS users as well as those who had abstained from AS use for 3 months, indicating a possible effect of AS on vitamin B absorption. Previous studies have also suggested a possible link between AS use and thrombotic risk through alterations in hemoglobin levels [136].

Lipid profile influence early atherogenesis. Therapeutic use of AAS has been shown in many studies to affect the individuals’ lipid profile. A meta-analysis including 19 studies and comprising 272 hypogonadal men showed that substitution therapy with intramuscularly administered testosterone results in a decrease in plasma HDL cholesterol levels. The same results were also demonstrated in a recent meta-analysis including 51 studies on men with low or low-to-normal plasma testosterone levels who received testosterone in different doses as therapy. Moreover, high-dose AAS abuse has been demonstrated to exert unfavourable direct and indirect effects, through AAS-associated hyperhomocysteaemia, on plasma lipid levels. In a nonblinded investigation on 19 bodybuilders, short-term (8 weeks) and long-term (> 14 weeks) high dosages of AAS administration markedly reduced HDL cholesterol. The suppressive effects of AAS administration on HDL plasma levels are dose dependent and depending on the type of AAS and route of administration can result in decrement of 40-70 percent. The adverse effects of high AAS dosages on plasma levels of LDL cholesterol have been shown in animal and human studies. Lipid profile impairment is causally implicated in vascular wall injury by promoting inflammatory processes in the arterial wall, macrophage recruitment, and uptake of LDL and oxidized LDL by macrophages which results in foam cell formation. The aforementioned processes, which contribute to establishment and progression of atherosclerotic plaques, can be depicted by molecular imaging techniques. 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) has been studied in a notable number of investigations and has been shown to correlate with the macrophage density in atherosclerotic plaques in humans and in animal models. Additionally, 18F-FDG PET depicts MI subsequent to coronary atherosclerosis. Molecular targeting of oxidized LDL and macrophage uptake of radiolabelled LDL has verified promising targets for visualizing vulnerable atherosclerotic plaques. Moreover, a recent pilot study reported feasibility of ultrasmall superparamagnetic particles of iron oxide (USPIO) in detecting inflammation in endothelial cells during atherogenesis with magnetic resonance imaging (MRI) [048].

Somatic adverse reactions of AAS abuse include disturbances in the lipid profile, cardiovascular effects, dermal manifestations, and endocrine adverse reactions. Decreased secretion of the pituitary luteinizizing hormone (LH) and follicle-stimulating hormone (FSH) is commonly reported. These effects result from the negative feedback of androgens on the hypothalamic–pituitary–gonadal axis, and possibly from the local suppressive effects of exogenous androgens on the testes. Long persistence of low levels of gonadotropins has been described in nandrolone abusers, with a significant correlation between 19-norandrosterone and LH and FSH. Abuse of AASs leads to increased levels of low-density lipoprotein (LDL) and apolipoprotein B (ApoB; the major component of the LDL particle), but also a decreased level of high-density lipoprotein (HDL) and apolipoprotein A1 (ApoA1; the major component of the HDL particle). A perturbation in the lipoprotein profile has been observed even after one single dose of testosterone in healthy volunteers through increased total cholesterol levels and induced expression of 3-hydroxy-3-methyl-glutaryl-CoA reductase, 2 days after administration. Stanozolol has been studied with respect to its effect
on HDL and found to give a 71 percent decrease in HDL levels after 7 days’ treatment in association with changes in hepatic triglyceride lipase. These effects on the lipid profile during long-term abuse are associated with an increased risk of coronary artery disease. In contrast to their unfavorable effects on lipids, AASs may favorably lower lipoprotein(a) (Lp[a]) concentrations. “Lp(a)” is an LDL-like particle and contains, in addition to LDL, a specific protein component, apolipoprotein(a) (apo[a]). High levels of Lp(a) have been reported as a risk factor for ischemic heart disease and peripheral vascular disease. To study the effect and time profile of different doses of testosterone enanthate on the blood lipid profile and gonadotropins 25 healthy male volunteers aged 27-43 years were given 500 mg, 250 mg, and 125 mg of testosterone enantate as single intramuscular doses of Testoviron® Depot. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), blood lipid profile (total cholesterol, plasma [p-] low-density lipoprotein, p-high-density lipoprotein [HDL], p-apolipoprotein A1 [ApoA1], p-apolipoprotein B, p-triglycerides, p-lipoprotein(a), serum [s-] testosterone, and 25-hydroxyvitamin D3) were analyzed prior to, and 4 and 14 days after dosing. Testosterone and epitestosterone in urine (testosterone/epitestosterone ratio) were analyzed prior to each dose after a washout period of 6-8 weeks. All doses investigated suppressed the LH and FSH concentrations in serum. LH remained suppressed 6 weeks after the 500 mg dose. These results indicate that testosterone has a more profound endocrine effect on the hypothalamic-pituitary-gonadal axis than was previously thought. There was no alteration in 25-hydroxyvitamin D3 levels after testosterone administration compared to baseline levels. The 250 and 500 mg doses induced decreased concentrations of ApoA1 and HDL, whereas the lowest dose (125 mg) did not have any effect on the lipid profile. It was concluded that a single doses of testosterone produced a dose-dependent increase in serum testosterone concentrations together with suppression of s-LH and s-FSH. Alterations in ApoA1 and HDL were observed after the two highest single doses. It is possible that long-time abuse of anabolic androgenic steroids will lead to alteration in vitamin D status. Knowledge and understanding of the side effects of anabolic androgenic steroids are important to the treatment and care of abusers of testosterone [137].

Although several reports have been reported of adverse cardiovascular effects associated with the use of supraphysiological doses and/or prolonged use of such drugs, changes in lipid profile have also been observed both at therapeutic doses and in the short term. A meta-analysis of 19 studies, totaling 272 men manifesting hypogonadism (44 ± 4 years old) who used physiological doses of intramuscular testosterone (179 ± 13 mg every 16 days for 6 months), was conducted in 2001. There was a reduction of 14 mg/dL (17-11 mg/dL) in total cholesterol, 5 mg/dL (8-1 mg/dL) in LDL cholesterol, 4 mg/dL (5-2 mg/dL) in HDL cholesterol, and 5 mg/dL (−6 to 4 mg/dL) in triglycerides. However, effect size was not significant. Only HDL cholesterol reduction tended to result in a significant outcome. Another meta-analysis of studies involving 1,083 middle-aged and older men (mean age 65 years) designed to study the prevention of loss of muscle mass and bone found a significant reduction in HDL cholesterol, at therapeutic doses between controls and experimental participants. Therefore, the evidence points to possibilities of damage only in HDL cholesterol, and these numbers are not for athletes. The reason for the absence of data from athletes is the fact that when athletes do use AAS, they use them in supraphysiological doses [138].

While the use of physiological doses promotes a mild reduction in serum concentration of HDL cholesterol, the self-administration of several AAS simultaneously (at least three drugs and up to nine drugs for those who used the most, without prescription, and in supraphysiological doses in all cases) during 14 weeks decreased the concentration of HDL cholesterol to less than half in 19 bodybuilders (31 ± 7 years old) who had undergone an average of seven cycles (range: 1–30) over an average period of time of 4.8 years (range: 1–14). This phenomenon was accompanied by a reduction, also by half, of apolipoprotein A1, which mediates the HDL cholesterol formation. Six weeks following cessation of the use of AAS, the worsening of the lipid profile still persisted. Halving in HDL cholesterol was also observed by Lane and colleagues in 10 youths who admitted using AAS compared to
nonusers. Although the administration of nandrolone decanoate for 8 weeks at physiological doses (200 mg/week) did not affect the HDL cholesterol or other serum lipoproteins, a single dose of 500 mg of testosterone increased the serum concentration of total cholesterol by 15 percent. Interestingly, molecular biology tests revealed that this increase was accompanied by increased mRNA and protein expression of HMG-CoA reductase, a key enzyme in the formation of cholesterol by the liver. The trend found in reduction of HDL cholesterol at physiological doses is confirmed by the very significant reduction following treatment with high doses of AAS. Although there are few studies, the data presented indicate an adverse effect of AAS use on HDL cholesterol [138].

An association between premature cardiovascular events and the misuse of AAS in athletes has been observed. This is believed to be primarily mediated through changes in the lipid profile. Although endurance exercise favorably affects the lipid profile primarily through an antiatherogenic effect of raising high-density lipoprotein (HDL) cholesterol and lowering triglycerides, heavy resistance training alone fails to show a similar effect. This implies that the effect of AAS on lipid profile may confounded by the type of training the athlete pursues. Multiple prospective studies of AAS effects on cholesterol have yielded varied results. The majority of results (studies ranging from 3 to 26 weeks) show no overall change in levels of total serum cholesterol; however, some individual studies show increases and others show a decrease in total cholesterol. Despite the varied results on total cholesterol, the effects on HDL seem more consistent. Reductions in HDL range from 39 to 70 percent depending on the type of AAS and also appear to be dose dependent. Several studies show reductions of HDL down into the teens, which, based on Framingham data, places these patients at a three times greater risk for coronary artery disease compared with men with HDL above 50 mg/dL. There even appears to be some variation in the dose effect based on gender. In one study of hemodialysis patients, weekly administration of nandrolone resulted in a reduction of HDL-2 and apolipoprotein A-1 levels, complemented by a corresponding increase in apolipoprotein B and triglycerides. The oral 17-alpha alkylated steroids, as opposed to parenteral nandrolone, seem to exert the greatest effects on lipids and lipoproteins, which can be seen as early as the first few days of administration. This reduction often reaches a plateau effect after 8 weeks of use. Although the direct mechanisms of action and impact on cardiovascular disease remain unproven this negative effect on HDL suggests a higher risk of atherogenesis. The alteration in lipid profile seems completely reversible upon discontinuation, but may take at least 4 to 12 weeks, often depending on dose and duration of steroid use [139].

In addition to HDL effects, an increase in low-density lipoprotein (LDL) appears to parallel the HDL reduction. Significant LDL increases were appreciated in just 8 weeks of anabolic steroid use in one study, and often had not returned to baseline 6 weeks after cessation of AAS use. Because HDL acts as a primary scavenger of LDL particles, LDL changes possibly reflect a secondary rather than primary effect. These alterations in HDL and LDL cholesterol are more profound in athletes engaged in heavy resistance sports taking AAS as compared with endurance athletes, possibly reflecting the influence of the athlete’s training regimen. In one arm (self-administered, prospective, nonblinded portion) of the study from the Netherlands, reductions in lipoprotein (a), which is an independent risk factor for vascular disease, seem to provide a slightly beneficial effect on the lipid profile. Reductions of as much as 50 percent of lipoprotein (a) were observed in as little as 8 weeks of AAS use, and remained decreased at 6 weeks postcessation. Longer duration of AAS did not correlate directly with further serum reductions, but did demonstrate a more prolonged return to baseline of lipoproteins. In the second phase (randomized controlled trial, double-blinded portion) of the Dutch study, both placebo groups and nandrolone decanoate both demonstrated reductions (19 % and 40 %, respectively) in lipoprotein (a) that was nonsignificant. One explanation for the difference is that the oral 17-alpha alkylated steroids, taken in the first portion, seem to exert the greatest effects on lipids and lipoproteins as opposed to the parenterally administered nandrolone used in the second arm. This is
mediated by the first-pass metabolism of the orally administered drugs through the liver. These effects can be seen as early as the first few days of administration, and seem to be more dependant on the type of steroid as opposed to the duration, although no long-term studies exist currently. Concentrations of lipoprotein (a) have been shown to have a close correlation with deposition in vascular walls, are often genetically determined, and seem resistant to current lipid [139].

Although several reports have been reported of adverse cardiovascular effects associated with the use of supraphysiological doses and/or prolonged use of such drugs, changes in lipid profile have also been observed both at therapeutic doses and in the short term. A meta-analysis of 19 studies, totaling 272 men manifesting hypogonadism (44 ± 4 years old) who used physiological doses of intramuscular testosterone (179 ± 13 mg every 16 days for 6 months), was conducted in 2001. There was a reduction of 14 mg/dL (17-11 mg/dL) in total cholesterol, 5 mg/dL (8-1 mg/dL) in LDL cholesterol, 4 mg/dL (5-2 mg/dL) in HDL cholesterol, and 5 mg/dL (~6 to 4 mg/dL) in triglycerides. However, effect size was not significant. Only HDL cholesterol reduction tended to result in a significant outcome. Another meta-analysis of studies involving 1,083 middle-aged and older men (mean age 65 years, range 50-78 years) designed to study the prevention of loss of muscle mass and bone found a significant reduction in HDL cholesterol, at therapeutic doses between controls and experimental participants. Therefore, the evidence points to possibilities of damage only in HDL cholesterol, and these numbers are not for athletes. The reason for the absence of data from athletes is the fact that when athletes do use AAS, they use them in supraphysiological doses [015].

While the use of physiological doses promotes a mild reduction in serum concentration of HDL cholesterol, the self-administration of several AAS simultaneously (at least three drugs and up to nine drugs for those who used the most, without prescription, and in supraphysiological doses in all cases) during 14 weeks decreased the concentration of HDL cholesterol to less than half in 19 bodybuilders (31 ± 7 years old) who had undergone an average of seven cycles (range: 1-30) over an average period of time of 5 years (range: 1-14). This phenomenon was accompanied by a reduction, also by half, of apolipoprotein A1, which mediates the HDL cholesterol formation. Six weeks following cessation of the use of AAS, the worsening of the lipid profile still persisted. Halving in HDL cholesterol was also observed in 10 youths who admitted using AAS compared to nonusers. Although the administration of nandrolone decanoate for 8 weeks at physiological doses (200 mg/week) did not affect the HDL cholesterol or other serum lipoproteins, a single dose of 500 mg of testosterone increased the serum concentration of total cholesterol by 15 percent. Interestingly, molecular biology tests revealed that this increase was accompanied by increased mRNA and protein expression of HMG-CoA reductase, a key enzyme in the formation of cholesterol by the liver. The trend found in reduction of HDL cholesterol at physiological doses is confirmed by the very significant reduction following treatment with high doses of AAS. Although there are few studies, the data presented strongly indicate an adverse effect of AAS use on HDL cholesterol [015].

Anabolic-androgenic steroids (AAS) are used to enhance physical performance and/or appearance. The aim of this study was to evaluate the influence of the concomitant use of alcohol, tobacco, cocaine, and AAS on blood lipid profiles of 145 asymptomatic male bodybuilders from the Northeast region of Brazil. Interviews, clinical exams, and serological evaluations were performed on all participants between 2007 and 2009. All subjects' self-reported use of testosterone or its derivatives, 118 individuals reported alcohol intake, 27-reported cigarette smoking, and 33 confirmed cocaine use. Four subjects were users of all drugs at the same time. Higher levels of total cholesterol and LDL-cholesterol were observed among concomitant users of alcohol, tobacco, cocaine, and AAS. The study's limitations are noted [140].
Altered lipid profiles in AAS users are reflected in increased low-density lipoprotein and decreased high-density lipoprotein. The oral C-17 alkylated steroids seem to exert the greatest effects on the lipid profile. Thrombus formation has been postulated by way of these adverse lipid changes and is supported further by findings of AAS-induced increased platelet aggregation, enhanced coagulation enzyme activity, and coronary vasospasm. Hypertension in AAS users has been reported and is likely the result of blood volume increases and fluid retention. This effect, as well as the finding of increased septal thickness and left ventricular mass reported in AAS users, can lead to significant detrimental cardiac remodeling [141].

The 17-alkylated compounds can provoke impairment of hepatic function and dyslipidemia. There are no consistent changes reported for total cholesterol. The oral and the parenteral forms of 17-a- alkylated steroids, though not the parenteral forms of androgen esters, have been associated with a lowering effect on high density lipoprotein cholesterol (HDL-C), thereby increasing the chance of the development of coronary heart disease (CHD). However, HDL-C fractions start increasing after cessation of AS use and tend to normalize in exercised men within 10 weeks [142].

**Two-ways action**

The aims of one study was to investigate the effects of anabolic androgenic steroids on the cardiac structure and the plasma lipoprotein profile isolated and in combination with exercise. Transgenic mice with a human lipaemic phenotype (expressing cholesteryl ester transfer protein on the LDL receptor knockout background) were used in this study. Sedentary and exercised mice (treadmill running, five times per week for 6 weeks) were treated with mesterolone (2 microg/g body weight) or vehicle (control-C) in the last 3 weeks. Four groups were compared: (i) exercise + mesterolone (Ex-M), (ii) exercise + vehicle (Ex-C), (iii) sedentary + mesterolone (Sed-M) and (iv) sedentary + vehicle (Sed-C). Arterial blood pressure and body mass increased in all groups along time, but Sed-M reached the highest values and Ex-C the lowest. Treatment with mesterolone increased total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-c) and very LDL-c (VLDL-c) plasma levels. However, exercise blunted some of these deleterious effects by increasing high-density lipoprotein cholesterol and decreasing LDL-c, VLDL-c and triglycerides. Exercise training induced beneficial effects, such as physiological cardiomyocyte hypertrophy, increase in myocardial circulation and decrease in cardiac interstitium. However, mesterolone impaired such physiological gains and in addition increased troponin T plasma levels both in sedentary and exercised mice. Thus, while mesterolone induced pro-atherogenic lipoprotein profile and pathogenic cardiac hypertrophy, exercise counteracted these effects and modified favourably both the lipoprotein profile and the cardiac remodelling induced by mesterolone [143].

**Postprandial triglyceridaemia, low-density lipoprotein and lipoprotein**

Although androgenic hormones decrease HDLC concentration, no direct evidence has linked them to atherosclerosis. The present study was undertaken to extend our ability to assess risk associated with androgen induced lipoprotein(Lp) changes by simultaneously gathering information about postprandial triglyceridaemia (PPT), LDL particle size, HDL and Lp(a) in men either taking exogenous androgens or with suppressed endogenous androgen concentrations. The experimental groups comprised nine male bodybuilders who self-administered anabolic-androgenic steroids (AAS) for a mean period of 6.5 weeks, and 10 healthy men whose testosterone concentration had been reversibly suppressed for 5 weeks using the GnRH agonist triptorelin (Decapeptyl; D-Trp6-LHRH). A separate group receiving no hormonal treatment provided analytical control (n=7). Lipoprotein size was assessed by
gradient gel electrophoresis categorisation (GGE), lipoprotein concentrations by immuno and enzymatic assays and PPT by a standardised oral fat tolerance test (65 g/m²). Testosterone concentration was significantly reduced on triptorelin from 7.32 ± 1.92 to 1.15 ± 0.57 ng/mL. High dose AAS use was confirmed by urinalysis. With AAS use, mean HDLC and Lp(a) concentrations and PPT decreased from 0.9 ± 0.3 to 0.7 ± 0.3 mmol/L, 125 ± 128 to 69 ± 73 U/L and 11.6 ± 10.0 mmol/L h to 7.5 ± 5.4 mmol/L h respectively. Mean total cholesterol and LDL were unchanged. LDL size was unchanged in six AAS users, decreased in one but remaining in the normal size range, and increased in two from small LDL to the normal range. Size changes in the latter two subjects were associated with 42 and 58 percent reductions in PPT respectively. In the triptorelin group, mean total cholesterol, HDLC and Lp(a) were increased from 4.8 ± 0.8 mmol/L to 5.2 ± 1.0 mmol/L, 1.1 ± 0.2 to 1.4 ± 0.3 mmol/L and 278 ± 149 to 377 ± 222 U/L respectively. Mean LDL concentration and PPT were unchanged. LDL particle size increased in four, decreased in two, and was unchanged in four subjects. LDL size decreased in two and showed no change in the other five control subjects. Other lipid measures were unchanged in the control group. Thus, apart from lowering HDLC concentrations, no other potentially atherogenic effects of endogenous androgens or AAS were observed. A suppression of Lp(a) as well as a reduced PPT and increased LDL size in predisposed individuals may be antiatherogenic effects of AAS [144].

**Total cholesterol**

The effects of AAS on serum total cholesterol metabolism are not determined in detail. Most prospective studies, investigating either low or high doses of single drug use or polydrug administration for periods from 3 to 26 weeks, reported no alterations of serum total cholesterol levels. Nevertheless, some studies found that AAS were able to induce an increase of serum total cholesterol levels, whereas others observed a decrease. The nature of this discrepancy of serum cholesterol response has yet to be established. However, the response of serum total cholesterol levels to nandrolone decanoate administration seems to be very consistent. The use of therapeutic and supratherapeutic doses of nandrolone decanoate does not seem to affect serum cholesterol levels. In strength athletes, testosterone enantate administered by intramuscular injection may have no effect on serum total cholesterol levels after 3 weeks of administration, but after 6 weeks a reduction of total cholesterol may occur. On the other hand, supratherapeutic doses of another testosterone substance (i.e. testosterone cipionate) do not exert significant effects on serum total cholesterol levels [012].

**High-density lipoprotein-cholesterol and its subfractions**

High-density lipoprotein (HDL)-cholesterol and its subfractions have been recognised as independent risk factors for the occurrence of cardiovascular disease. There is strong evidence that AAS administration will induce remarkable reductions of the serum levels of these lipoproteins. The suppressive effect varies between different androgenic-anabolic compounds, with decrements of HDL-cholesterol ranging from 39-70 percent. The most pronounced suppression has been observed in serum levels of HDL2-cholesterol rather than HDL3-cholesterol, with suppression ranging from 55 to 89 percent for HDL2-cholesterol and from 13 to 55 percent for HDL3-cholesterol. The reduction of serum HDL-cholesterol levels is mediated by hepatic triglyceride lipase (HTGL), an enzyme that regulates serum lipids and exposes the AAS-using athletes to an increased atherogenic risk. The orally taken 17-[alpha]-alkylated substances (such as stanozolol, oxymetholone and metandienone) exert much stronger effects than other AAS. The decline of HDL-cholesterol can be observed within a few days of starting steroid administration. After an initial strong negative effect, the suppression of the serum HDL-cholesterol and its subfractions continues at a more moderate
level. After 8 weeks of AAS administration no further decline of HDL-, HDL2- and HDL3-cholesterol can be observed. Short-term administration of androgens, such as testosterone enantate and cipionate, also depress serum HDL-cholesterol levels significantly. Effects of testosterone supplementation on lipoproteins, however, have been shown to be dose dependent. It was thus demonstrated that intramuscular testosterone 600 mg/week reduced HDL-cholesterol levels, whereas lower doses did not exert any effect on lipoprotein profiles. HDL-cholesterol suppression by 19-nortestosterone esters seem to follow another pattern since adverse effects in males have been demonstrated only after long-term administration, whereas in women alterations have been observed after short-term use of low doses. Parenteral administration of nandrolone decanoate for periods up to 2 months does not affect HDL-cholesterol and subfractions in healthy athletes. However, in clinical studies this steroid was found to affect HDL-cholesterol metabolism unfavourably in male haemodialysis patients when administered for more than 6 months. In women with postmenopausal osteoporosis a reduction of serum HDL-cholesterol levels was noticed even after 3 weeks. After steroid withdrawal, the disturbed lipid and lipoprotein profiles recover completely, although at least 4-12 weeks are needed to return to baseline values. It was demonstrated that recovery depends strongly on the duration of an AAS course [012].

Many studies have shown that AAS can cause dyslipidemia by increasing low-density lipoprotein as high as 596 mg/dL and decreasing high-density lipoprotein as low as 5 mg/dL. Alterations in high- and low-density lipoprotein levels occur in a dose-dependent manner within 9 weeks of self-administration of steroids. These changes could accelerate coronary artery atherosclerosis over the long term, resulting in an increased risk of coronary heart disease three to six times that of normal. The effects of androgens on lipid profile have been shown to be reversible after the discontinuation of administration [010].

**Reduction in plasma high density lipoprotein cholesterol and apolipoprotein**

The effects of testosterone (T) supplementation on insulin sensitivity, inflammation-sensitive markers, and apolipoproteins remain poorly understood. It is not known whether T's effects on plasma lipids, apolipoproteins, and insulin sensitivity are dose dependent, or whether significant anabolic effects can be achieved at T doses that do not adversely affect these cardiovascular risk factors. To determine the effects of different doses of T, 61 eugonadal men, 18-35 years of age, were randomly assigned to 1 of 5 groups to receive monthly injections of long-acting GnRH agonist to suppress endogenous T secretion and weekly injections of 25, 50, 125, 300, or 600 mg T enanthate for 20 wk. Dietary energy and protein intakes were standardized. Combined administration of GnRH agonist and graded doses of T enanthate resulted in nadir T concentrations of 253, 306, 542, 1345, and 2370 ng/dl at the 25-, 50-, 125-, 300-, and 600-mg doses, respectively. Plasma high density lipoprotein cholesterol and apolipoprotein A-I concentrations were inversely correlated with total and free T concentrations and were significantly decreased only in the 600 mg/week group. Serum total cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, triglycerides, apolipoprotein B, and apolipoprotein C-III were not significantly correlated with T dose or concentration. There was no significant change in total cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, triglycerides, apolipoprotein B, or apolipoprotein C-III levels at any dose. The insulin sensitivity index, glucose effectiveness, and acute insulin response to glucose, derived from the insulin-modified, frequently sampled, iv glucose tolerance test using the Bergman minimal model, did not change significantly at any dose. Circulating levels of C-reactive protein were not correlated with T concentrations and did not change with treatment in any group. Significant increments in fat-free mass, muscle size, and strength were observed at doses that did not affect cardiovascular risk factors. Over a wide range of doses, including those associated with significant gains in fat-free mass and muscle size, T had no adverse effect on insulin sensitivity, plasma lipids, apolipoproteins, or C-reactive protein. Only the highest dose of T (600 mg/week) was associated with a reduction in plasma high density lipoprotein cholesterol.
and apolipoprotein A-I. Long-term studies are needed to determine whether T supplementation of older men with low T levels affects atherosclerosis progression [145].

**Low-density lipoprotein-cholesterol**

In general, the administration of multiple AAS is likely to increase serum low-density lipoprotein (LDL)-cholesterol levels. The elevation parallels the decrease of HDL-cholesterol and may be observed within a few days after initiation of steroid use. Single anabolic steroid administration may exert different effects on serum LDL levels depending on the steroid and route of administration. Oral administration of stanozolol increased LDL levels, whereas the intramuscular injections of testosterone cipionate or testosterone enantate did not alter LDL levels [012].

**Triglycerides**

The effects on triglyceride metabolism appear to be more unequivocal. Most prospective studies in athletes did not observe any alteration of serum triglyceride levels due to AAS administration, although in one study an elevation of approximately 23 percent has been observed. The aberrant result of the latter study is hard to explain since in other studies of this Finnish research group with the same strength athletes as volunteers no effect on triglycerides were reported [012].

**Apolipoproteins and lipoprotein**

The misuse of androgenic-anabolic steroids (AASs) in young, healthy strength athletes has been associated with the occurrence of premature cardiovascular events. These events may in part be mediated by the adverse effects on serum lipid variables that have been linked to AAS administration. Previous studies have indicated that the use of AAS results in decreases in high density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (Apo-A1; the major component of the HDL particle), and increases in low density lipoprotein cholesterol (LDL-C). A growing number of strength athletes misuse AASs to obtain a well shaped body or increase muscular strength. Most athletes take AASs for periods of 8-12 weeks several times a year. Self administration of AASs may result in much higher doses than recommended, with possibly more severe side effects and more profound effects on serum lipids and lipoproteins. In particular, the orally active 17-alpha-alkyl steroids have been shown to have severe effects on LDL-C and HDL-C. Various studies have suggested that the concentration of lipoprotein(a) (Lp(a)) is an independent risk indicator for the development of vascular disease. The fat composition of Lp(a) is comparable to that of LDL-C, but the most important difference is the presence of a specific apoprotein (a). This protein is attached to apolipoprotein B (Apo-B) by a disulphide bridge. A close correlation has been reported between the serum concentration of Lp(a) and the accumulation of this particle in the vascular wall. The serum concentration of Lp(a) seems to be genetically determined and, when raised, cannot be lowered by alterations in food intake or taking cholesterol lowering drugs. Previous reports have suggested that, in contrast with their detrimental effects on lipids, AASs may favourably lower Lp(a) concentrations. To investigate the effects of two different regimens of androgenic-anabolic steroid (AAS) administration on serum lipid and lipoproteins, and recovery of these variables after drug cessation, as indicators of the risk for cardiovascular disease in healthy male strength athletes in a non-blinded study (study 1) serum lipoproteins and lipids were assessed in 19 subjects who self administered AASs for eight or 14 weeks, and in 16 non-using volunteers. In a randomised double blind, placebo controlled design, the effects of intramuscular administration of nandrolone decanoate (200 mg/week) for eight weeks on the same variables in 16 bodybuilders were studied (study 2).
Fasting serum concentrations of total cholesterol, triglycerides, HDL-cholesterol (HDL-C), HDL2-cholesterol (HDL2-C), HDL3-cholesterol (HDL3-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), and lipoprotein (a) (Lp(a)) were determined. In study 1 AAS administration led to decreases in serum concentrations of HDL-C, HDL2-C, HDL3-C, and Apo-A1, whereas Apo-B increased. Serum Lp(a) declined. Total cholesterol and triglycerides did not change significantly. Alterations after eight and 14 weeks of AAS administration were comparable. No changes occurred in the controls. Six weeks after AAS cessation, serum HDL-C, HDL2-C, Apo-A1, Apo-B, and Lp(a) had still not returned to baseline concentrations. Administration of AAS for 14 weeks was associated with slower recovery to pretreatment concentrations than administration for eight weeks. In study 2, nandrolone decanoate did not influence serum triglycerides, total cholesterol, HDL-C, HDL2-C, HDL3-C, Apo-A1, and Apo-B concentrations after four and eight weeks of intervention, nor six weeks after withdrawal. However, Lp(a) concentrations decreased significantly from 103 (68) to 65 (44) U/l in the nandrolone decanoate group, and in the placebo group a smaller reduction from 245 (245) to 201 (194) U/l was observed. Six weeks after the intervention period, Lp(a) concentrations had returned to baseline values in both groups. It was concluded that self administration of several AASs simultaneously for eight or 14 weeks produces comparable profound unfavourable effects on lipids and lipoproteins, leading to an increased atherogenic lipid profile, despite a beneficial effect on Lp(a) concentration. The changes persist after AAS withdrawal, and normalisation depends on the duration of the drug abuse. Eight weeks of administration of nandrolone decanoate does not affect lipid and lipoprotein concentrations, although it may selectively reduce Lp(a) concentrations. The effect of this on atherogenesis remains to be established [145].

Only a few studies have investigated the effects of AAS on apolipoproteins in healthy young athletes. These studies mainly focused on serum apolipoproteins A-1 and B levels. They demonstrated that AAS diminish serum apolipoprotein A-1 levels and induce elevations of apolipoprotein B levels. However, nandrolone decanoate does not seem to affect the apolipoproteins at all. These findings are not surprising since apolipoproteins are very closely related to HDL- and LDL-cholesterol and are in accordance with results in non exercising humans. However, the magnitude of changes may depend on the drug and dose administered. The 17-[alpha]-alkylated drugs (e.g. stanozolol) rather than testosterone esters are responsible for inducing more profound effects. The same holds true for polydrug regimens when compared with single-drug use. The time course until complete recovery of serum apolipoproteins after drug withdrawal depends on the duration of the AAS course used [012].

**Lipoprotein(a)**

Lipoprotein(a) [Lp(a)] has been recognised as an independent risk factor for cardiovascular disease. The fat composition of Lp(a) is comparable with that of LDL-cholesterol accompanied by the presence of a specific apoprotein(a). The serum levels of Lp(a) seem to be genetically determined and, when elevated, can be hardly influenced by nutrition and drugs. However, AAS have been demonstrated to improve serum Lp(a) levels in men and women. Research in AAS-abusing athletes has been started very recently and, therefore, only few data are available. In a cross-sectional study, it was observed that AAS-using bodybuilders possessed beneficial serum Lp(a) levels, while non-using bodybuilders showed atherogenic Lp(a) levels. In a series of prospective (blinded and unblinded) studies Hartgens and coworkers demonstrated a strong Lp(a)-lowering effect of polydrug regimens of AAS in strength athletes, while the effect of administration of intramuscular nandrolone decanoate 200 mg/week for 8 weeks was nonsignificant. More research is warranted to elucidate the effects on Lp(a), and the impact of unfavourable changes of serum lipids and lipoprotein levels in combination with a beneficially altered serum Lp(a) level [012].
In summary, many studies investigating therapeutic and supratherapeutic doses of AAS administration have consistently demonstrated that serum lipids and lipoproteins are unfavourably altered by these substances. However, the effects may vary considerably with regimen and types of AAS used, and with route of administration. Serum total cholesterol and triglyceride levels seem to remain unaffected by AAS abuse. Several AAS have been demonstrated to suppress serum HDL-cholesterol levels, with a more distinct effect on HDL2- rather than on HDL3-cholesterol. LDL levels will increase and parallels the pattern of HDL-cholesterol suppression. The effects on apolipoprotein A and B-1 are in line with the effects on HDL- and LDL-cholesterol, resulting in AAS-induced elevations of apolipoprotein A and a decline of apolipoprotein B-1. Recent research indicated that Lp(a) levels may be beneficially affected by the administration of a combination of several AAS in high doses. The unfavourable effects of alkylated AAS exceed those of testosterone esters. The influence of polydrug regimens on lipoprotein metabolism is more pronounced than the administration of a single steroid. Moreover, short-term administration of nandrolone decanoate, even at high doses, does not affect lipoprotein metabolism in young athletes. On the other hand, long-term use of nandrolone decanoate in patients alters lipoprotein levels considerably. The sometimes dramatic changes in serum lipids and lipoprotein levels exposes the AAS user to an increased cardiovascular risk, although the impact of short-term disturbances of the cardiovascular risk profile in otherwise healthy young athlete is unknown yet. This ignorance is enhanced by the possible beneficial alteration of Lp(a) levels. Disturbed serum lipids and lipoproteins may recover within a few months, although this is strongly dependent on duration of the AAS course rather than on the dosages used [012].

**Reduced removal from the plasma of chylomicron remnants**

To evaluate the effects of anabolic androgenic steroids (AAS) on chylomicron metabolism an artificial lipid emulsion labeled with radioactive cholesteryl ester (CE) and triglycerides (TG) mimicking chylomicrons was intravenously injected into individuals who regularly weight trained and made regular use of AAS (WT+AAS group), normolipidemic sedentary individuals (SDT group) and individuals who also regularly weight trained but did not use AAS (WT group). Fractional clearance rates (FCR) were determined by compartmental analysis for emulsion plasma decay curves. FCR-CE for the WT+AAS group was reduced (0.0073 ± 0.0079 per min, 0.0155 ± 0.0100 per min, 0.0149 ± 0.0160 per min, respectively), FCR-TG was similar for both the WT and SDT groups. HDL-C plasma concentrations were lower in the WT+AAS group when compared to the WT and SDT groups (22 ± 13; 41 ± 7; 38 ± 13 mg/dL, respectively). Hepatic triglyceride lipase activity was greater in the WT+AAS group when compared to the WT and SDT groups (7243 ± 1822; 3898 ± 1232; 2058 ± 749, respectively). However, no difference was observed for lipoprotein lipase activity. Data thus strongly suggest that AAS may reduce the removal from the plasma of chylomicron remnants, which are known atherogenic factors [146].

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Lipid profiles in rats

Dietary protein amount and source, hypertrophy resistance training (RT) and anabolic androgenic steroids (AAS) may affect body weight and plasma and hepatic lipid profile. 157 adult male Wistar rats were randomly distributed in 16 experimental groups resulting in: normal-protein (NP) or high-protein (HP) diets, whey or soy-protein diets, with or without RT and with or without AAS, for 3 months. Final body weight was lower in the RT and AAS groups compared to sedentary and non-AAS groups, respectively. Plasma total cholesterol (TC) was lower for the HP compared to the NP diets, for the whey compared to the soy-protein diets and for the AAS compared to the non-AAS groups. Plasma HDL-cholesterol was higher in the RT groups but lower for the AAS groups, the HP and the soy-protein diets. Plasma triglycerides (TAG) were lower for the HP diet, for the RT and the non-AAS groups. Liver TC was lower for the NP, for the soy protein and for the AAS groups. Liver TAG were lower for the whey-protein diet, RT and non-AAS groups. Some interactions were found, such as the greater effect of AAS on reducing body weight of rats that performed RT or ingested a HP diet. HDL-cholesterol was higher when RT was combined with HP diets or non-AAS and when HP diets were combined with non-AAS. Groups that combined RT with non-AAS administration obtained the lowest hepatic TAG. Among all the interventions tested, AAS was the factor that most negatively affected plasma and hepatic lipid profile, whereas HP diets and RT could benefit lipid profile, especially when combined [147].
MISCELEANOUS

Multiple organ failure

It was a report of a 42 year old male amateur body builder using anabolic androgenic steroids, who developed acute respiratory distress syndrome, acute kidney injury and refractory supraventricular tachycardia. He required extracorporeal membrane oxygenation, continuous veno-venous hemodialysis, and catheter ablation. It was thought that long-term anabolic androgenic steroid abuse predisposed the patient to developing multiple organ dysfunction syndromes from its immunomodulatory effects in an otherwise healthy patient. Anabolic androgenic steroid use should be part of the history taking process since it may complicate patient outcomes [148].

Effects on antioxidation after anabolic steroids

Reduced cardioprotection

The beneficial effects of exercise in reducing the incidence of cardiovascular diseases are well known and the abuse of anabolic androgenic steroids (AAS) has been associated to cardiovascular disorders. Previous studies showed that heart protection to ischemic events would be mediated by increasing the antioxidant enzyme activities. Here, we investigated the impact of exercise and high doses of the AAS nandrolone decanoate (DECA), 10 mg/kg body weight during 8 weeks, in cardiac tolerance to ischemic events as well as on the activity of antioxidant enzymes in rats. After a global ischemic event, hearts of control trained (CT) group recovered about 70 percent of left ventricular developed pressure, whereas DECA trained (DT), control sedentary (CS) and DECA sedentary (DS) animals recovered only about 20 percent. Similarly, heart infarct size was significantly lower in the CT group compared to animals of the three other groups. The activities of the antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) were significantly higher in CT animals than in the other three groups, whereas catalase activity was not affected in any group. Together, these results indicate that chronic treatment with DECA cause an impairment of exercise induction of antioxidant enzyme activities, leading to a reduced cardioprotection upon ischemic events [149].

Inflammation, oxidative stress, and vascular functioning

Increased systemic inflammation and oxidative stress participate in the mechanism of various cardiovascular diseases. These two phenomena are associated with venous thrombosis and endothelial dysfunction. Curiously, prolonged use of stanozolol decreased the mitochondrial oxidative stress of skeletal muscle in rats. However, hepatic oxidative stress has increased in rats at high doses (2 mg/kg body weight). Hepatic oxidative stress is associated with the production of C-reactive protein, a potent pro-inflammatory agent involved in vascular dysfunction, arterial hypertension, and ischemic heart disease. However, it is worth noting that the increase in hepatic oxidative stress was seen in rats, so it cannot be said that the same would occur in human AAS users. In human experiments, levels of homocysteine were significantly higher in users of AAS for 21 ± 2 years compared with a group that also used AAS for 21 ± 3 years, but discontinued the use for 3 months, and control groups of non-users of AAS. Homocysteine can be involved in the etiology of various cardiovascular diseases. Androgens can exert vasorelaxant effects, but chronic exposure of replacement doses decreases the vascular reactivity to vasodilators. In fact, analysis of pulse waves in response to glyceryltrinitrate shows that endothelium independent vasodilator function was impaired in young adult bodybuilders. The vasodilatation was reduced by half compared to previous users who discontinued the use and was only 30 percent of the value
obtained in a control group of AAS non-users. An impaired vasodilator functioning was also found in young adults manifesting hypogonadism (35 ± 4 years old) even at physiological doses used in testosterone replacement therapy. Finally, a lower vasodilator functioning was accompanied by an increased sympathetic nerve activity to the vasculature among AAS users based on microneurography measures. This adverse effect of AAS calls attention, but the data are inconsistent [015].

*Impaired exercise-induced cardioprotection of antioxidant enzymes*

High doses of anabolic androgenic steroids (AAS) impair the cardioprotective effects of exercise against ischemia/reperfusion (I/R) insult, possibly through cellular redox imbalance. Here, the effect of nandrolone decanoate (DECA) treatment on heart redox metabolism was investigated during I/R in sedentary and exercised rats. DECA treatment significantly reduced superoxide dismutase and glutathione reductase activities in exercised rats after heart reperfusion. Catalase and glutathione peroxidase activities were not affected by DECA in both sedentary and trained rats, regardless the I/R period. DECA also induced myocardial oxidative stress, as evidenced by the reduced levels of total reduced thiols after heart reperfusion in exercised rats treated with the anabolic steroid. These results indicate that cardiotoxic effects of supraphysiological doses of AAS involve reduced heart antioxidant capacity [149].

Uncertainty remains about possible cardiac adaptation to resistance training. Androgenic anabolic steroids (AAS) use plays a potential role and may have adverse cardiovascular effects. To elucidate the effect of resistance training and of AAS-use on cardiac dimensions and function cardiac magnetic resonance (CMR) were performed in 156 male subjects aged 18-40 years: 52 non-athletes (maximum of 3 exercise hours/week), 52 strength-endurance (high dynamic-high static, HD-HS) and 52 strength (low dynamic-high static, LD-HS) trained athletes (athletes ≥ 6 exercise hours/week). Twenty-eight LD-HS athletes denied and 24 admitted to AAS use for an average duration of 5 years (range 3 months-20 years). No significant differences were found between non-athletes and non-AAS-using LD-HS athletes. AAS-using LD-HS athletes had significantly larger LV and RV volumes and LV wall mass than non-AAS-using LD-HS athletes, but lower than HD-HS athletes. In comparison to all other groups AAS-using LD-HS athletes showed lower ejection fractions of both ventricles (LV/RV EF 51/48 % versus 55-57/51-52 %) and lower E/A ratios (LV/RV 1.5/1.2 versus 1.9-2.0/1.4-1.5) as an indirect measure of diastolic function. Linear regression models demonstrated a significant effect of AAS-use on LV EDV, LV EDM, systolic function and mitral valve E/A ratio. It was concluded that strength athletes who use AAS show significantly different cardiac dimensions and biventricular systolic dysfunction and impaired ventricular inflow as compared to non-athletes and non-AAS-using strength athletes. Increased ventricular volume and mass did not exceed that of strength-endurance athletes. These findings may help raise awareness of the consequences of AAS use [150].

*Experimental*

High doses of anabolic androgenic steroids (AAS) impair the cardioprotective effects of exercise against ischemia/reperfusion (I/R) insult, possibly through cellular redox imbalance. Here, the effect of nandrolone decanoate (DECA) treatment on heart redox metabolism was investigated during I/R in sedentary and exercised rats. DECA treatment significantly reduced superoxide dismutase and glutathione reductase activities in exercised rats after heart reperfusion. Catalase and glutathione peroxidase activities were not affected by DECA in both sedentary and trained rats, regardless the I/R period. DECA also induced myocardial oxidative stress, as evidenced by the reduced levels of total reduced thiols after heart reperfusion in exercised rats treated with the anabolic steroid. These results indicate that
cardiotoxic effects of supraphysiological doses of AAS involve reduced heart antioxidant capacity [151].

One study focuses on the short term effects of repeated low level administration of turinabol and methanabol on cardiac function in young rabbits (4 months-old). The experimental scheme consisted of two oral administration periods, lasting 1 month each, interrupted by 1-month wash-out period. Serial echocardiographic evaluation at the end of all three experimental periods was performed in all animals. Oxidative stress markers have also been monitored at the end of each administration period. Treated animals originally showed significantly increased myocardial mass and systolic cardiac output, which normalized at the end of the wash out period. Re-administration led to increased cardiac output, at the cost though of a progressive myocardial mass reduction. A dose-dependent trend towards impaired longitudinal systolic, diastolic and global myocardial function was also observed. The adverse effects were more pronounced in the methanabol group. For both anabolic steroids studied, the low dose had no significant effects on oxidative stress markers monitored, while the high dose created a hostile oxidative environment. In conclusion, anabolic administration has been found to create a possible deleterious long term effect on the growth of the immature heart and should be strongly discouraged especially in young human subjects [135].

**Homocysteine abnormalities**

Anabolic steroid use has been shown to have detrimental cardiac effects including left ventricular hypertrophy, increased thickening of the interventricular septum, dyslipidemia, cardiac arrhythmias, increased blood pressure, and most notably acute myocardial infarctions (MIs). Previous cases have reported multiple fatalities from the abuse of anabolic steroids as well as numerous incidents of acute MI. Furthermore, anabolic steroids have been linked to changes in homocysteine with increases so severe some patients develop hyperhomocysteinemia. Advanced research suggests that increased levels of homocysteine, including mild hyperhomocysteinemia, can lead to atherosclerosis of the coronary vessels as a result of damage to the endothelium and can be considered a risk factor for arterial vascular disease. A previous study showed that body-builders chronically taking anabolic steroids developed acute hyperhomocysteinemia. More research still needs to be conducted on the mechanism in which increased levels of homocysteine affect coronary vessels. We report the first case of a patient presenting to the emergency department (ED) with an acute MI due to anabolic steroids and associated elevated homocysteine levels. A 27-year-old male anabolic steroid user presented to the emergency department with chest pain radiating down his left arm. After initial assessment and electrocardiogram, the patient was diagnosed with an ST-elevation myocardial infarction (STEMI), and STEMI protocol was initiated. Cardiac catheterization revealed a 70 percent stenosis of the left anterior descending artery. Further in-patient testing revealed remarkably elevated homocysteine levels, which led to an additional diagnosis of hyperhomocysteinemia. Special attention should be paid to patients who abuse anabolic steroids due to their association with elevated homocysteine levels and subsequent stenosis of the coronary vessels and MI. The patient was found to have markedly high homocysteine levels (45.2 micromol/L) after anabolic steroid use. There has never been a case reported of a patient with a STEMI and hyperhomocysteinemia while taking anabolic steroids. This case is noteworthy because homocysteine levels should be considered when patients admit to anabolic steroids [152].

Hyperhomocysteinemia has been accepted as an independent risk factor for atherosclerosis and atherothrombosis. In recent years, several reports have appeared in the literature linking the use of anabolic steroids with acute vascular events in bodybuilders. In this study, we investigated whether hyperhomocysteinemia could contribute to the high vascular risk in
bodybuilders taking anabolic steroids. Twenty-three bodybuilders in different phases of their training cycle and six control athletes participated in our study. Anthropomorphic measures displayed a higher body mass index for bodybuilders in the competition phase than for bodybuilders in the work-out and build-up phases, and for control athletes. Homocysteine levels were 8.7 ± 1.6 micromol/L in control athletes, 8.5 ± 2.8 micromol/L in work-out phase bodybuilders, and 8.3 ± 1.5 micromol/L in competition phase bodybuilders, but 11.9 ± 3.1 micromol/l in build-up phase bodybuilders. Vitamin B12 and folate levels did not differ significantly between the four groups. The study shows that intake of anabolic steroids, as used typically by bodybuilders in the build-up phase, induces acute hyperhomocysteinemia and is likely to initiate an additional, potentially atherothrombotic mechanism in this group of athletes [153].

Experimental

Androgenic-anabolic steroids are used widely by many athletes in order to increase muscle mass and strength. Since plasma total homocysteine, an independent risk factor of vascular diseases, is higher in men than in women, it has been proposed that androgenic hormones could increase the plasma total homocysteine level and it might play some role in sudden death when used at supraphysiological doses. To study the association between the use of androgenic-anabolic steroids and plasma homocysteine level, nandrolone decanoate was administered in 3 and 10 mg/kg doses to male rats by intramuscular weekly injections. Control animals received the solvent of nandrolone decanoate. After 14 weeks, plasma total homocysteine level was measured. In order to make sure about the adequacy of doses and bioavailability of drug, testes parameters were also considered. While all testes parameters were suppressed significantly, no association between androgenic-anabolic steroids use and total homocysteine level was found. It is concluded that chronic administration of nandrolone decanoate does not have any significant effect on plasma total homocysteine of male rats. Thus, factors other than plasma total homocysteine level may contribute to increased cardiovascular events after chronic abuse of androgenic-anabolic steroids [154].

Studies not showing any cardiotoxic effects

Since the abuse of androgenic-anabolic steroids has been associated with the occurrence of serious cardiovascular disease in young athletes, we performed two studies to investigate the effects of short-term AAS administration on heart structure and function in experienced male strength athletes, with special reference to dose and duration of drug abuse. In Study 1 the effects of AAS were assessed in 17 experienced male strength athletes (age 31) who self-administered AAS for 8 or 12-16 weeks and in 15 non-using strength athletes (age 33) in a non-blinded design. In Study 2 the effects of administration of nandrolone decanoate (200 mg/wk i. m.) for eight weeks were investigated in 16 bodybuilders in a randomised double blind, placebo controlled design. In all subjects M-mode and two-dimensional Doppler-echocardiography were performed at baseline and after 8 weeks AAS administration. In the athletes of Study 1 who used AAS for 12-16 weeks a third echocardiogram was also made at the end of the AAS administration period. Echocardiographic examinations included the determination of the aortic diameter (AD), left atrium diameter (LA), left ventricular end diastolic diameter (LVEDD), interventricular septum thickness (IVS), posterior wall end diastolic wall thickness (PWEDWT), left ventricular mass (LVM), left ventricular mass index (LVMI), ejection fraction (EF) and right ventricular diameter (RVD). For assessment of the diastolic function measurements of E and A peak velocities and calculation of E/A ratio were used. In addition, acceleration and deceleration times of the E-top (ATM and DT, respectively) were determined. For evaluation of factors associated with stroke volume the aorta peak flow (AV) and left ventricular ejection times (LVET) were determined. In Study 1 eight weeks AAS self-administration did not result in changes of blood pressure or cardiac
size and function. Additionally, duration of AAS self-administration did not have any impact on these parameters. Study 2 revealed that eight weeks administration of nandrolone decanoate did not induce significant alterations in blood pressure and heart morphology and function. Short-term administration of AAS for periods up to 16 weeks did not lead to detectable echocardiographic alterations of heart morphology and systolic and diastolic function in experienced strength athletes. The administration regimen used nor the length of AAS abuse did influence the results. Moreover, it is concluded that echocardiographic evaluation may provide incomplete assessment of the actual cardiac condition in AAS users since it is not sensitive enough to detect alterations at the cellular level. Nevertheless, from the present study no conclusions can be drawn of the cardiotoxic effects of long term AAS abuse [155].

Effects on the cardiovascular system of dehydroepiandrosterone (DHEA)

An excess of steroid hormones such as mineralocorticoids has been linked to heart hypertrophy, arrhythmias, inflammation, fibrosis, and apoptosis as well as to endothelial and smooth muscle vascular dysfunctions. Benefits of antagonizing aldosterone action in patients with cardiovascular diseases (CVD) have demonstrated a causal relationship between steroid hormones and CVD. On the other hand, putatively protective steroid hormones such as dehydroepiandrosterone (DHEA) decrease with aging. DHEA, and particularly its sulfated derivative, DHEA sulfate (DHEA-S), are among the most abundant circulating steroid hormones. These two hormones are derived from cholesterol and are principally produced by the adrenal cortex; however, small amounts of them have been proposed to be produced by other organs such as the heart. Since the discovery of DHEA and its sulfated metabolite during the first half of the 20th century, many publications have hypothesized that the development of DHEA deficiencies with age might play a key role in the degradation of many functions and contribute to the genesis of several disorders, including cardiovascular defects. Other studies have reported a beneficial role for DHEA (S) in various physiologic or pathophysiologic conditions such as brain development, aging, osteoporosis, immune system-mediated rheumatologic diseases, diabetes mellitus (DM), obesity, chronic heart failure (particularly when linked with oxidative stress), and recently, vascular remodeling as occurring in pulmonary arterial hypertension. Nevertheless, only few marked beneficial effects have been clearly reported with DHEA supplementation in human and therefore, this subject is still controversial. Dehydroepiandrosterone (DHEA) and its sulfate ester, Dehydroepiandrosterone Sulfate (DHEA-S) have been considered as putative anti-aging hormones for many years. Indeed, while DHEAS is the most abundant circulating hormone, its concentration is markedly decreased upon aging and early epidemiologic trials have revealed a strong inverse correlation between the hormone concentrations and the occurrence of several dysfunctions frequently encountered in the elderly. Naturally, hormonal supplementation has been rapidly suggested to prevent DHEA (S) deficiency and therefore, age-related development of these pathologies, using the same strategy as estrogen replacement therapy proposed in postmenopausal women. All references were searched using PubMed and the following strategy: our initial selection included all articles in English and we sorted them with the following keywords: "DHEA or DHEA-S" and "heart or vascular or endothelium or cardiovascular disease". The search was limited to neither the publication date nor specific journals. The final selection was made according to the relevance of the article content with the aims of the review. According to these criteria, fewer than 10 percent of the articles retrieved at the first step were discarded. In the short review, it was focused on the cardiovascular action of DHEA. We started by analyzing evidences in favor of a strong inverse association between DHEA (S) levels and the cardiovascular risk as demonstrated in multiple observational epidemiologic studies for several decades. Then it was discussed the different trials aimed at supplementing DHEA (S), both in animals and human, for preventing cardiovascular diseases and we analyzed the possible reasons for the discrepancy observed
among the results of some studies. Finally, it was presented putative molecular mechanisms of action for DHEA (S), demonstrated in vitro in different models of vascular and cardiac cells, highlighting the complexity of the involved signaling pathways. It was concluded that the identification of the beneficial cardiovascular effects of DHEA (S) and a better understanding of the involved mechanisms should be helpful to develop new strategies or pharmacologic approaches for many lethal diseases in Western countries [156].

Cardiac effects of anabolic steroids in different sports

Bodybuilders or powerlifters

Increases in blood pressure and peripheral arterial resistance are known from experimental studies, but there are also effects on the heart muscle, primarily left ventricular hypertrophy with restricted diastolic function. Severe cardiac complications such as cardiac insufficiency, ventricular fibrillation, ventricular thromboses, myocardial infarction, or sudden cardiac death in individual strength athletes with acute AAS abuse have also been reported. In almost all studies, acute side effects were examined only during AAS intake or within weeks to a few months of their discontinuance. However, the extent to which these effects are reversible after discontinuing intake of these agents and the degree to which they leave permanent impairment are still controversial matters. To investigate the reversibility of adverse cardiovascular effects after chronic abuse of anabolic androgenic steroids (AAS) in athletes Doppler echocardiography and cycle ergometry including measurements of blood pressure at rest and during exercise were undertaken in 32 bodybuilders or powerlifters, including 15 athletes who had not been taking AAS for at least 12 months (ex-users) and 17 currently abusing AAS (users), as well as in 15 anabolic-free weightlifters. The ergometric performance in the subjects was within the normal range for untrained persons of the same age, even when considering the moderate exhaustion of the weightlifters (with a lower maximum heart rate towards the end of exercise). The typical training in bodybuilding and weightlifting, including the moderate endurance training on a cycle ergometer done by most of the athletes, does not result in significant increases in cycle ergometry performance. Systolic blood pressure was higher in users (140 ± 10 mmHg) than in ex-users (130 ± mmHg) or weightlifters (125 ± 10 mm Hg). The results suggest that the increases in blood pressure with AAS use are rather small and transient. Increased blood pressure values or a reduced fall in blood pressure during sleep have been described with AAS use, but not in all studies. These discrepancies probably reflect different preparations, dosages, and intake cycles. It has been reported that five months after discontinuing AAS intake, systolic blood pressure remained higher by 6 mm Hg at rest compared with an anabolic-free control group. In animal experiments an increase in peripheral resistance was still detectable six weeks after AAS use. Left ventricular muscle mass related to fat-free body mass and the ratio of mean left ventricular wall thickness to internal diameter were not significantly higher in users than in ex-users, but were lower in weightlifters. Left ventricular wall thickness related to fat-free body mass was also lower in weightlifters, but did not differ between users and ex-users. Left ventricular wall thickness was correlated with a point score estimating AAS abuse in users. In all groups, systolic left ventricular function was within the normal range. The maximum late transmitral Doppler flow velocity (Amax) was higher in users than in weightlifters. The reversible ST segment changes observed in one user after discontinuation of AAS use could be related to AAS intake. Only individual case descriptions of ECG changes with AAS abuse are found in published reports. In a previous investigation, ECG abnormalities could not be established. It was concluded that several years after discontinuation of anabolic steroid abuse, strength athletes still show a slight concentric left ventricular hypertrophy in comparison with AAS-free strength athletes [157].

It was compared cardiac parameters in weightlifters reporting long-term AAS use to those in
otherwise similar weightlifters without prior AAS exposure. It was performed 2D tissue-Doppler and speckle-tracking echocardiography to assess left ventricular (LV) ejection fraction, LV systolic strain, and conventional indices of diastolic function in long-term AAS users (n=12) and otherwise similar AAS nonusers (n=7). AAS users (median [quartile 1, quartile 3] cumulative lifetime AAS exposure, 468 [169, 520] weeks) closely resembled nonusers in age, prior duration of weightlifting, and current intensity of weight training. LV structural parameters were similar between the two groups; however, AAS users had significantly lower LV ejection fraction (51% [48, 54] versus 59% [58%, 62%]), longitudinal strain (17% [14%, 19%] vs 21% [20%, 23%]), and radial strain (38% [29%, 44%] vs 50% [44%, 62%]). Ten of the 12 AAS users showed LV ejection fractions below the accepted limit of normal (>55%). AAS users also demonstrated decreased diastolic function compared to nonusers as evidenced by a markedly lower early peak tissue velocity (7.4 [6.8, 7.9] cm/s vs 9.9 [8.3, 10.5] cm/s) and early-to-late diastolic filling ratio (0.93 [0.88, 1.39] vs 1.80 [1.48, 2.00]). It was concluded that cardiac dysfunction in long-term AAS users appears to be more severe than previously reported and may be sufficient to increase the risk of heart failure [158].

Combination with other substances

Combined cardiac effects of cocaine and nandrolone in the rat

Despite reports of an increase in the incidence of simultaneous cocaine and anabolic steroid abuse, potential adverse interactions between these two drugs on the cardiovascular system are largely unquantified. Cocaine has been reported to induce coronary vasoconstriction, cardiac arrhythmias and conduction delays. Anabolic steroids have been associated with cardiac hypertrophy and hypertension. Utilising both in vivo (radiotelemetry) and in vitro (isolated Langendorff-perfused heart) techniques, our aim was to determine whether anabolic steroids cause cardiac hypertrophy and alter cardiac function, and consequently alter the response of the heart to cocaine. It was found that 15 days of treatment of rats with nandrolone decanoate (20 mg/kg, s.c.) was not sufficient to cause hypertrophy, alter cardiac function or the spread of electrical activity through the heart. However, nandrolone pretreatment was found to significantly potentiate the heart rate response to cocaine (45 mg/kg, i.p.) in vivo. The study indicates that nandrolone significantly elevates the heart rate response to high dose cocaine without changing heart morphology. The mechanism of this interaction remains uncertain [159].

Increased risk of diabetes

Anabolic steroids decrease glucose tolerance and increase insulin resistance, which lead to hyperinsulinism and secondary diabetes mellitus with type II symptoms [20].

The case of a 36-year-old male professional bodybuilder was reported. He presented to the accident and emergency department with right upper quadrant pain. This was on the background of a 15-year history of anabolic steroid and growth hormone misuse. Examination revealed mild hepatomegaly and a random blood sugar of 30.2 mmol/L. There was no evidence of ketonuria or acidosis. Biochemical evidence of hepatitis was found, and the patient was in acute renal failure. He was given a sliding scale of insulin and an intravenous infusion of crystalloid. The hepatitis and hyperglycaemia settled with conservative treatment. It is believed that this is the first reported case of frank diabetes precipitated by supraphysiological recreational growth hormone misuse [160].

A 33-year-old male presented to the emergency department with complaints of polydipsia,
polyuria, nausea, headaches, blurry vision and malaise. Lab work revealed a serum glucose level of 1166 mg/dl (64.8 mmol/L). The patient admitted to completing a cycle of androgenic anabolic steroids (AASs) for bodybuilding. His regimen consisted of supraphysiologic intramuscular injections of a bovine growth hormone, trenbolone acetate and testosterone. The patient received intravenous fluids and insulin to restore metabolic balance. Previously healthy with a non-contributory family history, he was diagnosed with new onset diabetes.

Discussion: It has been demonstrated that AAS use, specifically growth hormone, can affect glucose homeostasis through increasing cellular insulin resistance and reducing glucose uptake. Excess growth hormone has been shown to cause symptoms of acromegaly which predisposes up to 40% of patients to diabetes. As trenbolone acetate is not indicated for human use and athletes are known to use supraphysiologic doses of this underground, performance enhancing drug, the correlation of the timing of events and the use of this veterinary growth hormone likely exacerbated an underlying condition or caused this new onset diabetes. It was reported a case of a young bodybuilder with no significant past medical history who was diagnosed with new onset diabetes associated with supraphysiologic self-injections of the bovine growth hormone, trenbolone acetate, combined with testosterone. AAS have the potential to induce or exacerbate diabetic conditions due to decreased glucose tolerance and increased insulin resistance [161].
A SUMMARY OF EFFECTS OF ANABOLIC STEROIDS ON THE HEART

Abuse of anabolic androgenic steroids (AAS) has been linked to a variety of different cardiovascular side effects. In case reports, acute myocardial infarction is the most common event presented, but other adverse cardiovascular effects such as left ventricular hypertrophy, reduced left ventricular function, arterial thrombosis, pulmonary embolism and several cases of sudden cardiac death have also been reported. However, to date there are no prospective, randomized, interventional studies on the long-term cardiovascular effects of abuse of AAS. In one review it was studied the relevant literature regarding several risk factors for cardiovascular disease where the effects of AAS have been scrutinized:

- echocardiographic studies show that supraphysiologic doses of AAS lead to both morphologic and functional changes of the heart. These include a tendency to produce myocardial hypertrophy, a possible increase of heart chamber diameters, unequivocal alterations of diastolic function and ventricular relaxation, and most likely a subclinically compromised left ventricular contractile function
- AAS induce a mild, but transient increase of blood pressure. However, the clinical significance of this effect remains modest
- AAS confer an enhanced pro-thrombotic state, most prominently through an activation of platelet aggregability. The concomitant effects on the humoral coagulation cascade are more complex and include activation of both pro-coagulatory and fibrinolytic pathways
- users of AAS often demonstrate unfavorable measurements of vascular reactivity involving endothelial-dependent or endothelial-independent vasodilatation. A degree of reversibility seems to be consistent, though
- there is a comprehensive body of evidence documenting that AAS induce various alterations of lipid metabolism. The most prominent changes are concomitant elevations of LDL and decreases of HDL, effects that increase the risk of coronary artery disease
- the use of AAS appears to confer an increased risk of life-threatening arrhythmia leading to sudden death, although the underlying mechanisms are still far from being elucidated

Taken together, various lines of evidence involving a variety of pathophysiologic mechanisms suggest an increased risk for cardiovascular disease in users of anabolic androgenic steroids [162].

Thus, the myocardial effects of AAS abuse can be summarized in three different categories including [043]:

- myocardial hypertrophy as result of
  o elevated muscle sympathetic nerve activity
  o direct anabolic effects of AAS
  o renin-angiotensin system activity induced collagen deposition and interstitial fibrosis
- left ventricular dysfunction as result of
  o AAS-induced myocardial hypertrophy
  o mitochondrial damage and apoptosis as consequences of Ca^{2+} signaling
  o rennin-angiotensin system activity and fibrosis
- cardiac arrhythmias as result of increased myocardial mass and reduction
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