Effects of Performance Enhancing Drugs on the Cardiovascular System

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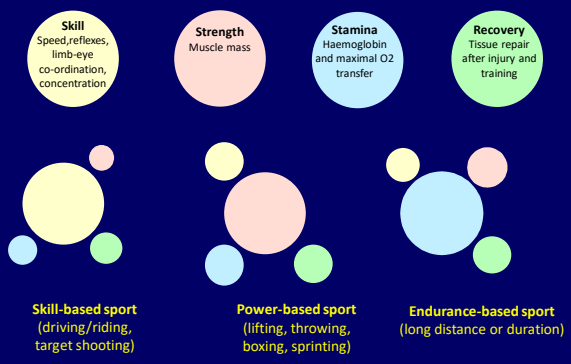
History

- Stories date back thousands of years to Ancient Olympic games
  - Ground horse hooves and sheep testicles
- In Chinese traditional medicine to bolster male body.
  - deer antler
  - tiger bone
  - bear gall bladder
  - ginseng and other roots
- Athletes in Late 19th/Early 20th century
  - Caffeine and strychnine
- Danish cyclist death in 1960 Olympic game
  - International Olympic Committee came out with first list of prohibited drugs.

Effects of Performance Enhancing Drugs on the Cardiovascular System

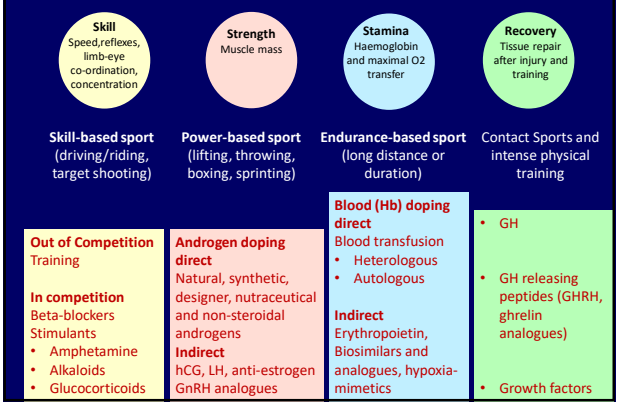
Anabolic Androgenic Steroids
Human Growth Hormone and IGF1
Erythropoietin
Stimulants
Beta blockers
Diuretics

Sports Performance- Skill, Strength, Stamina and Recovery



Performance Enhancing Hormones in Sports Doping. David J. Handelsman. In Endocrinology: Adult and Pediatric, Seventh Edition. Jameson, J. Larry

Sports Performance- Skill, Strength, Stamina and Recovery



Performance Enhancig Drugs and The CVS

- Case studies
- Postmortem studies
- Animal models
- Physiological effects are confounded by:
  - Self-reporting – unreliable
  - Different dosing levels
  - Different exposure duration
  - Quality of products
  - Multiple drug use

Anabolic Agents
Anabolic Androgenic Steroids

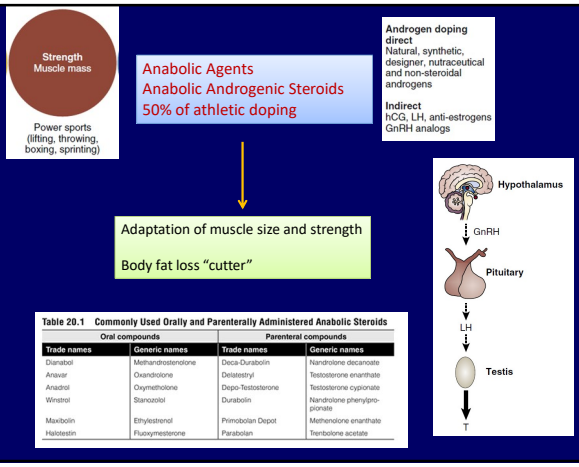


Table 20.1 Commonly Used Orally and Parenterally Administered Anabolic Steroids

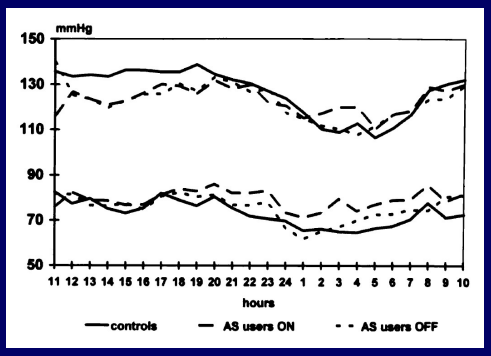
Oral compounds		Parenteral compounds	
Trade names	**Generic names**	**Trade names**	**Generic names**
Dianabol	Methandrostenolone	Deca-Durabolin	Nandrolone decanoate
Anavar	Oxandrolone	Delatestryl	Testosterone enanthate
Anadrol	Oxymetholone	Depo-Testosterone	Testosterone cypionate
Winstrol	Stanozolol	Durabolin	Nandrolone phenylpro-pionate
Maxibolin	Ethylestrenol	Primobolan Depot	Methenolone enanthate
Halotestin	Fluoxymesterone	Parabolan	Trenbolone acetate

Anabolic Androgenic Steroids

Hypertension - Controversial

- Higher at rest and during exercise. Adjusted for weight and bicept circumference no difference.
- ABPM. No difference with controls. ?less diurnal variation
- Affect corticosteroid/renin production

Riebe D et al. The blood pressure response to exercise in anabolic steroid users. Med Sci Sports Exerc. 1992 Jun;24(6):633-7.
J Clin Pharmacol. 1996 Dec;36(12):1132-40.
Palatini P et al. Cardiovascular effects of anabolic steroids in weight-trained subjects. J Clin Pharmacol. 1996 Dec;36(12):1132-40.
Gheshlaghi F. et al. Cardiovascular manifestations of anabolic steroids in association with demographic variables in body building athletes. J Res Med Sci. 2015 Feb;20(2):165-8.



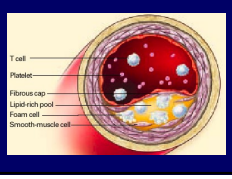
Palatini P et al. Cardiovascular effects of anabolic steroids in weight-trained subjects. J Clin Pharmacol. 1996 Dec;36(12):1132-40.

Anabolic Androgenic Steroids

Lipid metabolism – conflicting data

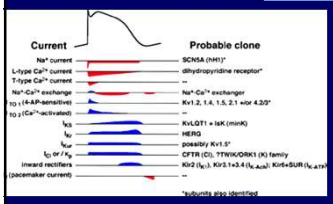
- ↑ Total cholesterol, ↑ LDL, ↓HDL
- Increase hepatic triglyceride lipase activity

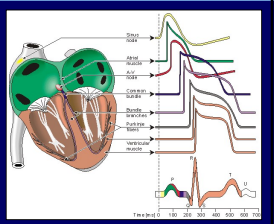
Predispose to premature atherosclerosis and CAD/strokes

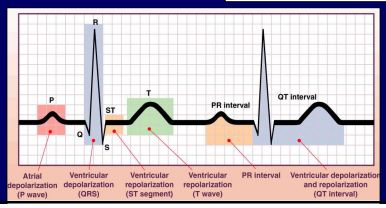


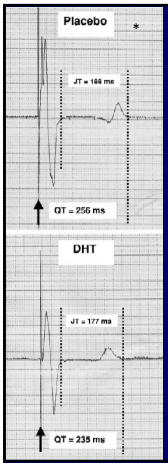
Cardiac Electrical Effects

Anabolic Androgenic Steroids









Anabolic Androgenic Steroids

Cardiac Electrical Effects

AAS shortens the QT interval and increases the densities of inward and delayed rectifier potassium currents in animal models

*Liu XK et al. In vivo androgen treatment shortens the QT interval and increases the densities of inward and delayed rectifier potassium currents in orchiectomized male rabbits. Cardiovasc Res. 2003 Jan;57(1):28-36.

Fulop L et al. Effects of sex hormones on ECG parameters and expression of cardiac ion channels in dogs. Acta Physiol 2006, 188, 163–171

Cardiac Electrical Effects — Anabolic Androgenic Steroids

Table 1. Body Size Variables, Blood Pressures, and Electrocardiographic Parameters of the Bodybuilders and Controls

	Group A (n = 90)	Group B (n = 86)	Group C (n = 79)	P value A versus B	P value A versus C	P value B versus C
Age (years)	31.4 ± 5	32.1 ± 4.6	33 ± 6	0.71	0.83	0.64
Height (cm)	178 ± 5	175 ± 8	179 ± 6	0.41	0.96	0.57
Weight (kg)	76 ± 9	79 ± 8	96 ± 8	0.53	0.001	0.003
Body surface area (m^2)	1.93 ± 0.11	1.98 ± 0.14	2.19 ± 0.16	0.69	0.021	0.035
Heart rate (bpm)	78 ± 10.3	69 ± 8.5	68 ± 8.9	0.07	0.073	0.59
Systolic blood pressure (mmHg)	130 ± 10	132 ± 11	135 ± 11	0.59	0.25	0.25
Diastolic Blood Pressure (mm Hg)	80 ± 8	78 ± 12	82 ± 10	0.35	0.27	0.39
QTc interval (ms)	418 ± 23.6	422 ± 24.5	367 ± 17.1	0.61	0.001	0.001

Group A = sedentary men; Group B = drug-free bodybuilders; Group C = drug user bodybuilders.

Bigi MA. Short QT interval: A novel predictor of androgen abuse in strength trained athletes. Ann Noninvasive Electrocardiol. 2009 Jan;14(1):35-9

Table 3. Comparison of Electrocardiographical Features of AAS User and Nonuser Bodybuilders

	AAS Nonuser (n = 18)	AAS User (n = 15)	P Value
QT (milliseconds)	370.3 ± 22.5	421.1 ± 22.7	<0.01
QTd (milliseconds)	39.5 ± 7.9	57.9 ± 7.1	<0.01
cQT	395.6 ± 42.7	459.7 ± 41.3	<0.01
cQTd	42.1 ± 7.9	63.5 ± 9.4	<0.01
QRS (milliseconds)	95.8 ± 10.1	97.3 ± 9.1	NS
JT (milliseconds)	276.6 ± 18.6	323.7 ± 25.3	<0.01
cJT	294.7 ± 32.6	352.8 ± 35.9	<0.01
Tp-e	77.1 ± 9.5	102.7 ± 9.2	<0.01
Tp-e/QT	0.21 ± 0.02	0.24 ± 0.02	<0.01
Tp-e/cQT	0.20 ± 0.03	0.22 ± 0.03	<0.01

Alizade E et al. The Effect of Chronic Anabolic-Androgenic Steroid Use on Tp-E Interval, Tp-E/Qt Ratio, and Tp-E/Qtc Ratio in Male Bodybuilders. Ann Noninvasive Electrocardiol. 2015 Nov;20(6):592-600

Cardiac Structural Changes — Anabolic Androgenic Steroids

Physiological changes vs. Drug induced

Left ventricular hypertrophy

Table 3 Echocardiographic data on the left ventricle

	Ex-users (n = 15)	Users (n = 17)	Weightlifters (n = 15)
LVMM (g)	232 ± 42	281 (54)*	204 (44)‡‡‡
LVMM per unit BSA (g/m^2)	112 (17)	132 (23)*	93 (12)‡‡‡‡
LVMM per unit FFM (g/kg)	3.16 (0.53)	3.32 (0.48)	2.43 (0.26)†††‡‡‡
EDD (mm)	54.0 (5.0)	56.5 (3.5)	54.0 (4.0)
EDD per unit BSA (mm/m^2)	26.0 (2.0)	26.5 (2.0)	25.0 (2.0)‡
EDD per unit FFM (mm/kg)	0.74 (0.08)	0.67 (0.05)*	0.66 (0.08)††
ESD (mm)	35.0 (4.5)	38.5 (2.5)*	36.0 (3.5)
IVS (mm)	11.5 (1.2)	12.3 (1.4)	10.3 (1.0)†‡‡‡
IVS per unit BSA (mm/m^2)	5.6 (0.6)	5.8 (0.7)	4.7 (0.5)†‡‡‡
IVS per unit FFM (mm/kg)	0.16 (0.02)	0.15 (0.02)	0.13 (0.02)†‡‡‡
LVPW (mm)	10.2 (0.8)	11.4 (1.3)*	9.4 (1.5)‡‡‡
LVPW per unit BSA (mm/m^2)	5.0 (0.5)	5.4 (0.6)	4.3 (0.5)†‡‡‡
LVPW per unit FFM (mm/kg)	0.14 (0.02)	0.14 (0.01)	0.11 (0.02)†‡‡‡

Values are mean (SD).
Users *v* ex-users: *p<0.05.
Ex-users *v* weightlifters: †p<0.05; ††p<0.01; †††p<0.001.
Users *v* weightlifters: ‡p<0.05; ‡‡‡p<0.001.
BSA, body surface area; EDD, end diastolic internal diameter; ESD, end systolic internal diameter; FFM, fat-free body mass; IVS, interventricular septum; LVMM, left ventricular muscle mass; LVPW, left ventricular posterior wall.

Greater:

- LV wall Txnss.
- LVEDV
- LV mass

A. Urhausen et al. Heart 2004;90:496–501

Cardiac Structural Changes — Anabolic Androgenic Steroids

Left ventricular hypertrophy - mechanism

Androgen Receptors Mediate Hypertrophy in Cardiac Myocytes

James D. Marsh, MD; Michael H. Lehmann, MD; Rebecca H. Ritchie, PhD; Judith K. Gwathmey, VMD, PhD; Glenn E. Green, MD; Rick J. Schiebinger, MD

Background—The role of androgens in producing cardiac hypertrophy by direct action on cardiac myocytes is uncertain. Accordingly, we tested the hypothesis that cardiac myocytes in adult men and women express an androgen receptor gene and that myocytes respond to androgens by a hypertrophic response.

Methods and Results—We used reverse transcription–polymerase chain reaction methods to demonstrate androgen receptor transcripts in multiple tissues and [^{3}H]phenylalanine incorporation and atrial natriuretic peptide secretion as markers of hypertrophy in cultured rat myocytes. Messenger RNA encoding androgen receptors was detected in myocytes of male and female adult rats, neonatal rat myocytes, rat heart, dog heart, and infant and adult human heart. Both testosterone and dihydrotestosterone produced a robust receptor-specific hypertrophic response in myocytes, determined by indices of protein synthesis and atrial natriuretic peptide secretion.

Conclusions—Androgen receptors are present in cardiac myocytes from multiple species, including normal men and women, in a context that permits androgens to modulate the cardiac phenotype and produce hypertrophy by direct, receptor-specific mechanisms. There are clinical implications for therapeutic or illicit use of androgens in humans. (***Circulation***. 1998;98:256-261.)

Cardiac Structural Changes — Anabolic Androgenic Steroids

Left ventricular hypertrophy - clinical effects

Table 4 Echocardiographic data for AS and NAS groups (data are mean ± SD)

Measure	AS	Non-AS
E ($m\ s^{-1}$)	0.67 ± 0.11	0.77 ± 0.20
A ($m\ s^{-1}$)	0.54 ± 0.10	0.38 ± 0.61†
E:A‡	1.31 (0.50)	1.88 (0.35)†
S' ($m\ s^{-1}$)	0.10 ± 0.01	0.10 ± 0.02
E' ($m\ s^{-1}$)	0.09 ± 0.02	0.13 ± 0.23†
A' ($m\ s^{-1}$)	0.10 ± 0.01	0.07 ± 0.01†
E':A'‡	0.99 (0.54)	1.78 (0.46)†
E:E'‡	7.19 (1.45)	5.66 (0.77)*
ε (%)	−14.2 ± 2.7	−16.6 ± 1.9*
Peak *S* SR (s^{-1})	−1.00 ± 0.23	−1.14 ± 0.11†
Peak *E* SR (s^{-1})	1.40 ± 0.38	1.65 ± 0.28
Peak *A* SR (s^{-1})	1.02 ± 0.36	0.72 ± 0.25*

E early diastolic filling, *A* late diastolic filling, *E:A* early:late diastolic ratio, *S'* systolic tissue velocity, *E'* early diastolic tissue velocity, *A'* late diastolic tissue velocity, *E':A'* early:late diastolic tissue velocity ratio, *ε* strain, *SR* strain rate

* $p < 0.05$
† $p < 0.005$
‡ Data given as median (interquartile range)

No sig. change in LVEF

↓ Diastolic function
- increase in collagen cross link and a decrease in myocardial elastance

Conflicting reports

Proposed Mechanism
- Alteration in myocyte calcium handling

PJ Angell et al. Eur J Appl Physiol (2014) 114:921–928

Cardiac Structural Changes — Anabolic Androgenic Steroids

Left ventricular hypertrophy - clinical effects

Table 3 CMR structural and functional measures in AS and NAS groups (data are mean ± SD)

	AS	Non-AS
Peak WT(mm)	13.0 ± 2.2	9.4 ± 1.3†
LV EDV (ml)	204.7 ± 25.4	187.5 ± 28.4*
LV ESV (ml)	81.1 ± 14.3	70.6 ± 14.7
LVM (g)	220 ± 45	163 ± 27*
Peak WT/FFM (mm $g^{-0.33}$)‡	0.46 (0.11)	0.40 (0.09)
LV EDV/FFM (ml g^{-1})‡	2.32 (0.46)	2.51 (0.28)
LV ESV/FFM (ml g^{-1})‡	0.97 (0.30)	0.97 (0.16)
LVM/FFM‡	2.56 (0.40)	2.43 (0.48)
LV mass/volume‡	1.10 (0.26)	0.88 (0.16)*
RV EDV (ml)	225.9 ± 40.8	199.8 ± 39.6
RV ESV (ml)	110.4 ± 24.7	83.1 ± 23.0*
RV EDV/FFM (ml g^{-1})‡	2.63 (0.72)	2.78 (0.62)
RV ESV/FFM (ml g^{-1})‡	1.27 (0.37)	1.15 (0.37)
LV SV(ml)	122 ± 13	117 ± 16
LV EF (%)	61 ± 3	63 ± 3
RV SV (ml)	115 ± 19	117 ± 18
RV EF (%)	51 ± 4	59 ± 5†
Fibrosis	Negative	Negative

LV left ventricle, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SV* stroke volume, *EF* ejection fraction, *LVM* left ventricular mass, *RV* right ventricle, *WT* wall thickness, *FFM* fat-free mass

* $p < 0.05$
† $p < 0.005$
‡ Data given as median (interquartile range)

Cardiac MRI/Echo

- **Right Ventricular dilatation and reduced EF**
- **↓ Diastolic function**

PJ Angell et al. Eur J Appl Physiol (2014) 114:921–928
E. Kasikcioglu et al. Int J Cardiol 2009;134:123-25

Cardiac Structural Changes — Anabolic Androgenic Steroids

Left ventricular hypertrophy - clinical effects - fibrosis

M. Lusetti et al

Table 1
shows main myocardial and coronar

Histological findings
Interstitial fibrosis
Perivascular fibrosis
Perineural fibrosis within the left v
Fibroadipous metaplasia
Contraction band necrosis
Myocyte segmentation
Intercalated disc widening
Contracted myocytes/distended m
Myocyte hypertrophy
Inflammatory infiltration
Coronary fatty streaks
Coronary intimal and media thicke

Proposed Mechanism
- Apoptotic cell death

Eur J Appl Physiol (2014) 114:921–928
DOI 10.1007/s00421-014-2820-2

ORIGINAL ARTICLE

Ventricular structure, function, and focal fibrosis in anabolic steroid users: a CMR study

Peter J. Angell · Tevfik F. Ismail · Andrew Jabbour · Gillian Smith · Annette Dahl · Ricardo Wage · Greg Whyte · Daniel J. Green · Sanjay Prasad · Keith George

Received: 12 September 2013 / Accepted: 8 January 2014 / Published online: 28 January 2014

Abstract
Purpose Anabolic steroid (AS) misuse is widespread amongst recreational bodybuilders; however, their effects on the cardiovascular system are uncertain. Our aim was to document the impact of AS use on cardiac structure, function and the presence of focal fibrosis using the gold standard cardiovascular magnetic resonance imaging (CMR).
Methods A cross-sectional cohort design was utilised with 21 strength-trained participants who underwent CMR imaging of the heart and speckle-tracking echocardiography. Thirteen participants (30 ± 5 years) taking AS for at least 2 years and currently on a "using"-cycle were compared with age and training-matched controls (n = 8; 29 ± 6 years) who self-reported never having taken AS (NAS).
Results AS users had higher absolute left ventricular (LV) mass (220 ± 45 g) compared to NAS (163 ± 27 g; $p < 0.05$) but this difference was removed when indexed to fat-free mass. AS had a reduced right ventricular (RV) ejection fraction (AS 51 ± 4 % vs. NAS 59 ± 5 %; $p < 0.05$) and a significantly lower left ventricular E'/A' myocardial tissue velocity ratio [AS 0.96(0.54) vs. NAS 1.78(0.46) $p < 0.05$] predominantly due to greater tissue velocities with atrial contraction. Peak LV longitudinal strain was lower in AS users (AS −14.2 ± 2.7 % vs. NAS −16.6 ± 1.9 %; $p < 0.05$). There was no evidence of focal fibrosis in any participant.
Conclusions AS use was associated with significant LV hypertrophy, albeit in-line with greater fat-free mass, reduced LV strain, diastolic function, and reduced RV ejection fraction in male bodybuilders. There was, however, no evidence of focal fibrosis in any AS user.

Zaugg M et al. J Cell Physiol. 2001 Apr;187(1):90-5
Journal of Forensic and Legal Medicine 33 (2015) 101e104
PJ Angell et al. Eur J Appl Physiol (2014) 114:921–928

Vascular function — Anabolic Androgenic Steroids

Endothelial dysfunction
- ❖ Nitic oxide mediated smooth muscle dilatation
- ❖ Affect endothelial proliferation and propagation

- Vascular stiffness
- Promote atherosclerosis
- Attenuate the effects of vasodilators
- Enhance the effects of vasoconstrictors
- Predispose to vasospasm

Resistance training may have a negative impact on vascular function

E Ammar et al. Pharmcol Res 2004 Sep;50(3):253-9.
S. D'Ascenzo et al. Toxicol Lett. 2007 Mar 8;169(2):129-36.

Haematological changes — Anabolic Androgenic Steroids

Testosterone/AAS

Reduce hepcidin levels – peptide that regulates iron bioavailabilty

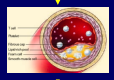
Stimulate erythropoiesis
↑ haematocrit → thrombosis → Vascular events

Bachman E et al. Testosterone suppresses hepcidin in men: a potential mechanism for testosterone-induced erythrocytosis. J Clin Endocrinol Metab 2010; 95: 4743–7.
Bachman E et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci 2014; 69: 725–35.

Anabolic Adrenergic Steroids

Atherogenic dyslipidaemic profile
? Hypertertension
?Haematocrit

IHD risk factors



LVH
? Electrophysiological changes
? Fibrosis
? Changes in RV/LV function

Arrhythmogenic substrate

Metabolic disturbances
Electrolyte disturbances
Temperature changes
Adrenergic surges

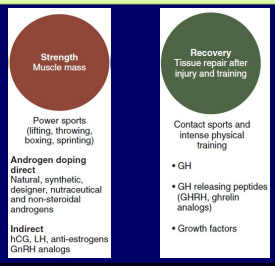
Myocardial infarction

Death

Human Growth Hormone
Insulin-like Growth Factor 1

HGH/IGF1: synthetically administered

Stimulate endogenous HGH by clonidine, levodopa, propranolol, amino acid supplements



Human Growth Hormone
Insulin-like Growth Factor 1

Skeletal Muscle

- **↑ Amino acids transport into muscle cells and protein synthesis**
- **↑ Lean muscle mass**
- **↑ Interstitial fibrosis and fluid retention "simulate hypertrophy"**
- **? ↑Muscle strength**
- **Alteration in lipid metabolism by lipolysis. ?↓ LDL and T. chol. ↑lipoprotein (a). No significant change TGL, HDL, apo B, apo A**

Human Growth Hormone
Insulin-like Growth Factor 1

Early phase hyperkinetic syndrome → ↑ heart rate and systolic output.

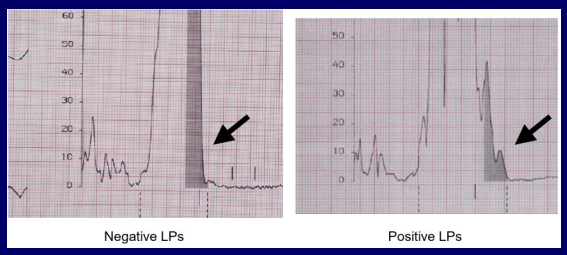
Concentric cardiac hypertrophy → diastolic dysfunction → impaired systolic function → heart failure.

Myocardium

- Myocyte hypertrophy. ↑ Collagen, fibrosis, cellular infiltration and myocyte necrosis → cardiomyopathy/arrhythmias

The American sprinter, Florence Griffith-Joyner (Flo Jo), purchased GH from fellow sprinter Darrell Robinson. She died at 38 years, post mortem was consistent with cardiomyopathy

Human Growth Hormone
Insulin-like Growth Factor 1



Significantly higher prevalence of LPs in acromegalic patients in comparison to healthy control population and their association with PVCs

Human Growth Hormone
Insulin-like Growth Factor 1

Metabolic

- Promote sodium retention → hypertension, ankle swelling
- Diabetes mellitus/insulin resistance

P. Maffei et al. Int J Cardiol 2005;104:197-203

Human Growth Hormone
Insulin-like Growth Factor 1

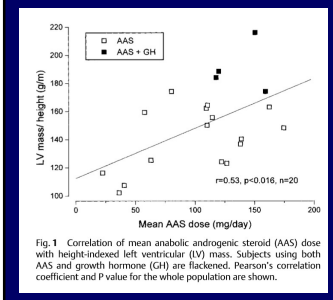


Fig. 1 Correlation of mean anabolic androgenic steroid (AAS) dose with height-indexed left ventricular (LV) mass. Subjects using both AAS and growth hormone (GH) are flackened. Pearson's correlation coefficient and P value for the whole population are shown.

Myocardial hypertrophy is associated dose-dependently with AAS abuse and concomitant use of GH leads to a marked concentric remodelling of the left ventricle.

TA Karila et al. Int J Sports Med 2003;24:337-43

Erythropoietin (EPO)

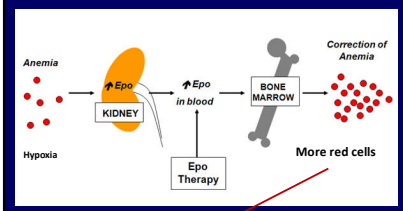
Stamina
Haemoglobin and maximal O2 transfer

Endurance-based sport
(long distance or duration)

Blood (Hb) doping
direct
Blood transfusion
- Heterologous
- Autologous

Indirect
Erythropoietin, Biosimilars and analogues, hypoxia-mimetics

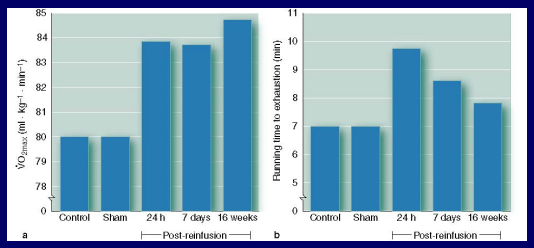
Erythropoietin (EPO)



- Higher Haematocrit
- Increase aerobic capacity
- Improve skeletal muscle performance
- Improve endurance
- No increase in cardiac output

Blood doping
High Altitude training
Synthetic EPO

Changes in $\dot{V}O_{2max}$ and Running Time to Exhaustion After Reinfusion of Red Blood Cells



Adapted, by permission, from F.J. Buick et al, 1980, "Effect of induced erythrocythemia on aerobic work capacity," *Journal of Applied Physiology* 48: 636-642.

Erythropoietin (EPO)

Higher Haematocrit → Polycythaemic

- Dose miscalculation and dehydration
- Undetectable cardiovascular disease

- ↑ Blood viscosity
- ↑ Afterload
- Hypertension
- LV dysfunction
- Thromboembolism – Strokes/MI/Peripheral embolism
- Reports of SCD
- Seizures

Autologous blood transfusion – complications of transfusions, poor storage/handling

Homologous blood transfusion – infection risks

Stimulants

Psychoactive agents that arouses or accelerates physiological activity thorough the actions of excitatory neurotransmitters or antagonise the actions of an inhibitory neurotransmitter.

- Amphetamines
- Cocaine
- Ephedrine alkaloids (ephedrine, pseudoephedrine)
- β-2 agonists

- Caffeine
- Nicotine

- ↑ Mental alertness/focus
- ↑ Psychological activity and motivation
- ↑ Physiological activity
- Improve locomotion
- Mask fatigue and extend exercise time

Stimulants

Sympathomimetic Drugs

- Amphetamines
- Cocaine
- Ephedrine alkaloids (ephedrine, pseudoephedrine)
- β-2 agonists

"Flight and fight response" vs. "Drug warm up" vs. "Exercise warm up"

Increase heart rate, BP and cardiac output → increase blood flow to skeletal muscle

Mobilise energy → glycogenolysis → glucose → heat

Heat → shifts the O2 dissociation curve to the right → improve tissue oxygenation

Stimulants

Sympathomimetic Drugs

Ephedrine alkaloids - ephedrine, pseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, norpseudoephedrine

Combined with Caffeine to enhance the cardiovascular effects

- Headaches
- Insomnia
- Stroke – haemorrhagic and thrombotic
- Cardiomyopathy
- MI/coronary spasm
- Supra- and ventricular arrhythmias
- Myocarditis
- Myocardial necrosis
- Death

Stimulants

Beta-2 agonist

Salbutamol/Clenbuterol - Selective β2 agonist. Higher doses → β1 stimulation
- asthma and exercise induced bronchospasm

β2 cardiac receptors – chronotropic and inotropic effects, myocyte growth

β2 peripheral vascular receptors – vasodilatation

- Anabolic actions – muscle building
- Fat-stripping agent
- Boost aerobic capacity

Stimulants

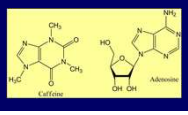
Beta-2 agonist

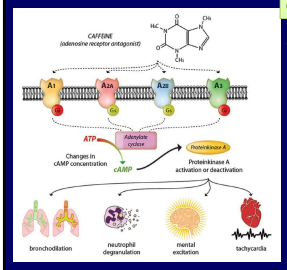
- Myocardial ischaemia/infarction
- Atrial fibrillation, SVT's, Ventricular arrhythmias
- Cardiac muscle hypertrophy
- Contraction band necrosis
- Cardiomyopathy
- QT prolongation (hypokalaemia) and metabolic disorders.
- Sudden cardiac death

- Cocaine
- Amphetamines

Stimulants

Caffeine





Reversible inhibitor of enzyme monoamine oxidase → higher levels of dopamine, epinephrine, norepinephrine and serotonin

- Psycoactive, reduce perception of fatigue, tremor, vasoconstriction, hypertension?,

Agonist of ryanodine receptor → Ca2+ release from the sarcoplasmic reticulum → Muscle contraction

- To increase performance
- Inotropic (high doses)

Stimulants

Caffeine and Sports Performance

- No significant increase in the power, strength or physical ability
- May improves endurance, by increasing resistance to fatigue or by increasing the activity of the nervous system

Arrhythmias
Hypertension (nonhabitual coffee drinkers)
Dehydration
Tremor
Insomnia
Nervousness
Mental distraction (higher doses)

Stimulants prohibited by World Anti-Doping Agency

Table 1 Stimulants prohibited in competition

Name	*Specified substance*[e]	*Metabolized to A/M*[b]	*Mode of action*[c]
Adrafinil adrenaline[d]			Monoamine
Amfepramone			Monoamine
Amiphenazole			Resp. stim.
Amphetamine			Monoamine
Amphetaminil		Yes A	Monoamine
Benzphetamine		Yes M	Monoamine
Benzylpiperazine			Monoamine
Bromantan			Monoamine
Cathine[d]	Yes		Monoamine
Clobenzorex		Yes A	Monoamine
Cocaine			Monoamine
Cropropamide	Yes		Resp. stim.
Crotetamide	Yes		Resp. stim.
Cyclazodone			Monoamine
Dimethylamphetamine		Yes M	Monoamine
Ephedrine[d]	Yes		Monoamine
Etamivan	Yes		Resp. stim.
Etilamphetamine		Yes A	Monoamine
Etilefrine			Monoamine

British Journal of Pharmacology (2008) 154 606–622

Table 1 *Continued*

Name	*Specified substance*[e]	*Metabolized to A/M*[b]	*Mode of action*[c]
Famprofazone	Yes	Yes M	Analgesic
Fenbutrazate			Monoamine
Fencamfamin			Monoamine
Fencamine		Yes M	Monoamine
Fenetylline		Yes A	Monoamine
Fenfluramine			Monoamine
Fenproporex		Yes A	Monoamine
Furfenorex		Yes M	Monoamine
Heptaminol	Yes		Monoamine
Isometheptene	Yes		Monoamine
Levmethamfetamine	Yes		Monoamine
Meclofenoxate	Yes		Nootropic
Mefenorex		Yes A	Monoamine
Mephentermine			Monoamine
Mesocarb		Yes A	Monoamine
Methamphetamine (D-)		Yes A[c]	Monoamine
Methylenedioxyamphetamine			Monoamine
Methylenedioxymethamphet.			Monoamine
Pmethylamphetamine	Yes		Monoamine
Methylephedrine[d]	Yes		Monoamine
Methylphenidate			Monoamine
Modafinil			Monoamine
Nikethamide	Yes		Resp. stim.
Norfenefrine	Yes		Monoamine
Norfenfluramine			Monoamine
Octopamine	Yes		Monoamine
Ortetamine	Yes		Monoamine
Oxilofrine	Yes		Monoamine
Parahydroxyamphetamine		Note[f]	Monoamine
Pemoline			
Pentetrazol			Resp. stim./GABA
Phendimetrazine			Monoamine
Phenmetrazine			Monoamine
Phenpromethamine	Yes		Monoamine
Phentermine			Monoamine
4-Phenylpiracetam (carphedon)			Nootropic
Prolintane			Monoamine
Propylhexedrine	Yes		Monoamine
Selegiline	Yes	Yes	MAOI
Sibutramine	Yes		Monoamine
Strychnine			Glycine
Tuaminoheptane and other substances with a similar chemical structure or similar biological effect(s)	Yes		Monoamine

Stimulants prohibited by World Anti-Doping Agency

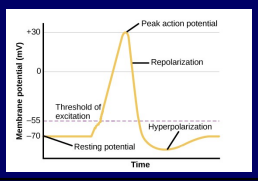
Strychnine - glycine receptor antagonist

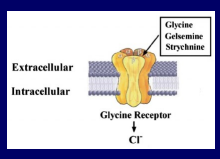
Rio 2016: Weightlifter Izzat Artykov stripped of bronze for doping

Kyrgyzstan's weightlifter Izzat Artykov, who won bronze in the men's 69 kilogram category, has tested positive for strychnine and will lose his medal. He's Rio's first medalist to test positive for a banned substance.

Strychnine:

Is one of the best known of all agents that increase excitability of neurons.
It *inhibits the action of some normally inhibitory transmitter substances*, especially glycine in the spinal cord.
Therefore, the effects of the excitatory transmitters become overwhelming, and the neurons become so excited that they go into rapidly repetitive discharge, resulting in severe tonic muscle spasms.





Beta-Blockers

- Prevent the binding of norepinephrine and decrease sympathetic nervous system activity
- May improve accuracy (for shooting sports, snooker, etc.)
- Decrease aerobic capacity but have no effect on strength, power, or muscular endurance
- Prolonged use can cause bradycardia, heart blockage, hypotension, bronchospasm, fatigue, and decreased motivation

Masking Agents

Diuretics

- Used to reduce body weight - before a competition
- Masking agent – to flush out traces of banned substances to avoid testing positive

Masking Agents

Diuretics

- Electrolyte imbalances - arrhythmias
- Dehydration
- Impaired thermoregulation

Case 1

39 yr. old male admitted on the 20th July 2016 with a history of right-sided facial, arm and leg weakness, difficulties moving his lips and an expressive dysphasia. Two days earlier he complained of left-sided face and arm weakness that lasted 20 seconds. For the preceding three weeks he noticed that his vision was blurred.

An urgent CT – no significant findings.

ECG showed atrial fibrillation with a ventricular rate of 130 beats per minute.

He works as a personal trainer.
Previously lost 12-14 stone (76 -88 kg) over the preceding 3½ year period
Using ephedrine, caffeine, anabolic androgenic steroids, thyroxine and caffeine.

PMx: nil.

FHx: mother died of a stroke at age 57 which may be related to a clot originating in her leg. He has a sister with three miscarriages.

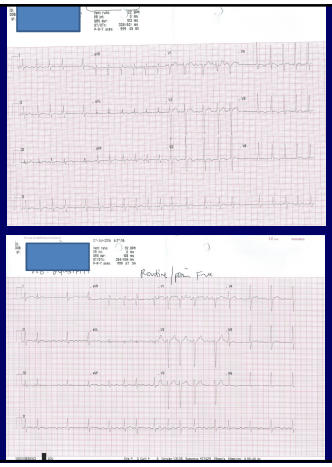
Case 1

Non smoker. Drinks alcohol occasionally and denies using any recreational drugs.

HB mildly elevated at 171 gm/L with a normal MCV, CRP, ferritin, TFT's, haemoglobin A1c, beta-2 microglobulin, ANA and anti-cardiolipin antibody. Although lupus anticoagulant screen was done it could not be interpreted given that he was on Apixaban. Creatinine was mildly elevated at 135 mmol/L, with sodium of 138 mmol/L, potassium 4.9 mmol/L and an eGFR of 51 ml/min, LDH was mildly elevated at 353 IU/L. He was negative for factor V Leiden.

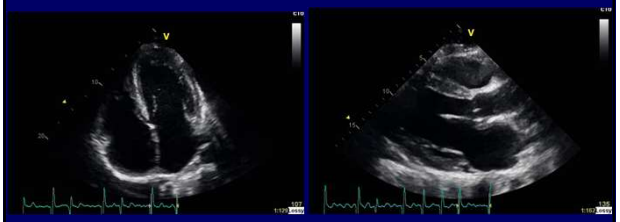
His ventricular rate was adequately controlled on bisoprolol 10 mg daily. He was also commenced on Ramipril and the dose was slowly titrated up to 5 mg bd, and Apixaban 5mg BD

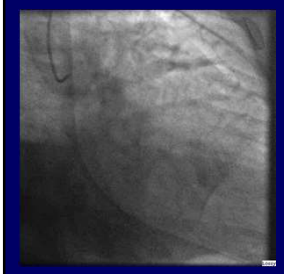
An inpatient echocardiogram demonstrated moderately dilated left ventricle (LVDD 6.5 cm, LVDS 4.97 cm) with significant LV systolic impairment. There was no significant valvular abnormalities. The right ventricular systolic pressure was 26 mmHg. Inferior vena-cava was dilated with poor inspiratory collapse.

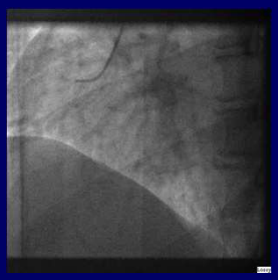


Case 1

Case 1







Cardiac MRI
Echo
DC cardioversion

Case 1

Over a 3.5 years

Started with DNP (dinitrophenol)

Ephhedrine 30-90mg
Caffeine 200-400 mg,
Aspirin

ECA stack. Daily. Occasionally omit stack 1-2 wks. up to 4 times over 3 years

T3 50mcg OD
Clembuterol 40-120 mcg OD

Stack for 3 wks. Six times over 3 yrs.

Test 250 (fast and slow acting testosterone)
Decabolin
Winstrol

Alternate

Test 300/400
Tren (trenbolone)
Anavar (oxandrolone)

Stack, twice wkly for 16 wks. Then stop for 3 months

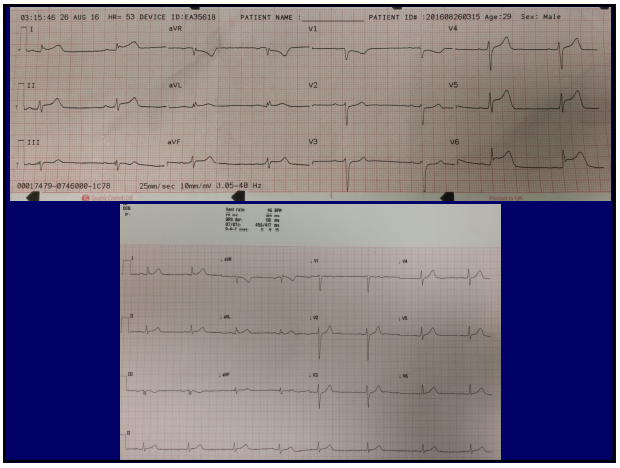
Case 2

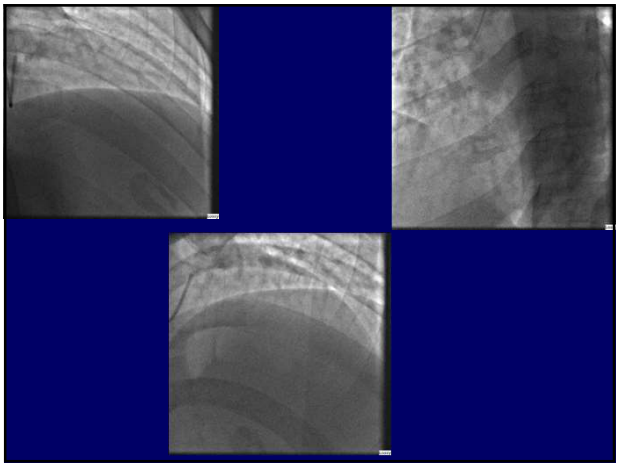
29 year male. Admitted in the early hours of the morning after awakening with acute onset heavy chest pain associated wit sweating.

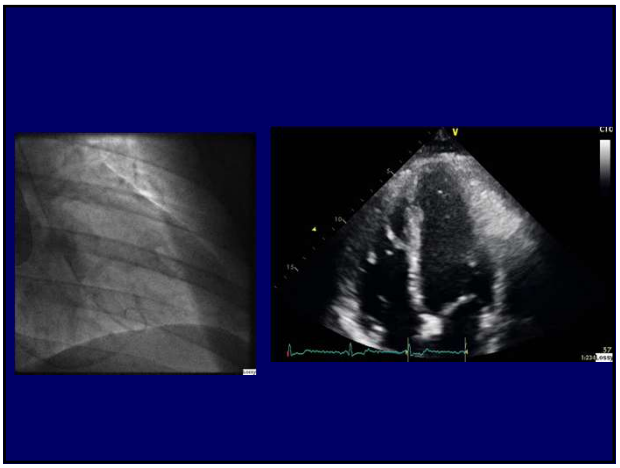
Smoker. Denied recreational drugs. No FHx of IHD

PMHx: Nil. Admits to using Test 400 and Stanvar (oxandrolone and stanozol) Winstrol)

Paramedics ECG ST↑ I, Avl, V5, V6.







Conclusion

- Doping in Sports have been around for centuries
- Some of the drugs/methods used can have significant and profound cardiovascular effects
- The pathophysiological mechanisms for the effects are not clearly understood.
- Current data are based on small studies, case reports and animal models.
- WADA exists to prevent unfair competitive sporting advantage and to protect the health of athletes