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Serious cardiovascular side effects of large doses of anabolic steroids in weight lifters

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Pathological cardiovascular manifestations are reported in four male patients, who had taken massive amounts of anabolic steroids while undergoing many years of strength training. One patient was referred because of ventricular fibrillation during exercise, one because of clinically manifest heart failure, and one because of arterial thrombus in his lower left leg. The fourth patient was persuaded to attend for a check-up because of a long history of massive use of anabolic steroids. All four patients had cardiac hypertrophy. Two of the patients had symptoms and signs of heart failure, and one of these two had a massive thrombosis in both right and left ventricles of his heart. After cessation of the use of anabolic steroids in the other patient with heart failure, left ventricular wall thickness reduced quickly from 12 to 10·5 mm, and fractional shortening increased from 14% to 27%. Endomyocardial biopsy revealed increased fibrosis in the myocardium in two of the three cases. HDL-cholesterol was 0·58 mmol . l^{-1} and 0·35 mmol . l^{-1} in the two patients still using multiple anabolic steroids at the time of investigation. The cardiovascular findings described in the present paper should warn all physicians and athletes about the possible serious acute and long-term side effects of the massive use of anabolic steroids.

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Key Words: Anabolic steroids, congestive heart failure, left ventricular hypertrophy, life threatening arrhythmia.

Introduction

Anabolic steroids stimulate cellular protein synthesis by androgen receptors, and promote growth in all organs that have the ability to grow[1] similar to androgens[2]. Their therapeutic use involves replacement therapy in hypogonadal males; they improve nitrogen balance in catabolic states, and stimulate erythropoiesis in the treatment of bone marrow failures[3]. Anabolic steroids have been used by athletes to improve physical performance[4].

Experimental studies have demonstrated that prolonged treatment with anabolic steroids leads to increased peripheral vascular resistance and dose-dependent cardiac hypertrophy together with depressed contractility of the heart[5,6]. In myocardial cell cultures, testosterone cypionate causes a significant release of lactate dehydrogenase indicating cellular injury[7].

In weight lifters, anabolic steroids increase ventricular wall thickness, end-diastolic volume and left ventricular mass, and isovolumetric relaxation time is prolonged significantly[8]. Autopsy findings in a 28-year-old weight lifter who had taken anabolic steroids in combination with a protein-rich diet containing 2–3 g cholesterol daily demonstrated coronary atherosclerosis and interstitial fibrosis in the myocardium and endocardium[9]. In several reports, the use of anabolic steroids has also been linked to arterial occlusion[10,11]. They are potentially atherogenic through their action on the lipid metabolism[12].

In the present paper we report four young men who had all used high doses of anabolic steroids for many years in combination with weight training and exhibited serious pathological cardiac manifestations.

Methodological aspects

It is often difficult to find competitive athletes for cardiovascular investigations who admit that they have taken anabolic steroids. The amount and use of steroids is a delicate matter. However, it was possible to obtain a detailed history of anabolic steroid use in three of the patients and the fourth admitted extensive use of these drugs.

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Table 1 The dosages and duration of use of the anabolic steroids during the last year prior to admission

Agent	Patient 1		Patient 2		Patient 3	
	mg/IU	months	mg/IU	months	mg	months
Methandienone (po)	750	8	762	7	1200	12
Mesterelone (po)	1050	12				
Oxymetholone (po)	110	0·7				
Stanatsolol (po)	870	3	690	2·5		
Methyltestosterone (po)	625	0·8	10	1 day		
Oxandrolone (po)	250	2	210	10 days		
Fluoxymesterone (po)	830	1				
Tamoxifen (po)	348	7	300	1		
Clenbuterol (po)	400 μg**	2	1575 μg**	1·5		
Bromokriptin (po)	45	2				
Testosterone-undecanoate (po)	2000	5 days	3318	0·5		
Stanatsol (im)	675	4	566	6	500	12
Testosterone (im)	2375	4	1700	7	4500	12
Testosterone-proprionate (im)	825	2	750	1		
Human corion gonadotropine (im)	13 750 IU	6	1300 IU	5		
Growth hormone (sc)	89 IU	3	120 IU	3		
Insulin (sc)	19 IU	4 days				

po = by mouth (per ora); im = by intramuscular injections, sc = by subcutaneous route; ** = dosages uncertain.

Routine echocardiography was performed in all of the patients, and because of left ventricular systolic and diastolic dysfunction, an endomyocardial biopsy was taken in three of the four. In the fourth patient, biopsy was contraindicated because of a ventricular thrombus. Maximal bicycle exercise testing was performed in three cases, and three of the patients had 24-h ECG recordings. Coronary angiography, thallium scintigraphy and programmed electrophysiological stimulation were performed, depending on clinical indications. The events leading to referral and patient histories are described individually.

Patients

Patient 1, uncomplicated, with left ventricular hypertrophy

A 33-year-old male, a close friend of patient 2, was referred for cardiac examination because of a long history of anabolic steroid use. He had been weight training for many years and had taken short periods of anabolic steroids since 1985. The present use of anabolic steroids began in December 1991 and during the years 1992–1993 he took steroids and other hormones according to the list shown in Table 1. Echocardiography showed increased left ventricular wall thickening and ventricular dilatation (Table 2). Endomyocardial biopsy revealed diffuse and spotty fibrosis of the heart, endocardial thickening and diffuse oedema. Blood pressure was 118/65 mmHg, pulse rate 51 beats . min^{-1}, and the ECG was considered normal. No pathological findings were found subsequent to the 24-h ambulatory ECG recording. Maximal working capacity on bicycle exercise testing was 300 W and no electrocardiographic abnormalities were present. The amount of high density lipoprotein in serum was significantly reduced (Table 3).

Patient 2, ventricular tachycardia during exercise

A 29-year-old male, who had been weight training for years, had taken anabolic steroids during several periods over the past 8 years. The present prolonged use of steroids began in 1989 (Table 1). In March 1993 he was preparing for a body-building competition by reducing his weight (11 kg in 17 days) and using massive doses of clenbuterol. At a routine exercise test at 250 W work level, a monomorphic ventricular tachycardia of 230 beats . min^{-1} started from a preceding sinus rate of 142 beats . min^{-1} (Fig. 1a). Exercise was stopped. After 1 min of rest, the rhythm degenerated into a polymorphic ventricular tachycardia, finally resembling ventricular fibrillation and causing unconsciousness (Fig. 1b). After cardioversion with 300 J and a few slow wide QRS complexes, the same monomorphic ventricular tachycardia started again, returning spontaneously to sinus rhythm in 20 s.

On arrival at hospital, the patient was in sinus rhythm. His blood pressure was 130/90 mmHg; serum sodium and potassium concentrations were 141 mmol . l^{-1} and 4·3 mmol . l^{-1}, respectively. Blood haemoglobin concentration was 155 g . l^{-1} and leucocyte count was normal. Blood glucose and lipid data are shown in the Table 3. There were no signs of myocardial ischaemia or injury in the resting ECG. In the high

Table 2 Echocardiographic data of the patients

	Patient 1 March	Patient 2		Patient 3			Patient 4 May
		March	August	March	July	December	
FS	33	30	33	14	19	27	13%
LVEDD	55	60	54	79	64	63	78 mm
LVESD	37	42	36	68	52	46	68 mm
LAD	26	35	40	35	31	26	51 mm
RVD	30	34	34	20	14	14	74 mm
IVST	14	14	13	12	12	11	11 mm
PWT	14	14	12	12	12	11	15 mm
E/A	1·4			1·5	1·2	1·7	
LVMi*	155	221	165	318	225	178	228 g m^{-2}

FS=fractional shortening; LAD=left atrial diameter; RVD=right ventricular diameter; IVST=interventricular septal thickness; PWT=posterior wall thickness; E/A=mitral flow E point/A point flow velocity index, LVMi=LVM/body surface area; *Calculated by cubic formula.

Table 3 Blood lipid profile and glucose data of the patients

Parameter	Patient 1	Patient 2	Patient 3*	Patient 4**
Total cholesterol	3·5	3·2	4·3	2·9 mmol l^{-1}
TG	0·7	2·48	1·28	0·77 mmol . l^{-1}
HDL	0·35	0·58	1·08	0·54 mmol . l^{-1}
B-glucose	—	3·2	4·3	7·4 mmol . l^{-1}

*about 1 month after stopping using anabolic steroids.
**about 1 week after stopping using testerone.

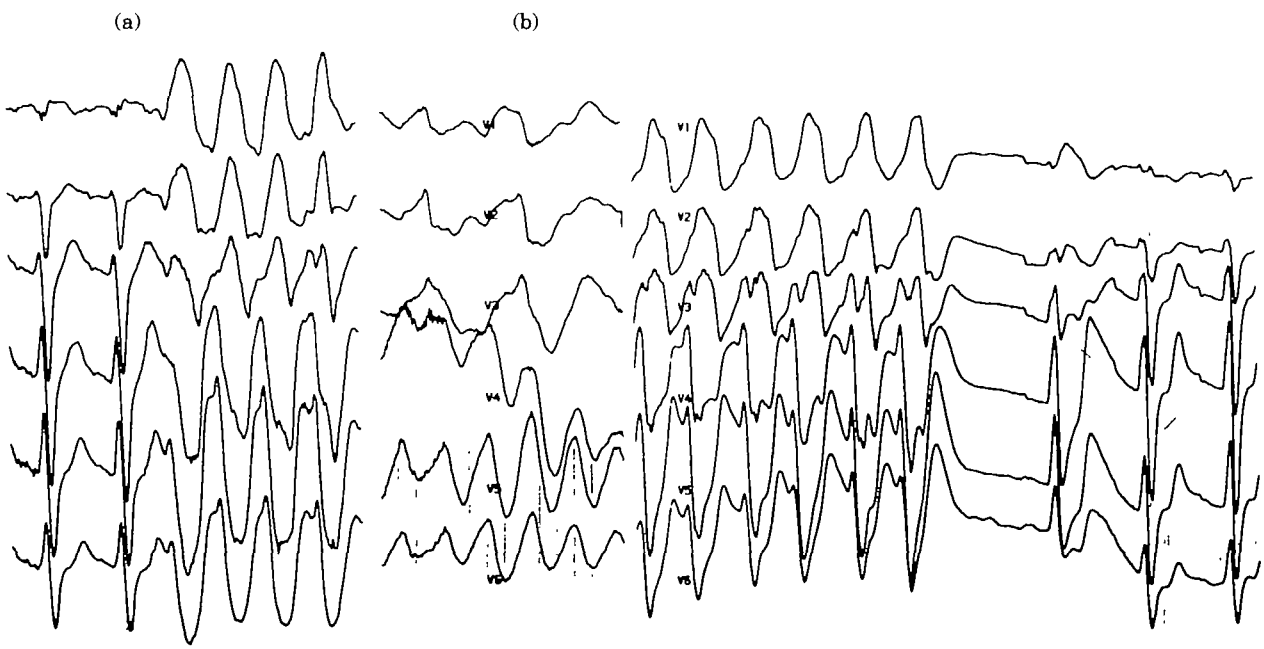

Figure 1 **(a) The start of ventricular tachycardia during exercise testing in patient 2. (b) Polymorphic ventricular tachycardia and ventricular fibrillation in patient 2 1 min later and cardioversion resulting in sinus rhythm 20 s later.**

resolution ECG, the filtered QRS duration was 126 ms, but no abnormal late potential was present. Echocardiography showed a dilated left ventricle and marked thickening of the left ventricular walls (Table 2). Fractional shortening was 30%. Angiography showed open epicardial coronary arteries, but coronary flow was slow. The small side branches of these arteries were barely visible. Left ventricular cineangiography revealed dilatation of the left ventricle with a 40% ejection fraction. Inferior and antero-apical walls were

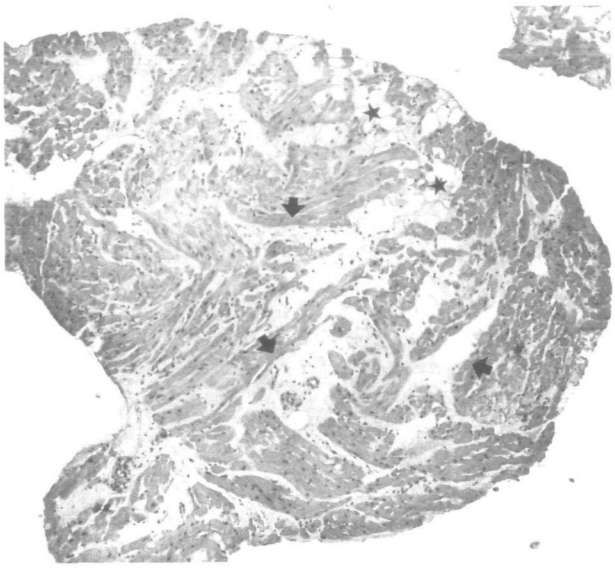

Figure 2 **Histology of endomyocardial biopsy from patient 2. Fibrous tissue has increased between the myocytes (arrows). A moderate amount of lipid droplets is also seen (★).**

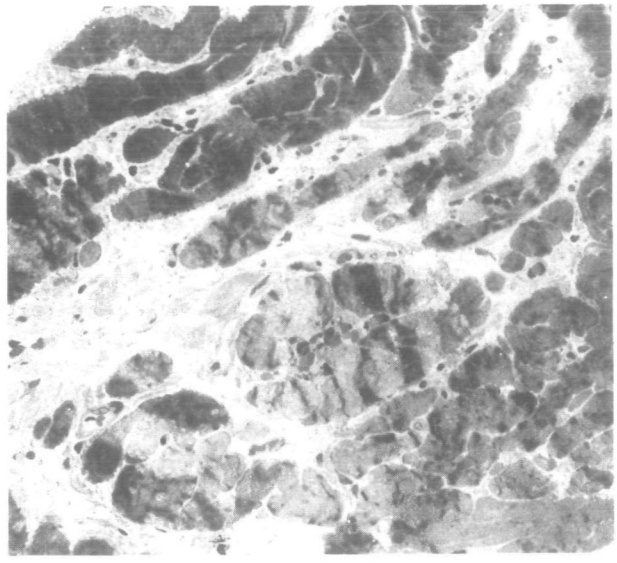

Figure 4 **Histology of an endomyocardial biopsy 6 months later from patient 2, who had stopped using anabolic steroids. Some fibrous strands are seen between the myocytes, but no lipid is detectable.**

hypokinetic. Cardiac output was $8{\cdot}61 \cdot min^{-1}$. The mean pulmonary artery pressure was 20 mmHg.

Programmed electrophysiological stimulation was performed. No ventricular tachycardia was inducible with or without isoprenaline infusion. A dual atrioventricular node was detected and during isoprenaline infusion atrioventricular nodal re-entrant tachycardia with a cycle length of 420 ms was induced. The antimyosin map was considered normal. One month later during a bicycle exercise test of up to 300 W, there were no signs of ischaemia on the ECG. The 24-h ambulatory ECG recording showed no spontaneous arrhythmia. The patient had no symptoms of angina. Endomyocardial biopsy revealed focal fibrosis of the left ventricle and fat degeneration, (Figs 2 and 3). No signs of granulocyte infiltrations were seen.

Five months later, after the cessation of the use of anabolic steroids, echocardiography showed that the fractional shortening was 33%, left ventricular dimensions were normalized and hypertrophy of the left ventricular walls had reduced slightly (Fig. 4). No ventricular tachycardia attacks were observed during follow-up, possibly because of cessation of the use of clenbuterol and anabolic steroids.

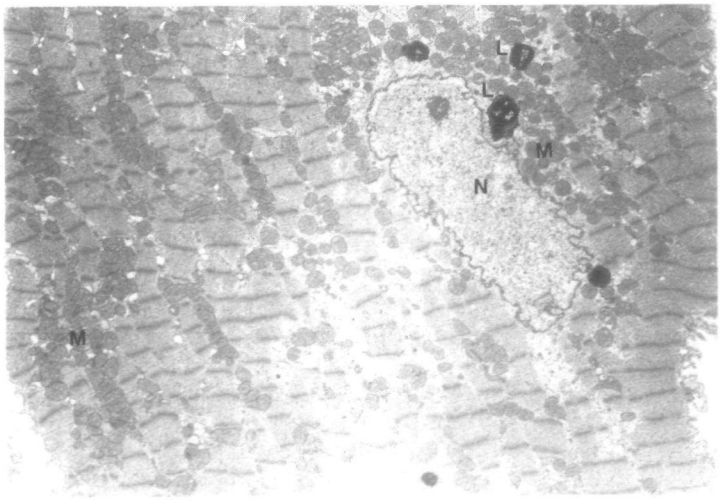

Figure 3 **Ultrastructure of myocardial cells from patient 2. The sarcoplasmic space is extended, and Z-bans are regular. Some droplets of lipofuscin pigment (L) are situated in the perinuclear space. Mitochondria (M) are numerous, and there is a slight variation in mitochondrial size and space.**

Patient 3, congestive heart failure

The patient was a 31-year-old male body-builder, who had taken anabolic steroids for 2 years (1986–1988) to increase muscle mass. From the beginning of 1991 until the day of examination, after a pause of 2·5 years, he started to take them again every week in approximately the doses described in Table 1. He was referred to the emergency department in October 1993 because of congestive heart failure. On admittance, the ECG showed left ventricular hypertrophy, the pulse rate was 70 beats . min^{-1} and blood pressure 120/70 mmHg. Echocardiography (Table 2) revealed left ventricular hypertrophy and dilatation. Left ventricular fractional shortening was 14%. After heart failure had been established, right-sided catheterization was performed. The mean right atrial pressure was 4 mmHg, mean pulmonary artery pressure 21 mmHg, and pulmonary wedge pressure 11 mmHg. Cardiac output was 6·1 l . min^{-1}, which was partly related to the high heart rate (89 min), and stroke volume was low (69 ml) in relation to left ventricular size.

Thallium scintigraphy demonstrated spotty, regular defects representing scar formation of the anterior and posterior walls of the left ventricular myocardium. Thallium washout was decreased indicating diffuse myopathy of the heart. During the ambulatory ECG performed in hospital, there were short periods of Wenckebach type AV-conduction disorders. Endomyocardial biopsy revealed some hypertrophy, variation in the size of the nuclei, but no fibrosis. Electron microscopy of endomyocardial biopsy samples showed some thickening of the Z-lines between the myocytes and the clusters of mitochondria of various sizes.

During the bicycle exercise test, T-wave inversions in leads V_3–V_6 became positive. The maximal working capacity was 150 W. Three successive ventricular beats were also recorded. Four months later, after the cessation of the use of the anabolic steroids, left ventricular hypertrophy was reduced and the fractional shortening of the left ventricle had increased from 14% up to 27%. The thickness of the interventricular septum and posterior wall had decreased by 1–2 mm (Table 2). The patient had started to lift weights again, but did not suffer from dyspnoea during exercise. Five months later, fractional shortening had increased up to 27%. Both systolic and diastolic dimensions had normalized (Table 2).

Patient 4, thrombus in both ventricles

A 27-year-old male had been lifting weights at championship level for many years and used anabolic steroids in massive doses, mainly testosterone. He had discontinued competing, but was still lifting weights and coaching other weight lifters. Unfortunately we were not successful in receiving the amounts and names of the steroids he used. He admitted, however, that he mainly used testosterone in very high doses and that he felt that it was the only way to gain strength. In 1989 he was diagnosed as suffering from cardiac dilatation of unknown aetiology. Two years later, he was put on the following medication: digitalis 0·25 mg . day^{-1}, ACE-inhibitor 25 mg × 2/day and furosemide 40 mg 2+2+ . day^{-1}. The patient was referred to the emergency department with an arterial thrombus in his left leg. An embolectomy was performed.

Echocardiography revealed a large lobular intraventricular thrombus in both right (4 × 4 cm) and left (5·5 × 2·4 cm) ventricles of his heart (Fig. 5). Dilatation of the left ventricle and hypertrophy of the posterior and interventricular septum were confirmed (Table 2). The right ventricular thrombus partly occluded the outflow tract of the right ventricle. His blood pressure was 125/70 mmHg. The ECG showed sinus rhythm and right bundle branch block. His total cholesterol level was low (Table 3). All tested components of his fibrinolytic cascade were normal. No right side invasive catheterizations were performed because of a risk of further embolization. Pulmonary perfusion maps were normal. He was unwilling to undergo further evaluation, such as coronary angiography and was lost for follow-up.

Discussion

Main findings

The side effects of anabolic steroids have been underestimated in order to legitimize their use in sport, and it is well known that non-competitive and even competitive weight lifters abuse anabolic steroids in the hope of improving performance.

This paper presents four subjects with serious clinical problems, all of whom took anabolic steroids in massive doses for many years while weight training. All four patients exhibited abnormal cardiac hypertrophy. Diffuse myocardial fibrosis could be shown in two of the three cases in whom biopsies were taken. Two of these patients had signs of heart failure (patients 3 and 4), and impairment of coronary flow (patient 2) or perfusion (patient 3) was shown in two. In addition, two different potentially lethal side effects, malignant ventricular arrhythmia and massive intracardial thrombosis (Fig. 5), were verified.

Heart failure and hypertrophy

Overt cardiac hypertrophy with increased wall thickening and left ventricular enlargement was present in all patients on the echocardiogram. Wall thicknesses were increased comparable to that found in aortic stenosis patients, and two of the patients suffered from congestive heart failure. In all four patients, the ventricular dimensions were enlarged, and in three fractional shortening was reduced. Previous echocardiographic studies have associated excessive use of anabolic steroids with

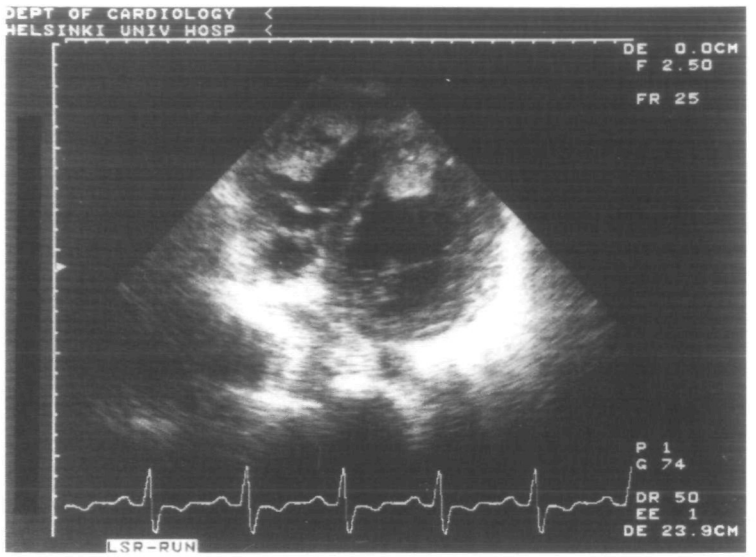

Figure 5 **Echocardiographic two-chamber view of patient 4 with a biventricular intracavity thrombosis. Both right and left ventricles are enlarged and left ventricular walls are thickened.**

cardiac hypertrophy and diastolic dysfunction of the heart[8]. The E/A ratio was only slightly reduced in two of our subjects (Table 2).

After cessation of the abuse of anabolic steroids, two of the patients demonstrated improved left ventricular function. However, the follow-up period was not long enough to see if the pathological changes and performance of the heart would recover completely. The patients began to use anabolic steroids again, despite the warnings given by the medical staff.

Experimental studies demonstrated that prolonged treatment with anabolic steroids leads to cardiac hypertrophy and increased peripheral vascular resistance[5]. In rats, prolonged high dose treatment anabolic steroids induce dose-dependent cardiac hypertrophy and depressed contractility[6].

It has also been shown that the myocardial hypertrophy induced by anabolic steroids is reversible, but that the reduced compliance of the left ventricle and the decreased inotropic capacity of the myocardium is irreversible[6]. Testosterone cypionate has been shown to significantly increase the beating activity and in myocardial cell cultures to induce release of lactate dehydrogenase indicating cellular injury[7]. When combined with training, some cells have even been observed to demonstrate necrotic signs, mitochondriolysis, myofibrinolysis and intracellular oedema[13]. In the right ventricular wall, anabolic steroids, together with exercise training also increase the activity of lysosymal hydrolytic enzymes and collagen concentration[14,15].

Autopsy findings in the 28-year-old weight lifter who had taken anabolic steroids in combination with a protein-rich diet containing 2–3 g cholesterol daily demonstrated interstitial fibrosis of the myocardium and endocardium[9].

It has recently been shown in hypertensive animals, that aldosterone increases fibrinogenesis and causes a reduction in the compliance of the myocardium. This can be prevented by spironolactone[16,17]. Synthetic steroids are known to interact with other steroid receptors like aldosterone[18]. The increased fibrosis of the hypertrophied myocardium observed after long-term use of anabolic steroids may be mediated by aldosterone-like effects.

Endomyocardial biopsy was performed on the right ventricular side. In general, the sample changes were related to hypertrophy, with variations in nuclear size and in the size of the myocytes. Increased interstitial fibrosis was observed in two of the biopsied patients. In one of two patients, variation in the thickness of the z-bands was seen in the electron microscopic analysis. These observed changes were more remarkable if the biopsies were performed in the left ventricle.

Androgens decrease elastic and increase fibrous proteins in arterial vascular tissue[19], and in weight lifters they have been reported to increase systolic and diastolic blood pressures[23,24]. All patients described here were, however, normotensive. Physical training is not known to lead to myocardial fibrosis, but rather to improve the pumping performance of the heart. Decreased perfusion as a result of microvascular changes or atherogenicity may have induced the fibrosis in these cases.

Atherogenesis

Anabolic steroids are also potentially atherogenic through their actions on lipid metabolism. They have been shown to decrease blood HDL levels and increase LDL levels significantly[12]. Lyndberg reported diffuse coronary atherosclerosis following the autopsy of a young body-builder who had used anabolic steroids[9]. The narrow coronary arteries observed in the third

patient may be an indication of enhanced, diffuse coronary sclerosis, which could have been elucidated by intravascular ultrasound.

Thrombogenesis

Our fourth patient presented with intraventricular thrombus on both the right and left side of his heart. In several earlier reports, the use of anabolic steroids has also been linked with arterial occlusion, but no direct evidence of connecting this outcome with the use of androgens has been reported[10,11]. Possible mechanisms for an increased risk of arterial thrombosis due to anabolic steroids included increased levels of several procoagulant factors, decreased fibrinolytic activity, increased platelet aggregation[19], decreased synthesis of prostacyclin[20] and increased endothelin release after vascular injury[21]. On the other hand, androgens have been shown to increase heparin cofactor II, Hageman factor, protein C and both free and total protein S concentrations[19,22]. In our patient, the specific mechanism for increased thrombogenesis was not investigated as he was rapidly anticoagulated.

Arrhythmias

There are no reports available concerning the possible arrhythmogenic effects of anabolic steroids. One of our patients experienced a potentially lethal ventricular arrhythmia on exercise testing at submaximal work levels. No signs of myocardial ischaemia or electrolyte imbalance could be found. The absence of late potentials and inducible ventricular tachycardia indicates the absence of an arrhythmogenic substrate. The dual atrioventricular node and electrophysiologically induced atrioventricular nodal re-entrant tachycardia did not play a role in the genesis of the clinical ventricular arrhythmia. Ambulatory ECG recording showed no continuous spontaneous arrhythmia. The lack of known factors predisposing to ventricular tachycardia and fibrillation indicates that the combination of the use of anabolic steroids, fasting, use of massive doses of clenbuterol, and physical exercise may predispose to serious ventricular arrhythmias. The behaviour of the ventricular tachycardia observed in our patient indicates increased automaticity as the possible electrophysiological mechanism of the arrhythmia.

Conclusion

As the number of athletes who have taken massive doses of anabolic steroids for long periods is possibly increasing, the findings of the present report are of most concern and should warn all physicians and athletes of the serious risks involved in the continuous use of large doses of anabolic steroids.

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