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Reversibility of the haemodynamic effects of anabolic steroids in rats

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Summary. The haemodynamic effects of 6 weeks nandrolone decanoate treatment (total dose 30 $mg \cdot kg^{-1}$) (SG I, $n=12$) and their reversibility were studied in anaesthetised, open-chest male rats exposed to 5 min isoproterenol (2.5 $\mu g \cdot kg^{-1}$) and $CaCl_2$ (25.0 $mg \cdot kg^{-1}$) loads. In SG I, the heart weight and its ratio to body weight were greater than in the untreated rats (CG I, $n=13$) ($p<0.05$ and $p<0.01$ respectively). The initial heart rate and the inotropic and chronotropic responses to isoproterenol were lower in SG I than in CG I ($p<0.05$ in all cases). Peripheral resistance decreased during both infusions in SG I but remained unaltered in CG I ($p<0.05$). 6 weeks after finishing anabolic steroid treatment (SG II, $n=11$), in the $CaCl_2$-test the ejection fraction ($p<0.05$) and stroke index were smaller than in control rats of the same age (CG II, $n=12$). Mean aortic pressure was lower in SG II than in CG II. In the $CaCl_2$-test peripheral resistance was initially higher, but decreased during the infusion in SG II while it increased in CG II ($p<0.05$ in both cases). In conclusion, anabolic steroid treatment reversibly reduces the left ventricular response to isoproterenol. It decreases peripheral vascular tone during inotropic loads. Six weeks after the cessation of treatment, the pumping efficiency of the heart is reduced.

Key words: $CaCl_2$ — Isoproterenol — Nandrolone — Ventricular volumes

Introduction

Anabolic steroids influence cellular protein synthesis through androgen receptors (Rogozkin 1979; Bergink et al. 1985) and, among many other organs, both cardiac muscle and major arteries contain considerable amounts of these receptors (Krieg et al. 1978; McGill and Sheridan 1981). Besides anabolic effects, long-term treatment with anabolic steroids affects the secretion of other hormones which may affect the cardiovascular system (Wright 1980), for example, they cause hyperinsulism (Wynn 1975). Androgens have been reported to cause hypertensive disease and vascular lesions similar to those found after corticosteroid treatment (Molteni et al. 1969).

Anabolic steroids change the pattern of plasma lipids in a way that is known to increase the risk of coronary artery sclerosis and ischemic heart disease (Wynn 1975; Webb 1984; Leeds et al. 1986). In addition, experimental studies have revealed that androgens cause degenerative and then regenerative changes in intracardiac sympathetic neurons in mice (Hartmann et al. 1986). They increase also the fragility of cardiac lysosomes, leading even to autophagy of the heart myocytes (Koenig et al. 1982). Furthermore, anabolic steroids cause myofibrillar disintegration and mitochondrial swelling in cardiac muscle cells (Behrendt and Boffin 1977).

Long-term treatment with anabolic steroids leads the canine left ventricle to work at larger volumes and to respond less to inotropic stimulus than the control heart (Rämö 1987). In addition, anabolic steroids increase peripheral resistance (Rämö 1987) and cause morphological changes in major arteries resembling those observed in early atherosclerosis (Appell 1983).

Most of the metabolic and hormonal changes disappear after the withdrawal of anabolic steroids (see review by Wright 1980). The purpose of this study was to see if the cardiovascular effects of anabolic steroids in rats resemble those ob-

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served in dogs and whether or not these effects revert within 6 weeks after the cessation of treatment. The evaluation of haemodynamic status was performed in situ during anaesthesia by open-chest instrumentation and the inotropic responses of the left ventricle were evaluated by administering isoproterenol and $CaCl_2$.

Materials and methods

Forty-eight male, laboratory bred, Sprague-Dawley rats, obtained from Alvslaboratorium, Skensved, Denmark, were used as experimental animals (age 10 weeks, average weight 231 ± 9 g). They were randomly divided into four groups: a 6 week sedentary group as controls (CG I, $n = 13$), a 6 week anabolic steroid treated group (SG I, $n = 12$), a 12 week sedentary group (CG II, $n = 12$) and a 6 week anabolic steroid treated group that was sedentary for 6 weeks subsequent to steroid treatment (SG II, $n = 11$). The steroid treated rats received nandrolone decanoate (DECA-DURABOLIN®, 25 $mg \cdot ml^{-1}$, Organon, Oss, Holland) 5.0 $mg \cdot kg^{-1} \cdot week^{-1}$ (total 30 $mg \cdot kg^{-1}$) injected intramuscularly twice a week. Untreated rats were injected with equal volumes of the steroid vehicle, arachidonic oil containing 10% benzyl alcohol. All rats were fed with standard laboratory food and water ad libitum and were weighed weekly.

Instrumentation. After the experimental period the rats were anaesthetised with intra-peritoneal urethane (Urethan, Merck, USA, 1 $mg \cdot kg^{-1}$). A polyethylene tube (volume 20 µl) was inserted into the left femoral vein for drug administration. The rats were heparinized intravenously (Heparin, Medica, Finland, 250 $IU \cdot kg^{-1}$) and a thermistor probe (Edwards American Laboratories, Irvine, USA, 4F cut to 2F) was inserted into the proximal aorta through the right iliac artery. The position of the probe was verified after the interventions. Aortic pressure was recorded with a catheter tip manometer (Millar, 3F, Millar Instruments, Texas, USA) introduced into the aortic arch through the left carotid artery. The right carotid artery was left intact. The rats were tracheostomized and artifially ventilated with a rodent respirator (Harvard 680 rodent respirator, Mills, USA, room air, 360 $ml \cdot min^{-1}$). Following midsternal thoracotomy, a polyethylene tube (volume 15 µl) was inserted into the left atrial auricle for thermal dilution indicator injections (0.9% saline at room temperature, 20 µl for each injection). Left ventricular pressures were recorded by a catheter tip manometer (Millar, 3F, Millar Instruments, Texas, USA) inserted into the ventricle through its apex after a small pericardial incision. The thoractomized area was covered with a saline gauze. The body temperature of the rats was kept constant with an infra-red lamp.

The manometers were connected via a control unit (TCB 100, Millar, Texas, USA) to an amplifier (Kyowa DA-110, Japan) and a display monitor (Wavetek 1901C, Indiana, USA). Thermal dilution curves were recorded by a thermal probe connected to a Wheatstone bridge (CBA 210, Wilton Webster, California, USA) and an amplifier (Kyowa DA-110, Japan). The ECG was recorded from standard limb leads II or III with subcutaneous needle electrodes. The signals were amplified by an ECG amplifier (Mingograph EM 34, Elema Schönander, Sweden). All signals were recorded on-line by a digital computer (Micro-PDP, DEC, USA) equipped with a 12-bit analog-to-digital converter (AXV-11).

The manometers were calibrated before insertion by taking a 2.5 s digital record at zero and a calibration level using a sampling rate of 25 Hz. A signal/noise ratio of more than 60 dB and resolution better than 0.2 mm Hg were obtained. The transducers were kept in distilled water overnight before use. The ECG and pressure signals were recorded simultaneously by taking 2.5 s digital recordings at a sampling rate of 1 kHz. Low pass filtering with a cut-off frequency of 300 Hz was employed when amplifying the pressure signals. The quality of the recordings was checked directly on the display monitor and by digital-to-analog conversions displayed on another oscilloscope. The thermal probe was calibrated before insertion at zero and at calibration levels and a resolution better than 0.004° C was obtained. The left ventricular thermal wash-out curves were recorded at a sampling rate of 500 Hz for 6 s. The time constant of the thermistor probe was 150 ms.

Interventions. 10 min after instrumentation, a 10 min isoproterenol (0.50 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 0.2 $ml \cdot min^{-1}$ for 5 min) and — after a 10 min interval — a 10 min $CaCl_2$ (5.0 $mg \cdot kg^{-1} \cdot min^{-1}$, 0.2 $ml \cdot min^{-1}$ for 5 min) infusion tests were carried out. The doses of both isoproterenol and $CaCl_2$ were experimentally adjusted to the highest level where no arrhytmias occurred (Karhunen et al. 1988). Pressure recordings were made at 2.5 min intervals and thermal dilutions at 5 min intervals during the tests.

After the loading tests, the hearts of the rats were excised, the large vessels and fat were removed and the hearts were weighed as a whole. Thereafter the right ventricle and atria were dissected. The right ventricle and the left ventricle with septum were weighed.

Data processing. The QRS complexes of the ECG were detected using a 5 step algorithm designed by Okada (1979). The onset of the systolic pressure rise and the electromechanical delay were determined according to an algorithm described by Kettunen et al. (1985), and the left ventricular end-diastolic pressure was defined at the onset of the ventricular pressure rise. A 5-point, second-order data fit derivation algorithm was used to determine peak values for the first derivative of the left ventricular pressure curve (dP/dt_{max}) (Marble et al. 1981). The parameters derived from ventricular pressure and ECG were calculated for all individual cycles during a given 2.5 s recording period, the mean values being accepted as the result. The analysis excluded premature beats.

Cardiac output was calculated as a mean obtained from three successive aortic thermal dilution curves by the method of Ganz and Swan (1974), further modified in dogs by Kettunen (1985). The stroke volume was obtained by dividing the cardiac output by the heart rate. Cardiac output and stroke volume are expressed as indices of 100 g of body weight. The end-diastolic volume and ejection fraction were determined by the down-slope method (Holt 1956; Kettunen 1985). Systemic vascular resistance was calculated by dividing the mean aortic pressure by cardiac output (Yang et al. 1978).

Statistical calculations. Relative changes of haemodynamic variables were obtained as means of percentage changes obtained in individual experiments. The one-way analysis of variance continued by a modified two-tailed (Bonferroni) t test for nonpaired data (independent samples) (Wallenstein et al. 1980) was used to calculate statistical significances between the groups. The data are given as means ± standard errors (SE).

Results

After the *6 week anabolic steroid treatment* the heart weight and its ratio to body weight were greater than in control rats ($p<0.01$ between the groups) (Table 1). The right ventricular weight and its proportion of the heart weight were smaller in SG I than in CG I ($p<0.05$ and $p<0.001$ between the groups, respectively).

Before the isoproterenol test, heart rate was lower (Table 2) and during the infusion it increased less (Fig. 1) in SG I than in CG I ($p<0.05$ between the groups). The dP/dt_{max} increased less in SG I during the isoproterenol test than in CG I ($p<0.05$ between the groups). In SG I, peripheral resistance decreased during isoproterenol infusion while remaining practically unaltered in CG I ($p<0.05$ between the groups).

Before the $CaCl_2$ infusion, the heart rate of SG I was lower than in CG I ($p<0.05$ between the groups) (Table 3) but it increased in SG I during the infusion while decreasing in CG I

Table 1. Body and heart weights after 6 weeks of anabolic steroid treatment with or without a subsequent 6 week sedentary period in rats (mean ± SE)

Parameter	CG I $n=13$	SG I $n=12$	SG II $n=11$	CG II $n=12$
BW, g	413 ± 8	410 ± 10	407 ± 22	442 ± 15
HW, g	1.36 ± 0.02*	1.44 ± 0.01	1.41 ± 0.05	1.42 ± 0.01
LVW, g	0.92 ± 0.01	0.96 ± 0.05	0.93 ± 0.06	0.96 ± 0.01
RVW, g	0.35 ± 0.02*	0.30 ± 0.02	0.27 ± 0.03**	0.36 ± 0.02
HW·100/BW	0.31 ± 0.01**	0.34 ± 0.01	0.35 ± 0.01**	0.32 ± 0.01
LVW·100/HW	67 ± 1	70 ± 2*	66 ± 1	67 ± 1
RVW·100/HW	26 ± 2***	22 ± 1*	19 ± 1**	25 ± 2

CG I = control group (6 weeks), SG I = anabolic steroid treated group, SG II = anabolic steroid treated sedentary group and CG II = control groups (12 weeks). BW = body weight, HW = whole heart weight, LVW = left ventricular weight, RVW = right ventricular weight. Statistical significances between the groups are: *=$p<0.05$, **=$p<0.01$ and ***=$p<0.001$

Table 2. Haemodynamic values before and at 5 min of isoproterenol infusion after 6 weeks anabolic steroid treatment with or without a following 6 week sedentary period (mean ± SE)

Variable	Time min	CG I $n=13$	SG I $n=12$	SG II $n=11$	CG II $n=12$
Heart rate.	0	240 ± 16*	223 ± 10	231 ± 13	237 ± 8
min^{-1}	5	264 ± 13*	236 ± 14	243 ± 14	255 ± 8
Stroke index	0	0.07 ± 0.01	0.10 ± 0.02	0.09 ± 0.01	0.10 ± 0.02
$ml\cdot(100\ g)^{-1}$	5	0.09 ± 0.01	0.12 ± 0.03	0.09 ± 0.01	0.12 ± 0.01
Cardiac index	0	19 ± 1	22 ± 3	18 ± 3	21 ± 1
$ml\cdot min^{-1}\ (100\ g)^{-1}$	5	22 ± 1	27 ± 3	20 ± 1	28 ± 1
End-diastolic	0	0.79 ± 0.05	0.85 ± 0.14	0.89 ± 0.12	0.88 ± 0.06
volume, ml	5	0.97 ± 0.11	1.04 ± 0.19	1.05 ± 0.15	0.93 ± 0.08
End-systolic	0	0.47 ± 0.03	0.51 ± 0.07	0.54 ± 0.09	0.53 ± 0.08
volume, ml	5	0.58 ± 0.08	0.60 ± 0.11	0.74 ± 0.13	0.61 ± 0.08
Ejection	0	0.40 ± 0.02	0.39 ± 0.02	0.39 ± 0.04	0.39 ± 0.02
fraction	5	0.42 ± 0.02	0.42 ± 0.02*	0.37 ± 0.02	0.40 ± 0.02
dP/dt_{max}	0	5138 ± 401	4907 ± 214	3497 ± 670	4744 ± 472
$mm\ Hg\cdot s^{-1}$	5	5382 ± 413	4979 ± 220	3932 ± 721	5176 ± 553
End-diastolic	0	2.9 ± 1.0	1.8 ± 1.1	2.0 ± 0.9	3.1 ± 1.1
pressure, mm Hg	5	3.8 ± 1.0	2.4 ± 1.0	3.3 ± 1.6	3.6 ± 1.0
Mean aortic	0	80 ± 3	74 ± 9	72 ± 14	85 ± 5
pressure, mm Hg	5	79 ± 4	63 ± 3	67 ± 12	88 ± 6
Peripheral resistance	0	75 ± 2	78 ± 6	84 ± 9	73 ± 4
$dyne\cdot s\cdot cm^{-5}\cdot 10^3$	5	77 ± 3*	54 ± 9	78 ± 14	66 ± 9

dP/dt_{max} = maximum derivate of left ventricular pressure rise. For further explanations, see Table 1. Statistical significances between the groups are: *=$p<0.05$

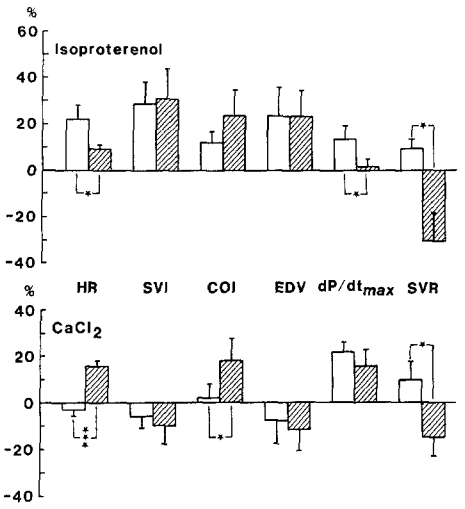

Fig. 1. Percentage changes of haemodynamic values after 5 min isoproterenol and $CaCl_2$ infusions after anabolic steroid treatment. HR = heart rate, SVI = stroke index, COI = cardiac index, EDV = end-diastolic volume, dP/dt_{max} = maximum derivate of left ventricular pressure rise and SVR = systemic vascular resistance. White column is the 6 week control group and lined column is the anabolic steroid treated group. Statistical significances between the groups: $*=p<0.05$ and $***=p<0.01$

($p<0.05$ between the groups) (Fig. 1). Cardiac index was initially smaller in SG I than in CG I ($p<0.05$ between the groups) and it increased in SG I while remaining unaltered in CG I. Peripheral resistance was initially greater, but decreased in SG I ($p<0.05$ between the groups) while it increased in CG I ($p<0.05$ between the groups).

6 weeks after the cessation of anabolic steroid treatment the heart weight to body weight ratio was greater in SG II than in CG II ($p<0.01$ between the groups) (Table 1). In SG II the right ventricular weight and its ratio to heart weight were smaller than in CG II ($p<0.01$ between the groups in both cases).

Before and after the isoproterenol test, heart rate did not differ significantly between SG II and CG II (Table 2) but its response to isoproterenol was slightly smaller in SG II than in CG II (Fig. 2). Stroke index was slightly smaller before the infusion in SG II than in CG II and did not increase during infusion as it did in the CG II ($p<0.05$ between the groups). Isoproterenol increased the left ventricular end-diastolic pressure in SG II more than in CG II ($16\pm8\%$ and $62\pm16\%$, respectively, $p<0.05$ between the groups).

During the $CaCl_2$ infusion, stroke index was slightly smaller in SG II than in CG II (Table 3). $CaCl_2$ increased the cardiac index in SG II and decreased it in CG II ($p<0.05$ between the groups) (Fig. 2). The ejection fraction was smaller in SG II before the infusion than in CG II ($p<0.05$ between the groups). Mean aortic pres-

Table 3. Haemodynamic values before and at 5 min of $CaCl_2$ infusion after 6 weeks anabolic steroid treatment with or without a following 6 week sedentary period (mean ± SE)

Parameter	Time min	CG I $n=13$	SG I $n=12$	SG II $n=11$	CG II $n=12$
Heart rate. min^{-1}	0	239±6*	213±14	226±12	228±10
	5	222±7*	254±17	240±13	219±11
Stroke index $ml\cdot(100\ g)^{-1}$	0	0.13±0.04	0.11±0.02	0.09±0.02	0.12±0.01
	5	0.12±0.01	0.10±0.02	0.09±0.01	0.10±0.01
Cardiac index $ml\cdot min^{-1}\ (100\ g)^{-1}$	0	27±2*	20±4	19±3	25±1
	5	28±2	23±5	23±4	23±7
End-diastolic volume, ml	0	1.07±0.16	0.97±0.17	1.35±0.20	1.20±0.10
	5	1.03±0.16	0.89±0.14	1.24±0.19	1.07±0.06
End-systolic volume, ml	0	0.67±0.09	0.58±0.09	0.80±0.14	0.70±0.08
	5	0.65±0.12	0.53±0.06*	0.76±0.12	0.64±0.05
Ejection fraction	0	0.41±0.02	0.39±0.02	0.35±0.03*	0.42±0.02
	5	0.42±0.02	0.38±0.02	0.36±0.03	0.41±0.03
dP/dt_{max} $mm\,Hg\cdot s^{-1}$	0	4576±442	4496±403	4569±321	4893±553
	5	5227±553	5023±246	5009±633	5587±574
End-diastolic pressure, mm Hg	0	4.0±1.2	4.2±1.6	3.0±0.9	3.6±1.3
	5	3.9±1.4	3.6±1.9	2.9±0.8	3.4±1.2
Mean aortic pressure, mm Hg	0	88±4	74±6	67±10*	87±5
	5	88±6	65±8	63±9*	90±5
Peripheral resistance $dyne\cdot s\cdot cm^{-5}\cdot 10^3$	0	60±4*	70±4	74±8*	59±5
	5	65±3	56±5	56±6	67±3

For explanations see Table 2. Statistical significances between the groups are: $*=p<0.05$

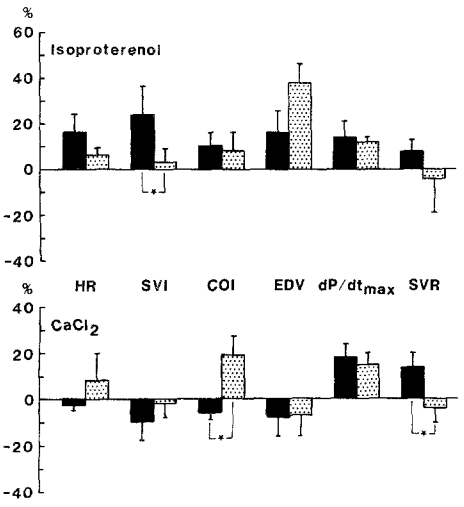

Fig. 2. Percentage changes of haemodynamic values after 5 min isoproterenol and $CaCl_2$ infusions 6 weeks after the cessation of anabolic steroid treatment. Black column is the 12 week control group and dotted column is the anabolic steroid treatment followed by a 6 week sedentary period. For abbreviations, see Fig. 1. Statistical significances between the groups: $*=p<0.05$

sure was lower in SG II than in CG II ($p<0.01$ between the groups). Peripheral resistance was higher before infusion but $CaCl_2$ decreased it in SG II while it increased it in CG II ($p<0.05$ between the groups).

Discussion

The present study demonstrated a hypertrophic effect of anabolic steroids on the heart as reported previously in the literature: already after 6 weeks anabolic steroid administration a slight, but statistically significant cardiac hypertrophy was observed (e.g. Koenig et al. 1982; Rämö 1987). This hypertrophy has been suggested to represent true hypertrophy, since the dry to wet weight ratio of the heart does not alter during steroid administration (Rämö 1987). The proportional weight of the right ventricle of the heart was, however, smaller after anabolic steroid treatment than in the control rats. This may be related to increased collagen biosynthesis in the right ventricular tissue after anabolic steroid treatment, as has recently been observed in dogs (Takala et al., unpublished work). The cardiac hypertrophy induced by anabolic steroids reversed in 6 weeks after the end of the treatment. The relative cardiac mass was still, however, increased in the steroid treated rats, since body weight did not increase in this group during the sedentary period subsequent to steroid treatment.

The heart rate of the anabolic steroid treated rats was slightly lower than in the control animals, as has been reported earlier at rest and during exercise in men (Holma 1977) and in dogs (Rämö 1987). According to the present results this negative chronotropic effect of anabolic steroids is attenuated by 6 weeks after the treatment. Even though the chronotropic response to isoproterenol during urethane anaesthesia should be the greater the lower the initial heart rate (Maggi and Meli 1986), the chronotropic and inotropic responses to isoproterenol were reduced in anabolic steroid treated rats, as occurs in dogs (Rämö 1987). These alterations may be related to the similar, degenerative changes in intracardiac sympathetic neurons observed after androgen administration in mice (Hartmann et al. 1986). Further, the present results obtained during isoproterenol infusion support previous observations that anabolic steroids reduce the chronotropic responses of the heart (van Arman and Drill 1958; Einfeldt 1978, Rämö 1987). Six weeks after the cessation of anabolic steroid treatment, the inotropic response of the left ventricle to isoproterenol, as assessed by dP/dt_{max}, was similar to that in controls of same age. The chronotropic response still showed a tendency to be reduced. The increases in heart rate during $CaCl_2$ infusion in anabolic steroid treated rats both before and after the sedentary period are unpredictable, since $CaCl_2$ should not affect heart rate or even reduce it (Kettunen 1985; Kettunen et al. 1985). As the urethane anaesthesia used here does not essentially interfere with the cardiovascular reflexes (Maggi and Meli 1986), this tachycardic effect probably represents a reflex response to the decrease in systemic vascular resistance during the $CaCl_2$ infusion. However, anaesthesia causes a certain instability of haemodynamic status (Wolf and Braunwald 1984), and therefore the present conclusions are based mainly on the relative changes in the haemodynamic variables.

The greater peripheral resistance before the $CaCl_2$ test in the steroid treated group may be related to the morphological changes in major arteries induced by anabolic steroids resembling those observed in early atherosclerosis (Appell 1983). Peripheral resistance and mean aortic pressure decreased, however, in the anabolic steroid treated group during the isoproterenol load. Since it has been reported that exogenous testosterone administration potentiates the peripheral effects of norepinephrine (Salt 1972; Baker et al. 1978),

anabolic steroid treatment seems somehow to modulate the control of vascular tone by potentiating peripheral beta- and alpha-adrenergic effects. Six weeks after the cessation of anabolic steroid treatment, peripheral resistance tended still to be higher and the mean aortic pressure remained lower in the steroid treated group than in the controls rats.

Anabolic steroid treatment did not, in spite of decreased heart rate, affect left ventricular volumes in rats, contrary to previous results observed in dogs (Rämö 1987). This controversy may be caused by the different effects of various anabolic steroid preparations on total blood volume (Gardner 1985). The pump performance of the left ventricle was aided during both inotropic loads by decreases in peripheral resistance in the anabolic steroid treated group. Six weeks after the cessation of anabolic steroid treatment, both end-diastolic and end-systolic volumes were, however, slightly larger than in the control group. In spite of a larger end-diastolic volume, the anabolic steroid treated left ventricle could not attain a stroke output similar to that of the control animals. In addition, the ejection fraction decreased during isoproterenol load and remained lower throughout the $CaCl_2$ test in the steroid treated group than in the control animals of the same age. Thus, the contractility of the left ventricle may be slightly decreased 6 weeks after the cessation of anabolic steroid treatment.

The differences in haemodynamic variables between the control and steroid groups were relatively small when expressed as percentage or absolute values. In addition, this paper confirms alterations in the basal haemodynamic status in the course of anaesthesia. Thus, meticulous following of the experimental protocol and intergroup comparisons only are to be preferred, especially when small animals like rats are used. These data suggest, however, the significance of haemodynamic differences in response to inotropic stimuli. Furthermore, anabolic steroid treatment seems to alter heart function in rodents in the same way as previously described in dogs (Rämö 1987). However, the clinical implications remain to be elucidated.

In conclusion, 6 weeks anabolic steroid treatment causes cardiac hypertrophy but does not affect the pumping performance of the rat heart. 6 weeks after the cessation of treatment the stroke output of the heart is reduced in spite of increased diasstolic filling of the left ventricle. Anabolic steroids reduce, reversibly, the chronotropic and inotropic responses of the left ventricle to beta-receptor stimulation. In addition, peripheral resistance tends to increase during steroid treatment and it does not revert in 6 weeks.

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