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Effects of an androgenic steroid on exercise-induced cardiac remodeling in rats

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Woodiwiss, A. J., B. Trifunovic, M. Philippides, and G. R. Norton. Effects of an androgenic steroid on exercise-induced cardiac remodeling in rats. *J. Appl. Physiol.* 88: 409–415, 2000.—Habitual exercise results in a rightward shift in left ventricular end diastolic (LVED) pressure-volume or internal dimension (P-D) relationships [left ventricular (LV) remodeling]. However, exercise-mediated LV hypertrophy (LVH) produces an increased LV relative wall thickness [ratio (*h*/*r*) of wall thickness (*h*) to internal radius (*r*)] and hence a decrement in diastolic wall stress despite LV remodeling. In this study, the effect of chronic administration of an androgenic steroid on exercise-induced LV remodeling and *h*/*r* was examined in rats. Habitual exercise on voluntary running wheels resulted in LVH and a rightward shift in the LVED P-D relationships. However, LVH was sufficient to increase LVED *h*/*r*. Androgenic steroid administration to exercised rats, without influencing the development of exercise-induced LVH, produced a further rightward shift in the LVED P-D relationship associated with an increased diameter intercept. As a consequence, LVED *h*/*r* was reduced to control values. The steroid-mediated effects were not associated with alterations in either the quantity or quality of LV collagen. In conclusion, high-dose androgenic steroid administration alters exercise-induced LV remodeling and subsequently reduces the beneficial effect of physiological LVH on LV *h*/*r*.

running; cardiac hypertrophy; eccentric remodeling

EXERCISE TRAINING MAY RESULT in physiological left ventricular (LV) hypertrophy (LVH) associated with increases in LV end diastolic (LVED) internal dimensions (5). The enhanced LVED internal dimensions associated with physiological cardiac hypertrophy are a consequence of LV remodeling with marked rightward shifts in LVED pressure (LVEDP)-volume relationships (8, 24). LV remodeling associated with exercise training is thought to be of benefit in that it allows for increments in filling volume, necessary to increase stroke volume during acute bouts of exercise, without producing excessive changes in filling pressures (8, 24). The increment in LV filling volume and hence in internal diameter and radius that accompanies exercise-induced LV remodeling is associated with appropriate increases in LV wall thickness because of the development of physiological LVH (24). Physiological LVH subsequently results in increments in ratios of LV wall thickness to radius (relative wall thickness) determined at a given filling pressure (24) with a consequent reduction in diastolic wall stress despite the enhanced internal radius.

Recently, we have shown in rats that high-dose androgenic steroid administration, similar to that used by athletes (4), produces a leftward shift in LVEDP-internal dimension relationships (22, 23). We were also able to show that high-dose androgenic steroid administration results in a reduction in LV weight in sedentary rats (22, 23). Furthermore, simultaneous anabolic steroid administration and exercise training have been reported to prevent the cardiac hypertrophy observed after endurance training in dogs (20). Both a leftward shift in LVEDP-internal dimension relationships and modifications in the extent to which physiological LVH occurs could influence the development of appropriate LV remodeling that accompanies chronic exercise. An attenuation of exercise-induced LV remodeling by steroid administration may account for the detrimental influence of steroids on exercise-induced enhancement of cardiac performance (17). The primary purpose of this study was therefore to examine the effect of chronic administration of high-dose androgenic steroids on the development of exercise-induced LV remodeling. The secondary purpose was to determine whether steroid-mediated effects on exercise-induced LV remodeling are accompanied by alterations in myocardial collagen concentration, solubility, and the ratio of collagen type I to type III.

METHODS

Experimental groups. Male Sprague-Dawley rats (OLAC) weighing 75–90 g were placed in voluntary exercise wheels for training selection. Training selection was carried out as previously described (24). Forty-one of 70 rats that ran on average >2 km/day over a 10-day period were chosen for the study. Selected rats were randomly assigned to an exercised group receiving the androgenic steroid (n = 11), an exercised group receiving the vehicle of the androgenic steroid (n = 10), a sedentary steroid-treated group (n = 10), and a sedentary vehicle-treated group (n = 10). The exercised steroid-treated and exercised control groups were allowed to exercise voluntarily for 16 wk before cardiac function was measured. The steroid-treated and exercise steroid-treated groups received a biweekly intramuscular injection 3.5 days apart (5 mg/kg) of the androgenic steroid nandrolone decanoate [ester-4-en-3-one, 17-[(1-oxodecyl)oxy]-, (17β)-17β-hydroxyester-4-en-3-decanoate; Deca Durabolin, Organon] as previously described

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(6, 22). This dose is comparable to that frequently used by athletes, 600 mg/wk or ~8 $mg \cdot kg^{-1} \cdot wk^{-1}$ (16). The exercised and sedentary control groups received a biweekly injection of arachis oil with 10% (vol/vol) benzyl alcohol, the vehicle for the androgenic steroid. Nandrolone decanoate and vehicle injections were started when rats reached 150–250 g, ~3 wk after exercise had been initiated. The sedentary steroid and control groups were housed individually without access to exercise wheels. Steroid and vehicle administration continued for a 3-mo period, and rats received standard laboratory rat chow and water ad libitum throughout this period. All rats were housed in a room that was lighted between 0600 and 1800.

Habitual exercise protocol. The exercised steroid-treated and exercised control rats were housed in separate cages attached to exercise-training wheels designed in our laboratory (24). Rats had free access to the training wheels through an opening between the cage and the wheel. The circumference of the wheel was 1 m, and the wheels were designed to allow rotation in only one direction to prevent coasting or unmeasured running. Distance, speed, and duration of exercise were monitored by using Cat Eye Micro Cyclocomputers (CC-6000, Cat Eye). The average distance run over the 16 wk was 2.15 ± 0.13 km/day for the exercised steroid-treated group and 2.30 ± 0.24 km/day for the exercised control rats. The average speeds were 1.09 ± 0.05 and 1.02 ± 0.09 km/h for the exercised steroid-treated and exercised control groups, respectively. Neither the average distance run nor the average speed was statistically different between the groups. Rats were allowed to exercise for 4 mo, and no significant decrease in daily performance was noted. It has been shown that moderately high levels of chronic exercise can be maintained for up to 7 mo in rats that are preselected for their desire to run (11). Lambert and Noakes (7) showed that a significant training effect, as indicated by an increased maximal oxygen consumption, would occur in rats that ran >1.66 km/day.

Assessment of LV diastolic geometry and performance. LV diastolic geometry and performance were determined in anesthetized, artificially ventilated, open-chest rats as previously described (13, 22, 24). Briefly, rats were anesthetized with 0.05 mg fentanyl and 2.5 mg droperidol (Jannsen Pharmaceutica), and a PP25 saline-filled polyethylene carotid catheter was inserted for measurement of blood pressure and heart rate. Positive pressure ventilation was initiated with a constant-volume respirator (Harvard Apparatus, Natick, MA), before a thoracotomy was performed. After a midline thoracotomy and parietal pericardectomy, a 21-gauge needle attached to a saline-filled PP25 polyethylene catheter coupled to a Gould P50 (Oxnard, CA) pressure transducer was inserted through the apex of the heart for the measurement of LVED LVEDPs. Only catheters with an amplitude-frequency response, as previously determined (13), that were uniform until 10 Hz were used in these studies. Piezoelectric transducers attached to an apparatus designed and validated in our laboratory (22, 24) were placed over the short axis of the LV to determine LV short-axis external diameters.

LVED short-axis external diameters (LVEDD) as well as LVEDP were recorded with a Hellige polygraph (Hellige, Servomed) over a range of filling volumes by injecting a modified Dextran-70 solution (14) through the arterial line until a LVEDP of 10–15 mmHg was obtained. Blood was subsequently withdrawn from the arterial line into a heparinized syringe so that LVEDP values returned to baseline levels. The same data were then obtained during inferior vena cava occlusion. Recordings obtained during fluid infusion and inferior vena cava occlusion were used for subsequent analysis. Only results free from changes in heart rate or occurrence of ventricular extrasystolic beats were used for analysis. Data collection was repeated at least three times to ensure reproducibility. Repeat infusions were carried out by using the blood that had previously been withdrawn to reduce filling volumes to baseline values.

LVED geometry was determined from the relationship between LVED wall thickness (h) and radius (r) at incremental LVEDPs. LV wall thickness was calculated from the formula $h = (\text{LVEDD}-2r)/2$, where

$$r = \sqrt[3]{[(\text{LVEDD}/2)^3 - \text{Vm}(3/4\pi)]}$$

and where Vm is ventricular wall volume and is equal to 0.943 × LV wet weight (13, 24). LVED chamber diastolic performance was determined from the relationship between LVEDP and LVED internal diameter ($2 \times r$). LVED chamber stiffness (k) was determined from the slope of the linearized relationship between LVEDP and internal diameter. LVED myocardial k was calculated from the slope of the linearized relationship between LVED stress and strain. LVED stress and strain were calculated from the formulae stress = $[1.36 \times \text{LVEDP} \times (2r)^2]/[\text{LVEDD}^2 - (2r)^2]$, and strain = $(\text{LVEDD} - \text{LVEDD}_0)/\text{LVEDD}_0$, where LVEDD_0 is the unstressed LVEDD (13, 24).

Assessment of LV collagen characteristics. Left ventricular hydroxyproline concentration ([HPRO]) was determined as previously described (13). Briefly, samples of LV tissue were placed in evacuated sealed tubes and hydrolyzed in 6 N HCl at 107°C for 16 h. Excess HCl was blown off by using nitrogen gas, and [HPRO] was determined spectrophotometrically according to the method of Stegemann and Stalder (19).

The methods of Mukherjee and Sen (12) as modified by us (13, 25) were used to assess the ratio of LV collagen type I to type III. LV tissue was homogenized and extracted, and then digested for 18 h at 25°C with cyanogen bromide (CNBr) in 70% formic acid. The [HPRO] of the digested supernatant was then determined as described above, and collagen solubility (%) was calculated as the ratio of [HPRO] in CNBr digested tissue to [HPRO] in the LV. CNBr digested tissue was separated by PAGE by using vertical gels of 3 and 12.5% stacking and separating, respectively (12, 13, 25). After staining of the gels with Coomassie blue, a Helena Laboratories EZ-scan was used to obtain densitometric readings of type I (G and H bands) and type III (M band) collagens, and the type I-to-type III ratio was calculated.

Data analysis. Regression analysis was used to determine the lines of best fit for LVEDP vs. LVED internal diameter and LVED stress vs. strain relationships. The LVEDP-LVED internal diameter and LVED stress-strain relationships were found to best fit an exponential function: LVEDP or LVED stress = $b \exp^{(m \text{ LVED internal diameter/strain})}$. These relationships were linearized for statistical analysis: ln LVEDP or LVED stress = ln b + m(LVED internal diameter/strain). Comparisons between the groups were made using ANOVA followed by Tukey's post hoc test. Values in the text are means ± SE. A P value of < 0.05 was accepted as statistically significant.

RESULTS

Heart weight. Habitual exercise in nontreated rats produced increased heart weight, LV wet weight, and LV dry weight (physiological cardiac hypertrophy) (Table 1). In contrast, androgenic steroid administration resulted in reduced body, heart, and LV weight (Table 1). However, despite the effect of nandrolone decanoate on cardiac growth in sedentary rats, the androgenic steroid failed to influence the development of cardiac

Table 1. *Effect of habitual exercise and nandrolone decanoate (steroid) administration on body and heart weight in rats*

	BW, g	HW, g	Wet LVW, g	Dry LVW, g	HW/BW, %
Exercise steroid ($n = 11$)	548 ± 16	1.59 ± 0.06§	1.17 ± 0.02§	0.23 ± 0.005§	0.287 ± 0.002§
Exercise control ($n = 10$)	505 ± 15	1.44 ± 0.03†	1.11 ± 0.04†	0.21 ± 0.006†	0.291 ± 0.004†
Steroid ($n = 10$)	433 ± 17*	1.13 ± 0.04*	0.88 ± 0.02*	0.17 ± 0.003*	0.262 ± 0.001‡
Control ($n = 10$)	528 ± 36	1.30 ± 0.02	0.99 ± 0.02	0.19 ± 0.003	0.245 ± 0.004

Values are means ± SE; *n*, no. of rats. BW, body weight; HW, heart weight; LVW, left ventricular weight; HW/BW, ratio of HW to BW. *$P <$ 0.05: steroid vs. exercise steroid, exercise control and control; §$P < 0.01$: exercise steroid vs. steroid; †$P < 0.05$: exercise control vs. control; ‡$P < 0.01$: steroid vs. control.

hypertrophy in exercised rats. Exercised steroid-treated rats developed the same increase in cardiac weights compared with their nontreated exercised counterparts (Table 1).

LVED relative wall thickness. LVED wall thickness-to-radius ratios (relative wall thickness) were increased, as determined over a physiological range of filling pressures (up to 10 mmHg) after habitual exercise in the untreated group of rats (data up to 8 mmHg are illustrated in Fig. 1). Alternatively, despite the same increase in LV weight in the exercised steroid-treated rats compared with exercised nontreated rats, relative wall thickness values in the exercise steroid-treated group were reduced to values similar to those determined in sedentary control rats, assessed between 0 and 8 mmHg (physiological range of filling pressures) (Fig. 2). At LVEDP values greater than 8 mmHg, relative wall thickness values were similar when the two exercised groups of rats were compared. The lack of change in relative wall thickness in exercised rats receiving an androgenic steroid, despite an exercise-induced increase in LV weight (Table 1), indicates that the androgenic steroid has changed the exercise-mediated remodeling process to a more eccentric pattern as determined over a range of physiological filling pressures.

LVEDP-internal diameter relationships. Habitual exercise mediated a rightward shift in the LVEDP-internal diameter relationship (Fig. 2) because of a decreased slope of the relationship (*chamber k*, Fig. 3*A*). In contrast, androgenic steroid administration to sedentary rats resulted in a leftward shift in the LVEDP-internal diameter relationship (Fig. 2) as a consequence of an increased *chamber k* (Fig. 3*A*). However, nandrolone decanoate given to exercised rats produced a rightward shift in the LVEDP-internal diameter relationship as determined over a physiological range of filling pressures (0–10 mmHg) in compari-

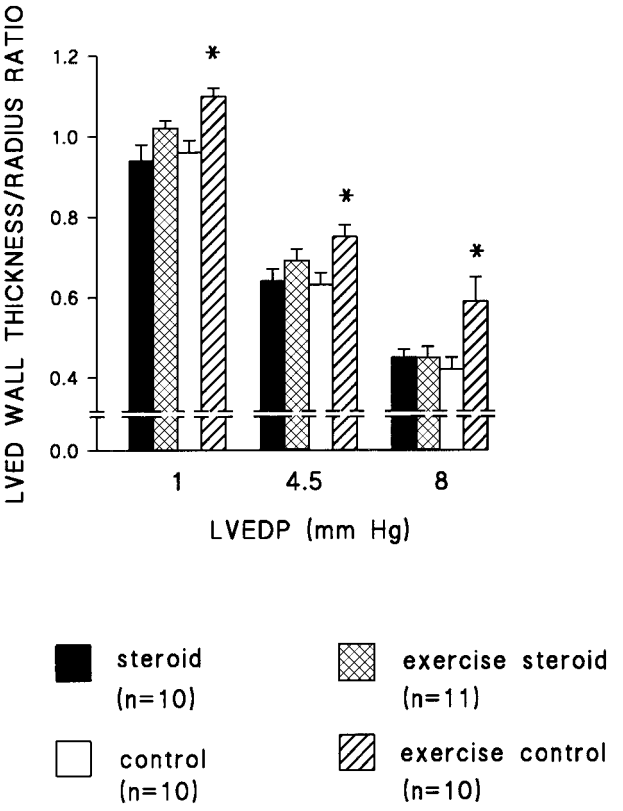

Fig. 1. Effect of nandrolone decanoate (steroid) and habitual exercise on left ventricular end diastolic (LVED) geometry in rats. Bar graphs show LVED wall thickness-to-radius ratio (relative wall thickness) as determined at incremental LVED pressures (LVEDP). *n*, Number of rats. *$P < 0.05$ vs. other three groups.

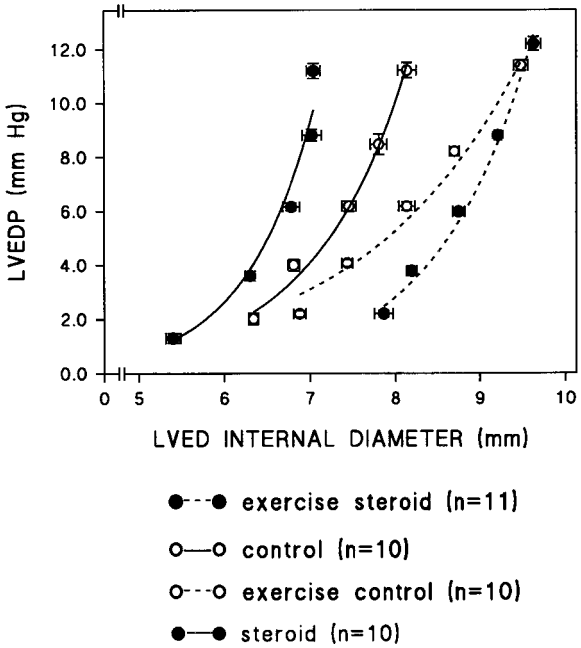

Fig. 2. Line graphs illustrate effect of steroid and habitual exercise on LVEDP vs. LVED internal diameter relationships. Statistical comparisons of slopes of linearized relationships and intercepts of these relationships are made in Fig. 3. *n*, Number of rats.

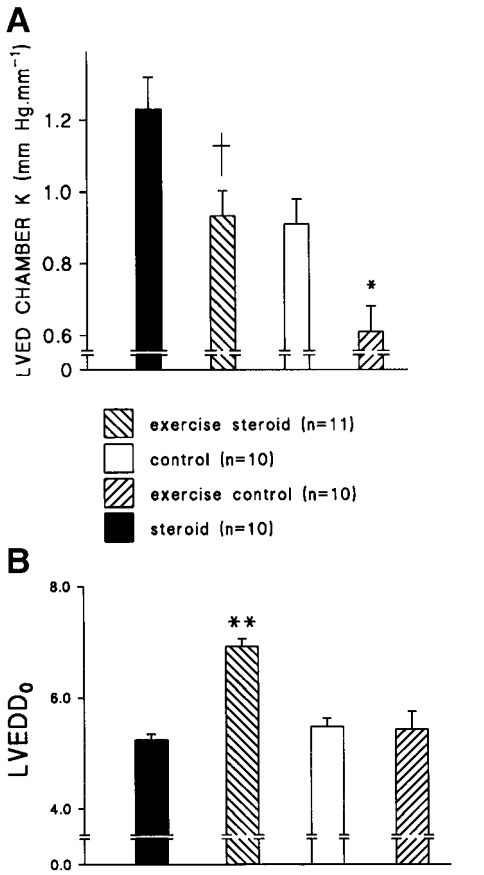

Fig. 3. Bar graphs illustrate effect of nandrolone decanoate (steroid) and habitual exercise on slope of linearized LVEDP vs. LVED internal diameter (LVEDD) relationships (*chamber k*; *A*) and intercept of these relationships [LVEDD at an LVEDP of 0 mmHg ($LVEDD_0$); *B*] in rats. *n*, Number of rats. $*P < 0.05$; $**P < 0.01$ vs. other groups, $\dagger P < 0.05$ vs. steroid and exercise control groups.

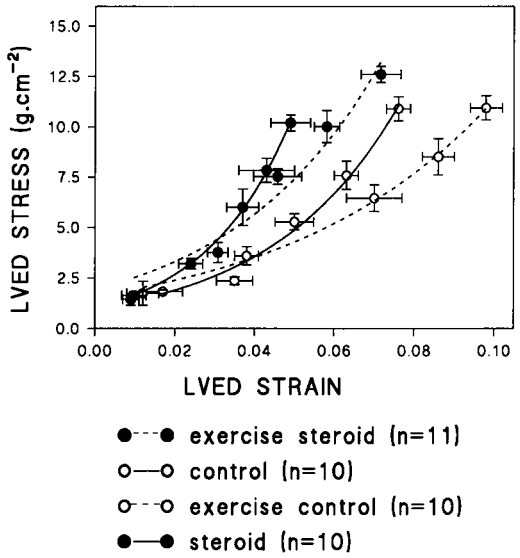

Fig. 4. Line graphs illustrate effect of nandrolone decanoate (steroid) and habitual exercise on LVED stress vs. strain relationships in rats. *n*, Number of rats. Statistical comparisons of slopes of linearized relationships are made in Fig. 5.

son to exercised nontreated rats, not because of changes in *chamber k*, which was increased in comparison to exercised, nontreated rats (Fig. 3*A*), but as a result of a marked increase in the diameter intercept of the relationship (Fig. 3*B*). The ability of nandrolone decanoate to prevent exercise-induced increases in LVED relative wall thickness, as determined over a physiological range of filling pressures (Fig. 1), was therefore attributed to a rightward shift in LVEDP-internal diameter relationships.

LVED stress-strain relationships. The reduced *chamber k* after habitual exercise was the consequence of a rightward shift in LVED stress-strain relationships (Fig. 4) and a decrease in *myocardial k* (Fig. 5). In contrast, the increase in *chamber k* after nandrolone decanoate administration was the consequence of a leftward shift in LVED stress-strain relationships (Fig. 4) and an increase in *myocardial k* (Fig. 5). Similarly, the increased *chamber k* after nandrolone decanoate given to exercised rats in comparison to untreated exercised rats (Fig. 3) was the consequence of attenuation of an exercise-induced rightward shift in LVED stress-strain relationships (Fig. 4) and a subsequent increase in *myocardial k* (Fig. 5).

LV collagen characteristics. LV collagen concentration was unchanged by habitual exercise, steroid administration, or their combination (Table 2). In addition, the solubility of LV collagen, the ratio of insoluble to soluble collagen, and the ratio of collagen type I to III were the same in all four groups. Hence, neither the decrease in *myocardial k* after habitual exercise nor the increase in *myocardial k* after nandrolone decanoate administration to exercised rats was attributed to alterations in the quantity or quality of collagen in the LV interstitium.

DISCUSSION

The main findings of this study are that supraphysiological doses of an androgenic steroid modify exercise-induced LV remodeling and prevent exercise-mediated

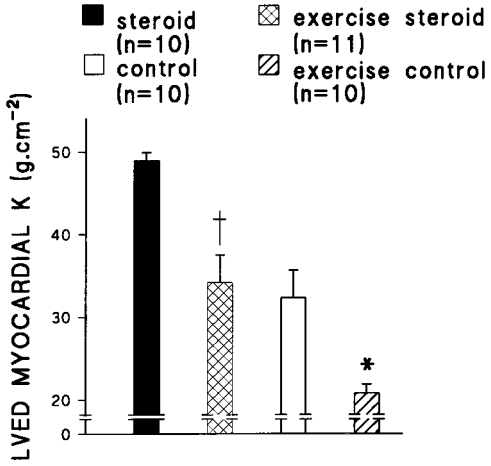

Fig. 5. Bar graphs illustrate effect of nandrolone decanoate (steroid) and habitual exercise on slopes of linearized LVED stress vs. strain relationships (*myocardial k*) depicted in Fig. 4 in rats. *n*, Number of rats. $*P < 0.05$ vs. other three groups and $\dagger P < 0.01$ vs. steroid and exercise control groups.

Table 2. *Effect of habitual exercise and nandrolone decanoate (steroid) administration on LV collagen characteristics in rats*

	[HPRO], μg/mg Dry LV	CNBr Sol, %	Insol/Sol	I/III
Exercise steroid ($n = 11$)	3.60 ± 0.12	46.0 ± 5.6	1.12 ± 0.27	2.76 ± 0.19
Exercised control ($n = 10$)	3.81 ± 0.20	46.6 ± 3.5	1.02 ± 0.12	2.81 ± 0.14
Steroid ($n = 10$)	3.81 ± 0.12	42.9 ± 3.9	0.95 ± 0.13	2.66 ± 0.25
Control ($n = 10$)	3.75 ± 0.07	42.6 ± 5.3	1.00 ± 0.36	2.80 ± 0.18

Values are means ± SE; *n*, no. of rats. [HPRO], hydroxyproline concentration; CNBr Sol, solubility to cyanogen bromide digestion; Insol/Sol, ratio of insoluble [HPRO] to soluble [HPRO]; I/III, ratio of type I to type III collagen.

increases in relative wall thickness without influencing the degree of cardiac growth in rats. Habitual exercise without steroid administration resulted in rightward shifts in LVEDP-internal diameter relationships but an increased LVED relative wall thickness as a consequence of appropriate LVH. Alternatively, nandrolone decanoate given to exercised rats augmented the exercise-induced rightward shift in the LVEDP-internal diameter relationship as determined over a physiological range of filling pressures and consequently reduced relative wall thickness values despite the presence of a similar increase in LV weight. The steroid-mediated effects on exercise-induced LV remodeling were not attributed to alterations in the LV interstitium.

In the present study, it is difficult to determine whether rats were performing short-duration, high-intensity exercise or endurance exercise. However, regarding total distances run (>2 km on average each day), it is hard to believe that the exercise was of a high intensity. In addition, the mean 24-h running speeds noted in each group are likely to reflect low- rather than high-intensity exercise. Furthermore, Lambert and Noakes (7) have shown endurance training effects after voluntary running in rats that run on average >1.66 km/day, a distance below that achieved by all rats recruited for the study. Voluntary running training was chosen in preference to swimming and treadmill exercise, as it avoids anxiety and hence a possible increase in central nervous system-mediated autonomic effects (2). As previously discussed (24), autonomic neurohumoral influences stimulate cardiac growth and may be responsible for a reduced appetite and hence body weight. Because steroid administration alone reduces somatic growth (22, 23), we wanted to avoid any potential further reduction in body weight as a consequence of forced exercise training. Body weight is not altered by voluntary running (24).

Consistent with effects previously described (22, 23), steroid administration to sedentary rats suppressed both somatic and cardiac growth. The decrease in body weight is attributed to a reduction in both calculated lean and fat mass (22). In contrast, steroid administration failed to alter the development of physiological LVH or somatic growth in exercised rats in the present study. Hence, androgenic-anabolic steroids have the ability to produce potential catabolic as well as anabolic effects on cardiac and somatic growth, depending on the experimental conditions. These data are congruous with effects described by Karhunen et al. (6), who showed an increase in heart weight associated with an exercise program in rats receiving an androgenic steroid. However, Liang et al. (9) found no differences in heart weights subsequent to either steroid administration or chronic exercise. This disparity is likely to be due to differences in the exercise protocols employed (voluntary training wheel as used by us vs. forced treadmill exercise as used by Liang et al.) and the frequency of the steroid administration (biweekly as used by us vs. once weekly as used by Liang et al.).

In this study, LVH in the exercised untreated group was associated with an increased LVED relative wall thickness determined at incremental filling pressures despite a rightward shift in the LVEDP-internal dimension relationships, an effect previously described by us (24). The increase in relative wall thickness was a consequence of physiological LVH. However, in the present study, administration of androgenic steroid to exercised animals resulted in a further rightward shift in the LVEDP-internal dimension relationships (assessed over a physiological range of filling pressures) and a consequent reduction in relative wall thickness despite similar increments in LV weights as noted in the untreated exercised group. According to La Place's law as applied to the heart, the result of such an effect of the androgenic steroid would be to increase LVED stress values as determined at a given filling pressure. Whether an enhanced LVED stress occurred at operating filling pressures in steroid-treated exercised rats was not evaluated in this study for practical reasons, as exercised rather than resting operating filling pressures would be of importance.

The effect of habitual exercise on LVEDP-internal dimension relationships (LV remodeling) in the present study was as a result of a reduced LVED chamber and in part myocardial stiffness. It is well known that running training is associated with increments in LVED dimensions as determined at rest (5) or during acute exercise (18). The enhanced LVED dimensions after habitual exercise are likely to reflect a combined effect of increments in blood volume (3) and LV remodeling. Exercise-mediated alterations in diastolic stiffness are thought to provide for a reduced LV filling pressure when filling volumes are increased during acute exercise (8, 24). As nandrolone decanoate augmented the exercise-induced rightward shift in diastolic pressure-internal dimension relationships, the androgenic steroid would not have influenced the ability of the LV to accomodate larger volumes of blood while maintaining relatively normal or low filling pressures during exercise.

The effect of nandrolone decanoate administration on LVEDP-internal dimension relationships and the subsequent detrimental impact on relative wall thickness in exercised rats was a consequence of an increase in the intercept of the LVEDP-internal diameter relationship and not of a decrease in the slope. Indeed, the

androgenic steroid produced an increased slope of the LVEDP-dimension relationship in exercised rats, similar to its effects in sedentary animals. The increase in the slope of the LVEDP-dimension relationship produced by androgenic steroids in both sedentary and exercised animals is thought to be a consequence of changes in myocardial diastolic stiffness (22, 23). In the present study, the androgenic steroid increased myocardial stiffness constants in both sedentary and exercised rats. The mechanisms through which the androgenic steroid produces increases in myocardial stiffness are thought to be modifications in myocardial active rather than passive properties (23). However, the steroid-induced effect on LV remodeling in exercised rats may be attributed to myofibrillar destruction, an effect that occurs with the combined influence of androgenic steroids and exercise (1) and could produce the same actions as catecholamine toxicity on LV geometry (21).

Consistent with previous studies (25), we showed that exercise-induced LVH is not associated with changes in myocardial collagen characteristics. Similarly, neither collagen concentration, the ratio of collagen type I to III, nor collagen solubility (an index of cross-linking) was altered by steroid administration alone (23) or in combination with exercise training in rats. These data are consistent with a previous study in dogs (20), where the authors report no change in collagen concentrations in the LV after the combination of exercise and anabolic steroid administration. Hence, it is more likely that myocardial active properties contribute toward the steroid-induced effect on LV remodeling in exercise-trained rats.

A potentially detrimental steroid-mediated effect on exercise-induced cardiac remodeling, as described in this study, has not been examined in humans. However, echocardiographic data obtained in weight lifters, a significant percentage of whom were taking androgenic steroids, showed increases in LV cavity volumes and dimensions together with an increased LV wall thickness (15). Although the authors of this study did not report on relative wall thickness values (15), the potentially beneficial actions of the increased LV wall thickness are likely to be offset by a detrimental influence on LV cavity volume.

In conclusion, we have shown that supraphysiological doses of an androgenic steroid augment an exercise-induced rightward shift in LVEDP-dimension relationships and subsequently reduce relative wall thickness values as determined over a physiological range of LV filling pressures in rats. Whether the influence of the androgenic steroid on exercise-induced LV remodeling produces increases in LV diastolic wall stress when filling volumes increase during exercise has yet to be determined. Moreover, whether the potentially detrimental influence of androgenic steroids on exercise-induced cardiac remodeling shown in this study occurs in humans and/or contributes toward sudden death in young athletes with physiological cardiac hypertrophy (10) has yet to be determined.

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