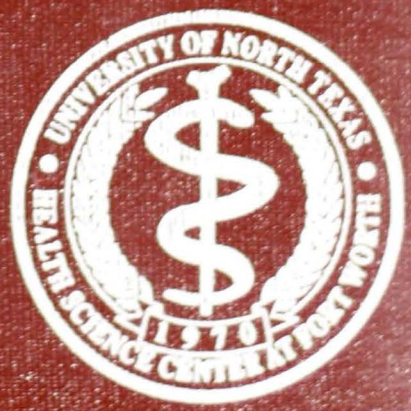
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Dickerman, Rob D., Androgens and Cardiovascular Disease Doctor of Philosophy (Biomedical Sciences), May, 1998; 111 pp; 10 tables, bibliography, 197 titles.

Anabolic steroids are commonly used by many muscle and strength dependent athletes due to their ability to enhance the hypertrophic effects of resistance training. The use of anabolic steroids by bodybuilders appears to carry significant health risks, most commonly reported are sudden death, myocardial infarction and cardiomyopathy. To investigate the effects of anabolic steroids on cardiovascular risks, a study was designed to analyze the effects of androgens on lipoprotein levels and structure/function of the heart. For the study on lipid-related risk, twelve competitive bodybuilders were recruited for a comprehensive analysis of serum apolipoprotein A-I, B, total cholesterol, HDL-cholesterol, LDL- cholesterol, and testosterone. Serum total cholesterol, HDL- and LDL-cholesterol, apolipoproteins A-I and B were significantly lower in the androgen-users. Consistent with previous reports, androgens were associated with decreases in HDL-cholesterol and apolipoprotein A-I. However, androgens were also associated with reduced serum total cholesterol, LDL-cholesterol and apolipoprotein B. Despite the significantly higher total cholesterol/HDL-cholesterol ratio, the low levels of serum total cholesterol levels (<5th percentile) in the androgen-users raises questions as to whether there is increased risk for cardiovascular disease and the exact role of androgens in cardiovascular risk.

To investigate the effects of anabolic steroids in pathologic concentric left ventricular hypertrophy, the effects of androgens on left ventricular size and function were analyzed. Previous investigations conducted on left ventricular size and function have yielded inconclusive results. Problems existing in each of the previous investigations were small body mass, short length of myocardial exposure time to resistance training (years of training), significantly different body mass between steroid-users and steroid-free subjects and monitoring/reporting of steroid use. These problems may have contributed to the discrepancies between studies. Therefore, we selectively recruited eight competitive heavy weight drug-free bodybuilders and eight matched competitive heavy weight bodybuilders on self-directed regimens of anabolic steroids for examination of left ventricular size and function via echocardiography. Increases in left ventricular posterior wall (LVPW) and ventricular septal thickness (VST) were apparent in the steroid-user group ($p< 0.05$). Ratio of echocardiographic findings to body mass index (BMI) revealed a significantly smaller left ventricular end diastolic dimension (LVDEd/BMI, $p< 0.05$) in the steroid-user. The smaller LVDEd in steroid-users is coupled with a significantly disproportionate septal and posterior wall thickness in steroid-users. There was no direct evidence of diastolic dysfunction. Thus, it appears from these studies that androgens alter lipoproteins leading to a questionable increased risk for cardiovascular disease and may potentiate concentric left ventricular hypertrophy without affecting cardiac function.

ANDROGENS AND CARDIOVASCULAR DISEASE

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ANDROGENS AND CARDIOVASCULAR DISEASE

DISSERTATION

Presented to the Graduate Council of the
Graduate School of Biomedical Sciences
University of North Texas Health Science Center at Fort Worth
in Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

By

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Fort Worth, Texas

May 1998

ACKNOWLEDGEMENTS

This Dissertation is dedicated to my wife, Paula K. Dickerman, for being my best friend and the sweetest person I have ever known. Paula thanks for keeping my head on straight and pushing me when others would have not. I love you. I would like to thank God for life, opportunity, experience, memories and most of all choice. I thank my mother, father and brother for unconditional love and support, I would not have made it without you all. I would also like to thank Pouch, CJJ, CN, KMG and JWE for being great friends.

A special thanks to my graduate supervisor Walter J. McConathy, Ph.D. for intellectual, technical, financial and moral support. Dr. McConathy thanks for allowing and supporting the steroid research, I feel we both found areas of interests that will carry on for years to come. Thanks for being a mentor and friend. Thanks to Eva Spudich and Laraine Horton for secretarial support and friendship.

I express my appreciation to Dean Thomas Yorio, Ph.D. and Robert Gracy, Ph.D. for believing in me from the start and giving me a chance. I would like to give a special thanks to Dr. N.Y. Zachariah for laboratory training, conference experience, support and friendship. Thanks to Frederick Schaller, D.O. a great cardiologist and special person. Thanks for having patience with myself and the subjects. Thanks to Steve Grant, Ph.D. for intellectual and moral support in this dissertation.

This dissertation was supported by grants to Rob D. Dickerman from Southern Medical Association (SMA) and Glaxo-Wellcome. The project was also supported by grants to Dr. Walter J. McConathy from the Department of Research and Biotechnology at University of North Texas Health Science Center.

This dissertation and my education were supported by the Department of Biomedical Sciences and the Department of Medicine of the University of North Texas Health Science Center at Fort Worth and the previously referenced extramural and intramural funding. The following publications are results of this support and training.

Dickerman, R.D., McConathy, W.J., Zachariah, N.Y. Testosterone, Sex Hormone-Binding Globulin, Lipoproteins, and vascular Risk. ***Journal of Cardiovascular Risk*** 4:363-366;1997.

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Dickerman, R.D., Schaller, F., McConathy, W.J. Aortic Valve Thickening Associated with Power Training: Is it Pressure Overload ? ***The American Journal of Cardiology*** In Press.

Dickerman, R.D., Schaller F., Zachariah, N.Y., McConathy, W.J. Left Ventricular Wall Thickening Does Occur in Elite Power Trained Athletes With or Without Anabolic Steroid Use. ***Cardiology*** In Press.

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Dickerman, R.D., Mooney, M. Myocardial Infarction and Quadruple Bypass Surgery in a 34 Year-Old Powerlifter Using Androgens. ***American Heart Journal*** In preparation.

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LIST OF ABBREVIATIONS

A	Active atrial contraction diastolic filling
ANOVA	Analysis of variance
Apo AI	Apolipoprotein A-I
Apo B	Apolipoprotein B
BMI	Body mass index
CHD	Coronary heart disease
DU	Drug-user
DF	Drug-free
E	Passive early diastolic filling
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HTGL	Hepatic triglyceride lipase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LVEDd	Left ventricular end-diastolic dimension
LVESd	Left ventricular end-systolic dimension
LVH	Left ventricular hypertrophy
LVPW	Left ventricular posterior wall
SHBG	Sex hormone-binding globulin
VST	Ventricular septal thickness

CHAPTER 1

INTRODUCTION

The questions addressed in this dissertation are based on numerous reports of sudden death[1-4], myocardial infarction[5-11] and hypertrophic cardiomyopathy [12-16] in athletes using anabolic steroids. Cross-sectional and interventional studies of testosterone and lipoprotein levels have yielded varying findings. Testosterone and estradiol levels have been reported to be either negatively or positively associated with levels of HDL-cholesterol, respectively [17,18]. Testosterone has been shown to decrease HDL-cholesterol to varying degrees depending on the androgen and route of administration. Testosterone's effect on LDL-cholesterol remains controversial. LDL-cholesterol levels have been shown to increase[19-22], decrease[23], or remain unaffected by androgen administration[24]. Reports of myocardial infarction and sudden death in bodybuilders using anabolic steroids [18-22] have often been thought to result from coronary heart disease in part due to anabolic steroid's deleterious effects on lipoprotein levels. The overall consensus in the majority of studies on testosterone and cholesterol metabolism is that androgens decrease serum HDL levels while increasing serum LDL levels.

Cardiomyopathy is the most common reported cause of cardiac death in athletes using anabolic steroids[1-4,12-16]. To date, the pathogenesis of anabolic steroid-induced cardiomyopathy is yet to be elucidated. The recent reports of cardiomyopathy[14] and sudden cardiac death[1] in athletes abusing anabolic steroids suggest that anabolic steroid abuse alone or when coupled with intense weight-lifting may promote pathological changes. Previous reports have indicated the presence of androgen receptors on cardiac muscle[25] and have experimentally shown that myocardial lesions develop from anabolic steroid therapy[26]. Despite the numerous reports on steroid related deaths, several investigations conducted on left ventricular size and function have yielded inconclusive results[27-32]. Previous reports on left ventricular function in bodybuilders on anabolic steroids and bodybuilders not on steroids have concluded that left ventricular mass is proportional to body mass and that left ventricular function is not impaired in bodybuilders using anabolic steroids[29]. To date there is only one report of left ventricular dysfunction in anabolic steroid using bodybuilders[30].

This dissertation is intended to examine whether anabolic steroids increase cardiovascular risk in elite resistance-trained athletes by either altering lipoprotein levels and/or when combined with intensive resistance-training, induce pathological functional and/or structural changes in the left ventricle.

BACKGROUND

Since the development of anabolic steroids in 1935, there use has been most often associated with athletes in quest of increasing muscle mass and strength. There are reportedly at least 1 million Americans who have used anabolic steroids to improve athletic performance or physical appearance, and many of these users may be adolescents[33]. The role anabolic steroids have in enhancing certain strength related performances is no longer disputed[34]. The beneficial effects of these steroids on athletic performance has accelerated their abuse and led to increasing doses without medical supervision.

Male gender has long been recognized as an important risk factor for coronary heart disease (CHD)[35-37]. The concurrence of several major risk factors for CHD in men has suggested a common underlying factor[38-40], and it has been hypothesized that this factor linking them may be the sex hormone milieu[39]. In contrast, the risk of atherosclerotic disease in premenopausal women is low but increases after menopause[41]. Estrogens have thus been postulated as a protective hormone against atherosclerosis, while testosterone has long been implicated as detrimental in men. It is possible that the increased risk for coronary atherosclero-

sis in postmenopausal females may be due not only to withdrawal of estrogen, but also the effects of unopposed androgens.

Testosterone has many important physiological functions, including effects on muscle, bone, central nervous system, prostate, bone marrow and sexual function[42]. However, the contribution of androgens, particularly testosterone, to the increased likelihood of coronary artery disease in men is unclear with respect to lipid metabolism. Supraphysiolgic levels of androgens via anabolic steroid abuse are thought to be deleterious secondary to there ability to affect lipoproteins[17-24]. To date the link between anabolic steroids and myocardial infarction is supported by several case reports[5-11]. The overall consensus in studies of athletes abusing anabolic steroids is that androgens decrease HDL-C while increasing LDL-C[50-53](Table 1).

Table 1. Summary of comparative observational studies of adverse lipoprotein metabolism secondary to androgenic-anabolic steroid use in strength-trained athletes.*

References	Subjects	Total Cholesterol	LDL-C	HDL-C
Cohen et al.[50]	9 male	291± 88.1	------	23.5± 9.1
Costill et al.[51]	9 male	218.1± 44.1	------	17.0± 6.5
Glazer et al.[52]	5 male	183± 27	138± 25	26± 10
Lenders et al.[53]	20 male	------	204± 21	26± 21

Values are expressed in mg/dl ± standard deviation.

*Melchert RB, Welder AA. Cardiovascular effects of androgenic-anabolic steroids. Med Sci Sports Exer. 27(9);1252-1262,1995.

The athlete's heart has been a topic of interest among cardiologists for decades[54]. Several years ago the upper limits of physiologic left ventricular hypertrophy (LVH) were redefined during an investigation of 947 Olympic aerobic and anaerobically trained athletes[55]. The authors concluded that a left ventricular

wall thickness beyond 13 mm was confined to elite rowers, canoers and cyclists. The authors went onto state that the presence of left ventricular wall thicknesses beyond 13 mm in elite resistance trained athletes would suggest alternative explanations, such as the diagnosis of pathologic hypertrophy or hypertrophic cardiomyopathy.

Numerous reports of sudden death and cardiomyopathy associated with anabolic steroids exist in the medical literature[1-4,12-16]. To date the exact relationship between anabolic steroid abuse and pathological cardiac growth remains to be elucidated. Studies on cardiac size and function in resistance trained athletes have yielded conflicting results[27-32]. Case reports of idiopathic cardiomyopathy in athletes who use anabolic steroids point to the possible role of steroids in cardiac pathology[1-4,14]. Animal studies on the effects of anabolic steroids in cardiac growth demonstrated an increase in cardiac size only when anabolic steroids were combined with exercise[43].

The conflicting results in previous echocardiographic investigations were maybe due to small body mass among subjects, short length of myocardial exposure time to resistance training (years of training), significantly different body mass between steroid-users and steroid-free subjects and monitoring/reporting of

steroid use [27-31]. Since cardiac growth is known to be dependent on several factors such as hormones, length of exposure to intense exercise, type of exercise - weight-lifting/pressure overload versus long distance runnning/volume overload, and individual body mass; controlling for these variables is essential[44].

The importance of length of cardiac exposure to resistance exercise is a point worth discussion and is the basis for our most recent article in review[45]. Current articles are now questioning their previous published results on increasing left ventricular wall thickening in power athletes and are disputing the occurrence of this physiological adaptation in power athletes unless anabolic steroids are used [46-48]. The origin of such arguments is based on the left ventricular responsiveness or lack thereof to the pressor response (hypertensive episodes) which occurs with weight-lifting. There is no debate that blood pressure elevates during weight-lifting, but the recent change of thought is that the short bursts of arterial hypertension that occur with weight-lifting are not sufficient in duration to induce left ventricular wall thickening[46-48]. Despite the numerous studies on blood pressure responses during weight lifting, and the attempts to elucidate the mechanisms responsible for blood pressure elevations, a study conducted over a decade ago remains the focus of scientists interested in the physiological and pathological effects of resistance training on blood pressure[49]. The study recorded mean systolic and diastolic arterial pressures in five drug-free human males during weight-lifting, the mean pressure

for the group was 320/250, with pressures in one subject exceeding 480/350 mmHg. These intermittent hypertensive episodes during weight-lifting were previously thought to lead to physiological adaptations within the myocardium in the form of concentric left ventricular hypertrophy[27-32,55].

Therefore, we set out to address several questions in these investigations on elite resistance trained athletes: First, do anabolic steroids induce pathological lipoprotein profiles leading to an increased risk for myocardial infarction and sudden death? Secondly, do anabolic steroids induce pathological left ventricular growth or affect left ventricular function? Thirdly, does left ventricular hypertrophy occur in resistance trained athletes with or without anabolic steroid use and could androgens potentiate left ventricular growth when coupled with resistance exercise ?

SPECIFIC AIMS

The primary objectives of this dissertation were to address the aforementioned questions and to further support or reject our hypothesis based on existing data in the literature. The current study tests the hypothesis that androgens increase cardiovascular risk by alterations in lipoproteins. Secondly, androgens do not induce left ventricular dysfunction, but may potentiate cardiac growth when combined with years of intermittent hypertensive episodes experienced with

rigorous resistance exercise. The following three specific aims were investigated.

I. To test the hypothesis that androgens increase cardiovascular risks by pathologically altering lipoprotein profiles.

II. To test the hypothesis that androgens potentiate left ventricular hypertrophy without affecting diastolic function.

III. To test the hypothesis that left ventricular wall thickening occurs in resistance trained athletes with or without anabolic steroid use.

Two studies were designed to investigate Specific Aims I and II. Specific Aim III was addressed as a follow-up investigation which included retrospective analysis of data collected in the second investigation. These studies are discussed in detail in the following chapters.

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Chapter II

TESTOSTERONE, SEX HORMONE-BINDING GLOBULIN, LIPOPROTEINS AND VASCULAR DISEASE RISK

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JOURNAL OF CARDIOVASCULAR RISK
1997;4:363-366

ABSTRACT

Background: A higher risk for coronary heart disease in males has pointed to testosterone as a risk factor. Lipoprotein levels have been reported to be altered by androgens thus increasing the risk for coronary heart disease (CHD), myocardial infarct, and sudden death. The increasing abuse of anabolic steroids and reports of sudden death and myocardial infarction in bodybuilders has raised concerns about increased cardiovascular risk in this population.

Methods: Twelve competitive bodybuilders were recruited for a comprehensive study on the cardiovascular risks associated with anabolic steroid use. Six competitive heavy weight bodybuilders on self-directed regimens of anabolic steroids (SU) and six competitive heavy weight drug-free bodybuilders (SF) were utilized for cardiovascular risk assessment. Apolipoprotein A-I, B, total cholesterol, HDL-cholesterol, LDL- cholesterol, triglycerides, testosterone, and sex hormone-binding globulin were determined in each athlete.

Results: Total cholesterol, HDL- and LDL-cholesterol, apolipoproteins A-I and B, and triglycerides were significantly lower in the SU group. As expected, testosterone was significantly higher in the SU group; sex hormone-binding globulin was significantly lower. While apolipoprotein and lipoprotein levels were lower in the SU group, the ratio of total cholesterol/HDL-cholesterol was significantly higher in

the SU.

Conclusions: Consistent with previous reports, androgens were associated with decreases in HDL-cholesterol and apolipoprotein A-I. However, androgens were also associated with reduced LDL-cholesterol and apolipoprotein B. Despite the significantly higher total cholesterol/HDL-cholesterol ratio, the low serum total cholesterol levels (<5th percentile) and low plasma triglyceride in the SU group raises questions as to the exact role of androgens in increasing risk for cardiovascular disease.

Keywords: androgens, coronary heart disease, lipoproteins

INTRODUCTION

Male gender has been recognized as an important risk factor for coronary heart disease (CHD)[1-3]. The concurrence of several major risk factors for CHD in men has suggested a common underlying factor[4-6], and it has been hypothesized that this factor linking them may be the sex hormone milieu[5]. In contrast, the risk of atherosclerotic disease in premenopausal women is low but increases after menopause[7]. Estrogens have thus been postulated as a protective hormone against atherosclerosis, while testosterone has long been implicated as detrimental in men. It is possible that the increased risk for coronary atherosclerosis in postmenopausal females may be due not only to withdrawal of estrogen, but also the effects of unopposed androgens.

Testosterone has many important physiological functions, including effects on muscle, bone, central nervous system, prostate, bone marrow, and sexual function[8]. However, the contribution of androgens, particularly testosterone, to the increased likelihood of coronary artery disease and cardiac dysfunction in men is unclear with respect to lipid metabolism. Cross-sectional and interventional studies of testosterone and lipoprotein levels have yielded varying findings. Testosterone and estradiol levels have both been reported to be either negatively or positively associated with levels of HDL-cholesterol, respectively[9,10]. Testosterone has been shown to decrease HDL-cholesterol to varying degrees depending on the androgen and route of administration. Testosterone's effect on LDL-cholesterol remains

controversial. LDL-cholesterol levels have been shown to increase[11-14], decrease[15], or remain unaffected by androgen administration[16].

Reports of myocardial infarction and sudden death in bodybuilders using anabolic steroids[17-19] have often been thought to result from coronary heart disease subsequent in part to anabolic steroid's deleterious effects on lipoprotein levels. The overall consensus in the majority of studies on testosterone and cholesterol metabolism is that androgens decrease serum HDL levels while increasing serum LDL levels. To help clarify the role of anabolic steroids in cardiovascular disease, six competitive heavy weight bodybuilders on self-directed regimens of anabolic steroids (SU) and six competitive heavy weight drug-free bodybuilders (SF) were recruited for cardiovascular risk assessment.

METHODS

Study Subjects: Twelve subjects were selectively recruited from the Dallas-Fort Worth metropolitan area based on their lean body mass, training regimens, drug history, level of competition and body mass index > 30.0 kg/m^2. Both steroid-users (SU) and lifetime steroid-free (SF) subjects were fully informed about the potential risks and benefits of the study and signed an informed consent form as approved by the University of North Texas Health Science Center Institutional Review Board. All subjects had been lifting weights for at least six years and most were in training for competition. The subjects were all involved in previous studies at UNTHSC

which documented their blood pressure status and each subject denied the use of any other medications. The SU group had been using steroids for six to fifteen years. The subject pool included nationally ranked heavyweight bodybuilders, a multi-world record powerlifter (squats > 1000 lbs). Anthropomorphic data was recorded on each subject. Each subject was aware of their own bodyfat percentage and was collected, based on the subject's knowledge. The subjects utilized in this investigation followed a highly regimented training and dietary schedule, most eating every two-three hours, thus non-fasting serum (20 ml) was collected on each subject for analytical studies.

Analytical methods: Serum testosterone was measured in duplicate by radioimmunoassay kits (Diagnostic Systems, Webster, TX). SHBG was measured by immunoradiometric assay (IRMA) kits (Diagnostic Systems, Webster, TX). Total cholesterol and triglycerides were determined on a routine serum chemistry analyzer. HDL-cholesterol was measured using standard HDL precipitating reagent (DMA Inc., Arlington, TX) on an Olympus serum analyzer at Corning Clinical Labs, Irving TX. LDL-cholesterol was calculated by the Freidwald formula[20]. Due to small serum sample size, apolipoprotein analysis was limited to apolipoproteins A-I and B which were measured on a Behring Nephelometer BNI (Corning Clinical Labs of Irving, TX).

RESULTS

The subjects examined in this investigations, in contrast to previous studies, were well matched with respect to age, weight, and years of training[12]. The SU subjects were larger and had less body fat (Table 1) though the differences were not significant ($p>0.05$). The body masses reported in this study are not only larger than previous studies, but the SF subjects were larger with respect to BMI than all previous reports on SU subjects[12,18-19].

As expected, serum testosterone and sex-hormone binding globulin demonstrated an inverse relationship within each group and were significantly different ($p<0.004$) between groups. Serum total cholesterol and triglyceride ($p<0.03$) were also significantly lower in the SU group (Table 2). In addition, the total cholesterol for the SU group was in the 5th percentile (<120 mg/dl)[21].

HDL- cholesterol and apo-AI levels were both significantly lower in the SU group consistent with previous reports[12,18-19]. However, contrary to previous reports LDL-cholesterol and apo-B levels ($p < 0.04$) were lower in the SU group (Table 3). Total cholesterol/HDL ratio was 3.7 in the SF group, which agrees with previous studies[22], however, despite lower LDL and total cholesterol, the SU group had a total cholesterol/HDL ratio of 4.6, inferring increased cardiovascular risk.

Statistically significant negative correlations were found for testosterone versus HDL in both the SU and SF groups. A significant negative correlation was also found for testosterone versus total cholesterol and LDL-C in the SF group.

SHBG was positively correlated only with total cholesterol and LDL-C in the SU group (Table 4).

DISCUSSION

Taken as a whole, our results concur with previous studies[1,12] that suggest anabolic steroids may increase cardiovascular risk by decreasing the levels of apolipoprotein A-I and HDL-cholesterol. However in selecting two such appropriately matched study groups, this study decreased many variables, such as diet and exercise that may alter apolipoprotein and lipoprotein levels. This allowed us to focus more on the suprapharmacological doses of testosterone, and in doing so, we were able to reveal new findings that conflict with previous reports[1,12-14].

Apolipoprotein A-I, the major apolipoprotein of HDL, is synthesized by the liver and its mode of regulation to date by androgens is unclear. The results of this study reveal a possible steroid regulation of both apolipoprotein A-I and apolipoprotein B levels, similar to that seen for SHBG. As androgen levels increase, a reciprocal decrease in apolipoprotein levels occurred. This inverse relationship between apo-A-I, apo-B, and SHBG to testosterone supports the view of the presence of androgen response elements in the genes for apo-A-I and apo-B. To date, studies addressing the possibility of androgens inhibiting apolipoprotein synthesis thus limiting the subsequent formation of lipoproteins are scant. Several mechanisms have been proposed to explain androgens ability to increase

cardiovascular risk, however to date the exact mode remains to be elucidated. The majority of reports have focused on androgens ability to increase hepatic triglyceride lipase (HTGL) levels[12,23-25], thus decreasing HDL-cholesterol levels and increasing risk[25-29]. These studies have shown that the route of administration, oral versus injected, and the type of anabolic steroid administered are the major determinants affecting the increase in HTGL. Of particular interest was a study[28] on the administration of testosterone enanthate alone versus coadministration of testosterone enanthate and testolactone (an aromatase inhibitor), which revealed a more significant increase in HTGL with coadministra-tion. The coadministration of an aromatase inhibitor increasing HTGL demonstrates the importance of aromatization for decreasing cardiovascular risks. However, this study demonstrated varying degrees of HTGL activity with oral and injectable anabolic steroids.

It appears, by mechanisms that remain to be elucidated, that the risk for coronary heart disease may be increased with anabolic steroid use. However, we would like to discuss several unique findings of this study that raise further questions as to the role of androgens in cardiovascular disease. First, total cholesterol was below the 5th percentile (< 120 mg/dl) for all of the steroid users, thus the amount of risk present when total circulating serum cholesterol levels are this low remains unclear. One would expect that risk would be relatively low but this point remains to be established. Secondly, the low serum total cholesterol may

be secondary to increased utilization for increasing muscle mass as seen in male puberty[30]. Is cholesterol being utilized to replace those cells damaged during intense workouts is also an open question. Next, in examining the diet of a few androgen using bodybuilders, it appears that they are receiving > 200% of the United States Recommended Daily Allowance (RDA) for cholesterol, yet serum cholesterol levels remain low. This high cholesterol diet is usually low in saturated fat. Thus, it may be the low saturated fat diet decreases the synthesis of cholesterol[31] and that the low serum cholesterol levels reflect adherence to an extremely rigid dietary regimen only or diet combined with androgen.

CONCLUSIONS

This investigation has demonstrated through the use of elite steroid-free and steroid-using bodybuilders that testosterone may suppress the levels of both apolipoprotein A-I and apolipoprotein B leading to subsequent alterations in lipoprotein profiles to levels that have questionable coronary heart disease risk. In addition, this study demonstrates the similar androgen response patterns of SHBG, and apolipoprotein A-I. For years testosterone has been known to decrease HDL-cholesterol, however previous studies have concluded that testosterone also increases LDL-cholesterol levels leading to a greater cardiovascular risk. This study disputes previous reports, and raises questions as to the exact role of testosterone in lipoprotein regulation and subsequent coronary heart disease.

Future research should focus on the role of sex steroids in apolipoprotein synthesis and the elucidation of steroid-response elements.

Acknowledgements: Thanks to Corning Clinical Laboratories, Irving, Texas, Osteopathic Medical Center of Texas, and North Texas Medical Specialty Laboratory. Special thanks to all the bodybuilders who volunteered for this study.

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; SHBG, sex hormone-binding globulin; CHD, coronary heart disease; SU, steroid user; and SF, steroid non-user.

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Table 1. ANTHROPOMORPHIC CHARACTERISTICS OF BODYBUILDERS

	Age	BMI	Body Fat
SF	26.2[a]	31.9[b]	11.1
n=6	(3.0)	(1.6)	(2.1)
SU	25.5	34.8	8.4
n=6	(6.0)	(2.7)	(2.5)

[a]Mean (SD).
[b]p = 0.0534 by Welch's approximate t-test.

Table 2. SERUM LIPID, SHBG, AND TESTOSTERONE LEVELS IN BODY-BUILDERS

	Testosterone	SHBG	Total Cholesterol	Triglyceride
	ug/ml	nM/l	mg/dl	mg/dl
SF	6.5[a,b]	22.3[b]	159.0[c]	136.7[c]
n=6	(1.3)	(2.7)	(41.3)	(56.5)
SU	18.8	10.3	107.8	63.5
n=6	(5.4)	(4.2)	(15.0)	(19.5)

[a]Mean (SD)
[b]$p < 0.004$ by Welch's approximate t-test.
[c]$p < 0.03$

Table 3. LIPOPROTEIN AND APOLIPOPROTEIN PARAMETERS IN BODYBUILDERS

	HDL	LDL	apo-AI	apo-B	TC/HDL
	mg/dl	mg/dl	mg/dl	mg/dl	
SF	42.7[a,b]	89	155.1[b]	126.0[c]	3.7[c]
n=6	(6.1)	(38.9)	(5.9)	(25.6)	(0.5)
SU	24.2	70.8	81.2	88.8	4.6
n=6	(5.8)	(10.2)	(25.5)	(18.0)	(0.8)

[a]Mean (SD)
[b]$p < 0.005$
[c]$p < 0.04$

Table 4. CORRELATION PARAMETERS OF TESTOSTERONE AND SHBG IN BODYBUILDERS.

	CORRELATION COEFFICIENT (r)[a]	p
SF (n = 6)		
Testosterone vs		
Total Cholesterol	-0.841	0.036
HDL	-0.851	0.032
LDL	-0.841	0.036
SU (n = 6)		
Testosterone vs		
HDL	-0.899	0.0149
SU (n = 6)		
SHBG vs		
Total Cholesterol	0.899	0.015
LDL	0.829	0.042

[a]Spearman correlation coefficients of all significant relationships, $p < 0.05$, found when correlating measured parameters for SU and SF groups.

TRANSITION I

The results of the initial investigation show that elevated testosterone levels, in elite bodybuilders ingesting a low saturated fat diet, lead to decreased serum levels of both apolipoprotein A-I and apolipoprotein B thus leading to a questionable increase in cardiovascular risk. However, the question remains as to the role of androgens in pathologic left ventricular hypertrophy and hypertrophic cardiomyopathy. Numerous reports of sudden death and cardiomyopathy associated with anabolic steroids exist in the medical literature and studies on cardiac size and function in resistance trained athletes have yielded conflicting results[1-6]. Case reports of idiopathic cardiomyopathy in athletes who use anabolic steroids point to the possible role of steroids in cardiac pathology[7-15]. Animals receiving methandienone (anabolic steroid) in doses per kilogram of bodyweight similar to those used by athletes demonstrate increased heart weight compared to control animals[16]. Of particular interest is a study examining systolic time intervals (left ventricular pumping efficiency) in canines receiving methandienone which only demonstrated abnormal pumping efficiency when exercise was combined with anabolic steroid treatment[17]. In addition, a recent examination of four bodybuilders self-administering high doses of anabolic steroids revealed significant left ventricular septal and posterior wall thickness, with 2 of 3 athletes exhibiting

significant fibrous endomyocardial deposition as determined by biopsy[18]. Therefore, we selectively recruited sixteen elite competitive heavy-weight bodybuilders from the metropolitan area based on their lean body mass, training regimens, drug history, level of competition and body mass index > 30.0 kg/m^2 for assessment of left ventricular size and function via two dimensional echocardiography.

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CHAPTER III

LEFT VENTRICULAR SIZE AND FUNCTION IN ELITE BODYBUILDERS USING ANABOLIC STEROIDS

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CLINICAL JOURNAL OF SPORT MEDICINE
1997;7(2):90-93

ABSTRACT

Background: Anabolic steroids have been implicated in numerous cases of hypertrophic cardiomyopathy and pathologic concentric left ventricular hypertrophy. To date there are conflicting studies on the role of anabolic steroids in left ventricular hypertrophy and cardaic function. The present study was designed to distinguish the role of anabolic steroids and resistance training in left ventricular hypertrophy and cardiac function.

Methods: Eight competitive heavy weight drug-free bodybuilders, and eight competitive heavy weight bodybuilders on self-directed regimens of anabolic steroids were recruited for an echocardiography study, the cardiologist and laboratory technician were blinded as to the subjects drug-status.

Results: Average body mass index (BMI, Kg/m^2) for drug and drug-free groups were not significantly different (34.1 ± 2.8 and 32.0 ± 4.3, respectively). Increases in left ventricular posterior wall (LVPW) and ventricular septal thickness (VST) were apparent in the DU group ($p< 0.05$). Ratio of echocardiographic findings to BMI revealed a significantly smaller left ventricular end diastolic dimension (LVDEd/BMI, $p< 0.05$) in the DU. The smaller LVDEd in DU is coupled with a significantly disproportionate septal and posterior wall thickness in DU's when indexed to body mass as compared to DF's. There was no direct evidence of diastolic dysfunction

detected by mitral inflow velocity patterns.

Conclusions: Anabolic steroids may potentiate concentric left ventricular hypertrophy with decreasing ventricular compliance without affecting cardiac function.

Key Words: concentric hypertrophy, resistance training, hypertrophic cardiomyopathy, compliance.

INTRODUCTION

High intensity weight-training is becoming an ever increasing popular form of exercise among athletes in quest of increasing muscle mass. Unfortunately, anabolic steroids are commonly used by many muscle and strength dependent athletes due to their ability to further enhance the hypertrophic effects of resistance training. The use of anabolic steroids by bodybuilders/powerlifters has become a recognizable health risk, due to the large amounts that are self-administered without medical supervision[1,2]. The role anabolic steroids have in enhancing certain strength related performances is no longer disputed[13]. However, the adverse side effects of these drugs when administered in suprapharmacological doses on myocardial hypertrophy and cardiac function remains unknown. The recent reports of hypertrophic cardiomyopathy[3] and sudden cardiac death[5] in athletes abusing anabolic steroids suggest that anabolic steroid abuse alone or when coupled with intense weight-lifting may promote pathological conditions. In addition, previous reports have indicated the presence of androgen receptors on cardiac muscle[15] and have experimentally shown that myocardial lesions develop from anabolic steroid therapy[1].

Despite the numerous reports on steroid related deaths, several investigations conducted on left ventricular size and function have yielded

inconclusive results. Previous reports on left ventricular function in bodybuilders on anabolic steroids and bodybuilders not on steroids have concluded that left ventricular mass is proportional to body mass and that left ventricular function is not impaired in bodybuilders using anabolic steroids[19]. To date there is only one report of left ventricular dysfunction in anabolic steroid using bodybuilders[20]. Problems existing in each of the previous investigations were small body mass, short length of myocardial exposure time to resistance training (years of training), significantly different body mass between drug users and drug-free subjects and monitoring/reporting of steroid use. These problems may have contributed to the discrepancies between studies. Therefore, we selectively recruited 16 of the largest bodybuilders in the Dallas-Fort Worth metropolitan area for an intensive investigation into the possible adverse affects of anabolic steroid abuse coupled with resistance training on cardiac size and function.

METHODS

Study Subjects: Sixteen subjects were selectively recruited from the metropolitan area based on their lean body mass, training regimens, drug history, level of competition and body mass index > 30.0 kg/m^2. Both drug-users (DU) and lifetime drug-free (DF) subjects were fully informed about the potential risks and

benefits of the study and signed an informed written consent form as approved by the University of North Texas Health Science Center (UNTHSC) Institutional Review Board. All subjects had been lifting weights for at least four years and most were in training for competition. The subjects were all involved in previous studies at UNTHSC which documented their blood pressure status, and each subject denied the use of any other medications. Prior to echocardiography, each subject was questioned in regard to family history of hypertension, sudden death, or cardiomyopathies. The subject pool included nationally ranked heavyweight bodybuilders and a multi-world record powerlifter (squats > 1000 lbs.). Physical and training characteristics were recorded for each subject (Table I). Body fat was not measured in all subjects, although each was aware of their own bodyfat percentage and was thus based on the subjects knowledge (Table I). Serum was collected from each subject after echocardiographic analysis for testosterone quantification by radioimmunoassay.

Protocol: Age, height, weight, and body mass index (BMI) were determined on each subject upon arrival. The subjects then underwent transthoracic echocardiography, performed in a resting state, on a SONOS 1000 echo-doppler sonography unit (HP) with 3.5 H^7 phased array transducer. The echocardiographer was blinded as to the drug status of the subjects. Doppler studies were performed in the apical four and two chamber views, recording inflow across the mitral valve. Echocardiographic measurements included left ventricular septal and posterior wall

thickness, left ventricular end-diastolic and end-systolic internal diameter, right ventricular end diastolic diameter, and left atrial dimension. Long and short axis measurements were made from the apical views and parasternal short axis projection. Chamber dimension and wall thickness were measured at end-systole and end-diastole in the parasternal short axis at a level one cm below the mitral annulus during normal resting respirations. Left ventricular mass was calculated from software package Rev 5 from Hewlett-Packard. The endocardium was traced during the systolic and diastolic phase of the cardiac cycle for determination of left ventricular ejection fraction using a modified Simpson's rule. Doppler inflow measurements included E and A wave peak velocities, E wave slope, and diastolic filling time. Diastolic dysfunction was defined as E/A ratio less than 1 or with high velocity, steep slope E wave. Ejection fraction is considered normal when $\geq$ 55 % . Wall thickness is normal when $\leq$ 1.1 cm.

Statistics: The unpaired t test with Welch's approximation for independent samples was used in analyzing the difference between the mean values of the two groups. Data are expressed as mean values $\pm$ standard deviation (SD) unless otherwise noted. A $p \leq 0.05$ was required to demonstrate statistical significance.

RESULTS

Anthropomorphic Characteristics: Table I contains mean physical and training characteristics of all subjects. In contrast to previous investigations the DU

and DF groups were well matched with respect to height, weight and body mass index (BMI) with the only exception being a significant difference in percent of body fat. The body masses reported in this study are not only larger than previous studies, but the DF subjects were larger than all previous reports on DU subjects. The number of years of training were also not significantly different between the two groups, thus eliminating differences in the time of cardiac exposure to resistance-training. Strength as assessed by maximum squat was different but not significantly.

Steroids: In Table I serum total testosterone levels are reported for each group and were determined in all subjects to confirm steroid use. All DU subjects reporting drug use had elevated testosterone levels. Serum testosterone levels were significantly higher in the DU ($p<0.0001$) and were on average 2.5 times higher than the highest level seen in the DF group (normal range, 2.8 - 8.8 ng/ml).

Cardiac size and function: Left ventricular dimensions that were significantly greater in the DU group than DF group are seen in Table II ($p < 0.05$). These included the left ventricular posterior wall (LVPW) and the ventricular septum (VST) thickness. However, left ventricular function assessed by percent fractional shortening (FS%), early diastolic filling velocity (E), velocity with atrial contraction (A) and E/A ratio were not significantly different between the two groups, although a lower trend was seen in the DU group. This lower average was due to smaller

end-diastolic dimensions among the DU. Left ventricular diastolic function assessed by the rate of posterior wall thinning, relaxation times, left ventricular filling rate and the Doppler pattern of left ventricular inflow was similar in the DU and DF groups. After normalizing for body mass effects, by the use of BMI (Table II), left ventricular end diastolic dimension (LVEDd/BMI) was significantly different ($p < 0.05$). In addition, ratios of ventricular septal thickness (VST) to left ventricular end-diastolic dimension (LVEDd) demonstrated that there is a disproportionate thickening of the ventricular septum in the DU group.

DISCUSSION

Previous reports on idiopathic cardiomyopathy[11,16,17] and recent reports on hypertrophic cardiomyopathy and sudden death in athletes abusing anabolic steroids[5,15] have raised concerns about the role of anabolic steroids in cardiac function and hypertrophic changes. To date, few studies have examined the possibility of these drugs promoting anabolism in cardiac muscle and the subsequent hypertrophic-induced dysfunction. In addition, previous studies have stated that echocardiographic measurements of diastolic filling velocity allow for the delineation between physiological and pathological hypertrophy[4]. This investigation has demonstrated that while disproportionate ventricular growth is apparent in the anabolic steroids users, there is no demonstrable diastolic dysfunction.

Hypertrophy of myocardial cells in response to pressure overload has both

beneficial and harmful consequences. Initial architectural and cellular alterations are adaptive processes of form to function that assist the heart to respond to acute pressure overload, however, long-term hypertrophy tends to accelerate the myocardial deterioration through abnormal gene expression[8]. Previous reports have suggested that as adult myocardial cells increase protein synthesis in response to chronic overload, they preferentially express genes that encode the fetal isoforms of several myocardial proteins[6]. This reflects the fact that adult cardiomyocytes are terminally differentiated cells that have not only lost the ability to divide, but also the capacity for rapid protein synthesis[10]. This investigation addressed the questions surrounding ventricular dysfunction associated with long-term training coupled with steroid use by examining athletes who have been using steroids and training intensively for up to fifteen years.

What is the ability of cardiomyocytes to differentiate between the constant pressure overload of the hypertensive patient versus the daily intermittent extreme pressure overload of intense weight-training? Previous reports have recorded mean systolic/diastolic arterial pressures of 480/350 mm Hg in top bodybuilders during resistance training[14]. In contrast to previous reports[18], we demonstrated a disproportionate ventricular septal thickening (VST/LVEDd) in the DU group, which tends to parallel the pathological concentric left ventricular hypertrophy experienced in hypertension. We believe this demonstration was due to the utilization of elite bodybuilders with long histories of both anabolic steroid use and intensive training.

Lastly, anabolic steroids have been reported to increase myocardial tissue sensitivity to catecholamines, which facilitates sarcomere shortening[12]. This could explain the decreased end-diastolic dimension in the DU group and may also explain the reports of myocardial infarction associated with anabolic steroid use[7].

CONCLUSIONS

This investigation suggests through the use of elite bodybuilders matched for size, strength and length of exposure to resistance training, that anabolic steroids may potentiate concentric left ventricular hypertrophy without affecting diastolic function. This study argues against previous reports of diastolic dysfunction in resistance athletes using anabolic steroids[20]. The disproportionate left ventricular hypertrophy, and septal thickening in the anabolic steroid user is most likely a physiological adaptation to the intense hypertensive episodes experienced with resistance training, brought about by the ergogenic effects of anabolic steroids. In addition, a recent report on bodybuilding twins, with one twin on anabolic steroids for over fifteen years, indicated that anabolic steroids did not induced cardiac dysfunction[21]. Future investigations should be conducted on aerobically exercising elite bodybuilders to unmask any possible latent dysfunction not apparent at rest.

Acknowledgements: Special thanks to the University of North Texas Health Science Center for partial funding of this study. Thanks to Kristi Cotton of Osteopathic Medical Center of Texas, Josephine Rivas and the Pathology Department at UNTHSC for assistance in serum collection and to Kevin Gallagher and Bart Robbins for assistance in subject handling. Special thanks to Drs. Xiangrong Shi and Patricia Gwirtz for expert advice and review.

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Table 1. Physical and Training Characteristics of Bodybuilders

Bodybuilder Group	Height	Weight	Age	BMI	Fat	Training	Maximum Squat	Testosterone Level
	m	Kg	Y	$Kg/(m)^2$	%	Years	Kg	ng/ml
DU	1.74	103.7	27.0	34.1	8.4[b]	10.9	313.6	20.3[c]
	±	±	±	±	±	±	±	±
n=8	0.04[a]	10.3	5.2	2.8	2.5	3.4	72.2	4.7
DF	1.79	102.0	26.9	32.0	11.1[b]	10.0	263.1	5.6[c]
	±	±	±	±	±	±	±	±
n=8	0.11	4.9	7.8	4.3	2.1	5.4	30.6	2.4

[a]Mean ± SD
[b]Significant difference by Welch approximate t-test, p = 0.0332.
[c]Significant difference, p = 0.0001.

Table 2. Echocardiographic Findings in Elite Bodybuilders

Measurement[a]	Drug Users	Drug-Free	p*
Pulse (bpm)	64.5 ± 7.3	69.2 ± 6.6	0.9764
LVEDd (cm)	5.56 ± 0.43	5.74 ± 0.37	0.3981
LVEDs (cm)	3.54 ± 0.34	3.59 ± 0.34	0.8152
Shortening Fraction (FS)%	36.0 ± 6.8	37.2 ± 4.5	0.6699
LVPW (cm)	1.21 ± 0.10	1.03 ± 0.20	0.0358
Ventricular Septum (VST) (cm)	1.12 ± 0.020	0.874 ± 0.245	0.0471
E	0.744 ± 0.157	0.869 ± 0.202	0.1890
A	0.468 ± 0.069	0.521 ± 0.080	0.1729
E/A	1.63 ± 0.46	1.67 ± 0.28	0.8206
LVEDd/BMI[a]	16.37± 1.35	18.09 ± 1.60	0.0357
LVPW/BMI[a]	3.58 ± 0.44	3.29 ± 0.85	0.4059
Ventricular Septum/BMI[a]	3.32 ± 0.75	2.80 ± 0.95	0.2444
LVEDd/Kg[a]	5.39 ± 0.47	5.63 ± 0.40	0.2899
LVPW/Kg[a]	1.18 ± 0.17	1.01 ± 0.21	0.0985
VST/Kg[a]	1.09 ± 0.25	0.86 ± 0.26	0.0945

Values are mean ± SD. LVEDd, left ventricular end diastolic dimension; LVEDs, left ventricular end systolic dimension; LVPW, left ventricular posterior wall; VS, ventricular septum. E, early diastolic filling velocity; A, velocity with atrial contraction.

* p level using 2-tailed unpaired t-test (Welch's approximate t) using INSTAT2 statistical software.

[a] All values multiplied by 100.

TRANSITION II

The following brief reports were published during both phases of this cardiovascular research project. The reports support the basis of this dissertation. The first report is on sudden cardiac death in a 20 year-old bodybuilder who lived in the metropolitan area. The second report is a comparative study of left ventricular size and function in fraternal twin bodybuilders who have lifted weights competitively for over 15 years, only one twin has used anabolic steroids for the past fifteen years. This study led to the larger echocardiographic investigation of sixteen bodybuilders that demonstrated androgens may potentiate left ventricular hypertrophy without diastolic dysfunction. The third report is on a 26 year-old bodybuilder, from the metropolitan area who suffered a sudden death secondary to bilateral pulmonary embolism. This report discusses the possible hypercoagulable state imposed by suprapharmacological levels of androgens. The fourth report is on a 33 year-old anabolic steroid-using bodybuilder who suffered idiopathic dilated cardiomyopathy. The subjects cardiac function dropped to 15 % and was recommended to undergo cardiac transplantation. The patient refused transplant and has almost fully recovered. The most recent report is aortic and mitral valve thickening in a 33 year-old professional bodybuilder. The pathogenesis of valvular thickening in such young athletes is at this point unclear. We discuss the possibility of pressure-overload, secondary to the years of extreme hypertensive episodes associated with resistance training. The contribution of androgens

remains unclear, but an indirect effect of there ability to potentiate the pressor response by enhancing strength is discussed, as the possible cause. The last report is based on the view stating left ventricular wall thickening does not occur in resistance trained athletes and attempts to redefine the upper limits of left ventricular wall thickness[1,2]. Recent reports, by authors who previously published papers on the upper limits of left ventricular wall thickness, now claim that left ventricular wall thickening does not occur in resistance trained athletes, unless they are using anabolic steroids[3,4]. We dispute this view and selectively examined four elite resistance trained athletes who use anabolic steroids and retrospectively examined seven drug-free and six anabolic steroid-using resistance trained athletes, which demonstrated that left ventricular wall thickening ($\geq$13 mm) occurs in elite power athletes with or without anabolic steroid use.

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CHAPTER IV

BRIEF REPORTS: ANDROGENS AND CARDIOVASCULAR DISEASE

SUDDEN CARDIAC DEATH IN A 20 YEAR-OLD BODYBUILDER USING ANABOLIC STEROIDS

Rob D. Dickerman, Frederick Schaller, Irvine Prather, Walter J. McConathy

CARDIOLOGY
1995;86:172-173

ABSTRACT

Anabolic steroid use is widespread and has been associated with a variety of pathological conditions. The subject of this case is a 20 year old amateur bodybuilder who died of sudden cardio-pulmonary arrest. He had no previous medical complaints but had a history of anabolic steroid abuse and a hypertrophic heart (515 g) at autopsy. This case presentation will discuss the cardiovascular effects of these drugs and the possible impact of long term abuse.

CASE REPORT

Anabolic steroids were reportedly first used during World War II by German troops in an effort to increase aggressiveness and strength. By 1954 anabolic steroids were being administered to Russian male and female athletes. Since such non-therapeutic use began, many studies have documented the harmful physical and psychological side effects of anabolic steroids[1-4]. Despite many reported medically adverse effects, anabolic steroid abuse is more common than ever.

There is no question of the ability of anabolic steroids to improve certain strength related performances in athletics. Typically, anabolic steroids are used by athletes in an attempt to gain muscle size and strength that may be beneficial in competitive athletics or improve appearance[5]. However, the human body has a

carefully balanced hormonal system that when upset by exogenous hormonal influences may react with serious consequences[6]. Recently, there have been case reports of acute myocardial infarction possibly related to anabolic steroid-abuse[7-9].

This case describes a 20 year old amateur bodybuilder who self-administered several anabolic steroids, and suffered an instantaneous cardiac death with idiopathic bilateral pulmonary hemorrhage. The 222-pound, 5 foot 11 inch (body mass index, 31.0), male bodybuilder with no past or family history of cardiac disease collapsed suddenly. Witnesses at the scene reported the bladder immediately voided and Cheyne-Stokes respirations followed. The patient was transferred by paramedics to Denton County Hospital where he never recovered. Autopsy was performed at the Tarrant County Medical Examiners office and the cause of death was ruled cardio-pulmonary arrest of natural causes. The parents of the deceased have given written consent for the publication of this case. The subject had a history of anabolic steroid use and had just completed a 3 month cycle of several anabolic steroids obtained in Mexico. Primobolan depot (methenolone depot), Testosterona (veterinarian testosterone enanthate), and Laurabolan (veterinarian nandrolone laurate). These drugs are commonly used by bodybuilders due to low cost and easy access in Mexico. In addition, it is not unusual for a weight lifter to be self-administering veterinarian steroids. The dosages obtained from his diary indicate at peak cycle, he was administering approximately 700 mg/week of anabolic steroids. This is neither an abnormal nor

extraordinary amount compared to previous steroid user interviews. The problem that arises in anabolic steroid users is one of unperceived pathological effects. The possibility of anabolic steroids having a causal role in pathological myocardial hypertrophy is discussed herein.

The heart of the deceased weighed 515 grams (normal heart 250 g) at autopsy with definitive signs of concentric left ventricular hypertrophy. Case reports of idiopathic cardiomyopathy in athletes who use anabolic steroids[10] point to the possible role of steroids in cardiac pathology. It has been shown that androgen receptors exist on the cardiac atrial and ventricular cells of primates[11], anabolic steroids cause complete dissolution of the sarcomere unit in the myocardium of rats[12], and guinea pigs receiving methandrostenolone (Dianabol) demonstrate myocardial intracellular edema, mitochondrial swelling, myofibrillar changes and cell necrosis[13]. Dogs who received methandienone in doses per kilogram of body weight similar to those used by athletes, demonstrate increased heart weight compared to control animals[14]. Drug-free vigorous weight training will increase left ventricular wall thickness and mass without hindering cardiac function. However, when combined with anabolic steroids cardiac hypertrophy could become pathologic. Therefore, the potential role of androgens in hypertrophic cardiomyopathy requires further investigation.

The autopsy report indicated that this 20 year old athlete had also developed mild atherosclerosis possibly accelerated by the anabolic steroids. Elevated

circulating levels of low density lipoprotein (LDL) cholesterol and lowered high density lipoprotein (HDL) cholesterol have been reported in powerlifters and bodybuilders abusing anabolic steroids[15]. To date, the mechanisms for altered cholesterol metabolism in athletes on anabolic steroids remains controversial and is under investigation. Case reports have also linked anabolic steroid use to thrombotic complications in several athletes[16,17]. In vitro experiments have demonstrated increased platelet aggregation induced by anabolic steroids[18]. Thus, the scenario for a cardiovascular events thickens with these hematologic effects.

In summary, it seems that the role of anabolic steroids in pathology is multivariate and requires further investigation. The combined effects of vigorous weight training, anabolic steroid use, and androgen sensitivity may have predisposed this young man to pathologic myocardial hypertrophy and subsequent sudden cardiac death. This case is indicative of the potential catastrophic effects of anabolic steroids and reinforces the warning against use of these drugs by athletes.

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ECHOCARDIOGRAPHY IN FRATERNAL TWIN BODYBUILDERS WITH ONE ABUSING ANABOLIC STEROIDS

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CARDIOLOGY
1997;88:50-51

ABSTRACT

Based on our previous Case Report on "Sudden Cardiac Death in a 20 Year-Old Bodybuilder Using Anabolic Steroids" Cardiology 1995;86: 172-173, we examined a unique set of fraternal twin bodybuyilders that were part of an ongoing investigation at the University of North Texas Health Science Center at Fort Worth into the role of testosterone in cardiovascular disease and cardiac dysfunction. Anabolic steroids and other ergogenic drugs are more popular today than ever. To date there have been numerous reports of steroid related deaths, cardiomyopathies and myocardial infarction[1-3]. However, there is no conclusive data on human subjects that demonstrates direct pathological myocardial adaptations related to anabolic steroid use. Anabolic steroids are thought to promote pathological concentric growth of heart muscle and thus may induce cardiomyopathies similar to those seen in acromegliacs.

CASE REPORT

Therefore, we performed an echocardiographic study on fraternal twins that have been lifting weights competitively as bodybuilders and powerlifters for approximately 20 years. One twin (steroid user, SU) has been using anabolic steroids for 15 of those 20 years, while the other twin has remained steroid-free (SF). Both of the subjects were extremely large with profound skeletal muscle hypertrophy. Each has held state and national titles in bodybuilding and

powerlifting, in addition one twin has been displayed in many top bodybuilding magazines. Their body mass indices were (SF) 31.6 kg/m^2 and (SU) 38.1 kg/m^2, respectively. Each had a body fat below 10 % and followed nearly the same diet and training regimen year round. Resting blood pressures were well within normal ranges for each. Serum testosterone was measured by radioimmunoassay on each and were 6.2 ng/ml and 11.5 ng/ml respectively (normal 2.8 - 8.8 ng/ml). While the SU subject had only a moderately elevated testosterone level at the time of echocardiography, he has had testosterone levels recorded in our laboratory several times with values > 25.0 ng/ml.

Echocardiographic findings were similar, with only small differences in the left ventricular posterior wall (LVPW) and ventricular septum (VST) seen (Table 1). Initially a larger left ventricular end-diastolic dimension (LVEDd) was seen in the SU twin, however upon normalizing the echocardiographic measurements for body mass, the LVEDd was actually smaller. Ventricular function assessed by passive early diastolic filling (E) and active atrial contraction diastolic filling (A) demonstrated that the SU had lower (E) and (A) values and a lower E/A ratio, thus establishing a trend towards a decrease in ventricular compliance (Table I).

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TABLE 1. ECHOCARDIOGRAPHIC PARAMETERS OF ELITE BODYBUILDING TWINS

MEASUREMENT	STEROID-USER	STEROID-FREE	RANGE OR MEAN OF NORMAL
LVPW	1.5	1.1	0.6 -1.1
VST	1.6	0.96	0.6 - 1.1
E	0.54	0.80	0.66 ± 0.14
A	0.40	0.50	0.38 ± 0.06
E/A	1.35	1.60	1.75 ± 0.40
LVEDd	6.1	5.6	3.5 - 6.0
LVESd	3.9	3.3	2.1 - 4.0
BMI	38.1	31.6	
LVEDd/BMI	0.160	0.177	

LVPW, left ventricular posterior wall; VST, ventricular septal thickness; E, early passive diastolic filling velocity; A, diastolic filling velocity with atrial contraction; LVEDd/BMI, ventricular end diastolic dimension/body mass index.

CARDIOVASCULAR COMPLICATIONS AND ANABOLIC STEROIDS

Rob D. Dickerman, Walter J. McConathy, Frederick Schaller, Nannepaga Zachariah

EUROPEAN HEART JOURNAL
1996;17:1915-1916

ABSTRACT

Anabolic steroids have become a popular drug among athletes and are known to have a multitude of pathological effects when administered in suprapharmacological doses. Sudden death due to right heart failure subsequent to venous thrombus formation in an athlete abusing anabolic steroids has not been previously reported. We are now reporting on the role of testosterone in coagulation and hope this will further direct attention to its probable role in the myocardial infarctions and strokes that occur in athletes using anabolic steroids.

CASE REPORT

This report involves a 26-year old competitive bodybuilder who suffered a sudden death due to right heart failure subsequent to a bilateral pulmonary embolism from deep venous thrombus of lower extremities. The 300-pound, 72 inch, male bodybuilder of very large muscular proportions [body mass index = 40.8 kg/m] collapsed suddenly while moving furniture. The patient was transferred by paramedics to a local community hospital where he never recovered. Autopsy was performed at the Medical Examiners office and the cause of death was ruled right heart failure due to a bilateral pulmonary embolus of natural causes. At autopsy, the heart weighed 440 g with moderate left ventricular hypertrophy. Examination of the aorta revealed no significant atherosclerotic changes. The subject had a history of anabolic steroid use and had been successfully competing in

bodybuilding contests for several years.

Recently, there have been a few case reports attempting to link thrombosis and anabolic steroid abuse[1,2]. The role of anabolic steroids in platelet aggregation has support in the literature. Sex differences alone have demonstrated profound differences in platelet aggregation. Male rats are 10 times more responsive to aggregating agents than females. Castration of males markedly reduces their platelet sensitivity to aggregation, whereas ovariectomy elevated the platelet sensitivity in female rats. In vitro, androgens at physiological concentrations consistently stimulate platelet aggregation[1]. Androgens and other sex steroids are known to be absorbed at platelet membranes modifying their surface properties, inducing potential and permeability changes[2]. Androgens may potentiate platelet aggregation through increased production of arachidonic acid, a precursor to the potent platelet aggregator thromboxane A2 or, in aortic smooth muscle, a decreased production of prostacyclin[3]. Recently, testosterone was shown to increase thromboxane A2 receptor density and responsiveness in rat aortas and platelets[4]. In addition, it has also been reported that androgen receptors exist in the vascular tissue, on cardiac atrial and ventricular cells of primates. To date, the function of these receptors is unknown.

Myocardial infarctions, stroke and other thrombotic complications have been reported in athletes abusing anabolic steroids[5]. Therefore, with the majority of anabolic steroid cases being related to myocardial infarctions and stroke, it seems

that the common denominator in all these cases is thrombus formation. The role of androgens in the complex coagulation system is far from being understood, however, this case and points at the role of androgens in thrombus formation and subsequent death.

Interestingly, there is the possibility of androgen regulation of certain plasma coagulation factors. Protein S is an anticoagulant produced in hepatocytes and leydig cells of the testis. Protein S functions as a cofactor with Protein C in the inactivation of Factors Va and VIIIa. In addition, Protein S deficiency leads to a predisposition for venous thrombus[6]. A portion of Protein S is structurally homologous to the steroid binding domain of sex hormone-binding globulin (SHBG). SHBG is a steroid binding protein that binds dihydrotestosterone, testosterone, and estradiol. SHBG is positively regulated by estrogens and negatively regulated by androgens. Thus, with the administration of anabolic steroids, SHBG levels drop dramatically allowing more free (unbound), biologically active steroids in the system. If Protein S is regulated by sex steroids, it is plausible that Protein S levels also decrease with elevated androgen levels, thus allowing for an increase in the activity of the coagulation system and subsequent thrombus formation.

In summary, laboratory animal data has demonstrated a strong correlation between increased thrombosis and elevated testosterone levels. While extrapolation to the human population is always difficult, quite plausible mechanisms exist to establish a rationale for such a link. This case will hopefully

lead to further studies on the role of androgens in thrombosis and further warn physicians and athletes about the pathological effects of anabolic steroids.

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ACUTE DILATED CARDIOMYOPATHY AND ANABOLIC STEROIDS IN A 33 YEAR-OLD BODYBUILDER

Rob D. Dickerman, Frederick Schaller, Walter J. McConathy

CARDIOVASCULAR PATHOBIOLOGY
1997;2(1):53-55

ABSTRACT

Viral myocarditis induced dilated cardiomyopathy is a serious illness that occurs idiopathically in otherwise normal patients. Viral myocarditis while not gender specific, predominates in males. A strong association between androgens and altered viral immunity has been demonstrated in laboratory animals and athletes administering anabolic steroids. We are reporting the first case of viral myocarditis induced cardiomyopathy related to anabolic steroids and have identified quite plausible mechanisms for the pathogenicity, with possible explanations for some of the sudden deaths associated with anabolic steroid use.

CASE REPORT

There have been numerous reports of anabolic steroid related cardiovascular events, and cardiomyopathies.[1-7] Hypertrophic cardiomyopathy and sudden death have been the most common causes of death reported with androgen abuse.[3-5] While the mechanisms by which androgens alter gene expression are well understood, the exact role in cardiomyopathies remains unclear.

A common phenomenon among anabolic steroid users is their susceptibility to acute viral illness, i.e. colds[8-9] This phenomenon has been explained by the anabolic steroids ability to depress humoral immune function.[10] Earlier studies demonstrated that anabolic steroid users had significantly lower humoral immunity, while increasing natural killer cells and CD-4 T cells.[11] The immunoglobulin

decreases are thought to be responsible for the susceptibility to viral illness. A recent report described a 24-year old bodybuilder, on anabolic steroids, who suffered a sudden death while exercising.[4] Histological examination of the myocardium showed fibrosis with adjacent hypertrophic myocytes, monocytic and lymphocytic infiltrate. The findings were all consistent with myocarditis, although no virus was detected. In light of the anabolic steroid immune suppression data and recent bodybuilder related myocarditis case report, we report a case of viral myocarditis in a 33-year old previously healthy bodybuilder using anabolic steroids and address the immunosuppressive risks of athletes using anabolic steroids.

A 33-year old male competitive bodybuilder was admitted to the emergency room complaining of shortness of breath and weakness. Two days previously he was performing 1,000 pound leg presses for repetitions and had felt strong and healthy. The night prior to admission, the patient suffered mild orthopnea, however awakened in the morning feeling well. Later the same day, he collapsed while walking to his truck. A friend rushed him to the emergency room. The physical examination revealed an extremely muscular man, 5" 10 inches tall, 245 pounds, with a bodyfat around 9 %, blood pressure 130/90, pulse 153 and irregular, point of maximal impulse enlarged and laterally displaced, irregular S_1 and S_2, S_3 was present, no murmurs, rubs or clicks, and the electrocardiogram revealed atrial fibrillation with left anterior hemiblock. Echocardiography demonstrated a grossly

dilated cardiomyopathy with global left ventricular hypokinesis. Subsequent cardiac catheterization was performed and revealed 15 % ejection fraction and normal coronary arteries. Further evaluation included viral titers, which were coxsackievirus 1:16, and echovirus 1:32. The patient revealed a 10 year history of anabolic steroid use, and competitive bodybuilding. The patient was not on any prescribed medications, but was self-administering four different anabolic steroids; deca-durabolin, testosterone cypionate, oxymetholone, and stanozolol. He did not deny previous bouts of colds and/or influenza, however, he could recall no colds or flu-like symptoms in the past year. The patient was admitted to intensive care pending cardiac transplantation. After 4 days in the hospital, his cardiac function had not improved, and was stabilized at 15 % ejection fraction. The patient rejected all notions of transplantation. After two weeks in the hospital his ejection fraction increased to 30 % and he was subsequently released. Eight weeks after original echocardiogram, his ejection fraction had increased to approximately 40 %. Septal wall motion remained reduced, but appeared to be improving. Left-ventricular end diastolic dimension remained markedly dilated at 73 mm (normal 35-57 mm). Two months after release from the hospital, the patients coxsackievirus convalescent titers were 1:8, thus as with most cases of viral myocarditis in North America, viral etiology remained unidentified.[12] The possibility of anabolic steroids having a causal role in the susceptibility and pathogenicity of viral induced cardiomyopathy will be discussed herein.

Myocarditis is predominately a male associated phenomenon.[13] Differences in male and female immune responses are well known. Males generally have an enhanced cellular immune response, while females usually mount better humoral immune responses as compared with males.[14-16] The different immune responses may, in part, explain the predominance of autoimmune diseases in females. Anabolic steroids significantly reduce IgA, IgM, and IgG, while significantly enhancing natural killer (NK) cells and CD-4 T-cells in athletes. The decreased immunoglobulins increase the susceptibility for viral illness, while increasing NK and CD-4 T-cells may lead to heightened tissue damage; this effect may promote the pathogenicity of viral myocarditis.

Previous studies have demonstrated that female resistance to coxsackievirus is complex but depends primarily on the protective effects of estrogens, while susceptibility in males and pregnant females results from elevated androgen levels.[17,18] Androgens enhance viral localization and replication in cardiomyocytes.[19] Earlier studies on coxsackievirus infection of male mice demonstrated that castration leads to reduced mortality, decreased myofiber necrosis, and depressed T-cytolytic activity, while testosterone administration led to increased mortality, myofiber necrosis, and T-cytolytic activity.[16] Most recently, it has been demonstrated in rats infected with coxsackievirus group B that the gender differences in CD-4 T cell response is the determining factor of virulence and pathogenicity.[20] Male rats infected with coxsackievirus group B respond to

cardiomyocytes with CD-4 T cells producing gamma-interferon and interleukin-2, while females infected respond with CD-4 T cells producing interleukin-4 and interleukin-5. Subsequent treatment of females with testosterone and males with estrogen alters the CD-4 T cell responses accordingly.

In summary, the role of anabolic steroids in viral susceptibility and pathogenicity is becoming clearer, and the increasing trend of anabolic steroid use among athletes for longer periods of time may lead to increasing cases of viral myocarditis. We believe this report may help explain some of the cases of sudden death in athletes abusing anabolic steroids and again may enlighten physicians of their potential dangers.

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AORTIC VALVE THICKENING ASSOCIATED WITH POWER TRAINING: IS IT PRESSURE-OVERLOAD?

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In Press
THE AMERICAN JOURNAL OF CARDIOLOGY

Previous reports have recorded mean systolic/diastolic arterial pressures as high as 480/350 mmHg during maximal weight-lifting, which subsequently contributes to structural alterations within the myocardium in the form of concentric left ventricular hypertrophy (1,2).

A 33 year-old male professional bodybuilder, 5'9, 280 lb, bodyfat 7 %, (subject A) and a 36 year-old male bodybuilder, 5'10, 290 lb, bodyfat 9% (subject B) voluntarily participated in an echocardiographic study at UNTHSC. The patients had negative family, medical and surgical histories. The patients adamantly denied recreational or intravenous drug use in his past. Physical examination revealed extremely muscular normotensive males, with regular heart rate and rhythm without murmur, rubs or gallops. Echocardiographic parameters were normal except for significant calcific thickening along the margins of the trileaflet aortic valves, which were without fused commissures. No reductions in excursion were found and the sinuses of valsalva were free of calcification. Significant concentric left ventricular hypertrophy was also evident in both subjects, with left ventricular posterior wall and ventricular septal thicknesses of 14 mm/14mm in subject A and 15 mm/16mm in subject B. Serum chemistry profiles were normal in both subjects.

There are numerous factors that have been correlated with thickened aortic valves, including systemic hypertension, age, hypercholesterolemia, diabetes mellitus, and chronic hypercalcemia (3). These valvular alterations are thought to occur concurrently with coronary artery disease and in elderly patients with long-standing hypertension (3). One must consider the extreme intermittent hypertensive episodes associated with resistance training as a possible cause of valvular thickening (1). A recent laboratory investigation on the effects of

systemic hypertension on valvular thickening found a direct relationship between afterload and aortic valve thickening (4). These authors stated that "previous clinical studies (3) indirectly support the view that a heavier pressure loading is an important predisposing factor in valvular thickening". In addition, despite the supposed balanced system of pressures i.e., Valsalva, muscle compression, etc, in the human to protect against the intermittent hypertension associated with weight-lifting; there has been a report of four weight-lifters suffering ascending aortic dissection during weight lifting (5). The possibility of the extreme afterload experienced with weightlifting causing valvular thickening is, in part, supported by our recent report on hiatal hernia occurring in a young bodybuilder secondary to the extreme intra-abdominal pressures generated with weightlifting (6). Hiatal hernias, like valvular thickening, were previously thought to be an age-related disease (7). It seems anabolic steroids may predispose athletes to pressure-overload pathological sequelae, through their inherent ability to increase muscle mass and strength, thus allowing generation of higher pressures (7).

In summary, this is the first report of aortic valve thickening occurring in two young healthy professional bodybuilders. We have raised the possibility that the extreme intermittent hypertensive episodes experienced with weightlifting may over time induce pathological anatomical valvular alterations, that may lead to compromised cardiac function. The possibility that anabolic steroids may accelerate valvular thickening is not without merit, however the exact mechanism remains to be elucidated. Further investigations are needed to elucidate the pathogical sequelae of competitive weightlifting, anabolic steroids and the extreme intermittent hypertensive episodes.

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LEFT VENTRICULAR WALL THICKENING DOES OCCUR IN ELITE POWER TRAINED ATHLETES WITH OR WITHOUT ANABOLIC STEROID USE

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In Press
CARDIOLOGY

ABSTRACT

Background Reports on the occurrence of left ventricular wall thickening in resistance-trained athletes have rejected the possibility for this physiological adaptation to occur without concomitant anabolic steroid abuse. Others have concluded short bursts of arterial hypertension that occur with maximal weight-lifting are not sufficient to induce left ventricular wall thickening and left ventricular wall thicknesses ≥ 13 mm should not be found in pure resistance-trained athletes.

Methods We examined four elite resistance-trained athletes by two dimensional echocardiography. In addition, we retrospectively examined the individual left ventricular dimensions of 13 bodybuilders from our previous echocardiographic studies.

Results All four elite resistance-trained athletes had left ventricular wall thicknesses beyond 13 mm. One of the elite bodybuilders has the largest left ventricular wall thickness (16 mm) ever reported in a power athlete. Retrospectively 43 % of the drug-free bodybuilders and 100 % of the steroid-users had left ventricular wall thicknesses beyond the normal range of 11 mm. In addition, one drug-free subject and three steroid-users were beyond the critical mark of 13 mm. No subjects demonstrated diastolic dysfunction.

Conclusions In contrast to previous reports, we have demonstrated that left

ventricular wall thicknesses ≥ 13 mm can be found routinely in elite resistance trained athletes. The use of anabolic steroids concomitant with intensive resistance exercise does appear to augment left ventricular size without dysfunction. Anabolic steroids may accelerate left ventricular wall thickening indirectly by increasing strength, thus augmenting the pressor response.

Keywords: left ventricular wall thickness, hypertrophic cardiomyopathy, anabolic steroids, androgens, resistance exercise, pressor response.

The athlete's heart has been a topic of interest among cardiologists for decades[1]. Several years ago the upper limits of physiologic left ventricular hypertrophy (LVH) were redefined during an investigation of 947 Olympic aerobic and anaerobically trained athletes[2]. The authors concluded that a left ventricular wall thickness ≥ 13 mm was confined to elite rowers, canoers and cyclists. The authors went onto state that the presence of left ventricular wall thicknesses ≥ 13 mm in elite resistance trained athletes would suggest alternative explanations, such as the diagnosis of pathologic hypertrophy or hypertrophic cardiomyopathy. A recent review on the athlete's heart has suggested the differential in pathologic versus physiologic LVH is found in the diastolic function[3]. Contrary to previous

reports[4] on concentric LVH in bodybuilders using anabolic steroids, our recent study concluded anabolic steroids may potentiate concentric left ventricular hypertrophy without diastolic dysfunction[5]. In addition, while the anabolic steroid-users had significantly larger left ventricular posterior wall and ventricular septal thicknesses, the drug-free group also demonstrated left ventricular wall thicknesses beyond the normal range. Based on the recent publications stating that LVH does not occur in resistance trained athletes[2,6,7] we decided to examine elite power athletes via two-dimensional echocardiography. In addition, we retrospectively examined the individual left ventricular dimensions in each subject from our previous echocardiographic investigation[5].

The four elite subjects that were examined included a 5'10, 285 lb., 36 year-old competitive steroid-using bodybuilder (SU-B1), that has lifted competitively for 18 years. The second subject was a 34 year-old, 6'1, 305 lb. bodybuilder who has used anabolic steroids and competed for over 10 years (SU-B2). The third subject was a 33 year-old, 280 lb. professional bodybuilder who has competed for 12 years (SU-B3). The last subject was a 31 year-old powerlifter, who is the current world record holder in powerlifting and squats > 1030 lbs. at a bodyweight of 240 lbs (SU-P). We retrospectively examined the individual left ventricular wall dimensions of thirteen elite bodybuilders, seven drug-free (DF) and six steroid-using (SU) subjects

from our previous investigation[5].

Echocardiography: The subjects underwent transthoracic echocardiography, performed in a resting state, on a SONOS 1000 echo-doppler sonography unit (HP) with 3.5 H7 phased array transducer. The echocardiographer was blinded as to the drug status of the subjects. Doppler studies were performed in the apical four and two chamber views, recording inflow across the mitral valve. Echocardiographic measurements included left ventricular septal and posterior wall thickness, left ventricular end-diastolic and end-systolic internal diameter, right ventricular end diastolic diameter, and left atrial dimension. Long and short axis measurements were made from the apical views and parasternal short axis projection. Chamber dimension and wall thickness were measured at end-systole and end-diastole in the parasternal short axis at a level one cm below the mitral annulus during normal resting respirations. Left ventricular mass was calculated from software package Rev 5 from Hewlett-Packard. The endocardium was traced during the systolic and diastolic phase of the cardiac cycle for determination of left ventricular ejection fraction using a modified Simpson's rule. Doppler inflow measurements included E and A wave peak velocities, E wave slope, and diastolic filling time. Diastolic dysfunction was defined as E/A ratio less than 1 or with high velocity, steep slope E wave. Wall thickness is considered normal when < 11 mm.

Four elite resistance-trained subjects had significant left ventricular wall thickening with normal wall motion and without diastolic dysfunction (Table 1). The steroid-using bodybuilder(SU-B1) had the largest left ventricular wall thicknesses (16 mm) ever reported in a resistance-trained athlete. The two other steroid-using bodybuilders (SU-B2, SU-B3) both had left ventricular wall thicknesses of 14 mm. The steroid-using powerlifter (SU-P) had left ventricular wall thicknesses of 14 mm, thus is also beyond the critical marker of 13 mm. In addition, the powerlifter demonstrated the greatest degree of concentric hypertrophy when normalizing for bodymass. Retrospectively 43 % (3 of 7) of our drug-free subjects and 100 % (n = 6) of steroid-using subjects had left ventricular dimensions beyond normal ranges < 11 mm. In addition, when using the value of 13 mm as the upper limit for physiologic left ventricular wall thicknesses, one drug-free subject and three steroid-users were found to be at or beyond this thickness (Table 2). As demonstrated by the E/A ratios, no subjects were found to have diastolic dysfunction.

Therefore, we dispute the most recent publications[2,6,7] that state left ventricular wall thickening does not occur in resistance trained athletes and that the short bursts of arterial hypertension that occur with weight lifting cannot stimulate left ventricular wall thickening. We have demonstrated by examining elite power

trained athletes, both on and off anabolic steroids, that left ventricular wall thickening does occur and if examining elite bodybuilders and powerlifters, one might find left ventricular wall thicknesses well beyond normal ranges.

There are several points that need to be discussed. Is left ventricular wall thickness dependent on strength? As seen in this study, our elite powerlifter demonstrated the greatest degree of left ventricular hypertrophy. The hypertensive response experienced with weight-lifting is the summed effects of a potent pressor response (includes the Valsalva maneuver and muscular compression of the blood vessels), and their magnitude, which is greatly dependent on the intensity of the exercise[8]. The Valsalva maneuver increases intra-abdominal and intrathoracic pressure leading to increases in arterial pressure[9]. The increasing intra-abdominal and intrathoracic pressures provide a mechanical stabilizing mechanism in the lumbar spine[10]. In fact, as lumbar spinal pressure increases, weight-lifters compensate by further increasing intra-abdominal pressure[11]. Therefore, the powerlifter, who is currently the strongest man in the world for the squat lift, is loading his lumbar spine significantly more than other lifters, and should be generating the highest pressures, thus developing a greater degree of compensatory left ventricular wall thickening. Secondly, the athletes examined in

this study and retrospectively are not only larger than previous studies, but the drug-free subjects were larger than all previous reports on steroid-using subjects[12-15]. In addition, all subjects had been training for at least five years and the number of years of training was not significantly different between the drug-free subjects and steroid-users, thus eliminating differences in the time of cardiac exposure to resistance-training. Lastly, it has been recently mentioned that the acute hypertensive episodes that occur with weight-lifting are not sufficient to induce left ventricular wall thickening[6,7]; this statement may reflect the caliber of bodybuilding subjects examined in previous studies. We suggest cardiomyocytes would respond to aortic pressures of 480/350 or even higher generated intermittently, five-six days per week for 5-15 years. A recent review on the athletes heart stated that there are some single cases of weight-lifters or bodybuilders demonstrating pronounced wall thickness, in such cases, the effect of anabolic steroids must be considered[3]. We question this statement, as demonstrated on our elite drug-free subjects, left ventricular wall thicknesses $\geq$ 13 mm can be found without anabolic steroids.

There is no longer a question regarding the ability of anabolic steroids to enhance strength and skeletal muscle hypertrophy[16]. Due to the numerous cases of sudden death and cardiomyopathy in athletes using anabolic steroids, physicians have been forced to question the direct effects of anabolic steroids on the

myocardium[17,18]. However, animal research has demonstrated that left ventricular wall thickening only occurs in animals when anabolic steroids are coupled with exercise[19]. Thus, it would follow that the larger left ventricular wall thicknesses we have seen in the anabolic steroid-users are secondary to the athletes increased strength and thus the ability to generate a greater pressor response leading to physiologic compensatory left ventricular hypertrophy.

In conclusion, left ventricular wall thicknesses ≥ 13 mm do occur in athletes with or without anabolic steroid use. Anabolic steroids may increase left ventricular wall thicknesses indirectly through there ability to increase strength, thus allowing a greater overall pressor response with weight-lifting.

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Table 1. Left Ventricular Dimensions of Four Elite Resistance Trained Athletes.

MEASUREMENT	SU-B1	SU-B2	SU-B3	SU-P	NORMAL RANGE
LVPW (mm)	15	14	14	14	6.0 - 11 mm
VS (mm)	16	14	14	14	6.0 - 11 mm
E	0.7	0.8	0.9	0.8	0.66 $\pm$ 0.14
A	0.6	0.7	0.6	0.5	0.38 $\pm$ 0.06
E/A	1.12	1.14	1.5	1.2	1.75 $\pm$ 0.40
LVEDd (mm)	62	57	58	56	35 - 60 mm
LVEDs (mm)	48	43	46	39	21 - 40 mm
BODY MASS (BMI-kg/m^2)	40.1	40.3	41.4	35.6	
LVPW/BMI	0.37	0.35	0.39	0.34	

SU-B, steroid-using bodybuilder; SU-P, steroid-using powerlifter; DF, drug-free bodybuilder; LVPW, left ventricular posterior wall; VS, ventricular septum; LVEDd, left ventricular end diastolic dimension; LVEDs, left ventricular end systolic dimension. E, early diastolic filling velocity; A, velocity with atrial contraction.

Table 2. Retrospective Analysis of Left Ventricular Wall Thicknesses in Elite Drug-Free and Steroid-Using Bodybuilders.

SUBJECT (years)	LVPW (mm)	VS (mm)	E	A	E/A	BMI (kg/m^2)
DF-1 (31)	12	12	0.8	0.43	1.9	31.6
DF-2 (18)	13	9	0.8	0.58	1.4	30.2
DF-3 (18)	12	12	1.3	0.6	2.2	28.3
SU-1 (22)	11	14	0.65	0.5	1.3	33.8
SU-2 (30)	12	9	0.9	0.75	1.2	34.3
SU-3 (24)	12	11	0.8	0.43	1.9	35.6
SU-4 (24)	12	9	0.75	0.46	1.6	31.8
SU-5 (31)	13	13	0.86	0.6	1.4	29.8
SU-6 (35)	12	13	1.0	0.4	2.5	32.4

DF, drug-free bodybuilder; SU, steroid-using bodybuilder; LVPW, left ventricular posterior wall; VS, ventricular septum; E, early diastolic filling velocity; A, velocity with atrial contraction.

CONCLUSIONS

It was first hypothesized that androgens would alter lipoprotein profiles leading to an increased risk for atherosclerosis. Contrary to previous findings and in support of our null hypothesis, apolipoprotein A-I, B, total cholesterol, HDL-C and LDL-C were all lower in the anabolic steroid-users leading to an overall net effect of a questionable increased risk for cardiovascular disease based on lipids. This was demonstrated by utilizing elite bodybuilders on anabolic steroids compared to elite drug-free bodybuilders following the same diet and training regimen. Despite the higher ratio of total cholesterol/HDL-C in the androgen-users, one must question the actual risk of atherosclerosis in subjects with serum total cholesterol levels < 120 mg/dl ie. 5th percentile. One must also consider the role of low saturated fat diet and the intensive resistance-training regimen in lowering serum cholesterol.

Questions that remain: Why are there so many reports of myocardial infarction associated with anabolic steroids? Upon reviewing all the case reports one will find that the majority of the cases on atherosclerosis are based on powerlifters, who do not follow the low saturated fat diet. In fact, it is probably the

case that androgens combined with a high saturated fat intake increases risk by increasing serum total cholesterol, LDL-C and lowering HDL-C.

Why is the total cholesterol so low in these elite bodybuilders? I propose that the bodybuilders on anabolic steroids are putting themselves into a constant state of growth and repair (anabolism), thus despite ingesting 300 % of the recommended daily allowance of cholesterol, there body is in such demand for myocyte repair and growth that the cholesterol is utilized, as seen in males during puberty (1). Would anabolic steroid therapy have the same effect on lipoproteins in normal males? I do not propose that androgens would have the same effect in normal males. This is due to the obvious anabolic state that our androgen-users were in via anabolic steroids combined with intensive weight-training, thus reutilizing cholesterol for repair. Secondly, the normal male does not follow the strict low saturated fat dietary regimen present in our subjects.

Chapter III. addressed the hypothesis that androgens may potentiate left ventricular hypertrophy without affecting diastolic function. The second investigation clearly demonstrated that androgens increase left ventricular posterior wall and ventricular septal thickness without affecting cardiac function. The physiological mechanism responsible for the increases in left ventricular wall thickness in the anabolic steroid-using subjects remains to be elucidated.

Several points are worth discussing: Could the left ventricular wall thickening be an indirect effect of the androgens via there ability to increase overall strength in the athlete, thus allowing a more potent pressor response during weight-lifting? This hypothesis was developed secondary to the findings in our strongest athlete, who is the current world-record holder in the squat, with a squat of 1032 lbs. at a bodyweight of 242 lbs. This powerlifter has a bodymass index of 35.6, which is significantly smaller than most of the bodybuilders examined, yet he had the largest left ventricular dimensions when normalizing for bodymass. Thus, it is proposed that androgens potentiate left ventricular hypertrophy secondary to there ability to increase strength thus allowing a more potent pressor response. To explain this physiologically, arterial pressure increases with maximal weight-lifting secondary to the summed effects of the pressor response which involves the Valsalva maneuver and muscular compression of the blood vessels and their magnitude, which is greatly dependent on the intensity of the exercise. The Valsalva maneuver increases intra-abdominal and intrathoracic pressure leading to increases in arterial pressure.

The increasing intra-abdominal and intrathoracic pressures provide a mechanical stabilizing mechanism in the lumbar spine. In fact, as lumbar spinal pressure increases, weight-lifters compensate by further increasing intra-abdominal

pressure. Therefore, the powerlifter, who is currently the strongest man in the world for the squat lift, is loading his lumbar spine significantly more than other lifters, and should be generating the highest pressures, thus explaining his left ventricular dimensions being the largest.

It has been proposed that androgens may have a direct effect on the myocardium, acting through the androgen receptor, increasing cardiac muscle protein synthesis, as seen in skeletal muscle. It is also quite possible that both androgens and resistance-training (elevated arterial pressures) are required to induce the left ventricular hypertrophy. Regardless of the mechanism and in contrast to other studies, I did demonstrate, by examining the largest subjects published to date, that anabolic steroids do potentiate left ventricular thickening without affecting cardiac function.

Lastly, the brief reports in Chapter IV provide further support of the two previous investigations. First, in regard to androgens not increasing cardiovascular risks in bodybuilders following low saturated fat diets, there were no findings of myocardial infarction or premature atherosclerotic lesions at autopsy in any of our reports. Secondly, our report on bodybuilding twins found that the androgen-using twin had significantly larger left ventricular wall thicknesses when normalizing for bodymass. This twin study lead to our larger investigation which further confirmed

our original findings. Lastly, our reports of cardiomyopathy in bodybuilders support the effects directly/indirectly of androgens on left ventricular wall thickening. The mechanism for sudden death remains to be elucidated but it has been previously proposed that enlarged left ventricles, when stressed, are more susceptible to fatal arrhythmia (2).

The last investigation of Chapter IV. on pathological left ventricular wall thickening is an area of particular interest. In this study, we found the largest left ventricular wall thicknesses ever reported in the literature. We again found no diastolic dysfunction. This study could lead to a redefining of the upper limit to left ventricular wall thickening in resistance trained athletes. In closing, despite the findings of no diastolic dysfunction in any of our studies, our reports of sudden death and findings of left ventricular wall thicknesses consistent with pathologic left ventricular hypertrophy or hypertrophic cardiomyopathy lead to this last question: Is it possible that the years of intensive resistance-training regimens, which induce intermittent supertensive (>480/350 mmHg) episodes, combined with anabolic steroids can induce such a degree of physiological left ventricular hypertrophy that it eventually becomes pathologic?

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SUGGESTIONS FOR FUTURE RESEARCH

Listed below are several potential investigations designed to further support the research presented in this dissertation and to build upon the concepts summarized above. The investigations described below are intended to: a) support the concept of androgens altering both apolipoprotein A-I and apolipoprotein B leading to a questionable increase in cardiovascular risk. b) support the concept that androgens induce left ventricular wall thickening without affecting cardiac function in resistance trained athletes.

I. To further test the hypothesis that androgens alter both apolipoprotein A-I and apolipoprotein B levels in bodybuilders following a low saturated fat diet. The following experiment will assist in elucidating the role of androgens versus low saturated fat diet in circulating apolipoprotein and cholesterol levels. Twelve elite competitive bodybuilders (six drug-free and six androgen-users) will be recruited from previous investigations. A three day dietary recall will be utilized on each subject during two phases. Phase I is a 8 week period of low saturated fat diet intake, ie., bodybuilding contest diet preparation. Phase II is a 8 week period of

moderately low saturated fat diet, ie., bodybuilding off-season. Serum will be collected on subjects during each phase of the study for analysis of apolipoprotein A-I, B, total and fractionated cholesterol, testosterone, dihydrotestosterone and estradiol. Dietary analysis via Nutricalc program will be performed on each 3-day dietary recall for total protein, saturated/unsaturated fat and cholesterol intake. Analysis can then be performed to determine the role of low saturated fat diet versus testosterone, dihydrotestosterone and estradiol on apolipoproteins and lipoproteins.

II. A second experiment can be designed to test the hypothesis developed during the second phase of this research. The hypothesis is that anabolic steroids indirectly effect left ventricular wall thickening by increasing skeletal muscle strength, thus allowing a more potent pressor response. Thus, the increases of left ventricular wall thickness seen in the anabolic steroid-users is merely a physiological adaptation to the extreme pressures generated during maximal lifting. This hypothesis is supported, in part, by our finding the greatest degree of left ventricular wall thickness/body mass in our strongest subject, who was by no means our largest subject. The experimental protocol would entail utilization of resistance trained athletes, anabolic steroid-users and drug-free subjects, as seen in Chapters II & III. Each subject would have a radial arterial line placed for measuring arterial pressure during maximal lifting on a 45 degree leg press. The experiment could use

subjects of various strengths (weight-lifted/bodymass) to assess the relationship of strength - arterial pressure generated - left ventricular wall thickness/bodymass. The outcome of this study would contribute significantly to the understanding of a pressor response threshold or plateau in humans and the contribution of anabolic steroids directly or indirectly on left ventricular thickening.

III. To investigate the possibility of pathologic left ventricular hypertrophy or hypertrophic cardiomyopathy occurring in these resistance-trained athletes with left ventricular wall thicknesses $\geq$ 13mm. A repeat echocardiographic investigation on all athletes with left ventricular wall thicknesses $\geq$ 13mm should be performed on these athletes while aerobically exercising. Each athlete will perform a cardiac stress test exercising on a stationary reclined bicycle, capable of holding athletes up to 300 lbs. The exercising cardiac stress test will allow for elucidation of any latent left ventricular dysfunction not apparent during rest. This investigation would assist in the understanding of left ventricular function in these athletes with enormous wall thicknesses and would support or reject the notion of fatal arrhythmia in these athletes.