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CARDIOVASCULAR TOXICITY OF ANABOLIC STEROIDS

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INTRODUCTION

There is widespread concern within the medical/drug regulatory community over an increase in the self-administration of anabolic, or more properly, anabolic-androgenic steroids (AAS; 1) for non-medicinal purposes (2, 3). Yet, the majority of those who self-administer AAS obviously feel that the benefit-risk ratio for these agents is acceptable. The opinion of the group can best be summarized by a quote from *The Underground Steroid Handbook II* (4),

> Steroids are prescription drugs. They have some dangerous side effects. These side effects are not unknown. Not all steroids have the same side effects, and of course, some people may be more sensitive than others. But death? That risk has been virtually non-existent in healthy athletes. Bottom line? Some steroids are more harmful than others; educated athletes know which ones are the harmful ones.

This publication is perhaps the most widely used guide to self-administration of AAS (5) and should be recommended to all who deal with steroid abuse, as an aid to understanding the mind-set of their patients.

There is, in fact, a growing opinion among experts in the field that serious toxic effects on the physiology of healthy athletes are rare (6). With our present state of knowledge, consensus is forming that

> these drugs represent more of an ethical dilemma than a major public health problem (7).

Nevertheless, virtually all authorities recognize that controlled studies with the very high doses and patterns used by the self-administering population are

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not available (see 5). That issue, and the potential for delayed, but as yet undescribed, toxicities create unease in the biomedical community. This is especially true for the growing cadre of women and adolescents who abuse AAS (3), but in whom few health studies have been conducted.

Media attention to the issue of AAS abuse has spurred discussion of the toxicity of AAS. No fewer than 23 review/commentary articles (2, 3, 5, 6, 8–26) related to AAS abuse and/or toxicology appeared during 1990–1992. Major reviews on aspects of AAS toxicity, including general toxicities (13, 15, 23, 27), psychiatric complications (8), hepatic dysfunction/carcinoma (28), serum lipid abnormalities (14), thrombosis (12), musculoskeletal pathology (20), illicit use (2, 3, 5, 17, 19, 26, 29), and adverse effects in specific subsets of abusers (30, 31) have been published within the past 5 years. The intensity of this scrutiny makes redundant any attempt to review the subject comprehensively. Common toxicities, their incidence, and severity are well described and easily recognized. In contrast, adverse circulatory responses to AAS ingestion are poorly detailed.

Adverse cardiovascular responses were among the earliest toxicities to be recognized following implementation of therapeutic AAS use. Palpitation, tachycardia, precordial pain, weakness, and edema were documented in 1939 in a eunuchoid patient treated with testosterone propionate (32, 33). The sole adverse response to AAS reported prior to that time was oligospermia (34). Testosterone itself was only isolated (35) and synthesized (36, 37) four years earlier. It was recognized later that testosterone and related steroids could cause hypertension and altered serum lipid profiles in a manner presumed to accelerate coronary heart disease (CHD) (38, 39).

However, epidemiological evidence of human cardiovascular disease in individuals exposed to AAS remains equivocal (30). In many ways, the data on circulatory dysfunction and AAS use exemplify the controversy that exists over steroid self- administration and public health. On one hand, there is both preclinical and human evidence that AAS can adversely affect circulatory structure and function: on the other, the available data are often contradictory and frequently incomplete or anecdotal. Because of these features, the previously cited quote from the *Underground Steroid Handbook II* (4) may provide a unique context within which to examine the issues of circulatory toxicity. The direct relevance of the chosen quotation to high-dose AAS abuse should assist in an examination of why it is so difficult to conclusively establish the potential for human toxicity. Specifically, three questions can be asked: Can we predict, from animal or human studies, the incidence of specific circulatory adverse effects? Do we know which AAS are more harmful than others? Is there a risk of increased cardiovascular morbidity and mortality in athletes using AAS? It is hoped that this treatment will serve as a useful approach to the study of AAS toxicity.

TOXICOLOGICAL ISSUES AND AAS

A multitude of AAS have been described, primarily in an attempt to dissociate anabolic from androgenic activity (40). Nevertheless, it has proven impossible to separate these activities completely (41, 42). Both actions result from binding to and stimulation of a common intracellular receptor, the androgen receptor, the structure of which has been elucidated (31, see 43). The androgen receptor appears to be identical in all tissues studied (31, 44-49). The differences observed between anabolic and androgenic actions of natural androgen receptor agonists have been reasoned to reside in differences between receptor number in the genitalia and extragenital tissues (42), in the relative activity of the enzyme 5α-reductase (50, 51), which converts testosterone to 5α-dihydrotestosterone (5α-DHT), and possibly in interactions with catabolic effects of glucocorticoids (52–54). The conclusion would be reached that, in normal human males, the classic androgen receptor is believed to be saturated, or near saturation, in most tissues by circulating levels of endogenous plasma androgens (31). Because of these facts, it has been hypothesized that nonandrogen receptors mediate some toxic effects of AAS (52). The receptors in question include a putative cardiac DHT receptor (55), as well as the progesterone, estrogen and glucocorticoid receptors.

Dose-response

A dose-response relationship for AAS and increased lean body mass in man has been demonstrated (56). Comparable data on the toxic effects of AAS have not been fully developed. Other reviewers have suggested that it is not possible to relate either dose or duration of AAS therapy to the most serious adverse responses (27, 28; Table 1, 2).

Interactions with Receptors

Chemical modifications of the testosterone molecule alter both the binding affinity and efficacy at the androgen receptor. This is exemplified by DHT, a ligand that possesses substantially greater affinity for the androgen receptor than does testosterone (42). Binding characteristics of AAS for neither the androgen nor the putative DHT receptor have been systematically examined.

Testosterone and a limited number of other AAS have been shown to bind to and activate endometrial progesterone receptors in experimental animals and in women (52, 57). Dimethyltestosterone and norethandrolone exerted biological effects through the progesterone receptor with potencies equivalent to that of progesterone (57). The administration of testosterone was associated with nuclear translocation of cytosolic progesterone receptors, in at least one study that found adverse circulatory effects (58).

The AAS can bind also to glucocorticoid receptors, usually with very low, but occasionally with substantial affinity (see 53). This binding has been reported to produce anabolic actions through antagonism of glucocorticoid-induced catabolism (54). Raaka et al (59) noted that 17α-methyltestosterone competed with glucocorticoids for an intracellular receptor and prevented activation of the receptor protein. However, Hickson et al (53) have examined the anabolic effects of exercise and AAS and suggest that the putative role as glucocorticoid antagonists requires additional examination. Interpretation of experimental results is complicated by the dynamics of hormone receptors during exercise. Training regimens that increase muscle mass are associated with increases in the concentrations of both androgen and glucocorticoid receptors in skeletal muscle, whereas similar effects do not occur following endurance training (53, 60). However, swimming-induced cardiac hypertrophy is associated neither with increases in cardiac androgen receptor number (61) nor with increased formation of activated cardiac glucocorticoid receptor complexes (53) in the rat. The relationships between toxic myocardial responses and androgen-glucocorticoid receptor interactions require careful and additional evaluation.

Metabolism

Chemical modifications of AAS alter interactions with metabolizing enzymes, such as 5α-reductase (42, 62) and 17β-hydroxysteroid dehydrogenase (62), and have the potential to alter the responses to AAS administration. Testosterone, and certain other AAS, can be aromatized to yield estradiol (63). This is emphasized by the demonstration of serum estradiol levels comparable to those found in adult, fertile women following a characteristic "stacking" regimen of high-dose AAS in male power athletes (64). The degree of aromatization, and the tissues in which this occurs, can be expected to significantly modify the responses to stimulation of the androgen receptor, in at least some circumstances. Estrogens exerted a permissive effect on the anabolic action of androgen receptor stimulation in rat skeletal muscle (54). In contrast, estradiol inhibited AAS-induced effects on rabbit endometrial tissues (52). The extent to which modification of androgen receptor-mediated events is altered by the presence of estradiol or other estrogens in cardiovascular tissues is unknown.

Multiple factors can contribute to AAS-induced toxic responses. However, comprehensive studies of metabolic disposition and receptor binding characteristics of commonly abused steroids remain unavailable. In particular, few data are available on potential receptor interactions that may occur following self-administration of multiple agents in high doses.

RELATIONSHIP BETWEEN AAS AND CIRCULATORY PATHOPHYSIOLOGY

Preclinical data

STEROID-BINDING RECEPTORS The circulatory system and associated regulatory tissues possess androgen receptors that are specific, saturable, and of high affinity. Cardiac ventricular (55, 61, 62, 65–67) and atrial (66, 67) muscle, aorta (67, 68), pulmonary (55) and peripheral arteries (67), adrenal gland (69, 70), and central cardiovascular regulatory regions (71) contain receptors. Autoradiographic studies indicate that the binding sites are found on cardiac myocytes, but not interstitial tissue (66, 67). Binding does not differ in the aorta when endothelial/intimal tissue is removed, suggesting predominant binding to vascular muscle (68), a fact corroborated by autoradiographic studies in baboon arteries (67). A complete absence of androgen-binding receptors was reported in the canine vena cava (68). Specific androgen-binding sites in circulatory tissues have been found in several species (55, 61, 65–68, 71). The levels of the receptor sites vary, depending upon tissue, species, and experimental handling but are low, when compared to noncirculatory tissues, such as prostate (42). Heart from uncastrated adult male rats, as an example, contains lower numbers of androgen receptors when compared to already low values in skeletal muscle from similar rats or to heart tissue from normal adult female or castrated male rats (65). Affinities of the receptor sites are more uniform, with Kd values for the selective androgen receptor agonist [^{3}H]R1881 ranging from 1.3 to 1.8 x 10^{-10}M (61) to 1.56 x 10^{-9}M (66).

Testosterone is presumed to be the active endogenous ligand at the heart muscle androgen receptor (72), as demonstrated by direct measurements of testosterone levels in heart tissue that exceed those of 5α-DHT, and/or on high cardiac levels of 5α-androstanediols, metabolites of 5α-DHT (65, 72). However, nuclear uptake of [^{3}H]-DHT, but not [^{3}H]-testosterone has been shown in baboon heart muscle cells, suggesting that heart tissue contains receptors specific for DHT and not for testosterone (55).

The binding characteristics of AAS to the cardiac androgen receptor have not been fully described. The rank order of potency for displacement of [^{3}H]testosterone was shown to be nandrolone > testosterone > DHT ≥ progesterone in rat heart (65). Estradiol exerted a weak, but demonstrable competition. However, Bergink et al (62) noted, also in rat heart muscle, that nandrolone and testosterone exhibited roughly equal degrees of binding. Horwitz & Horwitz (68) showed that progesterone competed significantly for binding to the androgen receptor isolated from canine aortic tissue, while

McGill et al (66) indicated that progesterone exerted no significant competition for binding to the androgen receptor isolated from cardiac tissue of nonhuman primates. A systematic basis for the discrepancies between the results of these studies is not evident. Nevertheless, it is apparent that at least one commonly abused AAS, other than testosterone, can bind to the cardiac androgen receptor with high affinity. Moreover, there is some indication of similarities in binding characteristics between progesterone, estrogen, and androgen receptors.

HYPERTENSION In 1940 (38), testosterone was reported to cause hypertension in the rat. In 1953 (73), hypertension, nephrosclerosis, and cardiac lesions were described following administration of methylandrostenediol to uninephrectomized rats drinking 1% saline. The hypertension was shown to be dependent upon the adrenal gland (74). Subsequent studies, summarized by Brownie (75), determined that this class of steroids inhibited 11β-hydroxylation of 11-deoxycorticosterone (DOC) to corticosterone and that increased levels of DOC are responsible for hypertension in the rat. Gallant et al (76) have shown that testosterone administration selectively reduces mRNA levels coding for cytochrome P-$450_{11\beta}$, suggesting that AAS act at the level of the genome to inhibit transcription and reduce 11β-hydroxylase activity.

Anabolic-androgenic steroids exert multiple actions that could contribute to the development of hypertension. Enhanced reactivity of isolated vessels to norepinephrine has been shown in several species following administration of testosterone or methyltestosterone (77–79). Administration of AAS increased responsiveness to tyramine, but not to angiotensin, indicating that the response is specific to both exogenously applied and endogenously released catecholamines (79). Testosterone is a selective and potent inhibitor of extraneuronal norepinephrine uptake in rat heart (80). More recently, testosterone was shown to produce small increases in norepinephrine content and in dopamine β-hydroxylase activity in the rat vas deferens (81). These alterations were time-dependent, appearing following 5–7 days of AAS treatment. In contrast, one day administration of testosterone has been shown to depress vascular responsiveness in the canine hind-limb (82).

The complexity of this issue is illustrated by experiments examining the effects of testosterone and physical aerobic training on catecholaminergic neuron structure and content in the mouse heart (83). Over a 6-week period of treatment, noradrenergic neurons were found initially (at 1 and 3 weeks) to undergo degenerative changes, which were followed by evidence of adaptive regeneration. The results were consistent with recognized neuronal responses to overstimulation and to the trophic actions of exercise and testosterone on neurobiology (see 83). The most pronounced evidence for regeneration was noted in mice receiving both training and testosterone. These data emphasize the desirability of following the responses induced by AAS

carefully across time, since examination of data from single time points can be very misleading. The AAS are fundamental growth factors. Thus, a complicating aspect of any evaluation of the toxic effects caused by these agents is that injurious effects are likely to be modified by the anabolic activity.

Testosterone increases levels of renin mRNA in the kidney, brain, and adrenal gland (84) and increases plasma renin activity, apparently by increasing renal renin secretion (85). Moreover, membrane binding of angiotensin and aldosteronogenesis was stimulated by testosterone hemisuccinate in bovine adrenal glomerulosa cells, although this effect was noted only after washing the androgen from cell preparations (86). Biliary excretion and plasma clearance rates of aldosterone (87) and plasma levels of arginine vasopressin (88) were reduced by treatment with testosterone.

Generally, however, in the rat, AAS-induced increases in blood pressure are small, unless other insults (e.g. uninephrectomy or 1% saline ingestion) occur concomitantly (75, 89). Exceptions can be found (82, 90) and interesting differences between AAS in the potential to cause hypertension have been described (89). Ganten et al (91) have shown that testosterone is critical for full development of hypertension in young (9-week old) stroke-prone spontaneously hypertensive rats (SHRsp). However, neither castration nor administration of a testosterone receptor antagonist, flutamide, would reduce pressure in established hypertension in 25-week old SHRsp, suggesting that testosterone's greatest effects on blood pressure occurred in young organisms and that it did not contribute directly to the maintenance of established hypertension. Factors affecting human hypertension during AAS use are poorly described (75) and deserve further study.

OTHER CIRCULATORY CHANGES Testosterone has been reported to modify the structure of components of the circulatory system. However, both positive (e.g. increased repair of damaged myocardium) and negative (e.g. ventricular hypertrophy, myofibrillar damage) effects of AAS administration have been shown. Anabolic effects of testosterone on cardiac muscle were first described in 1936 (92). Since then, cardiomegaly has been described in animals treated with testosterone (89, 93–96) and other AAS (73, 90, 97–103). The AAS improve myocardial tissue repair following a variety of insults. The data from animal studies were sufficiently convincing to encourage a series of therapeutic trials (for review see 104). Although the results were not impressive enough to stimulate further development as a clinical modality, the fact remains that AAS alter myocardial remodeling following injury. This relationship has not always been considered in evaluation of the toxic responses to AAS administration.

Administration of methandrostenolone for 13 weeks altered myocyte ultrastructure by increasing noncontractile, intermediate filaments in left

ventricular muscle cells, in the female rat (105). A study, using the same design but with drug treatment conducted over a 3-week period, noted ultrastructural changes similar to those found in congestive heart failure, i.e. swollen, misshapen mitochondria with disarray and/or dissolution of sarcomeres (106). Myofibrillar damage was suspected following administration of methandrostenolone or aerobic training in the guinea pig, where the ratio of myofibrillar elements to mitochondria was reduced (107). Concurrent administration of methandrostenolone and training exacerbated the changes, causing disintegration of intercalated discs, mitochondriolysis, myofibrillolysis, and intracellular edema. Similar findings were noted in mice treated with androstenolone and physical training (108). The possible relationships between these findings and studies of cardiac sympathetic neurons (83) deserve additional scrutiny. Many of the responses designated as degenerative may, in fact, represent stages in ventricular remodeling and growth induced or accelerated by AAS. Conclusions derived from examination of tissue at single times following AAS administration may yield confounding results.

Evidence for functional alterations in myocardial performance by AAS was noted as early as 1958 (109). Again, both positive and negative effects of AAS were reported. Norethandrolone and testosterone produced initial increases in contractility of the isolated rabbit heart. However, a delayed depression of contractility and a bradycardia occurred following the initial period of stimulation. It is significant that similar effects were noted with administration of progesterone. In anesthetized dogs, norethandrolone and progesterone, but not testosterone, caused reversion of auricular flutter to sinus rhythm. Ramo (101) treated dogs for six weeks with high-dose methandienone. Cardiomegaly and bradycardia to submaximal exercise were noted in steroid-treated animals. Functional studies of the left ventricle, under morphine-pentobarbital anesthesia, determined that steroid treatment reduced isoproterenol-induced dP/dt_{max} and heart rate, while peripheral vascular resistance (PVR), end-systolic, end-diastolic, and stroke volumes increased relative to those in control dogs. Similar findings were reported following treatment of rats with nandrolone decanoate for six weeks (100). These results indicate that high-dose steroids exert adverse effects on cardiac pumping ability and circulatory regulation in untrained anesthetized animals.

Such conclusions were extended by studies comparing the effects of physical endurance training with those of high-dose steroids or a combination of training and steroid administration. Endurance training lowered PVR while increasing left ventricular stroke work in conscious dogs, both following submaximal exercise and stimulation with intravenous isoproterenol. These beneficial effects were attenuated by concomitant administration of methandienone (110). Similar findings were reported in anesthetized rats treated with nandrolone decanoate (111). Moreover, after a subsequent 6-week

sedentary period, AAS-treated rats demonstrated decreased left ventricular filling and elevated PVR values to isoproterenol challenge. The adverse effects of AAS treatment persisted following physical deconditioning in rats.

Effects of AAS on the structure of the vasculature have been reported. Administration of high doses of testosterone to normotensive male rats increased aortic elastin and collagen content, a response that, potentially, could contribute to atherosclerosis (112). Neither blood pressure nor heart weight were influenced by testosterone. This vascular remodeling is not unlike that which occurs in response to arterial hypertension. Subsequent studies from the same laboratory, however, demonstrated that administration of an androgen antagonist, cyproterone, actually inhibited hypertension-induced increases in aortic elastin and collagen, without altering the increments in these proteins seen during normal growth (113). This effect could be interpreted as protective in nature. Conclusions as to the nature of the responses to AAS were further complicated by the fact that neither gonadectomy early in life nor administration of a second antiandrogen had any effect on aortic composition in normotensive or hypertensive rats (113).

Gaynor (114) described reductions in elastin-associated microfibrils in the aortae of rabbits treated with high doses of testosterone. Higher concentrations of aortic collagen and elastin, as well as a higher collagen/elastin ratio, were observed in rats receiving testosterone (115). However, systemic blood pressure also increased in the testosterone-treated rats, which may have contributed to the alterations in vascular wall-connective tissue proteins. Aortic collagen and elastin increased in rabbits fed an atherogenic diet and treated with either testosterone or progesterone (58). The potential involvement of nonandrogen receptors was indicated by the demonstration that the effects of both testosterone and progesterone were associated with nuclear translocation of vascular progesterone receptors.

INTERACTIONS WITH COCAINE Recently, focus has been placed on the potential for adverse interactions between AAS and other drugs of abuse, most notably cocaine (116). Very little data have been reported on this subject. In a single study, the toxic interactions between cocaine and nandrolone decanoate have been examined in the spontaneously hypertensive rat (SHR) (Y. T. Tseng, T. Kimura, B. Hoskins, R. W. Rockhold, I. K. Ho, submitted for publication). Nandrolone decanoate (20 mg/kg, s.c., daily), cocaine hydrochloride (20 mg/kg, s.c., b.i.d.), both nandrolone and cocaine, or vehicle were administered to 7-week old SHR for 6 weeks. The normal rate of development of hypertension was accelerated equally in all three drug treatment groups. The greatest degree of left ventricular hypertrophy and of increases in left ventricular volume were noted in the nandrolone and cocaine group. Finally, nandrolone and nandrolone plus cocaine, but not cocaine

alone, caused hyaline myocardial necrosis, reactive inflammation and fibrosis. The greatest amount of myocardial damage was noted in the nandrolone plus cocaine group. The data confirm the ability of AAS to increase arterial pressure in susceptible rats and to induce myocardial toxic changes. Both cocaine and AAS can exert adverse circulatory responses in the SHR. However, cocaine does not appear to increase dramatically the circulatory toxicity of AAS.

LIPIDS AND CHD The literature documenting responses of serum lipids to AAS administration in animals and man, prior to 1972, was reviewed by Solyom (117). Since then, a majority of studies have examined steroid effects on lipid profiles in man, as comprehensively reviewed by Glazer (14). Only scattered references are available examining the effects of AAS on plasma lipids in animals, which is due, in part, to the difficulties in extrapolating animal data to the human situation (118). Indeed, Fogelberg et al (119), who tested the effects of stanozolol on atherogenesis in a rabbit model of diet-induced atherosclerosis, concluded that the model was not well suited for studying the effects of steroids on blood lipid profiles. In contrast, administration of nandrolone phenpropionate to rats reduces plasma high density lipoprotein (HDL) and increases the low density lipoprotein (LDL) fraction, in the absence of changes in total plasma cholesterol (120). These latter effects are similar to the pattern noted in humans (14, 117).

Human Data

Actions have been attributed to this group of drugs which would be expected to greatly increase risk for atherosclerotic CHD. These include changes in circulating lipid profiles, left ventricular hypertrophy, increases in blood volume, and hypertension. Animal study results comprise the basis for most of these conclusions. However, clinical data do not always confirm these widely held beliefs. It is not possible, with the present data, to conclude that AAS use causes an increased incidence of circulatory dysfunction.

HYPERTENSION Steroid-induced hypertension is an adverse effect of which athletes who self-administer steroids are most aware (4, 5). Indeed, references to hypertensive effects during self-administration are so common as to indicate that this is a reproducible phenomenon in power athletes (4). There is little support for this view in the scientific literature. No changes in blood pressure were observed in 21 men and 4 women with hyperlipoproteinemias treated with therapeutic levels of oxandrolone for 3 months (121). Similarly, no change in blood pressure was seen in healthy men (not competitive athletes) treated with either testosterone, testosterone and testolactone, or methyltestosterone (122). In male athletes, blood pressure was unchanged,

either during treatment with methandienone (123) or during maintenance (not pre-competition) self-administration cycling regimens (124). It is significant that blood pressure did not change in the study by Holma (123), despite a 15% increase in total blood volume. Thompson et al (125) and Urhausen et al (126) compared comprehensive echocardiographic and electrocardiographic measurements of left ventricular function in male power athletes who were taking competitive regimens of steroids and those who were steroid free. In one case (126), the athletes were of top national ranking. Blood pressure was not elevated above normal values in either group. Normal arterial pressure was reported in a steroid-using male bodybuilder with significant left ventricular hypertrophy (127).

Other studies, also in male power athletes, have noted slight (approx. 5 mm Hg) increases in systolic blood pressure (128–130). However, Freed et al (128) documented the exclusion of one steroid user who experienced a syncopal episode during lifting and who was consistently hypertensive on a low-dose regimen of methandienone. An earlier study by this group noted that increases in pressure of from 3 to 10 mm Hg were common and that much greater increases in pressure could be observed in a subset of athletes taking steroids (129). This was verified by reported increases in mean diastolic pressure of from 74 to 86 mm Hg in athletes self-administering AAS (131). Interestingly, no increases in blood pressure were observed in a second, double-blinded group receiving only high-dose nandrolone decanoate (131).

Hypertension is not a reliable response to AAS administration, but may occur in selected male patients or athletes. No data are available with respect to the possible effects of these agents on blood pressure in women and/or adolescents. Anecdotal observations in body builders suggest that different steroids can be grouped according to their propensity to cause hypertension (4). This observation is not yet supported by the scientific literature. There are no human data with which to address specific mechanisms (e.g. renal impairment, 11β-hydroxylase inhibition) by which AAS might increase blood pressure. Identification of the factors that predispose specific individuals to the hypertensive effects of AAS are clearly indicated.

VENTRICULAR FUNCTION Six studies using echocardiographic measures to determine left ventricular dimensions and function have been reported (125–127, 132–134). Evidence suggestive of mild impairment of diastolic function has been presented in top-ranking, competitive athletes self-administering steroids (126). Ventricular end diastolic diameter/kg body mass was reduced while absolute left ventricular posterior wall thickness, end diastolic volume, and relaxation index were increased in AAS users compared to nonusers. The authors concluded that AAS use during intense training caused minor concentric increases in left ventricular wall thickness and impairment

of diastolic function. Decreases in diastolic filling indices in five nationally competitive athletes who admitted to AAS use have been reported (132). Salke et al (133) found an increase in left ventricular septal wall thickness/mm^2 of body surface area in steroid-using body builders. However, all other indices of left ventricular structure and function were similar to those in body builders not using AAS. Isolated case reports of myocardial hypertrophy have been reported in association with AAS use in athletes (127, 135, 136) and in an infant (137). In contrast, two detailed, comprehensive studies were unable to detail any significant differences in left ventricular function or structure between body builders using steroids and nonusers (125, 134).

BLOOD VOLUME AAS are commonly believed to increase plasma volume through erythropoetic and renal sodium-retaining actions. The earliest references to human testosterone toxicity indicate edema as a consequence to therapy (32, 33). Stimulation of erythropoesis is a reproducible response following administration of AAS. However, the effect of steroids on plasma volume can vary, depending upon the agent and/or the characteristics of the recipient. Verwilghen et al (138) initially reported, in three female patients, that nandrolone could decrease plasma volume. Nandrolone decreased plasma volume in nonanemic men under treatment for impotence and in patients with refractory anemia and sickle cell disease, while patients with malignancies demonstrated increases in plasma volume (139). These effects may not be unique to nandrolone, since hemoconcentration was noted in such patients during treatment with testosterone cypionate (139–141). Testosterone enanthate increases plasma volume in nonanemic patients (139, 141, 142). However, reexamination of the effects of testosterone enanthate in 15 patients with primary hypogonadism identified a subset of patients with marked (>48%) increases in hematocrit that were associated with decreases in plasma volume (143). Three of these patients subsequently suffered stroke or transient ischemic attacks. The cause of the decrease in plasma volume caused by AAS is not known. Effects in athletes are less well studied. Certainly, "street" pharmacology suggests that edema is a common sequel to high-dose AAS administration (4). A 15% increase in total blood volume in well-trained athletes taking methandienone, which was evident both at rest and during exercise, has been reported (123). While fluid retention and edema must be considered more common adverse responses, the possibility should be recognized that steroid-induced hemoconcentration, due to decreases in plasma volume, can occur and may predispose to toxic thrombotic events.

LIPIDS AND CHD Human data linking AAS with changes in plasma lipoproteins and the potential for accelerating coronary atherosclerosis were presented

initially by Oliver & Boyd in 1956 (39), and have been reviewed comprehensively (14). This latter review concluded that steroid administration reduced levels of total HDL by 52% and of HDLb by 78%, while elevating LDL by 36%. However, the changes in lipoproteins are readily reversible. For example, HDL levels generally were noted to return within 3 to 5 weeks following cessation of steroid use. Overall, it was estimated that a three- to sixfold increase in the risk of CHD was associated with AAS use. This conclusion was moderated by the admission that other factors, such as cycling of steroid use, might complicate the risk analysis.

RELATIONSHIP TO PHYSICAL CONDITIONING Until recently, self-administration of AAS has been restricted to a relatively small group of male athletes, with unique physical and behavioral characteristics. Most of these characteristics, e.g. diet, exercise, youth, general abstinence from smoking, etc, are thought to reduce cardiovascular risk (13, 124). Kleiner et al (124) examined cardiovascular risk factors in 18 active male body builders who used steroids and 17 who did not. Nonusers exhibited only average risk, despite dietary patterns that should have greatly increased risk, an effect attributed to the protective actions of rigorous training. Steroid users had a much greater increase in calculated risk, which was maintained after cessation of steroid use for six months in 44% of the group. However, no data are available concerning longer term sequelae in the groups studied. An emphasis needs to be placed on collection of data with which to construct statistics on morbidity and mortality.

INCIDENCE OF MORBID EVENTS The primary medical concerns with the toxic effects of AAS are their potential for acceleration of atherosclerotic disease, for production of thrombosis, and, ultimately, for precipitation of occlusive or embolic circulatory events in man. There is little evidence to support acceleration of atherosclerosis by AAS, but other adverse circulatory events, which may have a common theme of thrombosis (12), have appeared in the literature. Excluding the sequelae to hepatic dysfunction and carcinoma, 26 serious circulatory events have been documented in the recent literature (1976–present), in patients receiving steroids therapeutically (Table 1). It should be noted that the number of life-threatening events is less than 26. Table 1 includes less serious circulatory system-related problems such as hematuria/cystitis, obstructive sleep apnea, and benign intracranial hypertension. Three additional cases reported by Krauss et al (143) included one patient who presented with a transient ischemic attack during testosterone enanthate therapy for impotence. Two other patients suffered strokes, although these

Table 1 Morbid circulatory events associated with therapeutic administration of AAS

	Diagnosis	No. of patients	Age/Sex	Therapeutic indication	Drug/Approx. total dose	Reference
Cerebrovascular						
	Superior sagittal sinus thrombosis with seizures	3	39/M 26/M 52/F	Hypoplastic anemia	Fluoxymesterone/3g Methenolone enanthate/25g Fluoxymesterone/14g	144
	Cerebral hemorrhagic infarction	1	22/M	Hypoplastic anemia	Oxymetholone/2g	145
	Cerebral vascular accident	1	21/M	Hypogonadal hypogonadism	Testosterone enanthate/3.6–36g[a]	146
	Cerebral vascular accident with angina	1	49/M	Anemia of chronic renal failure	Oxymetholone/4.1g	147
	Intracranial hypertension with seizures	1	60/F	Chronic low back pain	Stanozolol/3g	148
	Benign intracranial hypertension	3	23/F 36/F 24/F	Endometriosis Menorrhagia Endometriosis	Danazol/50g Danazol/113g Danazol/73g	149
	Cerebral vascular accident (delayed)	2	?/M	Erectile impotence	Testosterone enanthate/3.9–24.2g	143
	Transient ischemic attacks	1	?/M	Erectile impotence	Testosterone enanthate/26.5g	143
	Transient ischemic attack	1	64/M	Congenital protein-C deficiency	Stanozolol/0.5 g	150
Acute Hemorrhagic						
	Splenic rupture	1	69/M	Myelodysplastic syndrome	Oxymetholone/33g	151
Other						
	Cystitis/hematuria	10	28–56/7F,3M	Hereditary angioneurotic edema	Danazol/180–1,386g	152
	Obstructive sleep apnea	1	54/F	Anemia of chronic renal failure	Nandrolone decanoate/2.4g	153

[a] Surreptitious self-administration suspected, upper dose estimated from blood levels.

incidents did not appear until 9 months and 2 years, respectively, after cessation of testosterone therapy.

Hepatotoxic effects of AAS have been reviewed in detail (15, 28). Although AAS clearly cause liver injury and neoplastic changes, the incidence of death due to these changes is rare (15, 28), with the exception of peliosis hepatitis, which often has a fatal outcome (28). A single patient in Table 1 presented with splenic rupture, secondary to splenic peliosis, which may have been related to therapeutic administration of oxymetholone for treatment of refractory anemia (151). Distinct abnormalities in coagulation profiles were observed in this patient, which are consistent with a hypothesis that AAS increase risk of thrombosis (12).

These data indicating the possible association of severe adverse effects of steroids in patients, who might be debilitated or have disease pathologies, have not been convincing to those who advocate self-administration of steroids for athletes (4). Table 2 presents a summary of severe adverse effects related to the cardiovascular system reported in active athletes who were documented or suspected of AAS use. Eleven cases could be identified in the scientific literature.

At first inspection, the data summarized in Table 2 implicate AAS as causative agents in diverse circulatory pathologies. There are, however, several factors deserving closer consideration before this conclusion can be accepted. Each reported case represents an isolated incident, with a single exception (155). In some cases, the association with AAS use was based on meager evidence (156). In others, the details concerning the type and dosage of steroids were not available (154, 158–160, 162, 163). However, considering the obsessive nature of many body builders to their athletic endeavors (116), the pressure within the groups using these agents to enhance performance (7), and the secretive nature of athletes concerning AAS use, it is surprising that any documentation has been forthcoming.

The fact remains that intensive physical training conveys risks that can confound analysis of the published cases. Maron et al (164) identified significant cardiac structural abnormalities in 29 highly conditioned athletes who died suddenly, the most common of which was hypertrophic cardiomyopathy. Nineteen individuals were diagnosed with left ventricular hypertrophy. Fourteen of these cases showed left ventricular wall thickness > 13 mm, which has recently been identified as the upper limit of normal for highly trained athletes (165). Cardiomegaly was identified in four of the cases presented in Table 2 (135, 136, 158, 161). However, the extent to which that cardiomegaly resulted from training or steroid use cannot be determined. A greater risk may be that imposed by steroid use on thrombosis (12). A majority of the adverse events seen following both therapeutic and self-administration are, or can be assumed to result from. thrombotic or embolic incidents.

Table 2 Morbid circulatory events associated with AAS self-administration

	Diagnosis	No. of individuals	Age/Sex	Exercise preference	Drugs/Approx. duration of use	Reference
Cerebrovascular						
	Cerebrovascular accident with cardiomyopathy	1	32/M	Body builder	Multiple/16 yrs	136
	Stroke with seizure	1	34/M	Body builder	Multiple, unspecified/4 yrs	154
Thrombotic						
	Carotid/peripheral arterial ischemic events	1	28/M	Body builder	Multiple/3 yrs	155
	Pulmonary embolism	1	20/M	Body builder	Metanabol/unknown	156
Cardiac						
	Acute myocardial infarction	1	22/M	Power lifter	Multiple/unspecified	157
	Acute myocardial infarction with coronary atherosclerosis	1	28/M	Body builder	Multiple/undetermined	158
	Acute myocardial infarction with coronary atherosclerosis	1	23/M	Body builder	Unspecified/5 yrs	159 160
	Sudden cardiac death	1	21/M	Body builder	Testosterone cypionate, Nandrolone decanoate/"several months"	135
	Congestive heart failure	1	41/M	Body builder	Multiple/3 yrs	161
Acute Hemorrhagic						
	Bleeding esophageal varices	1	30/M	Body builder	Stanozolol, Methandienone, Oxandrolone/18 mo	162
	Rupture of hepatic tumor	1	27/M	Body builder	Unspecified/3 yrs	163

CONCLUSIONS

Experimental data suggest that AAS can cause cardiac dysfunction and should predispose to accelerated atherosclerosis. Thorough treatment of the literature frequently reveals that these data are accompanied by evidence that mitigates their impact. Anabolic responses may fundamentally alter putative deleterious actions of AAS on circulatory structure and function. In some cases, processes inherent to anabolic remodeling may have been mistakenly termed deleterious. Thus, the conclusions must be reached that it is not yet possible to predict what the nature of adverse circulatory responses may be or when they might occur, nor do sufficient data exist to permit discrimination between individual steroid agents as causative agents.

Eleven cases of catastrophic circulatory events have been reported since 1987 in the "worst-case" scenario of AAS use, i.e. following uncontrolled, high-dose, polypharmaceutic self-administration. The reluctance of individuals from this group to admit AAS use and the difficulty of identifying AAS as a causative factor in circulatory incidents are balanced by the intensity of medical interest in reporting assumed cases. What remains is a body of evidence showing circulatory pathology that would not be anticipated to occur in the population in question. Unfortunately, in the absence of appropriate statistical data, it is impossible to critically evaluate incidence rates. The data presently available do not support the hysteria that is commonly aimed at AAS abuse. Nevertheless, the data also indicate that a definite risk of morbid circulatory dysfunction does exist in some individuals, including athletes, using high-dose AAS. The pressing investigative questions will be to more completely define those individuals for whom AAS pose increased risk and what factors may predispose to increased risk in any given individual.

Much needs to be learned of the effects of high-dose AAS on both animal and human circulatory systems. Areas that deserve prospective consideration have been identified. Of these, clearly the most useful would be the epidemiology of circulatory dysfunction in high-risk subgroups, especially adolescents. The priorities for basic research should include characterization of nonandrogenic receptor and nonreceptor-mediated effects resulting from high-dose AAS use, and determination of the influence of intensive physical training on circulatory responses to AAS exposure. With respect to effects on cardiovascular structure and function, the past half century of study should be considered as a stepping stone to, rather than as the pinnacle of, our understanding of AAS, both as individual agents and as a drug class.

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