



## The Cardiac Toxicity of Anabolic Steroids

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Anabolic steroids are synthetic derivatives of testosterone that were developed as adjunct therapy for a variety of medical conditions. Today they are most commonly used to enhance athletic performance and muscular development. Both illicit and medically indicated anabolic steroid use have been temporally associated with many subsequent defects within each of the body systems. Testosterone is the preferred ligand of the human androgen receptor in the myocardium and directly modulates transcription, translation, and enzyme function. Consequent alterations of cellular pathology and organ physiology are similar to those seen with heart failure and cardiomyopathy. Hypertension, ventricular remodeling, myocardial ischemia, and sudden cardiac death have each been temporally and causally associated with anabolic steroid use in humans. These effects persist long after use has been discontinued and have significant impact on subsequent morbidity and mortality. The mechanisms of cardiac disease as a result of anabolic steroid use are discussed in this review.

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In 1932, testosterone and its derivatives were definitively determined to be the male sex hormones responsible for the extent of androgenic maturation during development. Therapeutic trials and interventions were discussed in the literature as early as 1939 for eunuchoid syndromes, impotence, depression, starvation, cryptorchidism, major surgery, and burns.<sup>1-3</sup> The first suggestion that these drugs might enhance physi-

cal performance occurred later that same year.<sup>4</sup> Mass trials conducted by Nazi Germany on their own soldiers during World War II, combined with concurrent animal studies, provided compelling data to support these theories.<sup>5</sup> Subsequent experiments with returning prisoners of war suffering from catabolic states associated with starvation and major trauma were less convincing.<sup>6</sup>

During the 1954 Vienna world weight lifting championships, the Russian national team introduced the use of anabolic steroids (AS) as ergogenic aids.<sup>7</sup> By the 1964 Olympics, athletes from around the world were consuming the drugs.<sup>8</sup> In a survey of weight lifters at the 1968 United States Olympic Training camp, 100% had taken some form of the substance. During the 1972 Olympics held in Munich, 68% of those competing in middle or short distance and field events admitted to having taken AS as part of their preparation for the games.<sup>9</sup> Proliferation of AS use throughout international competition had reached such epidemic proportions that by the 1976 Olympic games they were declared banned substances.<sup>7</sup>

Nonmedical use of AS in the United States was first reported among power athletes during the

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0033-0620/98/4101-0001\$8.00/0

1960s. The decade that followed saw proliferation of the substance throughout almost all venues of competitive sport.<sup>10,11</sup> By the mid-1980s, studies suggested that the fastest-growing population of nonmedical steroid users in the United States had never formally competed in any sport.<sup>12,13</sup> Consumption of AS has been estimated to be as high as 80% among power athletes and as much as 50% among athletes in general.<sup>14</sup> A 1984 study of 250 weight lifters by Frankle et al<sup>15</sup> found 110 who admitted to AS use. In 1985, Dezelsky et al<sup>12</sup> found that steroid use among intercollegiate athletes had increased from 15% in 1970 to 20% in 1984. The popular press reported extensive AS use throughout professional football during the early 1980s<sup>16</sup> and later went on to describe more prevalent use in the National Collegiate Athletic Association.<sup>17</sup>

It is still unclear whether disqualifying Ben Johnson from the 1988 Olympic games for using AS provided any more than public testimony to the performance-enhancing efficacy of AS.<sup>18,19</sup> In a study of 46 private and public high schools later that same year, 7% of male seniors surveyed had used AS. More than two thirds of them admitted to having started before 15 years of age.<sup>20</sup> In 1989, Johnson et al<sup>21</sup> reported the range of steroid use among male students at six Arkansas high schools to be from 9% to 19%, with a mean of 11%.<sup>21</sup> In that same year, a single high school study of 2,113 students found the prevalence rate of AS abuse among male students to be 7% and that among female students to be 2%.<sup>22</sup>

Improving athletic performance is the driving force behind AS use and it has infiltrated all levels of sport at all ages.<sup>21,23,24</sup> Recent studies have shown that although 65% to 84% of adolescent AS users participated in organized sports, as many as 27% were using the substances to improve their physical appearance.<sup>20-22,25</sup> The developmental tasks of adolescence may place teenagers at an increased risk for using AS.<sup>25</sup> Johnson et al<sup>21</sup> determined that among adolescents 43% of nonusers personally knew someone using AS, and a majority of both users (51%) and nonusers (57%) received their information about the drugs from their friends.<sup>21</sup> Dissemination of information regarding administration, dosages, and side effects has been largely anecdotal.<sup>6,25</sup> For years Volumes I and II of *The Underground Steroid Handbook* were considered the definitive reference for nonmedi-

cal AS use. This compendium actually consists of a collection of nonquantified observations from numerous AS users whose experiences encompass many different sports, drugs, and training regimens.<sup>19,25</sup>

A recent search on the Internet found no less than 3,600 websites regarding administration and procurement of AS. More than 100 different AS are available as oral or injectable preparations and are readily attainable in most metropolitan areas.<sup>6,15,26</sup> Although all are available by prescription, only 20% to 50% are actually obtained this way.<sup>18</sup> Most are procured through the black market, smuggled from foreign countries, or synthesized at clandestine laboratories.<sup>6,7</sup> The Food and Drug Administration estimated that during 1990 the sale of illicit AS amounted to be between 300 and 500 million dollars.<sup>27</sup> As legal restrictions have become greater, the integrity and purity of the various preparations, as well as the availability of clean syringes, has diminished and led to significant increases in morbidity and mortality from these sources.<sup>3,28</sup>

### Toxicity

Most AS toxicity, however, can be attributed to dosage and administration techniques.<sup>6,18,27,28</sup> In 1984, Burkett and Falduto<sup>26</sup> reported that the actual doses that are typically consumed are 10 to 100 times the normal therapeutic dose, and in one population of 24 weight lifters the lowest dose was still 350% of the usual therapeutic dose.<sup>28</sup> Other studies have described doses as much as 1,000 times those prescribed for appropriate medical conditions.<sup>13,29,30</sup> Very often multiple steroids are taken simultaneously by alternately increasing and then tapering the doses of particular drugs either in parallel, in series, or both, for a specific training effect.<sup>3,6,7,27,28</sup> Such pyramid schedules, called "stacking," not only involve suprapharmacological doses, but are usually taken over cycles lasting anywhere from 4 to 48 weeks.<sup>6,7,31</sup>

The toxicity of AS use is perceived very differently between the medical and athletic communities.<sup>19,28</sup> In 1990, Goldberg et al<sup>32</sup> showed that, despite comprehensive steroid education programs, the attitudes of high school football players toward AS use were not significantly altered.<sup>32</sup> Though the extent and longevity of the effects of

hormone supplementation are still unclear, that AS can significantly improve strength-related performance indices has been demonstrated repeatedly both empirically and through peer review.<sup>3,7,19,29,33</sup>

According to *The Underground Steroid Handbook II* in 1989, "(t)he more that you take, the more that you'll grow . . .," "(t)here is no such thing as taking too much steroid . . .," and, ". . . (the) risk (of side effects) has been virtually non-existent in healthy athletes."<sup>19</sup> Although there is sufficient evidence to counter such claims, it has been difficult to predict the nature, mechanisms, or even doses, at which adverse responses to AS use can be expected to occur.<sup>34</sup> Though the explanation for this is no doubt multifactorial, the single greatest confounding factor may well be the massive discrepancies between the doses that are used in monitored controlled studies versus the comparatively random suprapharmacological doses that are consumed every day.<sup>25,34</sup>

Nonmedical use of AS have been temporally associated with many subsequent defects of the endocrine, cardiovascular, reproductive, immunologic, genitourinary, psychiatric, and gastrointestinal systems. Though direct pathological evidence linking therapy to outcome is lacking, the same side effects have been documented within each of these systems after medically indicated AS use for skeletal disorders, osteoporosis, anemias, hormone deficiency states, and certain malignancies.<sup>3,6,7,27,29,34</sup> Direct cardiac complications include thrombotic and nonthrombotic ischemic events,<sup>35-39</sup> arrhythmia,<sup>40</sup> hypertension,<sup>6,31,33,41</sup> and cardiomyopathy.<sup>36,42,43</sup>

Between 1988 and 1991, Rockhold<sup>34</sup> described eight morbid circulatory events associated with AS use. Since that review was published in 1993, at least nine more cases have been reported.<sup>35-38,40,44,45</sup> Testosterone and its naturally occurring derivatives are known to modulate transcription,<sup>46</sup> translation,<sup>47</sup> and enzyme function.<sup>48-51</sup> Exogenous androgens that are administered with or without exercise result in alterations of cellular pathology<sup>52-55</sup> and organ physiology.<sup>56,57</sup> Supplementation of AS exacerbates the normal cardiac adaptive mechanisms to exercise<sup>58,59</sup> and the ensuing physiologic insult.<sup>34,37,60</sup> These changes persist well after the cessation of AS use<sup>61</sup> and appear to have significant impact on subsequent morbidity and mortality.<sup>34,62</sup> This re-

view discusses the alterations of cardiac physiology that occur with AS use.

## Clinical Pathophysiology

### Hypertension

Volume II of *The Underground Steroid Handbook* notes hypertension to be a transient effect of AS that resolves with completion of the cycle and leaves no residual defects.<sup>19</sup> Clinical evidence to support this is inconclusive. Although aerobic training increases the capacity of the cardiac pump,<sup>63,64</sup> AS both counteract exercise-induced functional adaptations of the heart<sup>65,66</sup> and alter the reserve capacity of the left ventricle.<sup>66,67</sup> Studies of active male body builders using AS showed significantly greater risk of subsequent cardiac disease compared with those who were drug free. In one study, elevated risk persisted in 44% of the test group for up to 6 months after discontinuing steroids.<sup>57</sup>

In studies of healthy noncompetitive male athletes treated with testosterone alone, testosterone and testolactone, and methyltestosterone, significant elevation of blood pressure did not occur.<sup>68</sup> Whether consumption was self-administered<sup>69</sup> or carefully monitored, power athletes taking high-dose AS did not develop hypertension compared with similar athletes who were drug free.<sup>70,71</sup> Olssen et al<sup>72</sup> followed 21 men and four women with hyperlipoproteinemias who received 3 months of oxandrolone therapy, and they were unable to show changes in blood pressure.<sup>72</sup> Because increased total blood volume can occur secondary to AS use without increased arterial blood pressure, androgens may be attenuating measurable hypertension by concomitantly altering the normal adaptive mechanisms of the vasculature.<sup>73</sup>

In contrast to the preceding studies, Lenders and others have found that, in power athletes, not only does systolic pressure increase as much as 10 mm Hg, but AS administration exacerbates hypertension even further.<sup>74,75</sup> Investigation of the effects of AS in humans are often confounded by differences between the amount of a drug taken in the gym and that allowable in a study.<sup>29,76</sup> In athletes self-administering large doses of multiple AS, mean diastolic pressure increased from 74 to 86 mm Hg, whereas no change in blood pressure

was reported in a double-blind clinical study using therapeutic doses of nandrolone decanoate.<sup>77</sup>

Grollman et al<sup>69</sup> were the first to find that animals treated with testosterone developed hypertension. Subsequent studies associated AS not only with hypertension, but with nephrosclerosis and other cardiac lesions.<sup>78,79</sup> In stroke-prone spontaneously hypertensive rats (SHRsp), neither castration nor androgen receptor antagonism by flutamide decreased blood pressure after 25 weeks. The authors concluded that in the SHRsp, testosterone is required to initiate hypertension but not to maintain it.<sup>80</sup> Other studies have indicated that testosterone can both selectively inhibit extraneuronal uptake of neuroamines and increase the vascular response to norepinephrine.<sup>81,82</sup> Androgens might thereby initiate or potentiate hypertension by stimulating tissues distant to the myocardium.<sup>34,81,82</sup>

Elevated concentrations of 11-deoxycortisone (DOC) causes hypertension in the rat.<sup>34</sup> Testosterone increases DOC in the adrenal gland by selectively inhibiting transcription of the mRNA-encoding cytochrome P-450<sub>11 $\beta$</sub> ,<sup>46</sup> thus reducing 11 $\beta$ -hydroxylase activity and subsequently inhibiting the conversion of DOC to cortisone.<sup>34</sup> In the bovine adrenal glomerulosa, testosterone hemisuccinate stimulates aldosteronogenesis and membrane binding of angiotensin.<sup>83</sup> Wagner et al<sup>84</sup> have documented that the expression of renin mRNA in the adrenal gland, kidney, and brain is both tissue-specific and androgen-dependent.<sup>84</sup> Renal renin secretion, and consequent plasma renin activity, is increased by exogenous testosterone.<sup>85</sup> Androgens further stimulate renal hypertension by decreasing plasma levels of arginine vasopressin<sup>86</sup> and hepatic clearance of aldosterone.<sup>87</sup>

### *Hypertrophy*

Resistance training stimulates hypertrophy of the left ventricular wall and interventricular septum independent of exogenous steroid administration.<sup>59</sup> Echocardiograms of experienced age-matched male weight lifters showed that those actively consuming AS had greater left ventricular mass, increased interventricular septal thickness, and decreased VO<sub>2max</sub>, compared with those ei-

ther not taking steroids at all or having stopped 2 months previously. When compared with subjects who had recently stopped, those who were actively consuming AS were also found to have greater left ventricular diameter and posterior wall thickness during diastole.<sup>61</sup> Supplementation with AS therefore pathologically alters the normal physiological adaptations that occur after exercise.<sup>59</sup>

Urhausen et al<sup>71</sup> have recently suggested that in body builders taking AS, sustained increases in heart rate and blood pressure may result in compensatory hypertrophy of the left ventricular wall. The proportion of these increased physiological parameters attributable to AS, as opposed to resulting from the exercise itself, is unclear.<sup>71</sup> Two recent studies of body builders taking AS were unable to find appreciable amounts of cardiac hypertrophy.<sup>70,88</sup> However, echocardiograms of 21 body builders that admitted to AS use showed not only increased left ventricular posterior wall thickness and end-diastolic volumes, but decreased ratios of ventricular end-diastolic diameter to body mass. The authors concluded that AS coupled with intense exercise training results in concentric hypertrophy of the left ventricular wall and impaired diastolic function.<sup>71</sup>

Previously undetected congenital cardiac conditions are responsible for most cases of sudden cardiac death (SCD) in athletes that are younger than 30 years of age.<sup>89</sup> In 29 cases of highly conditioned athletes with SCD, the most common structural abnormality was hypertrophic cardiomyopathy.<sup>62</sup> Of the patients studied, 19 had significant left ventricular hypertrophy, and 14 had left ventricular wall thickness at the upper limit of normal for highly trained athletes.<sup>62,90</sup> Dickerman et al<sup>44</sup> have described cardiomegaly with concentric left ventricular hypertrophy in a 20-year-old man who suffered SCD after 3 months of self-administering massive doses of methenolone depot, veterinary testosterone enanthate, and veterinary nandrolone laurate.<sup>44</sup>

Many case studies of athletes who self-administered large amounts of AS have documented grossly hypertrophied hearts at autopsy,<sup>43,68,91,92</sup> and one study has even found cardiomegaly in an infant who was exposed to AS.<sup>93</sup> Three cases of SCD occurring in adult male athletes taking AS found cardiomegaly and petechial surface hemor-

rhaging in association with normal valves and coronary arteries. Pathological studies from each subject showed generalized and focal fibrosis, significant myofibrillar disarray, and hypertrophy of the interventricular septum and left ventricular free wall.<sup>37,43</sup>

*Ventricular remodeling.* AS alter myocardial remodeling after injury.<sup>34</sup> The effects of AS on wall thickness become evident on echocardiogram within 3 months.<sup>94</sup> Pearson et al<sup>95</sup> found that the hearts of nationally competitive weight lifters that admitted to AS use show decreased diastolic filling and impaired left ventricular function.<sup>95</sup> In another study of body builders using AS, the only significant increase noted was in the ratio of left ventricular wall thickness to body surface area. All other indices of left ventricular structure and function were similar to those found in drug-free weight lifters.<sup>42</sup>

Sachtleben et al<sup>61</sup> compared male weight lifters that used AS with controls 8 weeks after finishing a cycle, and then again at the peak of their next cycle. Echocardiograms showed that AS users at peak cycle have left ventricular mass and interventricular septal thickness during diastole that is significantly greater than that of either non-steroid users or steroid users 8 weeks after termination of a cycle. In contrast to the control group, both the peak-cycle and the off-cycle AS cohorts had greater left ventricular posterior wall thickness and internal diameter during diastole.<sup>61</sup> In AS users, the ratio of ventricular end-diastolic diameter per kilogram body mass decreases as left ventricular posterior wall thickness and end-diastolic volume increase with the development of concentric hypertrophy.<sup>71</sup>

The remodeling that occurs secondary to AS is not associated with increased shortening fraction and persists beyond discontinuation.<sup>61</sup> Ferenchick<sup>96</sup> has recently discussed cardiomyopathy in athletes as a direct result of AS use. Cardiomyopathy was associated with chronic AS use in a former National Football League player who subsequently needed a heart transplant.<sup>97</sup> Autopsy results from tissue samples of the left ventricular free wall of two football players who took oxymesterone showed cardiomegaly, disorganized myofibrils of varying fiber size, fanning of myocytes with focal fibrosis, and thickening of the walls of the intramural arteries.<sup>37</sup> Animal<sup>98</sup> and human studies<sup>37</sup> both indicate that AS-

induced cardiomyopathy is the result of increased myocardial fibrosis, particularly in the subepicardium and central aspects of the left ventricle.<sup>43</sup>

Administration of testosterone,<sup>47,99,100</sup> or any of a host of other AS,<sup>58,66,67,101,102</sup> has generated significant cardiomegaly in many different animal models. In dogs treated with methandienone cardiac hypertrophy was documented within 6 weeks.<sup>103</sup> Rats that were exposed to chronic hypoxia and at least 5 weeks of testosterone treatments generated right ventricular hypertrophy.<sup>99</sup> In another rat study, nandrolone decanoate injections stimulated cardiomegaly that reversed after cessation of treatment.<sup>67</sup> Although myocardial hypertrophy associated with AS use has been quite reproducible in animals, the actual mechanisms by which this might occur are still vague.<sup>60</sup>

### *Myocardial Ischemia*

Case studies associating AS use with myocardial infarction (MI) and SCD abound in the literature.<sup>35-40,43,44</sup> AS potentiate many pathological mechanisms known to precipitate heart disease.<sup>34,60</sup> Power lifters consuming AS have a greater risk of atherosclerosis secondary to increased concentrations of low-density lipoprotein (LDL) cholesterol and decreased concentrations of high-density lipoprotein (HDL) cholesterol.<sup>104</sup> Increased cardiac risk occurs with the deposition of cholesterol plaques within the coronary vessels and subsequent thrombus formation at sites of plaque rupture.<sup>105</sup> AS predispose thrombus formation by stimulating platelet aggregation<sup>106</sup> and increasing the activity of specific enzymes of coagulation.<sup>107</sup> Thrombotic and arteriosclerotic heart disease can each independently increase the risk of coronary vasospasm.<sup>60</sup> Aberrant coronary vascular pathological conditions after AS use have been well documented and may occur as the result of a number of different mechanisms.<sup>108</sup>

*Lipids.* Clinical trials and human case studies find that AS cause significant elevations of LDL with concomitant reductions of HDL and HDLb (Fig 1).<sup>39,104,109</sup> Although these are reversible changes, the consequent risk of cardiac disease is at least tripled.<sup>109</sup> Some AS not only may alter lipid profiles but also may produce abnormal endothelial function by impairing the release of endothelium-derived relaxing factor.<sup>110</sup> AS admin-



immediate and delayed alterations of pre-coagulant factor VIII in response to exercise training. Similar changes also were noted in healthy adults who were receiving stanozolol, suggesting that AS administration with exercise could synergistically increase the potential for thrombosis.<sup>120</sup>

Platelet aggregation studies of a 22-year-old power lifter admitted for MI with hypercholesterolemia and AS use showed hyperaggregability of 16 U/min, compared with a control value of 5 U/min.<sup>39</sup> Recent case studies in the literature describe three athletes who suffered large infarcts after self-administering AS. Cardiac catheterization showed extensive thrombosis in each.<sup>35,36</sup> Shiozawa et al<sup>121</sup> described cerebral sinus thrombosis in association with AS. Catheterization studies of two elderly patients who suffered MI while receiving metenolone enanthate therapy for aplastic anemia showed multiple thrombi.<sup>122</sup>

Platelet responsiveness to aggregating stimuli in male rats was found to be 10-fold that found in female rats. With castration, aggregability was decreased in the males but increased in the females. The same study showed that pretreatment with testosterone both attenuated the loss of aggregability found in castrated males and enhanced the platelet aggregation of both sexes.<sup>114</sup> AS can enhance platelet aggregation and thrombus formation by increasing the production of thromboxane A<sub>2</sub>, decreasing the production of prostaglandin PGI<sub>2</sub>, or both.<sup>107,115</sup> They also may increase thrombin activity secondary to activation of factor Xa after androgenic stimulation of factor IX, and possibly VII.<sup>60,115,123</sup>

**Vasospasm.** Anabolic steroids have also been associated with coronary artery vasospasm and MI in the absence of both atherosclerosis and thrombosis (Fig 1).<sup>37,43</sup> In the coronary arteries, nitric oxide functions as an endothelial-derived relaxing factor that increases the activity of guanylyl cyclase.<sup>51,124</sup> Guanylyl cyclase converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP), which subsequently stimulates smooth muscle relaxation.<sup>125,126</sup> Exogenous androgens are associated with increased concentrations of serum LDL that might directly contribute to atherosclerosis<sup>104,109</sup> and possibly coronary artery vasospasm.<sup>60,113</sup> Some amount of the excess LDL may become oxidized at the arterial endothelium<sup>113</sup> and consequently impair endothelium-dependent arterial relaxation by in-

hibiting nitric oxide production and therefore decreasing cGMP levels.<sup>119,127</sup> Green et al<sup>119</sup> found that vasodilatation of the brachial artery in response to methacholine and sodium nitroprusside was significantly inhibited in men who were self-administering nandrolone. The authors concluded that anabolic steroids lead to a state of hyperactive vascular reactivity that may increase the likelihood of coronary artery occlusion.<sup>119</sup>

There are a number of other mechanisms by which steroids might induce vasospasm. Ferrer et al<sup>51</sup> have shown that decreased relaxation of the thoracic aorta after chronic nandrolone therapy is associated with decreased concentrations of arterial endothelial cGMP, suggesting that androgens also may directly inhibit guanylyl cyclase itself.<sup>51</sup> Greenberg et al<sup>82</sup> and others<sup>115</sup> have discussed arterial spasm secondary to decreased vascular endothelial prostacyclin I<sub>2</sub> after anabolic steroid administration. Alternately, decreased capillary density after compensatory hypertrophy and longer periods of coronary artery compression secondary to diastolic dysfunction may additionally lower the threshold for vasospasm.<sup>43</sup>

## Cellular Pathophysiology

### *Intracellular*

Morphological alterations of the myocardium as direct consequences of AS have been well documented.<sup>52,53,60,128</sup> The histological changes that occur are exacerbated by endurance exercise and are similar to those observed in the early phases of left ventricular failure.<sup>53,58</sup> Behrendt and others<sup>128,129</sup> have found that, after exposure to methandrostenolone (Dianabol; Novartis, East Hanover, NJ), the mitochondria within the rat left ventricle enlarge, become rounded with the appearance of membranous defects and an electron-lucent matrix, and then elongate, leaving only a sparse matrix material and a few cristae. Guinea pigs treated with Dianabol show mitochondrial destruction and an increased ratio of mitochondria to myofibrils.<sup>53</sup> Electron microscopy of the contractile apparatus within myocardium similarly treated shows completely destroyed sarcomeres, regional disappearance of ribosomes and polysomes, thickening and stretching of the I-band, and noncontractile globular networks of

disrupted fragments of both thick and thin filaments.<sup>52,129</sup>

AS have variable effects on myocyte enzyme function, and studies indicate that in situ specific enzyme systems may be under some amount of androgenic control.<sup>48,49,129</sup> Endogenous androgens regulate cell growth and enzyme activity within the lysosomes and inner mitochondrial membrane of rat ventricular myocytes.<sup>49</sup> Koenig et al<sup>130</sup> have illustrated that within rat ventricular myocytes testosterone can induce polyamines to function as intracellular messengers that activate ornithine decarboxylase, stimulating calcium fluxes and alterations of membrane transport.<sup>130</sup> Chainy and Kanungo<sup>131</sup> showed that, within the hearts of castrated rats, testosterone increases pyruvate kinase activity. In sedentary pig myocardium, methandrostenolone induced decreases in malate dehydrogenase, isocitrate dehydrogenase, and hexokinase activity that were reversible with endurance training.<sup>50</sup> In the left ventricle of guinea pigs exercised on an inclined treadmill, Dianabol decreased both the total lactate dehydrogenase (LDH) and the concentration of LDH subunits, temporally associating exercise-induced adaptation with AS-induced myocardial cell injury.<sup>48</sup>

Hemodynamic conditions that result in compensatory cardiac hypertrophy and hypertension preferentially induce expression of the  $\beta$  myosin heavy chain (MHC) isoenzyme.<sup>132</sup> Lengsfeld et al<sup>100</sup> have shown that testosterone favors the expression of the  $\alpha$ -MHC isoenzyme despite increasing degrees of hemodynamic stimuli. Polymerase chain reaction studies of the rat myocardium have found the relative distributions of mRNA encoding the  $\alpha$ - and  $\beta$ -MHC isoforms to be identical. Testosterone consequently regulates expression of the  $\alpha$ -MHC isoforms at the pretranslational level in a manner that is independent of hemodynamic load or cardiac hypertrophy.<sup>47</sup>

### *Extracellular*

AS induce intrafibrillar collagen dysplasia and subsequent alterations in muscle load without compromising tendon composition.<sup>133,134</sup> Physical exercise<sup>135,136</sup> or transient increases in aortic pressure<sup>137</sup> elevate myocardial collagen content in direct proportion to the degree of hypertrophy that ensues, thereby maintaining a constant ratio

between the collagen and noncollagen proteins of the heart.<sup>63</sup> Carey et al<sup>138</sup> and others have shown that compensatory hypertrophy secondary to chronic volume or pressure overload may result in increased collagen deposition within the myocardium.<sup>139</sup> The extracellular space of rat myocardium treated with Dianabol is occupied by bundles of collagen fibrils, and the cells appear separated as during the early stages of fibrosis.<sup>129</sup> In the canine right ventricle, increased hydroxyproline concentration in both the endocardium and epicardium indicates that AS both enhance exercise-induced increases in collagen concentration and stimulate transmural redistribution of collagen synthesis.<sup>63</sup>

Testosterone is a potent and selective inhibitor of extraneuronal norepinephrine uptake in the heart.<sup>140</sup> Administered with exercise, testosterone induced degenerative changes within the intracardiac sympathetic neurons of the mouse at 1 and 3 weeks, with adaptive regeneration at 6 weeks.<sup>141</sup> These changes appear to be the direct result of AS. However, this is another instance in which the indirect vascular response is potentially more cardiotoxic.<sup>34,60</sup> Both testosterone and methyltestosterone have been shown to enhance vascular reactivity to norepinephrine and subsequently generate hypertension.<sup>81,82</sup> Decreased arterial endothelial cGMP secondary to nandrolone-induced inhibition of guanylyl cyclase occurs in the rabbit aorta and has been suggested as a possible mechanism of coronary artery vasospasm after high-dose AS in humans.<sup>51,60</sup>

Guinea pigs administered Dianabol for 4 weeks show not only degradation of the functional syncytium of the myocardium but an imbalance of cellular compartments and organelles.<sup>53</sup> Recent studies by Welder et al<sup>54</sup> and Melchert et al<sup>55</sup> have shown that AS cause direct cardiotoxicity in both a concentration- and time-dependent fashion. The loss of cell viability caused by AS toxicity may in some part be the result of alterations of intracellular ion concentrations after decreased plasma membrane integrity and the inability to synthesize high-energy phosphates.<sup>54,55</sup> Such direct cell injury with tissue necrosis results in fibrotic areas of the myocardium that are predisposed to potentially fatal ventricular arrhythmias and SCD.<sup>60,142</sup>

## Molecular Biology

### Biochemistry

Whether given orally or parenterally, AS are rapidly absorbed during their first pass through the liver, inactivated by a series of reduction reactions (phase I metabolism), conjugated with glucuronides or sulfates (phase II metabolism), and then excreted into the urine.<sup>143,144</sup> Synthetic AS derived from chemical modifications of the testosterone molecule are designed to reduce the rate of metabolic inactivation, overwhelm catabolic pathways, sustain higher serum concentrations for greater periods, or maximize anabolic efficacy at lower concentrations.<sup>7,145</sup>

The three most common modifications of the testosterone molecule to achieve these ends are (type A) esterification of the 17 $\beta$ -hydroxyl group, (type B) alkylation of the 17 $\alpha$ -position, and (type C) modification of the steroid ring structure.<sup>6,7,143,145</sup> Each structurally different compound will have not only different binding affinity and efficacy at the human androgen receptor (hAR) than does testosterone, but different relative androgenic and anabolic characteristics as well.<sup>146</sup> Evidence for this is shown in situ when testosterone is reduced by 5 $\alpha$ -reductase to dihydrotestosterone (DHT). The modified derivative possesses substantially greater affinity for the hAR than does testosterone and is actually the preferred ligand in skeletal muscle.<sup>144,146</sup>

### Receptors

The hAR appears to be identical in all cell types.<sup>7,35,147-149</sup> The manifestations of steroid stimuli are therefore a composite of (1) the ratio of the number of receptors in the extragenital tissue compared with that in the genitalia<sup>34,146</sup>; (2) the relative activity of the enzyme 5 $\alpha$ -reductase within the separate sites<sup>150,151</sup>; (3) concomitant glucocorticoid activity<sup>152,153</sup>; and (4) the type and amount of other steroid hormone receptors that may be expressed within the cells.<sup>34,144,154</sup> AS binding to the hAR generates conformational changes within the protein that expose the DNA-binding domain to particular segments of the genome.<sup>147</sup> These segments consist of unique consensus nucleotide sequences that have been shown to be steroid hormone receptor-responsive elements within DNA, thereby allowing for

modulation of specific gene transcription.<sup>144,147,154</sup> This is the mechanism by which AS, acting through their receptors, function as morphogens that direct the expression of tissue phenotype.<sup>148</sup>

Normal circulating concentrations of endogenous plasma androgens are typically sufficient to saturate the hAR. Therefore, at least some of the toxicity and anabolic response associated with AS administration may be mediated by interaction with nonandrogen receptors.<sup>7,34</sup> Human studies have noted that testosterone, as well as some synthetic androgens, can bind and activate progesterone receptors.<sup>155,156</sup> Dimethyltestosterone and norethandrolone, both synthetic AS, have been shown not only to bind and stimulate the progesterone receptor with efficacy equivalent to that of progesterone, but also to promote nuclear translocation of cytosolic progesterone receptors.<sup>155,157</sup>

Human glucocorticoid receptors that also can bind AS have been described in human skeletal muscle.<sup>158</sup> At physiological androgen levels, glucocorticoids exert a well-documented catabolic effect on skeletal muscle that may be inhibited by supraphysiological concentrations of anabolic steroids.<sup>153,159</sup> The synthetic AS 17 $\alpha$ -methyltestosterone, very popular among nonmedical users, has been shown to prevent activation of the glucocorticoid receptor by adhering to a site within its DNA-binding domain.<sup>160</sup> In the presence of glucocorticoids and estrogen, testosterone and its non-aromatizable analog trenbolone, each were shown to prevent the catabolic actions of endogenous glucocorticoids by interacting with the glucocorticoid receptor.<sup>153</sup>

### Myocardial Receptors

Skeletal muscle hypertrophy secondary to AS is primarily attributable to androgenic inhibition of glucocorticoid activity.<sup>153</sup> This is significantly different from the heart, in which both androgens and glucocorticoids have anabolic functions.<sup>161</sup> Glucocorticoid administration in cardiac tissue has been shown to increase myocardial growth by inhibiting protein degradation.<sup>161,162</sup> After exercise-induced cardiac hypertrophy, the myocardium shows increased concentrations of glucocorticoid receptors and greater binding of glucocorticoid hormones. Each of these alterations of glucocorticoid mechanics occurs after the initial hypertrophic response, and although they clearly contrib-

ute to adaptive processes within the heart, it is unlikely that they initiate them.<sup>161</sup>

Although the absence of androgens significantly reduces the rate of cardiac hypertrophy in response to aortic banding,<sup>163</sup> their presence initiates alterations within the myocardium secondary to either sustained physiological stress or exogenous administration.<sup>34,37,60</sup> In humans, there is a dose-response relationship between AS and lean body mass in which the hAR is the limiting factor.<sup>161,164,165</sup> The cardiovascular system has been shown to possess specific, saturatable, high-affinity androgen receptors.<sup>34</sup> Although they are not found within interstitial tissues,<sup>164,166</sup> they have been identified within ventricular<sup>161,164,166,169</sup> and atrial<sup>164,166</sup> muscle, as well as within the aortic,<sup>164,170</sup> pulmonary,<sup>167</sup> and peripheral vasculature.<sup>164</sup>

In hypertrophied skeletal muscle, the hAR is more abundant and has greater affinity for androgens than in control tissue.<sup>171</sup> In the enlarged heart, the hAR shows neither of these changes, suggesting that different mechanistic roles may exist for androgens in cardiac hypertrophy.<sup>161</sup> In androgenic end organs, stimulation of the hAR with the testosterone derivative DHT induces cellular hyperplasia.<sup>3,23,60,172</sup> Although the 5 $\alpha$ -reductase activity of skeletal muscle is greater than that of cardiac, the concentrations of the enzyme within both sites is extremely low. Therefore, compared with other organs in the body, DHT cannot accumulate in significant amounts, and hyperplasia is not considered to occur within either skeletal or cardiac muscle.<sup>144,146,173</sup> The myocardial activity of 3 $\alpha$ -hydroxysteroid dehydrogenase is significantly greater than that found in skeletal muscle and subsequently causes further accumulation of testosterone at the expense of DHT.<sup>169,174</sup> Consequently testosterone is considered to be the active endogenous ligand at the hAR in myocardial tissue.<sup>175</sup>

### Conclusion

AS are synthetic derivatives of testosterone and the preferred ligand of the hAR in the heart.<sup>175</sup> Within myocardial tissues, steroids modulate transcription,<sup>46</sup> translation,<sup>55</sup> and enzyme function.<sup>48-51</sup> The normal adaptive mechanisms of the heart in response to growth,<sup>161,162</sup> exercise,<sup>58,59</sup> and physiological insult<sup>34,37</sup> are under the influ-

ence of both endogenous and exogenous steroids.<sup>60</sup> Exogenous androgens administered with or without exercise result in alterations of cellular pathology<sup>52-55</sup> and organ physiology<sup>56,57</sup> that are similar to those seen with heart failure and cardiomyopathy.<sup>37,43,96</sup> Hypertension,<sup>74,75</sup> ventricular remodeling,<sup>42,61,94,95</sup> myocardial ischemia,<sup>34,60</sup> and SCD<sup>37,43</sup> have all been temporally and causally associated with AS use in humans. These changes persist well after the cessation of AS<sup>61</sup> and have significant impact on subsequent morbidity and mortality.<sup>34,62</sup>

### Acknowledgment

The authors thank Drs Calvin Eng, James Scheuer, and Edmund Sonnenblick for their critical review of this manuscript.

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