Original Articles

Long-Term Anabolic-Androgenic Steroid Use Is Associated With Left Ventricular Dysfunction

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Background—Although illicit anabolic-androgenic steroid (AAS) use is widespread, the cardiac effects of long-term AAS use remain inadequately characterized. We compared cardiac parameters in weightlifters reporting long-term AAS use to those in otherwise similar weightlifters without prior AAS exposure.

Methods and Results—We performed 2D tissue-Doppler and speckle-tracking echocardiography to assess left ventricular (LV) ejection fraction, LV systolic strain, and conventional indices of diastolic function in long-term AAS users (n=12) and otherwise similar AAS nonusers (n=7). AAS users (median [quartile 1, quartile 3] cumulative lifetime AAS exposure, 468 [169, 520] weeks) closely resembled nonusers in age, prior duration of weightlifting, and current intensity of weight training. LV structural parameters were similar between the two groups; however, AAS users had significantly lower LV ejection fraction (50.6% [48.4, 53.6] versus 59.1% [58.0%, 61.7%]; $P=0.003$ by two-tailed Wilcoxon rank sum test), longitudinal strain (16.9% [14.0%, 19.0%] versus 21.0% [20.2%, 22.9%]; $P=0.004$), and radial strain (38.3% [28.5%, 43.7%] versus 50.1% [44.3%, 61.8%]; $P=0.02$). Ten of the 12 AAS users showed LV ejection fractions below the accepted limit of normal ($\geq55\%$). AAS users also demonstrated decreased diastolic function compared to nonusers as evidenced by a markedly lower early peak tissue velocity (7.4 [6.8, 7.9] cm/s versus 9.9 [8.3, 10.5] cm/s; $P=0.005$) and early-to-late diastolic filling ratio (0.93 [0.88, 1.39] versus 1.80 [1.48, 2.00]; $P=0.003$).

Conclusions—Cardiac dysfunction in long-term AAS users appears to be more severe than previously reported and may be sufficient to increase the risk of heart failure. (*Circ Heart Fail*. 2010;3:472-476.)

Key Words: myocardial contraction ■ mechanics ■ systole ■ diastole ■ anabolic agent

The anabolic androgenic steroids (AAS) are a family of drugs that includes the male hormone testosterone and its synthetic derivatives. More than 1 million American men and women have used these drugs illicitly to gain muscle and lose body fat.[1–5] Long-term illicit use of supraphysiologic doses of AAS may cause adverse cardiovascular effects, but these remain poorly understood.[5–7] Early work examining cardiac function in AAS users produced inconsistent results.[8,9] Recent studies using modern imaging techniques have found evidence of overt left ventricular (LV) diastolic dysfunction[10–12] and subclinical LV systolic impairment (reduced systolic strain with normal LV ejection fraction) in AAS users.[10] In addition, numerous case reports of cardiac death among AAS users suggest a causal link between AAS use and cardiovascular disease.[13–19]

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Illicit AAS use did not become widespread in the general population until the 1980s, and thus, the first large wave of

long-term illicit users only now is reaching middle age.[5] Therefore, it has recently become both more feasible and increasingly critical to study cardiac structure and function in this population. Accordingly, we conducted a preliminary study comparing cardiac parameters in long-term male AAS-using weightlifters and age-matched male weightlifters reporting no AAS exposure.

Methods

Study Population

Using methods to maximize the representativeness of the sample and minimize selection bias as previously described in detail,[20,21] we recruited AAS users and nonusers by advertising in gymnasiums frequented by male weightlifters and other athletes known to have a high prevalence of AAS use. Briefly, our advertising indicated that we were conducting psychological and medical evaluations of experienced male weightlifters, but neither the focus of the study on AAS nor the specific hypotheses being tested were disclosed either in the advertising or in telephone screening of candidate study participants. All participants provided written informed consent

before initiating the study as approved by the McLean Hospital (Belmont, Mass) Institutional Review Board.

The evaluation included demographic information and determination of height, weight, and body fat.[22,23] Body fat was determined on the basis of 6 skinfold measurements with calipers, using the equations of Jackson and Pollock.[22] From these data, we calculated the fat-free mass index, which is an index of muscularity developed in our laboratory and previously described in detail.[23] Using an interview protocol described in previous studies,[20,21,24] we then elicited self-reported history of AAS use, including specific drugs, dosages, and durations. Estimated weeks of lifetime AAS use together with average weekly AAS dose and maximum lifetime weekly AAS dose were calculated using testosterone equivalence as previously described.[21,24] We also elicited a detailed history of lifetime alcohol and classical illicit substance use (cannabis, amphetamines, cocaine, opioids, etc) through a structured clinical interview,[25] as well as a history of use of other performance-enhancing drugs (eg, human growth hormone), again with estimates of total lifetime exposure as previously described.[20,21,24,26] Finally, we acquired traditional medical historical and exercise exposure data, including lifetime duration of weightlifting, current number of hours per week of weightlifting, and current number of hours of non-weightlifting exercise activity.

Echocardiography

Transthoracic echocardiography was performed using a commercially available system (Vivid-I, GE Healthcare). Participants were studied after >1 hour of rest. Images were obtained using 2D (frame rate, 25 to 75/s) Doppler and color-tissue Doppler (frame rate, >100/s) imaging and were acquired from standard parasternal and apical views. All data were stored digitally and subsequently analyzed offline. Standard measurements were performed in accordance with current guidelines.[27] LV ejection fraction was calculated using the modified Simpson (biplane) technique, with a value <55% considered abnormal.[27] LV mass was calculated with the area-length method, and a body surface indexed LV mass >103 g/m² was used to define LV hypertrophy.[27] Tissue velocity measurements were obtained offline from colorized 2D images. Peak systolic strain was measured from the apical 4-chamber view (longitudinal) and the parasternal short-axis view (radial) using speckle-tracking analysis; reported values represent average strain in the 6 wall segments designated by the processing software. Reported tissue velocity and strain values are the average of 3 consecutive cardiac cycles.

Measurement Variability

Two investigators blinded to each other's measurements independently measured LV mass, tissue velocity, and strain in 10 of the 19 study participants. Interobserver variability was quantified using the intraclass correlation coefficient. The intraclass correlation coefficient, the ratio of between-subject to total variability, reflects both within-subject and between-subject variability (see online-only Data Supplement).

Statistical Analyses

Differences between groups were assessed using the nonparametric Wilcoxon rank sum test because sample sizes were too small to permit an assumption of normality. Differences in proportions were assessed by Fisher exact test. Group-wise comparisons of cardiac parameters were assessed using linear regression on ranked data to adjust for body surface area and hours of training per week. Linear regression with ranked data also was used to examine the relationships between AAS exposure measures (lifetime weeks of use, estimated total lifetime dose of AAS, and maximum weekly dose of AAS) and cardiac parameters. Alpha was set at 0.01, 2-tailed, to partly control for multiple comparisons.

Results

Study Participants

We studied 12 AAS users and 7 nonusers. Although blood pressure and exercise capacity were not measured at the time of

Table 1. Characteristics of AAS Users and AAS Nonusers

Characteristic	AAS Users (n=12)	AAS Nonusers (n=7)	*P*
Age, y	40.0 (35.8, 43.6)	40.5 (37.9, 44.9)	0.55
Years of regular weightlifting	17.5 (12.3, 20.4)	15.0 (13.0, 22.0)	0.97
Hours of exercise per week†	5.5 (4.0, 7.4)	4.0 (3.0, 15.0)	0.67
Body mass index, kg/m²	30.3 (28.5, 32.1)	28.4 (26.9, 31.8)	0.35
Body surface area, m²	2.16 (2.02, 2.22)	2.02 (1.91, 2.26)	0.67
Fat-free mass index, kg/m²	26.6 (24.5, 27.9)	24.0 (22.7, 25.2)	0.01

Data are presented as median (quartile 1, quartile 3).
*All *P* values are from 2-tailed Wilcoxon rank sum test.
†Hours of weight training and other intense athletic activity.

evaluation, none of the participants had a history of hypertension, atherosclerotic vascular disease, heart failure, or exercise intolerance. AAS users reported taking median (quartile 1, quartile 3) weekly doses of 675 (513, 950) mg of testosterone equivalent for 468 (169, 520) lifetime weeks. The groups were similar in age, prior duration of weightlifting, current number of hours per week of weight training and other intense athletic activity, body mass index, and body surface area, but as expected, AAS users were significantly more muscular than nonusers as measured by fat-free mass index (Table 1). In other words, the AAS users had a similar body mass index to nonusers because the former group had more muscle but less body fat. Four of the 12 AAS users were currently taking supraphysiologic doses of AAS at the time of evaluation; 3 were currently taking only physiologic doses of testosterone at 50 to 100 mg/week; 1 had discontinued a course of supraphysiologic AAS 3 weeks prior to evaluation; and the remaining 4 had not used AAS for at least 6 months prior to the evaluation.

Six (50%) of the AAS users but none of the nonusers reported a past history of opioid, cocaine, or alcohol dependence. None of the participants reported amphetamine dependence. Two (17%) AAS users but none of the nonusers reported cannabis dependence, 1 past and 1 current. None of the participants reported a history of cigarette use. Nine (75%) AAS users but none of the nonusers reported at least some use of human growth hormone, and 6 of these reported human growth hormone use for >3 months. We assessed for possible cardiac effects of these other forms of drug use in exploratory analyses as described later.

Cardiac Structure and Function

All LV structural parameters were similar between groups (Table 2). Six (50%) AAS users and 5 (71%) nonusers met criteria for LV hypertrophy (P=0.63). However, AAS users differed significantly from nonusers in several complementary and independently derived indices of systolic function (Table 2). LV ejection fraction was abnormal (≤55%) in 10 (83%) AAS users but only in 1 (14%) nonuser, who had an LV ejection fraction of 54% (P=0.003) (Figure 1). Relative systolic dysfunction was further evidenced by significantly lower LV peak systolic strain among AAS users.

LV diastolic function also differed between the groups (Table 2). Compared to nonusers, AAS users showed lower early diastolic transmitral blood flow velocity and early peak tissue velocity with preserved or increased late diastolic

Table 2. Left Ventricular Structure and Function in AAS Users and AAS Nonusers

Measure	AAS Users (n=12)	AAS Nonusers (n=7)	P*
Structural parameters			
Posterior wall thickness, mm	11.1 (10.3, 1.9)	11.0 (10.2, 11.0)	0.31
Interventricular septal thickness, mm	10.8 (9.1, 11.7)	10.9 (10.3, 11.6)	0.67
End-diastolic diameter, mm	49.3 (47.8, 52.5)	49.1 (44.5, 50.4)	0.45
Mass, g	230 (195, 270)	237 (210, 243)	0.83
Systolic function parameters			
LV ejection fraction, %	50.6 (48.4, 53.6)	59.1 (58.0, 61.7)	0.003
Longitudinal strain, %	16.9 (14.0, 19.0)	21.0 (20.2, 21.9)	0.004
Radial strain, %	38.3 (28.5, 43.7)	50.1 (44.3, 61.8)	0.02
Peak systolic tissue velocity, cm/s†	6.2 (5.3, 7.0)	6.3 (5.8, 6.8)	0.50
Diastolic function parameters			
E-wave, cm/s	64.0 (55.5, 78.5)	77.0 (67.0, 86.0)	0.05
A-wave, cm/s	61.5 (55.3, 65.8)	43.0 (36.0, 54.0)	0.02
E/A ratio	0.93 (0.88, 1.39)	1.80 (1.48, 2.00)	0.003
Early peak tissue velocity, cm/s	7.4 (6.8, 7.9)	9.9 (8.3, 10.5)	0.005
Peak late diastolic tissue velocity, cm/s	5.1 (4.1, 5.7)	5.6 (4.4, 7.4)	0.25

Data are presented as median (quartile 1, quartile 3). E-wave indicates early diastolic transmitral blood flow velocity and A-wave, late diastolic transmitral blood flow velocity.

*All *P* values are from 2-tailed Wilcoxon rank sum test.

†Measured at basal lateral segment of the left ventricle.

filling as evidenced by late diastolic transmitral blood flow velocity and peak tissue velocity. This pattern of diminished early diastolic function and enhanced late diastolic function, a hallmark of impaired LV relaxation,[28] was reflected by a significantly lower ratio of early-to-late diastolic filling (E/A ratio). Representative examples of diastolic tissue velocity profiles for both groups are shown in Figure 2.

Associations Among AAS Use, Exercise Exposure, and Cardiac Parameters

We performed analyses that adjusted for cardiac structural measurements for body surface area and hours of weekly exercise training for all of the outcome measures in Table 2 and found that the differences between groups remained highly significant. In addition, we performed exploratory analyses that tested for outlier bias by comparing groups after excluding the nonuser with the highest LV ejection fraction and the nonuser with the highest E/A ratio. In both cases, all of the differences in Table 2 remained highly significant at $P<0.01$.

In further exploratory analyses within the AAS user group, we found no statistically significant associations between AAS exposure variables (lifetime weeks of exposure, total lifetime dose of AAS, and maximum weekly dose used) and the outcome measures in Table 2. We also performed an exploratory analysis excluding the 6 AAS users with past cocaine, opioid, or alcohol dependence and compared the remaining 6 AAS users to the
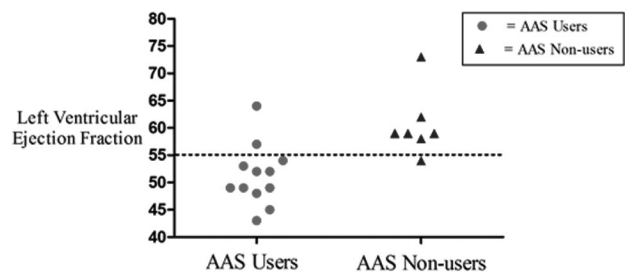

Figure 1. LV ejection fraction in AAS users and AAS nonusers. Circles indicate AAS users and triangles, AAS nonusers.

nonusers. In this analysis, differences between the 6 AAS users with no history of other illicit drug use and the 7 nonusers remained statistically significant ($P<0.05$) for LV ejection fraction, longitudinal strain, peak early diastolic tissue velocity, and E/A ratio. We then performed a similar analysis excluding the 6 AAS users reporting >3 months of lifetime human growth hormone use. Again, group difference for LV ejection fraction, longitudinal strain, peak early diastolic tissue velocity, and E/A ratio remained similar to those found during the analyses, including all 12 AAS users.

Finally, we performed exploratory analyses comparing the 7 nonusers with each of the 3 subgroups of AAS users, namely the 4 users currently taking supraphysiologic doses of AAS, the 4 users who had not used AAS for at least 6 months, and the 4 remaining users who were either taking only physiological doses of testosterone (n=3) or who had recently stopped a course of AAS (n=1). Each subgroup showed similar deficits relative to the nonusers on LV ejection fraction, LV systolic strain measures, and E/A ratio, tentatively suggesting that these deficits were not specifically associated with current AAS use or current AAS dose.

Discussion

Results from this study are consistent with previous findings showing LV diastolic dysfunction[10–12] and subclinical LV systolic impairment[10] in AAS users. However, our results suggest that the cardiac impairment in long-term AAS users may be more severe than previously reported. Specifically, long-term AAS users were found to have significant LV systolic dysfunction both by relative standards (compared to the AAS nonuser cohort) and by absolute standards (as defined by current clinical practice). To our knowledge, this study is the first to demonstrate an association between long-term AAS use and a clinically relevant reduction in LV ejection fraction.

There is a well-established relationship between LV dysfunction and exposure both to certain medications[29] and to some drugs of abuse.[30–32] Further, the prognostic importance of toxin-induced cardiac dysfunction has been well documented.[33–36] Data from this study suggest that AAS, particularly when used over long durations, may be another important cause of toxin-mediated myocardial impairment. Although confirmatory data are required, results from this study suggest that AAS exposure should be a diagnostic consideration among persons with asymptomatic LV dysfunction or incident heart failure.

Although several previous studies have reported mild cardiac dysfunction, LV dysfunction among our AAS users was more
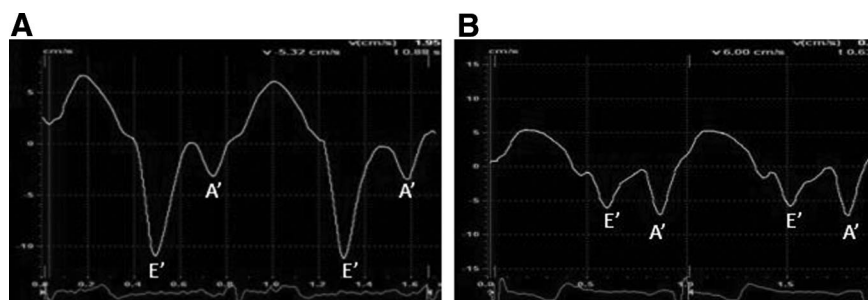
Figure 2. Representative tissue-Doppler velocity tracings of normal diastolic profile in an AAS nonuser (A) and an abnormal functional profile in a long-term AAS user (B).

severe than previously reported. Several hypotheses might explain this discrepancy. First, our AAS users were several years older, on average, than those in 2 of the 3 most recent studies.[10,12] Second, these previous studies selected top-level competitive bodybuilders,[10] squad athletes,[12] or individuals from bodybuilding studios,[12] thus possibly favoring healthier individuals with better cardiac function than the largely noncompetitive individuals[21] in our study. Finally, the specific AAS compounds and dosages typically used by our American participants may have differed from those of participants in previous studies, which were largely conducted in Europe.

It is noteworthy that our analysis revealed no significant relationship between cumulative AAS use and cardiac dysfunction. This observation suggests that AAS-associated cardiotoxicity might be only partially and unpredictably related to lifetime dose in a manner similar to the cardiac toxicity of alcohol.[37] Further work is required to determine whether cardiac function is influenced by factors such as the recency of AAS use (eg, current versus long past), specific AAS used (eg, possibly more toxic oral agents[5,38] versus injectable agents), duration of exposure to very high doses (eg, $\geq$2000 mg/wk), or concomitant use of other drugs (eg, human growth hormone[39,40]).

There are several important limitations to this study. First, our sample might not be representative of the overall source population of long-term AAS users or comparison weightlifters. Although we used recruitment procedures designed to generate a sample that is maximally representative,[20,21] it is possible that the group of AAS users in the present study is not entirely representative of the overall population. Second, our sample sizes were small and unequal. However, this limitation would likely produce false-negative findings (ie, type II errors) rather than false-positive results due to the reduced statistical power afforded by small sample sizes. Therefore, the highly statistically significant findings in the present study, despite the small sample size, suggest that the association between AAS use and cardiac pathology may be particularly strong (ie, a very large effect size). Conversely, the possibility of a type II error must be considered in instances where group comparisons were not significant. For example, the lack of association between AAS exposure and cardiac dysfunction must be interpreted with caution. Future study with adequate statistical power is warranted to examine this issue. A third limitation is our reliance on participants' self-reporting of AAS use. We recognize that errors based on self-report could have arisen if actual AAS users denied use and were misclassified as nonusers; individuals classified as nonusers had unknowingly ingested supplements contaminated with actual AAS; or individuals classified as users had ingested only counterfeit black market AAS and, hence, had not used genuine drugs. However, each form of misclassification would only narrow the differences between groups, causing us to underestimate the true association of AAS use with cardiac pathology. A fourth limitation is our use of retrospective exercise exposure assessment and the possibility that AAS-users differed from nonusers with respect to exercise intensity. However, it is unlikely that this factor contributed to our observations because no prior studies have demonstrated LV dysfunction secondary to intense, sustained exercise training. Finally, the cross-sectional nature of this exploratory study does not permit definitive conclusions about the long-term clinical implications of our findings and represents an important area of future work.

In summary, data from the present study suggest that AAS-induced LV dysfunction may be greater than previously reported. The reductions in LV systolic function observed in this group of AAS users are of a magnitude shown to increase the risk of heart failure and sudden cardiac death in other populations.[41,42] Further work is needed to confirm our findings and to determine the extent to which AAS-associated cardiac dysfunction leads to adverse clinical outcomes.

Sources of Funding

Disclosures

None.

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CLINICAL PERSPECTIVE

Well over 1 million Americans, most of them men, have used illicit anabolic-androgenic steroids (AAS) to gain muscle mass for athletic purposes or simply to enhance personal appearance. Because illicit AAS use did not become widespread in the general population until the 1980s, it is only now that the first large wave of long-term illicit AAS users is approaching middle age. Preliminary data suggest that long-term exposure to supraphysiologic doses of AAS has cardiotoxic effects, but the nature and severity of these effects remain inadequately characterized. This study compared 12 long-term AAS users and 7 age-matched weightlifters who reported similar exercise levels but no AAS use. The AAS group showed striking impairments of cardiac contraction and relaxation (systolic and diastolic function) similar to that observed in well-established forms of cardiomyopathy. In particular, the AAS users showed markedly reduced left ventricular systolic function (lower left ventricular ejection fraction, longitudinal strain, and radial strain) and impaired left ventricular diastolic function (reduced early peak tissue velocity and ratio of early-to-late diastolic filling) compared with nonusers. These findings suggest that long-term AAS use may be associated with clinically relevant cardiac dysfunction and that AAS use should be considered as a potential cause of cardiomyopathy.