



Cardiovascular Toxicity of Illicit Anabolic-Androgenic Steroid Use

BACKGROUND: Millions of individuals have used illicit anabolic-androgenic steroids (AAS), but the long-term cardiovascular associations of these drugs remain incompletely understood.

METHODS: Using a cross-sectional cohort design, we recruited 140 experienced male weightlifters 34 to 54 years of age, comprising 86 men reporting ≥ 2 years of cumulative lifetime AAS use and 54 nonusing men. Using transthoracic echocardiography and coronary computed tomography angiography, we assessed 3 primary outcome measures: left ventricular (LV) systolic function (left ventricular ejection fraction), LV diastolic function (early relaxation velocity), and coronary atherosclerosis (coronary artery plaque volume).

RESULTS: Compared with nonusers, AAS users demonstrated relatively reduced LV systolic function (mean \pm SD left ventricular ejection fraction = $52\pm 11\%$ versus $63\pm 8\%$; $P<0.001$) and diastolic function (early relaxation velocity = 9.3 ± 2.4 cm/second versus 11.1 ± 2.0 cm/second; $P<0.001$). Users currently taking AAS at the time of evaluation ($N=58$) showed significantly reduced LV systolic (left ventricular ejection fraction = $49\pm 10\%$ versus $58\pm 10\%$; $P<0.001$) and diastolic function (early relaxation velocity = 8.9 ± 2.4 cm/second versus 10.1 ± 2.4 cm/second; $P=0.035$) compared with users currently off-drug ($N=28$). In addition, AAS users demonstrated higher coronary artery plaque volume than nonusers (median [interquartile range] 3 [0, 174] mL³ versus 0 [0, 69] mL³; $P=0.012$). Lifetime AAS dose was strongly associated with coronary atherosclerotic burden (increase [95% confidence interval] in rank of plaque volume for each 10-year increase in cumulative duration of AAS use: 0.60 SD units [0.16–1.03 SD units]; $P=0.008$).

CONCLUSIONS: Long-term AAS use appears to be associated with myocardial dysfunction and accelerated coronary atherosclerosis. These forms of AAS-associated adverse cardiovascular phenotypes may represent a previously underrecognized public-health problem.

Aaron L. Baggish, MD,
MPH

Rory B. Weiner, MD
Gen Kanayama, MD, PhD
James I. Hudson, MD, ScD
Michael T. Lu, MD
Udo Hoffmann, MD, MPH
Harrison G. Pope, Jr, MD,
MPH

Correspondence to: Aaron L. Baggish, MD, Division of Cardiology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, or Harrison G. Pope, Jr, MD, MPH, McLean Hospital, 115 Mill Street, Belmont, MA 02478. E-mail abaggish@partners.org or hpope@mclean.harvard.edu

Sources of Funding, see page 2000

Key Words: anabolic-androgenic steroids ■ atherosclerosis ■ cardiology ■ cardiomyopathy ■ diastolic dysfunction ■ men

© 2017 American Heart Association, Inc.

Clinical Perspective

What Is New?

- Millions of individuals have used anabolic-androgenic steroids (AAS) to gain muscle for athletic purposes or personal appearance.
- Preliminary findings have suggested that long-term AAS exposure may lead to both cardiomyopathy and atherosclerotic disease, but previous studies have been small or methodologically limited.
- Here, in the first large controlled study of its type, we demonstrate that long-term AAS use is associated with both systolic and diastolic myocardial dysfunction, as well as coronary atherosclerosis.
- Systolic functional deficits appear to recover after AAS discontinuation, whereas diastolic dysfunction appears less reversible.
- Atherosclerotic disease appears strongly associated with lifetime duration of AAS exposure.

What Are the Clinical Implications?

- Widespread illicit AAS use first appeared in the general population in the 1980s, and thus most AAS users are still young or middle-aged today.
- Thus, when clinicians encounter young or middle-age men who exhibit evidence of unexplained left ventricular dysfunction or premature coronary artery disease, the possibility of cardiotoxicity because of long-term AAS use should be considered in the differential diagnosis.
- It is notable that $\approx 80\%$ of contemporary AAS users are simply recreational weightlifters rather than competitive athletes, and thus the possibility of AAS use should be considered even in individuals who do not identify themselves as athletes.

An estimated 2.9 to 4.0 million Americans have used supraphysiologic doses of illicit anabolic-androgenic steroids (AAS), including testosterone and its synthetic relatives, to gain muscle mass for athletics or personal appearance.¹ About 1 million of these individuals, almost all of whom are male, have developed AAS dependence, often leading to years of chronic AAS exposure.² Illicit AAS use did not become widespread in the general US population until the 1980s.³ Thus, the oldest AAS users, who initiated AAS as youths in the 1980s, are only now reaching middle age, when the adverse effects of long-term use may become apparent. Therefore, these effects remain incompletely understood.

Previous studies have suggested an association between AAS use and cardiovascular disease, with a pathophysiologic link first proposed by early case reports of sudden cardiac death or ischemic stroke among young AAS-using men.⁴⁻⁶ Subsequently, preclinical studies have shown that AAS exposure at supraphysiologic doses causes dyslipidemia,⁷⁻⁹ stimulates cardiomyocyte hy-

per trophy,^{10,11} impairs coronary arterial function,^{12,13} reduces cardiac β -adrenoreceptor sensitivity,¹⁴ potentiates oxidative cardiac stress,¹⁵ lowers arrhythmic thresholds,¹⁶ and induces myocyte apoptosis.¹⁷ Most recently, investigations utilizing noninvasive cardiac imaging in human users have demonstrated preliminary evidence of AAS cardiotoxicity in the forms of myocardial dysfunction,¹⁸⁻²² myocardial fibrosis,²³ and increased coronary artery calcification.²⁴

In aggregate, data from these earlier studies suggest that illicit AAS use may cause a form of cardiomyopathy characterized by decreased left ventricular (LV) function^{18,19,21-23,25,26} and may increase the risk of atherosclerotic disease.^{1,7,8,24} To date, definitive associations between AAS exposure and either myocardial or coronary artery disease have yet to be demonstrated in a large human study. To address this issue, we conducted comprehensive cardiovascular evaluations of 86 long-term AAS users and 54 nonusers.

METHODS

Study Design

We conducted an observational study using a cross-sectional cohort design. We have previously presented the formal properties of this design,²⁷ which has been used both explicitly²⁸⁻³¹ and implicitly^{32,33} in many earlier studies. This method identifies a dynamic cohort of individuals drawn from a given source population who in principle could have been enumerated in the past and followed to the present (termed the conceptual cohort). Instead of sampling from the conceptual cohort, one samples in the present from those currently available (the study cohort). With this design, estimates of effects derived from the study cohort are valid with respect to the conceptual cohort, subject to similar conditions for validity as other retrospective designs (eg, retrospective cohort and case-control studies).²⁷ We chose the cross-sectional cohort design because it can efficiently assess the association of outcomes with an uncommon exposure (eg, AAS use) in the same manner that a case-control design can efficiently assess the association of exposures with an uncommon outcome.

For the present study, we sampled from a source population of men who lift weights in gymnasiums and then compared exposed (ie, AAS-using) and nonexposed (ie, non-AAS-using) men from this group. We chose this source population because almost all long-term AAS users are male² and lift weights regularly.^{1,34} We did not recruit from sporting venues because most AAS users are not competitive athletes but simply recreational weightlifters.^{1,35,36}

Although this approach minimized the effects of confounding variables inherent to weightlifting, we considered that weightlifting or its associated lifestyle might be associated with specific cardiovascular characteristics. Therefore, in an ancillary study, we recruited a group of nonweightlifting and non-AAS-using men (frequency-matched in age to the weightlifters but never weightlifting >30 minutes per week at any time since 18 years of age), drawn from a roster of potential study volunteers maintained by Massachusetts General Hospital,

and compared these nonweightlifters to the subgroup of non-AAS-using weightlifters from the primary study. These 2 groups (AAS nonusers and nonweightlifting and non-AAS-using men) exhibited no scientifically important or statistically significant differences on measures of cardiovascular physiology or pathology (Tables I–III in the online-only Data Supplement), indicating that weightlifting per se, of the duration and intensity selected by our recruitment techniques, was associated with little or no cardiovascular adaptation or pathology.

Participants

As described in our previous cross-sectional cohort studies involving AAS,^{28,29} we advertised in gymnasiums for men 34 to 54 years of age who could bench-press 275 pounds for at least one repetition, currently or in the past to recruit AAS users and nonusers. On telephone screening, advertisement respondents were invited to participate without inquiring about AAS use to minimize selection bias that might arise if they knew in advance the exposure variable of interest. It is notable that AAS are typically ingested in courses or cycles, with deliberate intervening off-drug intervals.¹ Thus, our design anticipated that the AAS-using weightlifters would include 2 subgroups: those on-drug and those off-drug at the time of evaluation. We excluded AAS users reporting <2 years of cumulative lifetime AAS exposure. We imposed no specific exclusions for medical or psychiatric history.

Evaluation

Qualifying participants were evaluated at a screening interview, where they provided written informed consent for the study as approved by the McLean Hospital Institutional Review Board. We then obtained demographic data, lifetime exercise history (ie, exercise modalities, duration, intensity, and consistency), and fat-free mass index, a validated measure of muscularity.^{29,37,38} Psychiatric and substance-use histories were obtained using the Structured Clinical Interview for DSM–IV.³⁹ We next assessed history of AAS use, including age at onset of use, maximum weekly dose of AAS (calculated as mg of testosterone equivalent),⁴⁰ cumulative lifetime years of use, lifetime dose ingested, time of most recent use, and types and doses of AAS taken during most recent (or current) use. We also assessed use of other performance-enhancing substances, including over-the-counter substances (eg, creatine) and illicit drugs (eg, human growth hormone, clenbuterol). Participants then provided urine samples to be tested for AAS^{29,38} and head or axillary hair to be tested for opiates, cannabis, phencyclidine, amphetamines, and cocaine.^{29,38} Men showing urine or hair findings inconsistent with their reported substance-use history were excluded from further evaluation. We also excluded men denying AAS use but exhibiting a fat-free mass index >26 kg/m² together with body fat <10% based on previous work showing that a combination of leanness and muscularity beyond these limits strongly suggests surreptitious AAS use.^{37,41}

Men found to qualify after the screening interviews were then referred for a cardiovascular evaluation performed by investigators blinded to AAS status to characterize LV structure, LV function, and coronary atherosclerosis. Two-dimensional transthoracic echocardiography (iE33, Philips Medical Systems) was used to develop profiles of LV structure and function as

previously detailed by our group.⁴² The primary outcome variables for LV systolic and diastolic function were left ventricular ejection fraction (LVEF) as measured using the modified biplane method of disks⁴³ and early LV relaxation velocity (E′; average of basal septum and lateral wall values⁴⁴), respectively. Second, coronary computerized tomography angiography (CTA) was performed using a dual-source 128-slice CT scanner (Definition Flash, Siemens Medical Systems), with a primary outcome variable of total coronary artery plaque volume.⁴⁵ Secondary CTA measures included number of atherosclerotic coronary segments, degree of stenosis of the worst segment, and Agatston calcium score.⁴⁶ Detailed echocardiographic and CTA methods are provided in the online-only Data Supplement.

Statistical Analysis

Based on our pilot data¹⁸ and those of others,^{1,24} our primary hypotheses were that AAS users would exhibit: (1) decreased LVEF, (2) decreased E′, and (3) increased coronary plaque volume compared with non-AAS-using weightlifters. We further hypothesized that within the AAS-user group, greater pathology on these variables would be associated with currency of AAS use (ie, on-drug versus off-drug status at the time of evaluation) and with cumulative lifetime duration of AAS exposure.

Using linear regression, we estimated the mean difference between groups on the outcome measures (technically, the estimated mean difference was the estimated beta coefficient corresponding to group status in a linear model that also included a set of covariates and was fitted using ordinary least-squares linear regression). To control for confounding, our primary analysis adjusted for a set of plausible confounding variables including: age; race/ethnicity (modeled as black versus all others); history of tobacco use, cocaine dependence, and alcohol dependence; weekly hours of aerobic activity in the last 10 years (modeled in tertiles of the distribution); and reported family history of coronary artery disease as defined by the presence of angina, myocardial infarction, angioplasty/stent, or coronary bypass surgery in a first-degree relative. For echocardiographic measures, we additionally adjusted for body surface area as calculated by the Mosteller formula. To explore the relationship between LV mass, a potentially important mechanistic mediator of LV functional impairment, and our primary functional outcome variables, we performed post hoc analyses examining the association of LV mass index with LVEF and E′ among AAS users and nonusers. Specifically, we used linear regression with the same set of potential confounding variables and the addition of a term for AAS-user versus nonuser group status to examine the relationships between LV mass index (LV mass in g/body surface area in m²) and the primary cardiac function outcomes. Also, because resting heart rate could influence cardiac functional outcomes, we performed additional analyses of the primary cardiac functional outcomes by adding resting heart rate as a covariate. Note that heart rate may influence functional outcomes and also might be affected by current AAS use. In the latter eventuality, the estimated mean difference between groups adjusted for resting heart rate would likely be biased toward the null (ie, would potentially represent an overadjustment), thus producing an underestimate of the effect of AAS use.

In subsequent sensitivity analyses assessing the influence of adjustments using alternative sets of potential confounders,

we repeated all comparisons (1) with no adjustment for any covariates, (2) with the adjustment covariates reduced to only age and race (plus body surface area for echocardiographic measures), and (3) with the adjustment covariates augmented to include hypertension and dyslipidemia (as defined in [Tables X–X in the online-only Data Supplement](#)). It is important to note that the augmented set of covariates would be expected to yield underestimates of the effect of AAS use because hypertension and dyslipidemia are often effects of AAS use,^{1,7,9,47} and adjustment for these variables would consequently adjust out effects of AAS mediated by these variables.

Because the distributions of coronary CTA measures contained many zero values (ie, no measurable coronary artery disease), we used ranked data for these analyses. Within the AAS-user group, we evaluated the association of all outcome measures with duration of use and currency of use (ie, on-drug versus off-drug) using linear regression with adjustment for the same set of covariates. To aid in interpretation of comparisons between groups and associations within groups involving rank-transformed data, we used standard deviation (SD) units to express the estimated difference in ranks for binary predictor variables and the estimated change in ranks for each 1-unit increase in continuous predictor variables. The SD units were calculated by dividing the estimated beta coefficient for the predictor variable from the linear regression model by the SD of the ranks for the entire sample used for a given model.

All models were fitted using Stata 14.1 software (StataCorp). We set $\alpha=0.05$, 2-tailed. We did not perform corrections for multiple comparisons, so that the statistical significance of *P*-values for secondary outcomes, particularly those between 0.01 and 0.05, should be interpreted with caution.

RESULTS

Participants

Sample

We screened 165 men, of whom 25 were excluded from medical evaluation as follows: 10 qualified for participation but withdrew before medical evaluation (9 AAS users, 1 nonuser), 12 reported AAS use of <2 years duration, and 3 showed findings on drug testing or fat-free mass index inconsistent with their self-reports. The remaining sample comprised 86 AAS users and 54 nonusers. Among the AAS users, 58 (67%) were on-drug and 28 (33%) off-drug at evaluation. The off-drug users had last used AAS a median (interquartile range) of 15 (5, 70) months before evaluation.

Characteristics

AAS users and nonusers were similar on most characteristics (Table 1), but users showed higher body mass index and fat-free mass index, consistent with known effects of AAS.

Cardiometabolic Features

Compared with nonusers, AAS users displayed higher blood pressure (mean±SD systolic, 118±11 versus 115±10 mmHg; diastolic, 76±9 versus 72±9 mmHg) and a higher prevalence of dyslipidemia (N [%] with low-

density lipoprotein cholesterol >160 mg/dL: 20 [23%] versus 7 [13%]).

Cardiac Structure and Function

For the primary outcome variables of LVEF and E' , AAS users showed significant deficits compared with nonusers (Table 2). In models further adjusted for resting heart rate, the estimated mean differences between groups were reduced by 15%, and this change had no impact on the statistical significance of these findings ($P<0.001$ for both). On other measures, AAS users exhibited higher LV mass index, thicker LV walls, and more concentric LV geometry than nonusers. On subsequent analyses examining the association of outcomes with duration and currency of AAS use, currency of use was strongly associated with greater pathology (Figure 1 and [Table IV in the online-only Data Supplement](#)). Specifically, 41 (71%) of the 58 on-drug users showed LVEFs falling below the normal threshold of 52%,⁴³ whereas off-drug users showed largely normal LVEFs. Twenty-nine (50%) on-drug users fell below the normal E' threshold of 8.5 cm/second,⁴⁴ with off-drug users showing only partially normalized E' . Similar associations with currency of AAS use were found across other echocardiographic measures ([Table IV in the online-only Data Supplement](#)). In contrast, we found no significant associations between duration of AAS use and the primary outcome variables (for each additional 10 years of AAS exposure, the estimated mean change [95% confidence interval] in LVEF was -3.3% [-8.3 to 1.6], $P=0.19$; and the estimated mean change in E' was 0.1 cm/second [-1.0 to 1.2 cm/second], $P=0.90$).

Because LVEF and E' differed by group (ie, AAS user versus nonuser) and by subgroup based on currency of use (ie, current versus past AAS users), we further tested for interactions of group and subgroup status with LV mass index for each of these associations and found evidence for a significant interaction with AAS user group status ($P=0.046$ and $P=0.016$ for LVEF and E' , respectively) but not for currency of use among AAS users ($P=0.21$ and $P=0.86$, respectively). Therefore, we assessed the associations separately for AAS users and nonusers. Examining LVEF, among AAS users, a significant association occurred between increased LV mass index and decreased LVEF (estimated mean change [95% confidence interval] in LVEF for each 10 g increase in LV mass index -1.6% [-2.4 to -0.8], $P<0.001$). In contrast, among the nonusers, no significant association occurred between LV mass index and LVEF (estimated mean change in LVEF for each 10 g increase in LV mass index -0.2% [-1.5 to 1.2], $P=0.80$). Examining E' , among AAS users, a significant association occurred between increased LV mass index and reduced E' (estimated mean change in E' for each 10 g increase in LV mass index -0.31 cm/second [-0.49 to -0.13 cm/second], $P<0.001$). Among nonusers, the

Table 1. Characteristics of Anabolic-Androgenic Steroid Users and Nonusers*

Characteristics	Users	Nonusers	P Value
	(N=86)	(N=54)	
Demographic features			
Age, y	42 (39–47)	43 (38–49)	0.79
Race†			
White	80 (93)	41 (76)	
Black	6 (7)	12 (22)	0.006
Asian	0	1 (2)	
Ethnic background†			
Not Hispanic	76 (89)	52 (96)	0.13
Hispanic	10 (11)	2 (4)	
Anthropomorphic measures			
Height, m	1.8 (1.7–1.8)	1.8 (1.7–1.8)	0.16
Body surface area, m ² ‡	2.2 (2.1–2.3)	2.2 (2.0–2.3)	0.19
Body mass index§	31 (29–33)	29 (27–31)	<0.001
Fat-free mass index¶	26 (24–28)	23 (21–25)	<0.001
Exercise measures			
Age at onset of regular weightlifting, y	16 (14–20)	16 (15–20)	0.97
Lifetime duration of regular weightlifting, y	21 (15–26)	20 (12–28)	0.78
Time spent in aerobic exercise per week			
0–30 min	30 (35)	19 (35)	
31–120 min	24 (28)	22 (41)	0.18
>120 min	32 (37)	13 (24)	
Other potential cardiovascular risk factors			
Family history of coronary artery disease**	25 (29)	12 (22)	0.37
Lifetime history of substance use			
Regular cigarette smoking††	27 (31)	19 (35)	0.64
Alcohol dependence‡‡	12 (14)	7 (13)	0.87
Cocaine dependence‡‡	13 (15)	5 (9)	0.31
AAS use			
Age at onset of AAS use, y	23 (19–30)	—	
Cumulative lifetime total duration of AAS use, y	7.4 (4.0–11.6)	—	
Cumulative lifetime dose of AAS, g	366 (166–608)	—	

AAS indicates anabolic-androgenic steroids.

*Data are reported as median (interquartile range) or n (%) as appropriate. P values were obtained from a Wilcoxon rank-sum test or Fisher exact test.

†Race and ethnic background were self-reported.

‡By Mosteller formula.

§The body mass index is the weight in kilograms divided by the square of the height in meters.

¶The fat-free mass index is calculated as $(W(1-BF)/H^2) + 6.1(1.8-H)$, where W=weight in kg, H=height in m, and BF=percent body fat.³⁷

||Any self-reported aerobic exercise beyond ordinary daily activities.

**At least 1 first-degree relative reported to have had coronary artery disease, angina, heart attack, angioplasty/stent, or coronary artery bypass surgery.

††Any cigarette smoking beyond brief experimentation.

‡‡By the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*.³⁹

Table 2. Echocardiographic Findings in Anabolic-Androgenic Steroid Users and Nonusers*

Variable	Users (N=86)	Nonusers (N=54)	Comparison	
			Estimated Difference (95% Confidence Interval)†	P Value
Primary outcomes				
Left ventricular ejection fraction, %	52±11	63±8	-10 (-14 to -7)	<0.001
Average early left ventricular E', cm/s	9.3±2.4	11.1±2.0	-1.9 (-2.7 to -1.0)	<0.001
Secondary outcomes				
Resting heart rate, beats/min	65±5	62±6	2.7 (0.7 to 4.7)	0.008
Left atrial diameter, cm‡	3.6±0.5	3.5±0.5	0.1 (-0.1 to 0.2)	0.42
Longitudinal 4-chamber strain§	-16±4	-20±3	4.6 (3.2-6.0)	<0.001
Early lateral ventricular E', cm/s	10.6±3.1	12.5±2.3	-1.8 (-2.9 to -0.8)	<0.001
Early septal ventricular E', cm/s	8.0±2.2	9.8±2.1	-1.9 (-2.7 to -1.1)	<0.001
Left ventricular end diastolic internal diameter, cm	5.0±0.6	4.8±0.5	0.1 (-0.1 to 0.3)	0.30
Left ventricular end systolic internal diameter, cm‡	3.6±0.7	3.2±0.5	0.3 (0.0 to 0.5)	0.018
Left ventricular end diastolic volume, mL	125±38	119±28	-0.5 (-13 to 12)	0.94
Left ventricular end systolic volume, mL	61±27	45±15	13 (5 to 21)	0.003
Interventricular septum thickness, cm	1.2±0.2	1.1±0.1	0.2 (0.1 to 0.2)	<0.001
Posterior wall thickness, cm	1.2±0.2	1.1±0.2	0.1 (0.0 to 0.2)	0.003
Left ventricular mass, g	245±62	192±40	44 (24 to 63)	<0.001
Left ventricular mass/body surface area, g/m ²	111±61	89±18	21 (11 to 30)	<0.001
Left ventricular mass/height, g/m	138±33	107±22	27 (16 to 38)	<0.001
Left ventricular mass/height ^{2.7} , g/m ^{2.7}	52±13	40±8	11 (7 to 16)	<0.001
Relative wall thickness	0.49±0.11	0.45±0.08	0.050 (0.014 to 0.087)	0.007

AAS indicates anabolic-androgenic steroids; and E', relaxation velocity.

*Data are reported as means±SD.

†Estimated mean differences between groups adjusted for age, race, family history of coronary artery disease, cocaine dependence, regular tobacco use, alcohol dependence, aerobic exercise in the past 10 y, and body surface area by the Mosteller formula.

‡N=85 AAS users.

§N=84 AAS users.

relationship was of approximately equal magnitude but in the opposite direction, with a significant association between increased LV mass index and increased E' (estimated mean change in E' for each 10 g increase in LV mass index 0.36 cm/second [0.04–0.68 cm/second], $P<0.001$).

Coronary Artery Atherosclerosis

AAS users showed significantly higher coronary plaque volume than nonusers (Table 3 and Figure 2). On examining the association of CTA measures with currency and duration of AAS use, we found strong associations between lifetime duration of use on all angiographic measures of coronary pathology (Table 4 and Figure 3). However, we found no significant association between currency of use and plaque volume (estimated mean difference between on-drug and off-drug users in ranks:

-0.07 SD units [-0.56 to 0.41], $P=0.76$). It is notable that 3 (3%) AAS users had experienced earlier myocardial infarctions because of underlying atherosclerotic disease, documented by cardiac catheterization, occurring at 38 years of age (ST-segment myocardial infarction with complete occlusion of left anterior descending artery), 43 years of age (non-ST-segment myocardial infarction with 99% occlusion of both the right coronary and left circumflex coronary arteries), and 46 years of age (ST-elevation myocardial infarction with complete occlusion of a second obtuse marginal artery) and after 17, 11, and 5 years of cumulative lifetime AAS exposure, respectively. In addition, 1 AAS user had presented at 42 years of age after 20 years of cumulative lifetime AAS exposure with congestive heart failure and underwent stenting of the left circumflex and first obtuse marginal arteries. None of the 54 nonusers had a history of myocardial infarction or stenting.

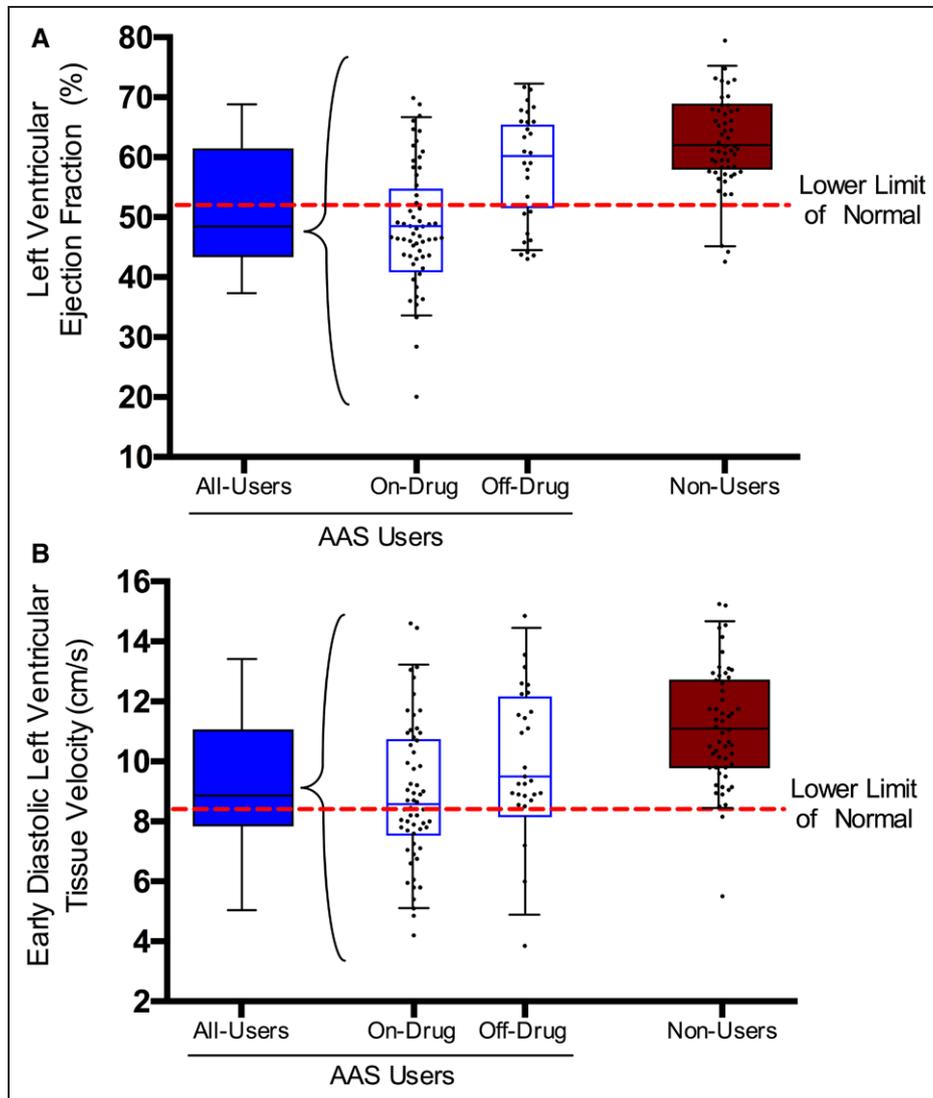


Figure 1. Left ventricular systolic and diastolic function in anabolic-androgenic steroid users and comparison nonusers.

A, Boxplots of left ventricular ejection fraction in anabolic-androgenic steroid (AAS) users (N=86), shown as an entire group (**Left**) and as subgroups of individuals who were on-drug (N=58) and off-drug (N=28) at the time of evaluation (**Middle**); and nonusers (N=54) (**Right**). On this variable, the estimated mean difference (95% confidence interval) between on-drug and off-drug AAS users, adjusted for covariates as described in the text, is -9.5% (-13.8 to -5.2), $P<0.001$; for on-drug AAS users versus nonusers, the difference is -13.6% (-17.3 to -9.8), $P<0.001$; and for off-drug AAS users versus nonusers, the difference is -4.1% (-8.6 to 0.3), $P=0.072$. **B**, Left ventricular early relaxation velocity in the same 4 groups. On this variable, the mean difference between on-drug and off-drug AAS users is -1.1 (-2.1 to -0.1) cm/second, $P=0.035$; for on-drug AAS users versus nonusers, the difference is -2.2 (-3.1 to -1.4) cm/second, $P<0.001$; and for off-drug AAS users versus nonusers, the difference is -1.1 (-2.2 to -0.1) cm/second, $P=0.035$.

Sensitivity Analyses

Assessing the influence of alternative sets of potential confounders, using models with both reduced and augmented sets of covariates, we obtained results similar to those of the primary analysis, with $<15\%$ change in the estimates for the primary outcomes and preservation of statistical significance for all results identified as such in the primary analysis (Tables V–VII in the online-only Data Supplement). We also reanalyzed the echocardiographic findings while omitting the 3 men with previous myocardial

infarctions. This analysis produced negligible changes in the findings, with the estimated mean differences between users and nonusers on the 2 primary outcome variables changing by $<2\%$ when these 3 men were excluded.

DISCUSSION

Illicit AAS use is widespread, but its long-term adverse effects remain poorly understood. A growing literature, largely comprised of case reports and small observa-

Table 3. Computed Tomography Coronary Angiography Findings in Anabolic-Androgenic Steroid Users and Nonusers*

Variable	Users (N=84)	Nonusers (N=53)	Comparison	
			Estimated Difference in Standardized Ranks (95% Confidence Interval)†	P Value
Primary outcome				
Plaque volume, mm ³ ‡	3 (0–174)	0 (0–69)	0.46 (0.10–0.82)	0.012
Secondary outcomes				
Degree of stenosis for most severe stenosis§	0.5 (0–1)	0.5 (0–1)	0.37 (–0.00 to 0.75)	0.052
Number of diseased coronary artery segments¶	0.5 (0–2)	1 (0–1)	0.36 (–0.01 to 0.74)	0.059
Agatston calcium score‡	0 (0–25)	0 (0–1)	0.18 (–0.17 to 0.52)	0.31

AAS indicates anabolic-androgenic steroids; and CI, confidence interval.

*Data are shown as median (interquartile range).

†Estimated mean difference between groups in rank, measured in standard deviation units, adjusted for age, race, family history of coronary artery disease, cocaine dependence, alcohol dependence, tobacco use, and aerobic exercise in the past 10 y (see text).

‡Four AAS users had received percutaneous coronary interventions, and thus their plaque volume and calcium score could not be quantified accurately. However, all 4 men showed extensive plaque as evidenced by their number of diseased segments and degree of stenosis for most severe stenosis. Therefore, for purposes of calculation, they were assigned the median values for plaque volume and calcium score, respectively, from among all study participants with nonzero plaque volume and calcium scores. If these cases were omitted entirely, then the estimated mean difference (95% confidence interval) between groups in standardized rank would be 0.43 (0.04–0.81) for plaque volume and 0.13 (–0.26 to 0.51) for calcium score.

§Represents the worst degree of stenosis of any coronary artery, on a scale of 0–4, where 0=0% stenosis, 1=1% to 25%, 2=26% to 49%, 3=50% to 69%, and 4=70% to 99%.

¶Represents the number of coronary artery segments showing any disease, with scores ranging from 0 to 10 diseased segments.

tional studies, suggests that AAS use may cause cardiovascular disease. We undertook the present study to examine cardiovascular health measures among long-term AAS users and otherwise similar nonusers with the following 4 key findings. First, AAS users demonstrated substantial impairment of LV systolic function as assessed by LVEF and longitudinal strain. This finding was driven almost entirely by those AAS users who were on-drug at the time of evaluation, suggesting that LV dysfunction

may be a dynamically related to AAS-use patterns. Second, AAS users also showed impaired LV diastolic dysfunction, both relative to nonusers and also as defined by current diagnostic criteria.⁴⁴ In contrast to systolic function, which appeared largely normal among off-drug AAS users, LV diastolic function was impaired in both on-drug and off-drug users, suggesting a more permanent form of acquired pathology. Third, AAS users had significantly more LV hypertrophy, as reflected by LV mass index, than nonusers, suggesting an anabolic effect on cardiac muscle mass. In addition, the magnitude of LV hypertrophy among AAS users was directly related to the degrees of both systolic and diastolic function, suggesting a mechanistic link between LV hypertrophy and functional deterioration. Fourth, AAS use was associated with increased coronary atherosclerosis, and the severity of atherosclerotic disease was strongly associated with cumulative lifetime duration of AAS use. In aggregate, our findings suggest that long-term AAS use is associated with adverse cardiovascular phenotypes characterized by both myocardial pathology and coronary artery pathology, which may represent a clinically substantial and largely unrecognized public health problem.

Several scientific and clinical implications emerge from this study. First, improved identification of the adverse cardiovascular associations of AAS use may deter potential future users. Second, clinicians may be better informed about the potential adverse cardiovascular effects of AAS. It is important to note that participants in the present study were not elite or professional athletes, the small subset of the general population most commonly tied to AAS exposure, but rather a sample of middle-age men representing a reasonably broad socioeconomic and racial/ethnic distribution. Thus, when comparable men are found to have impaired LV function or premature coronary artery disease, it seems prudent for clinicians to now include AAS use on the differential diagnosis of possible causes. Third, data derived from the present cross-sectional study provide a foundation for critical future work. The hypothesis that some cardiovascular phenotypes associated with AAS use may wax and wane with drug exposure (eg, LV systolic dysfunction) while others may be more permanent, perhaps irreversible (eg, LV diastolic dysfunction and coronary atherosclerosis), deserves rigorous assessment. Longitudinal studies of illicit AAS users with hard clinical endpoints, and with interventions to impact drug exposure patterns and treat detected disease, are also of importance.

Limitations

Several threats regarding the internal validity of this study, as previously delineated in general for cross-sectional cohort studies,^{27,29} deserve consideration. First, bias might arise through exiting from the under-

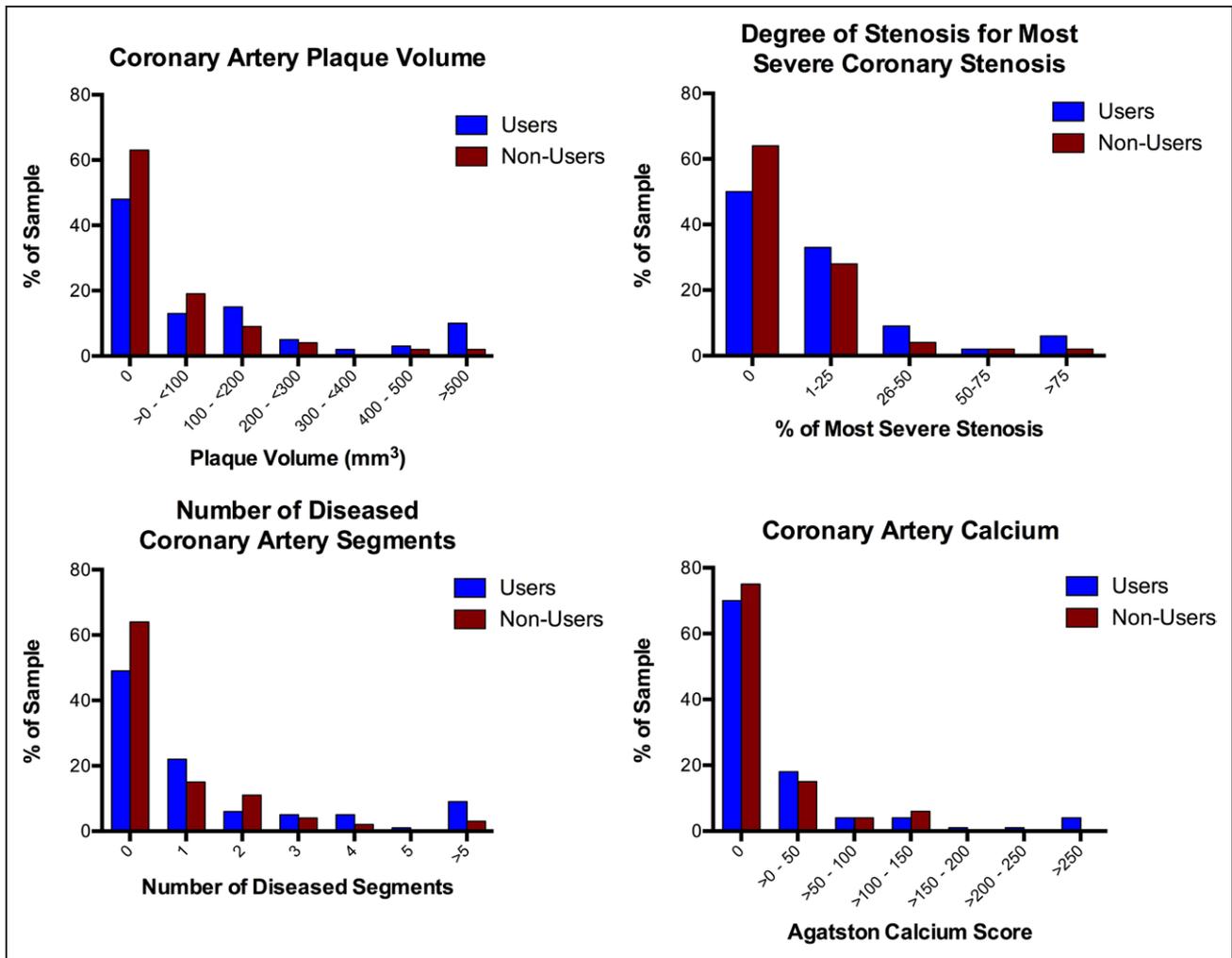


Figure 2. Distribution of computed tomography coronary angiography measures in anabolic-androgenic steroid users and nonusers.

Histograms displaying distribution of coronary artery plaque volume, degree of stenosis for most severe stenosis, number of diseased coronary artery segments, and coronary artery calcium for anabolic-androgenic steroid (AAS) users (N=84) and nonusers (N=53). The histograms for plaque volume and calcium score include for men with imputed values, as described in the footnote to Table 3.

lying conceptual cohort (ie, becoming unavailable for study in the present) that is differential with respect to exposure status. For example, AAS users might be more likely than nonusers to develop cardiovascular morbidity, stop weightlifting, and hence be unavailable for recruitment. Any resulting bias, however, would likely underestimate the effects of AAS use. Second, as in all observational studies, we cannot exclude residual confounding. However, given the lack of confounding seen with our measured potential confounders—as evidenced by similar estimates in sensitivity analyses using both reduced and augmented sets of potential confounders—it is unlikely that substantial residual bias remains because of unmeasured confounders. Third, because both AAS users and nonusers were weightlifters, the effects of AAS might be clouded if weightlifting contributed to cardiovascular pathology. However, our ancillary study

comparing non-AAS-using weightlifters with nonweightlifters demonstrated that weightlifting alone (of the duration and intensity exhibited by our sample) had little effect on cardiac adaptation or pathology. Fourth, bias could arise from measurement error, particularly in the exposure variables (eg, misclassifying surreptitious AAS users as nonusers or inaccurately assessing the type, duration, dose, and currency of use). In particular, AAS users provided retrospective accounts, often spanning many years of time, of the use of illicit drugs of uncertain potency or authenticity. As such, estimates of participants' lifetime duration of AAS use and total lifetime AAS dose were only approximations. The effect of these various sources of measurement error would be expected to be differential for between-group comparisons (because of the potential for inclusion of surreptitious AAS users in the nonuser group and the much less likely inclusion of

Table 4. Association of Computed Tomography Coronary Angiography Variables With Lifetime Duration of Anabolic-Androgenic Steroid Use

Variable	Increase in Standardized Rank per 10-y Increase in Duration of Lifetime AAS Use (95% Confidence Interval)*	P Value
Primary outcome		
Plaque volume, mm ³ †	0.60 (0.16–1.03)	0.008
Secondary outcomes		
Degree of stenosis for most severe stenosis‡	0.68 (0.26–1.10)	0.002
Number of diseased coronary artery segments§	0.75 (0.31–1.19)	<0.001
Agatston calcium score†	0.49 (0.06–0.92)	0.025

AAS indicates anabolic-androgenic steroids.

*Estimated increase in rank, measured in standard deviation units, for each 10-y increase in cumulative lifetime duration of AAS use, adjusted for age, race, family history of coronary artery disease, cocaine dependence, alcohol dependence, tobacco use, and aerobic exercise in the past 10 y (see text).

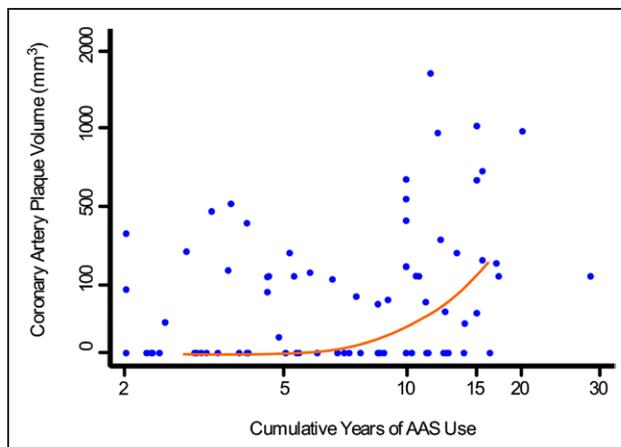
†Four AAS users had received previous percutaneous coronary interventions, and thus their plaque volume and calcium scores could not be measured accurately. However, all 4 of these men exhibited extensive plaque as evidenced by their number of diseased segments and degree of stenosis for most severe stenosis. Therefore, for purposes of calculation, they were assigned the median values for plaque volume and calcium score, respectively, from among all study participants with nonzero plaque volume and calcium scores. If these cases were omitted entirely, then the increase (95% confidence interval) in standardized rank per 10 y of AAS exposure would be 0.61 (0.11–1.12) for plaque volume and 0.48 (–0.04 to 0.99) for calcium score.

‡The worst degree of stenosis of any coronary artery, on a scale of 0–4, where 0=0% stenosis, 1=1% to 25%, 2=26% to 49%, 3=50% to 69%, and 4=70% to 99%.

§Represents the number of coronary artery segments showing any disease, with scores ranging from 0 to 10 diseased segments.

individuals falsely reporting AAS use in the user group) and random for within-group comparisons among AAS users (because of the low likelihood of an association between cardiac outcomes and error in the predictor variables). Both of these sources would likely bias results toward the null, thereby yielding an underestimate of the effects of AAS use.

Potential threats to external validity (generalizability) also require consideration. First, we recruited AAS users from gymnasiums. Thus, our results might not generalize to other AAS-using groups (eg, elite athletes). However, most AAS users are recreational weightlifters, and thus our results likely generalize to the population of AAS users of greatest public health importance. Second, despite the demographic diversity of our sample, white

**Figure 3. Relationship between coronary artery plaque volume and cumulative lifetime duration of anabolic-androgenic steroid exposure.**

Scatter plot displaying coronary artery plaque volume and cumulative years of lifetime anabolic-androgenic steroid (AAS) exposure, with a median spline (red line) fitted to the data to aid in the visualization of the relationship between these variables. Because of the highly right-skewed distributions, the data are presented on a transformed scale (square root transformation for coronary artery plaque volume; logarithmic transformation for cumulative years of AAS use).

non-Hispanic men were overrepresented, and therefore our results might not generalize to the full racial/ethnic spectrum of AAS users. Overall, however, these potential threats to internal and external validity appear modest. Thus, our findings likely represent reasonably unbiased estimates of the associations of AAS exposure with adverse cardiovascular phenotypes.

CONCLUSION

Our findings suggest that AAS use is associated with LV dysfunction and premature coronary artery disease. These findings may inform public health initiatives to curb drug exposure and provide clinicians with information that will translate into improved patient care.

SOURCES OF FUNDING

This study was supported by grant R01 DA-029141 from the National Institute on Drug Abuse (to Drs Pope, Kanayama, Hudson, Baggish, Weiner, and Hoffmann).

DISCLOSURES

Drs Pope, Kanayama, Hudson, Baggish, Weiner, and Hoffmann have received grant support for this study from the National Institute on Drug Abuse. Dr Hoffmann has received grants from HeartFlow and KOWA. Dr Pope has received expert witness fees for cases involving anabolic-androgenic steroids from the McNeil, Leddy, & Sheahan Law Firm and the US District Attorney

for Eastern New York. Drs Kanayama and Weiner report no additional conflicts of interest. Dr Lu reports no conflicts of interest.

AFFILIATIONS

From Cardiovascular Performance Program, Division of Cardiology, Massachusetts General Hospital, Boston (A.L.B., R.B.W.); Department of Medicine, Harvard Medical School, Boston, MA (A.L.B., R.B.W.); Biological Psychiatry Laboratory and Psychiatric Epidemiology Research Program, McLean Hospital, Belmont, MA (G.K., J.I.H., H.G.P.); Department of Psychiatry, Harvard Medical School, Boston, MA (G.K., J.I.H., H.G.P.); Cardiac MR PET CT Program, Massachusetts General Hospital and Department of Radiology, Harvard Medical School, Boston (M.T.L., U.H.).

FOOTNOTES

Received December 15, 2016; accepted March 13, 2017.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.026945/-/DC1>.

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Circulation is available at <http://circ.ahajournals.org>.

REFERENCES

- Pope HG Jr, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. *Endocr Rev*. 2014;35:341–375. doi: 10.1210/er.2013-1058.
- Pope HG Jr, Kanayama G, Athey A, Ryan E, Hudson JI, Baggish A. The lifetime prevalence of anabolic-androgenic steroid use and dependence in Americans: current best estimates. *Am J Addict*. 2014;23:371–377. doi: 10.1111/j.1521-0391.2013.12118.x.
- Kanayama G, Hudson JI, Pope HG Jr. Long-term psychiatric and medical consequences of anabolic-androgenic steroid abuse: a looming public health concern? *Drug Alcohol Depend*. 2008;98:1–12. doi: 10.1016/j.drugalcdep.2008.05.004.
- McNutt RA, Ferenchick GS, Kirilin PC, Hamlin NJ. Acute myocardial infarction in a 22-year-old world class weight lifter using anabolic steroids. *Am J Cardiol*. 1988;62:164.
- Bowman S. Anabolic steroids and infarction. *BMJ*. 1990;300:750.
- Ferenchick GS, Adelman S. Myocardial infarction associated with anabolic steroid use in a previously healthy 37-year-old weight lifter. *Am Heart J*. 1992;124:507–508.
- Gårevik N, Strahm E, Garle M, Lundmark J, Ståhle L, Ekström L, Rane A. Long term perturbation of endocrine parameters and cholesterol metabolism after discontinued abuse of anabolic androgenic steroids. *J Steroid Biochem Mol Biol*. 2011;127:295–300. doi: 10.1016/j.jsbmb.2011.08.005.
- Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med*. 2004;34:513–554.
- Thompson PD, Cullinane EM, Sady SP, Chenevert C, Saritelli AL, Sady MA, Herbert PN. Contrasting effects of testosterone and stanozolol on serum lipoprotein levels. *JAMA*. 1989;261:1165–1168.
- Cabral AM, Vasquez EC, Moysés MR, Antonio A. Sex hormone modulation of ventricular hypertrophy in sinoaortic denervated rats. *Hypertension*. 1988;11(2 Pt 2):I93–I97.
- Malhotra A, Buttrick P, Scheuer J. Effects of sex hormones on development of physiological and pathological cardiac hypertrophy in male and female rats. *Am J Physiol*. 1990;259(3 Pt 2):H866–H871.
- Tagarakis CV, Bloch W, Hartmann G, Hollmann W, Addicks K. Anabolic steroids impair the exercise-induced growth of the cardiac capillary bed. *Int J Sports Med*. 2000;21:412–418. doi: 10.1055/s-2000-3835.
- Tagarakis CV, Bloch W, Hartmann G, Hollmann W, Addicks K. Testosterone-propionate impairs the response of the cardiac capillary bed to exercise. *Med Sci Sports Exerc*. 2000;32:946–953.
- Norton GR, Trifunovic B, Woodiwiss AJ. Attenuated beta-adrenoceptor-mediated cardiac contractile responses following androgenic steroid administration to sedentary rats. *Eur J Appl Physiol*. 2000;81:310–316. doi: 10.1007/s004210050048.
- Frankenfeld SP, Oliveira LP, Ortenzi VH, Rego-Monteiro IC, Chaves EA, Ferreira AC, Leitão AC, Carvalho DP, Fortunato RS. The anabolic androgenic steroid nandrolone decanoate disrupts redox homeostasis in liver, heart and kidney of male Wistar rats. *PLoS One*. 2014;9:e102699. doi: 10.1371/journal.pone.0102699.
- Medei E, Marocolo M, Rodrigues Dde C, Arantes PC, Takiya CM, Silva J, Rondinelli E, Goldenberg RC, de Carvalho AC, Nascimento JH. Chronic treatment with anabolic steroids induces ventricular repolarization disturbances: cellular, ionic and molecular mechanism. *J Mol Cell Cardiol*. 2010;49:165–175. doi: 10.1016/j.yjmcc.2010.04.014.
- Zaugg M, Jamali NZ, Lucchinetti E, Xu W, Alam M, Shafiq SA, Siddiqui MA. Anabolic-androgenic steroids induce apoptotic cell death in adult rat ventricular myocytes. *J Cell Physiol*. 2001;187:90–95.
- Baggish AL, Weiner RB, Kanayama G, Hudson JI, Picard MH, Hutter AM Jr, Pope HG Jr. Long-term anabolic-androgenic steroid use is associated with left ventricular dysfunction. *Circ Heart Fail*. 2010;3:472–476. doi: 10.1161/CIRCHEARTFAILURE.109.931063.
- D'Andrea A, Caso P, Salerno G, Scarafilo R, De Corato G, Mita C, Di Salvo G, Severino S, Cuomo S, Liccardo B, Esposito N, Calabrò R. Left ventricular early myocardial dysfunction after chronic misuse of anabolic androgenic steroids: a Doppler myocardial and strain imaging analysis. *Br J Sports Med*. 2007;41:149–155. doi: 10.1136/bjism.2006.030171.
- Krieg A, Scharhag J, Albers T, Kindermann W, Urhausen A. Cardiac tissue Doppler in steroid users. *Int J Sports Med*. 2007;28:638–643. doi: 10.1055/s-2007-964848.
- Luijckx T, Velthuis BK, Backx FJ, Buckens CF, Prakken NH, Rienks R, Mali WP, Cramer MJ. Anabolic androgenic steroid use is associated with ventricular dysfunction on cardiac MRI in strength trained athletes. *Int J Cardiol*. 2013;167:664–668. doi: 10.1016/j.ijcard.2012.03.072.
- Nottin S, Nguyen LD, Terbah M, Obert P. Cardiovascular effects of androgenic anabolic steroids in male bodybuilders determined by tissue Doppler imaging. *Am J Cardiol*. 2006;97:912–915. doi: 10.1016/j.amjcard.2005.10.026.
- Angell PJ, Ismail TF, Jabbour A, Smith G, Dahl A, Wage R, Whyte G, Green DJ, Prasad S, George K. Ventricular structure, function, and focal fibrosis in anabolic steroid users: a CMR study. *Eur J Appl Physiol*. 2015;114:921–928.
- Santora LJ, Marin J, Vangrow J, Minegar C, Robinson M, Mora J, Friede G. Coronary calcification in body builders using anabolic steroids. *Prev Cardiol*. 2006;9:198–201.
- Hassan NA, Salem MF, Sayed MA. Doping and effects of anabolic androgenic steroids on the heart: histological, ultrastructural, and echocardiographic assessment in strength athletes. *Hum Exp Toxicol*. 2009;28:273–283. doi: 10.1177/0960327109104821.
- Kasikcioglu E, Oflaz H, Umman B, Bugra Z. Androgenic anabolic steroids also impair right ventricular function. *Int J Cardiol*. 2009;134:123–125. doi: 10.1016/j.ijcard.2007.12.027.
- Hudson JI, Pope HG Jr, Glynn RJ. The cross-sectional cohort study: an underutilized design. *Epidemiology*. 2005;16:355–359.

28. Kanayama G, DeLuca J, Meehan WP 3rd, Hudson JI, Isaacs S, Baggish A, Weiner R, Micheli L, Pope HG Jr. Ruptured tendons in anabolic-androgenic steroid users: a cross-sectional cohort study. *Am J Sports Med*. 2015;43:2638–2644. doi: 10.1177/0363546515602010.
29. Pope HG Jr, Kanayama G, Hudson JI. Risk factors for illicit anabolic-androgenic steroid use in male weightlifters: a cross-sectional cohort study. *Biol Psychiatry*. 2012;71:254–261. doi: 10.1016/j.biopsych.2011.06.024.
30. Arnold B, Arana B, Mäusezahl D, Hubbard A, Colford JM Jr. Evaluation of a pre-existing, 3-year household water treatment and handwashing intervention in rural Guatemala. *Int J Epidemiol*. 2009;38:1651–1661. doi: 10.1093/ije/dyp241.
31. Ljungman C, Kahan T, Schiöler L, Hjerpe P, Wettermark B, Boström KB, Manhem K. Antihypertensive treatment and control according to gender, education, country of birth and psychiatric disorder: the Swedish Primary Care Cardiovascular Database (SPCCD). *J Hum Hypertens*. 2015;29:385–393. doi: 10.1038/jhh.2014.100.
32. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1999;56:617–626.
33. Whitlock G, Norton R, Clark T, Pledger M, Jackson R, MacMahon S. Motor vehicle driver injury and socioeconomic status: a cohort study with prospective and retrospective driver injuries. *J Epidemiol Community Health*. 2003;57:512–516.
34. Bahrke MS, Yesalis CE, Kopstein AN, Stephens JA. Risk factors associated with anabolic-androgenic steroid use among adolescents. *Sports Med*. 2000;29:397–405.
35. Ip EJ, Barnett MJ, Tenerowicz MJ, Perry PJ. The Anabolic 500 survey: characteristics of male users versus nonusers of anabolic-androgenic steroids for strength training. *Pharmacotherapy*. 2011;31:757–766. doi: 10.1592/phco.31.8.757.
36. Parkinson AB, Evans NA. Anabolic androgenic steroids: a survey of 500 users. *Med Sci Sports Exerc*. 2006;38:644–651. doi: 10.1249/01.mss.0000210194.56834.5d.
37. Kouri EM, Pope HG Jr, Katz DL, Oliva P. Fat-free mass index in users and nonusers of anabolic-androgenic steroids. *Clin J Sport Med*. 1995;5:223–228.
38. Kanayama G, Pope HG, Cohane G, Hudson JI. Risk factors for anabolic-androgenic steroid use among weightlifters: a case-control study. *Drug Alcohol Depend*. 2003;71:77–86.
39. First M, Spitzer R, Gibbon M, Williams J. Structured Clinical Interview for DSM–IV Axis I Disorders–Patient Edition. New York: Biometrics Research Department, New York State Psychiatric Institute; 2001.
40. Pope HG, Katz DL. Psychiatric effects of exogenous anabolic-androgenic steroids. In: Wolkowitz OM, Rothschild AJ, eds. *Psychoneuroendocrinology: The scientific basis of clinical practice*. Washington, DC: American Psychiatric Press; 2003:331–358.
41. Pope HG, Kanayama G. Can you tell if your patient is using anabolic steroids? *Curr Psychiatry Prim Care*. 2005;1:28–34.
42. Weiner RB, Wang F, Isaacs SK, Malhotra R, Berkstresser B, Kim JH, Hutter AM Jr, Picard MH, Wang TJ, Baggish AL. Blood pressure and left ventricular hypertrophy during American-style football participation. *Circulation*. 2013;128:524–531. doi: 10.1161/CIRCULATIONAHA.113.003522.
43. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1.e14–39.e14.
44. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314. doi: 10.1016/j.echo.2016.01.011.
45. Maurovich-Horvat P, Ferencik M, Bamberg F, Hoffmann U. Methods of plaque quantification and characterization by cardiac computed tomography. *J Cardiovasc Comput Tomogr*. 2009;3(Suppl 2):S91–S98. doi: 10.1016/j.jcct.2009.10.012.
46. Hoffmann MH, Shi H, Schmitz BL, Schmid FT, Lieberknecht M, Schulze R, Ludwig B, Kroschel U, Jahnke N, Haerer W, Brambs HJ, Aschoff AJ. Noninvasive coronary angiography with multislice computed tomography. *JAMA*. 2005;293:2471–2478. doi: 10.1001/jama.293.20.2471.
47. Hartgens F, Rietjens G, Keizer HA, Kuipers H, Wolffenbuttel BH. Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a). *Br J Sports Med*. 2004;38:253–259.