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Cardiovascular phenotype of long-term anabolic-androgenic steroid abusers compared with strength-trained athletes

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Introduction: Abuse of anabolic-androgenic steroids (AAS) has been linked to a variety of different cardiovascular (CV) side effects, but still the clinical effects of AAS abuse on CV risk are not clear. The aim of this study was to assess the CV phenotype of a large cohort of men with long-term AAS use compared with strength-trained athletes without AAS use.

Methods: Fifty one strength-trained men with ≥3 years of AAS use was compared with twenty one strength-trained competing athletes. We verified substance abuse and non-abuse by blood and urine analyses. The participants underwent comprehensive CV evaluation including laboratory analyses, 12-lead ECG with measurement of QT dispersion, exercise ECG, 24 h ECG with analyses of heart rate variability, signal averaged ECG, basic transthoracic echocardiography, and coronary computed tomography angiography (CCTA).

Results: Hemoglobin levels and hematocrit were higher among the AAS users compared with non-users (16.8 vs. 15.0 g/dl, and 0.50% vs. 0.44%, respectively, both $p < 0.01$) and HDL cholesterol significantly lower (0.69 vs. 1.25 mmol/L, $p < 0.01$). Maximal exercise capacity was 270 and 280 W in the AAS and the non-user group, respectively ($p = 0.04$). Echocardiography showed thicker intraventricular septum and left ventricular (LV) posterior wall among AAS users ($p < 0.01$ for both), while LV ejection fraction was lower (50 vs. 54%, $p = 0.02$). Seven AAS users (17%) had evidence of coronary artery disease on CCTA. There were no differences in ECG measures between the groups.

Conclusions: A divergent CV phenotype dominated by increased CV risk, accelerated coronary artery disease, and concentric myocardial hypertrophy was revealed among the AAS users.

KEYWORDS

anabolic-androgenic steroids, cardiovascular phenotype, coronary artery disease, myocardial remodeling

1 | INTRODUCTION

The use of illicit anabolic-androgenic steroids (AAS) has become highly prevalent across the globe.[1] People use AAS because of their performance-enhancing properties, characterized by increased muscle strength and muscle size, and for aesthetic reasons. The abuse is widespread among competitive bodybuilders, while the highest numbers are found among recreational weightlifters.[2] Frequently, AAS users maintain long-term systemic exposure to supraphysiological doses.[3] The long-term effects of AAS use remain poorly known. Numerous case reports have suggested an association between AAS use and a range of different cardiovascular (CV) diseases; myocardial hypertrophy, heart failure, myocardial infarction, and sudden cardiac death are among the most frequently reported.[4–6] These case reports have prompted experimental studies that demonstrate that AAS are capable of inducing a range of maladaptive CV changes. Among these are premature atherosclerosis, left ventricular hypertrophy, altered cardiac function, and pro-arrhythmic effects.[7–10] Most studies regarding AAS use are small and/or evaluate the cardiac effects of short-term AAS use.

Common principles regarding AAS use are stacking (i.e., the routine of using multiple AAS simultaneously), cyclic administration, and the use of accessory drugs.[11] Most of the previous studies on AAS users have relied on self-reporting to estimate drug exposure. Therefore, the full extent of drug exposure is difficult to determine, and often, there is a high degree of uncertainty regarding the type and concentration of substances used.

Based on the above considerations, today's knowledge appears insufficient to capture the totality and importance of long-term AAS use on CV health. We attempted a broad CV evaluation of long-term AAS users by laboratory analyses and non-invasive cardiac examinations including coronary CT angiography, and compared them with strength-trained athletes without AAS use. Based on previous studies, our hypothesis was that chronic AAS use would confer dyslipidemia, adverse myocardial remodeling, and coronary atherosclerosis, and also might increase the risk of arrhythmias.

2 | METHODS

2.1 | Study design

This was a cross-sectional study comparing two groups of strength-trained men: long-term AAS users and non-users.

2.2 | Study population

Inclusion criteria were strength-trained men with long-term AAS use, aged 18 to 65 years, recruited from recreational gyms in Norway. We defined long-term AAS exposure as cumulative use for ≥3 years. We did not differentiate between users on- versus off-drugs (on- and off-cycle) at the time of examination. Cumulative AAS exposure <3 years and former AAS use (>6 months since drug withdrawal) were the exclusion criteria. Non-users were defined as those who reported never to have used any substance-enhancing drugs or stimulating agents. Medical conditions were not exclusion criteria.

2.2.1 | AAS use

Self-reporting and interviewing served as screening tools for AAS exposure, and were supported by blood and urine analyses. Administration of exogenous testosterone and/or its synthetic derivatives in supraphysiological doses results in a markedly increased free androgen index (FAI = testosterone [nmol/L]/sex hormone-binding globulin [SHBG] [nmol/L] × 100) in addition to the suppression of the pituitary hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In case of SHBG suppression to below the limit of detection (<2.0 nmol/L), the SHBG level was set at 2.0 nmol/L. Urine was tested using conventional AAS doping analyses, including tests for anabolic androgenic steroids and their metabolites, and stimulating agents.

2.3 | Control group

The control group consisted of strength-trained men of similar age as the study group who reported never to have used any performance-enhancing drug. These men had been practicing strength training for at least 5 years and were recruited from the elite strength training milieu in Norway, in collaboration with "Olympiatoppen," an organization that is part of the Norwegian Olympic and Paralympic Committee and Confederation of Sports. These environments routinely perform mandatory doping tests on their elite athletes. The recruitment period was 2005–2016.

2.4 | Clinical characteristics

Heart rate, resting blood pressure, height, weight, body mass index (BMI), and body surface area (BSA,

calculated using the formula of Du Bois[12]), served as baseline characteristics.

2.5 | Laboratory analyses

Blood samples were drawn in fasting condition before intake of any medications. For routine analyses, conventional methods were used. Hormonal tests included LH, FSH, testosterone, SHBG, and estradiol. We derived FAI from testosterone and SHBG, as described above.

2.6 | Electrocardiograms

Standard 12-lead ECG was obtained from resting, recumbent study participants. Various machines were used, paper speed was 50 mm/s, amplification 10 mm/mV, and the low-pass filter was set to 35 Hz. QRS amplitudes were measured manually, and Sokolow–Lyon index ($S_{V1-2} + R_{V5-6}$) ≥37 mm and Cornell voltage QRS duration product (($R_{aVL} + S_{V3}$) QRS duration) >2440 mm ms served as left ventricular hypertrophy (LVH) criteria. QRS duration was measured automatically, and also served as a marker for myocardial fibrosis.

QT dispersion (QTd) was defined as the difference between the longest and the shortest QT intervals between the 12 different ECG leads. Bundle branch block was an exclusion criterion.

24 h ambulatory ECG was performed with Schiller-MT-200 Holter-ECG. Nighttime was set at 23:00–07:00 h. The participants continued their daily activities during the registration period. The number of premature ventricular contractions (PVCs) was registered. Frequent PVCs was defined as ≥10 PVCs/h.

Heart rate variability (HRV): We used daytime registrations from the 24 h ECG recordings to get computer-derived standard time-domain parameters. The parameters included were as follows: the standard deviation of the RR intervals for normal sinus beats over 16 h (SDNN); SDNN corrected for heart rate (cSDNN); the standard deviation of the average RR intervals for normal sinus beats for five minutes segments (SDANN); the root mean square of the differences between consecutive RR intervals for normal sinus beats (RMSSD); the proportion of adjacent NN intervals greater than 50 ms of the total number of NN intervals (pNN50).[13] NN interval is the RR interval for normal sinus beats. All the calculations were computer-derived except from cSDNN that was calculated manually using the formula cSDNN = SDNN/e(HR/58.8),[14] since there is an exponential association between SDNN and HR; SDNN increases with decreasing HR.[15] SDNN, cSDNN, and SDANN reflect overall HRV, while RMSSD and pNN50 reflect high frequency HRV.

Signal Averaged ECG (SAECG) was carried out to reveal left ventricular late potentials, referring to low-amplitude signals appearing after the end of the standard QRS complex. We used the orthogonal leads (X, Y, and Z) and a 40 Hz high-pass bidirectional filter. At least 300 QRS complexes were averaged to obtain an adequately low noise level (<0.5 μV). Bundle branch block in resting ECG was an exclusion criterion. The following measures were computer-derived and used to define late potentials; (1) filtered QRS duration (fQRS) >114 ms; (2) terminal (last 40 ms) root mean square (RMS) voltage <20 μV; and (3) duration of low amplitude signal (LAS) >38 ms. The presence of at least two criteria defined an abnormal SAECG, indicating left ventricular late potentials. Results were grouped as normal or abnormal SAECG.

Exercise ECG was performed on a bicycle ergometer in a sitting position. The protocol started on 50 W and increased by 20 W/min until exhaustion. Cardiac parameters (heart rate, blood pressure, and electrocardiogram) were monitored for each step during the procedure. Criteria for early test abortion included severe chest pain, pathological ST-segment changes, systolic blood pressure >220 mmHg, diastolic blood pressure >120 mmHg, reduction in systolic blood pressure by ≥30 mmHg, and tachyarrhythmia.

2.7 | 24 h ambulatory blood pressure

Appropriate cuff size was assured in all individuals. Measurements were obtained every 30 min during daytime (07:00–24:00 h) and every 60 min during nighttime (24:00–07:00 h). Criteria for a valid test result were (a) ≥70% valid measurements and (b) at least 10 valid daytime and 5 valid nighttime measurements. The participants continued their daily activities during the registration period. We defined hypertension as 24 h BP ≥130/80 mmHg in accordance with the recommendations from European Society of Cardiology and European Society of Hypertension.[16]

2.8 | Basic transthoracic echocardiography

Standard transthoracic two-dimensional and M-mode were performed as recommended by the American Society of Echocardiography.[17] Images were obtained using GE Vivid E7. All recordings were analyzed blinded and off-line by two experienced cardiologists using commercially available customized software within a personal computer workstation (EchoPAC 108.1.0, GE Vingmed).

Images from the following views were obtained: parasternal long- and short-axis, and apical four-chamber, two-chamber and long-axis. Left ventricular ejection fraction (LVEF) served as the primary outcome variable for systolic heart function, determined by using the biplane method of disks. Left ventricular (LV) mass was calculated by the linear method with the Cube formula (LV mass $= 0.8 \times 1.04 \times ((\text{IVSd} + \text{LVIDd} + \text{LVPWd})^3 - \text{LVIDd}^3) + 0.6$ g).[18] LV mass was indexed to BSA calculated by the formula of Du Bois. Relative wall thickness (RWT) was calculated by the formula $(2 \times \text{LVPWd})/\text{LVIDd}$.[17]

2.9 | Coronary CT angiography

We performed coronary CT angiography (CCTA) using a dual-source 128-slice CT scanner (Definition Flash; Siemens Medical Systems). The primary outcome variable was the worst degree of stenosis in a coronary segment. Secondary CCTA measures included calcium score (Agatston score) and the number of coronary arteries affected by atherosclerosis. We divided the coronary artery pathology into (1) proximal and (2) mid-peripheral locations. Proximal locations included parts of the left main artery, the left anterior descending artery, the left circumflex artery, and the right coronary artery. In case of a dominant marginal branch, we classified this as a proximal location. For stenosis grading, a quantitative method was used[19]: normal (no coronary plaque), minimal (plaque with <25% stenosis), mild (25%–49% stenosis), moderate (50%–69% stenosis), severe (70%–99% stenosis), and occluded (≥99% stenosis). Stenosis grade >50% defined a significant stenosis. Heart rate-lowering intravenous beta-blockers were given according to the institutional imaging protocol to ensure acceptable imaging quality and minimize the radiation dose. We obtained ECG-gated images upon administration of intravenous contrast agent.

2.10 | Ethics

Written informed consent was obtained from all study participants, and ethical approval was given by the Regional Committee for Medical and Health Research Ethics in Norway.

2.11 | Statistical analyses

Data are expressed as median (25th–75th percentile) due to small sample sizes, unless otherwise specified. Differences between groups were assessed by Wilcoxon rank-sum test for numerical variables, and Fisher's exact or Chi-squared test for categorical variables. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using Stata 16 software.

3 | RESULTS

3.1 | Clinical characteristics

Seventy-two strength-trained men aged 20 to 62 years were included; 51 AAS users and 21 non-users. Ethnicity of the entire cohort was white Caucasians, except six subjects in the AAS user group where there were two of West African origin, one of North African origin, and three of Asian origin. Baseline characteristics are shown in Table 1. There were no differences in age, body composition, or resting systolic blood pressure between the two groups, but the resting diastolic blood pressure was significantly higher in the AAS group (Table 1). Four AAS users (8%) had known previous acute myocardial infarction; one of them complicated by cardiac arrest.

All participants had been involved in strength training for many years. Most of the participants in the non-user group were competing nationally, internationally, or both. Some of the participants in the AAS group had also been competing, while the rest were recreational bodybuilders.

Forty-eight (94%) of the AAS users had cumulative AAS exposure for 5 years or more (Table 1), and of these, 17 for at least 10 years. All of them mixed synthetic and non-synthetic AAS (stacking) in supraphysiological doses. They reported AAS doses as substantial. Thirty-two (63%) of the users reported simultaneous use of other performance-enhancing substances, stimulating agents, and/or substances to reduce adverse effects of the AAS. Substances frequently reported were ephedrine, clenbuterol, human growth hormone, insulin, thyroxine, cocaine, amphetamine, tamoxifen, clomiphene, and HCG.

3.2 | Laboratory analyses

AAS users had higher levels of hemoglobin (16.8 versus 15.0 g/dl, $p < 0.01$) and hematocrit (0.50 versus 0.44, $p < 0.01$) compared with non-users (Table 2). Median HDL cholesterol in the AAS group was 0.69 compared with 1.25 mmol/L in the non-user group ($p < 0.01$), whereas total cholesterol and LDL cholesterol did not differ between the groups.

AAS users had markedly suppressed luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Testosterone had high variability in the AAS group, but did not differ significantly between users and non-users ($p = 0.21$). In three users, SHBG was <2 nmol/L. Median FAI was significantly higher in users than non-users (328 versus 56, $p < 0.01$). We obtained urine samples from fifty

TABLE 1 Baseline characteristics

	AAS users ($n = 51$)	Non users ($n = 21$)	p Value
Characteristics			
Age (years)	33 (28–37)	33 (29–42)	0.62
AAS use ≥5 years (n, %)	48 (94)[a]	—	
Systolic blood pressure (mmHg)	129 (117–136)	123 (116–130)[b]	0.38
Diastolic blood pressure (mmHg)	78 (72–87)	70 (68–79)[b]	0.02
Medical history			
Previous CVD (n, %)	4 (8)	0	0.32
Treated hypertension (n, %)	1 (2)	0	1.00
Smoking history (n, %)	3 (6)	3 (14)	0.35
Current smoking (n, %)	3 (6)	0 (0)	
Family history of CAD (n, %)	6 (12)	3 (14)	0.71
Body composition			
Height (cm)	178 (172–183)	180 (174–184)	0.43
Weight (kg)	99 (91–113)	95 (87–119)	0.54
BMI (kg/m^2)	31.8 (29.4–34.5)	29.3 (26.6–35.3)	0.19
BSA (m^2)	2.18 (2.04–2.33)	2.15 (2.09–2.39)	0.98

Note: Data are presented as median (25th–75th-percentile) unless otherwise indicated.

Abbreviations: BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CVD, cardiovascular disease.

[a]Three registered AAS duration 3–5 years.

[b]$n = 19$.

of the AAS users, of whom five had negative samples. None of the twenty non-users who had their urine analyzed, had a positive urine sample.

3.3 | Electrocardiograms

3.3.1 | Resting ECG

Heart rate was higher in the AAS group compared with the non-user group ($p < 0.01$) (Table 3). Neither QRS duration, nor Sokolow-Lyon index or Cornell voltage QRS duration product differed between the two groups. Left ventricular hypertrophy was diagnosed by one or both algorithms in nine (18%) men in the AAS group and one (5%) of the non-users ($p = 0.26$).

3.3.2 | QT dispersion

QT dispersion did not differ between the groups ($p = 0.65$).

3.3.3 | 24-h ambulatory ECG

Short recording time, mostly due to the lack of nighttime recordings, resulted in exclusion of five test results in the AAS group and one in the non-user group. Mean heart rate was higher among users compared with non-users ($p < 0.01$). No arrhythmia was detected. Six (20%) users and one (11%) non-user had frequent PVCs. The highest number of PVCs was 6851/24 h (6% of the total heartbeats) registered in one of the AAS users.

3.3.4 | Heart rate variability

SDNN was significantly lower among AAS users ($p = 0.02$). However, SDNN corrected by heart rate (cSDNN), a better measure of overall HRV in this population due to higher HR among the AAS users, did not differ between the two groups. pNN50 differed significantly between the groups ($p < 0.01$).

3.3.5 | Signal averaged ECG

Two (6%) in the AAS group and two (10%) in the non-user group had at least two abnormal signal averaged ECG criteria indicating left ventricular late potentials. The difference was not statistically significant ($p = 0.63$). Prolonged fQRS duration was the most common abnormality among those with late potentials, seen in six AAS users (19%) and three non-users (15%).

TABLE 2 Laboratory analyses

	AAS users ($n = 51$)	Non users ($n = 21$)	p Value
Hemoglobin (g/dl)	16.8 (15.9–17.3)	15.0 (14.4–15.6)	<0.01*
Hematocrit (%)	0.50 (0.48–0.51)[a]	0.44 (0.43–0.45)	<0.01*
Thrombocytes ($\times 10^9$/L)	247 (190–286)	204 (185–247)	0.03
White blood cells ($\times 10^9$/L)	5.6 (4.6–6.8)	5.5 (4.2–5.7)	0.04
CRP (mg/L)	0.7 (0.0–1.1)[b]	1.1 (0.6–1.9)	0.16
Creatinine (μmol/L)	94 (85–109)[a]	89 (84–102)	0.90
Total cholesterol (mmol/L)	4.2 (3.5–5.2)	4.6 (4.0–5.1)	0.21
LDL-cholesterol (mmol/L)	2.7 (2.4–4.2)[a]	2.9 (2.1–3.4)	0.53
HDL-cholesterol (mmol/L)	0.69 (0.37–1.12)	1.25 (1.13–1.54)	<0.01*
T-Cholesterol/HDL ratio	5.9 (3.6–11.4)	3.3 (2.8–4.4)	<0.01*
FSH (U/L)	<1.0 (<1.0–<1.0)	3.4 (2.6–3.9)	<0.01*
LH (U/L)	<0.6 (<0.6–<0.6)	3.1 (2.8–3.8)	<0.01*
Testosterone (nmol/L)	25.8 (8.4–43.5)	16.0 (10.0–18.9)	0.21
SHBG (nmol/L)	7 (4–14)	31 (26–39)	<0.01*
FAI	328 (78–825)	56 (38–64)	<0.01*

Note: Data are presented as median (25th–75th-percentile) unless otherwise indicated. *$p < 0.001$.

Abbreviations: FAI, free androgen index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.

[a]$n = 50$.

[b]$n = 48$.

3.3.6 | Exercise ECG

We did not prematurely stop any tests due to the predefined abortion criteria. Despite their larger body mass, the AAS group had a lower maximal exercise capacity, 270 W, compared with 280 W in the non-user group ($p = 0.04$) (Table 4). Maximal exercise capacity estimated in metabolic equivalents (METs) did, however, not differ significantly between the groups ($p = 0.14$). All tests were negative for signs of ischemia and arrhythmias.

3.4 | 24 h ambulatory blood pressure

There were no differences in blood pressure measurements between the two groups (small number of valid test results) (Table 5).

3.5 | Basic transthoracic echocardiography

The results are shown in Table 6. AAS users had significantly thicker heart walls compared with non-users: interventricular septum (IVSd) 12 versus 10 mm ($p < 0.01$) and posterior wall thickness (PWd) 11 versus 9 mm ($p < 0.01$). Twenty-two (46%) users and one (5%) non-user had left ventricular hypertrophy (LVH), defined as LV mass index >116 g/m^2 ($p < 0.01$). Concentric hypertrophy was found in thirteen AAS users and none of the non-users (p 0.01). Left ventricular ejection fraction (LVEF) was lower among users (50% vs. 54%, $p = 0.02$).

3.6 | Coronary CT angiography

Coronary CT angiography was performed only in the AAS group (Table 7). Seven of the participants had pathological test results (17%), all affecting a proximal part of at least one of the coronary arteries (Table 8). Agatston score was elevated in five of the seven pathological examinations.

4 | DISCUSSION

In this study, we have performed a broad evaluation of CV health in long-term AAS users. Our results showed that the AAS users had a CV phenotype that differed from the phenotype of non-using athletes in more than one way. Our main findings were as follows: (1) AAS users had an adverse lipid profile and secondary polycythemia, (2) AAS users had no ECG findings indicating an increased risk of ventricular arrhythmias, (3) AAS users had reduced exercise capacity compared with non-users, (4) AAS users showed signs of structural myocardial remodeling evaluated by echocardiographic measures, and (5) a notable proportion of the AAS users had evidence of CAD when examined by CCTA.

TABLE 3 ECG, QT dispersion, 24 h ECG, and signal averaged ECG

	AAS users ($n = 51$)	Non-users ($n = 21$)	p Value
ECG			
Heart rate (bpm)	73 (63–85)	63 (55–65)	<0.01*
Sokolow-Lyon index (mm)	24 (21–31)[a]	22 (19–27)	0.23
>37 mm (n, %)	5 (10)[a]	1 (5)	0.66
Cornell voltage product (mm × ms)	1304 (800–1692)[a]	1100 (800–1196)	0.08
>2440 mm × ms (n, %)	6 (12)[a]	0 (0)	0.17
LVH (n, %)	9 (18)[a]	1 (5)	0.26
QRS duration (ms)	96 (90–104)	100 (94–100)	0.58
QT dispersion (ms)	58 (42–66)[b]	59 (44–72)[c]	0.65
24 h ECG	$n = 32$	$n = 9$	
Sinus rhythm (n, %)	32 (100)	9 (100)	
24 h heart rate (bpm)	80 (72–85)	65 (62–75)	<0.01**
Daytime heart rate (bpm)	84 (78–90)	72 (62–80)	<0.01**
Nighttime heart rate (bpm)	66 (60–74)	56 (49–63)	0.02
Frequent PVCs (n, %)	6 (20)	1 (11)	1.00
Heart rate variability	$n = 33$	$n = 10$	
SDNN (ms)	114 (96–137)	164 (122–187)	0.02
cSDNN (ms)	60 (50–79)	68 (62–82)	0.18
SDANN (ms)	92 (78–135)	122 (99–170)	0.09
rMSSD (ms)	39 (28–54)	52 (36–61)	0.28
pNN50 (%)	5 (2–8)	21 (11–32)	<0.01**
Signal averaged ECG	$n = 32$	$n = 20$	
Filtered QRS duration (ms)	107 (98–113)	108 (105–113)	0.27
RMS voltage (μV)	56 (39–79)	38 (33–53)	0.02
LAS duration (ms)	23 (19–32)	24 (19–33)	0.83
Filtered QRS duration >114 ms (n, %)	6 (19)	3 (15)	1.00
RMS voltage <20 μV (n, %)	1 (3)	2 (10)	0.55
LAS duration >38 ms (n, %)	2 (6)	1 (5)	1.00
Late potentials[d] (n, %)	2 (6)	2 (10)	0.63

Note: Data are presented as median (25th–75th-percentile) unless otherwise indicated. *$p < 0.001$. **$0.001 < p < 0.01$.

Abbreviations: cSDNN, SDNN corrected for heart rate; LAS, low amplitude signal; LVH, left ventricular hypertrophy; pNN50, the proportion of successive NN intervals greater than 50 ms of the total number of NN intervals; PVCs, premature ventricular contractions; RMS, root mean square; rMSSD, the square root of the mean squared differences of successive RR intervals for normal sinus beats; SDANN, the standard deviation of the average RR intervals for normal sinus beats for five minutes segments; SDNN, the standard deviation of the RR intervals for normal sinus beats over 16 h.

[a]$n = 50$.

[b]$n = 29$.

[c]$n = 10$.

[d]Characteristics of a late potential include 2 or 3 of the following: (1) fQRS > 114 ms; (2) RMS voltage < 20 μV; and/or (3) LAS > 38 ms.

4.1 | Coronary risk factors and coronary atherosclerosis

We found markedly reduced HDL cholesterol values among the AAS users compared with non-users, but no differences in total cholesterol or LDL values. The reduction in HDL leads to a significant difference in total cholesterol/HDL ratio. A decrease in HDL values has previously been demonstrated,[20] and other studies have also reported increased LDL values in people using AAS.[21] Hemoglobin

TABLE 4 Exercise ECG

	AAS users ($n = 42$)	Non users ($n = 12$)	p Value
Maximal heart rate (beats/min)	169 (161–180)	178 (172–184)	0.13
>85% target HR (n, %)	32 (76)	10 (83)	0.71
Maximal exercise capacity (W)	270 (230–290)	280 (260–350)	0.04
Maximal exercise capacity (METs)	9.6 (8.6–10.8)	11.2 (8.6–13.6)	0.14
Test duration (min)	12:39	14:08	

Note: Data are presented as median (25th–75th-percentile) unless otherwise indicated.

TABLE 5 24 h blood pressure

	AAS users ($n = 6$)	Non-users ($n = 2$)	p Value
24 h systolic blood pressure (mmHg)	121 (105–138)	117 (113–121)	0.86
24 h diastolic blood pressure (mmHg)	70 (69–74)	76 (69–83)	0.79
Daytime systolic BP (mmHg)	124 (107–138)	119 (115–122)	0.86
Daytime diastolic BP (mmHg)	75 (72–78)	78 (70–85)	1.00
Night-time systolic BP (mmHg)	112 (99–141)	112 (107–117)	1.00
Night-time diastolic BP (mmHg)	63 (62–71)	72 (67–76)	0.43

Note: Data are presented as median (25th–75th-percentile) unless otherwise indicated.

TABLE 6 Basic transthoracic echocardiography

	AAS users $n = 48$	Non-users $n = 21$	p Value
IVSd (mm)	12 (10–13)	10 (9–11)	<0.01*
LVPWd (mm)	11 (10–13)	9 (8–9)	<0.01*
LVIDd (mm)	55 (53–60)	57 (55–59)	0.23
LV mass (g)	254 (213–313)	213 (174–222)	<0.01*
LV mass index (g/m^2)	112 (101–138)	93 (84–105)	<0.01*
LV mass index >116 g/m^2 (n, %)	22 (46)	1 (5)	<0.01**
Relative wall thickness	0.39 (0.36–0.46)	0.31 (0.28–0.33)	<0.01*
Concentric hypertrophy (n, %)	13 (27)	0 (0)	0.01
LVEF, biplane (%)	50 (44–53)[a]	54 (51–56)	0.02

Note: Data are presented as median (25th–75th-percentile) unless otherwise indicated. *$p < 0.001$. **$0.001 < p < 0.01$.

Abbreviations: IVSd, interventricular septal thickness at end-diastole; LV, left ventricular; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension at end-diastole; LVPWd, left ventricular posterior wall thickness at end-diastole.

[a]$n = 47$.

and hematocrit levels were significantly higher in the AAS group. Erythropoiesis and increased hematocrit levels are both associated with testosterone exposure,[22] and this relationship might be dose-dependent.[23] Adverse lipid profile and polycythemia, as described in the present study, are the possible risk factors for premature coronary atherosclerosis.[24,25]

Of the AAS users undergoing CCTA, 17% had evidence of CAD. Two had previous CAD; one of these had significant coronary stenosis. Although most of the stenoses were graded as minimal, four out of seven had disease affecting all three main arteries, indicating more extensive CAD. Median age for the persons examined by CCTA was 33 (30–37) years. We do not have comparative data from

TABLE 7 Coronary CT angiography among AAS users

	AAS users $n = 41$ (100%)	Agatston score[a] (Score values)
Coronary locations		
Proximal/Dominant branch		
Minimal stenosis (<25%)	4 (10)	19 (4–47)
Mild stenosis (25%–49%)	2 (5)	—[b]
Moderate stenosis (50%–69%)	1 (2)	2872
Severe stenosis (70%–99%)		
Occlusion		
Mid-peripheral branch		
Minimal stenosis (<25%)		
Mild stenosis (25%–49%)		
Moderate stenosis (50%–69%)		
Severe stenosis (70%–99%)		
Occlusion		
Normal	31 (76)	0 (0–0)
Not conclusive/No intravenous contrast	3 (7)[c]	0 (0–0)

Abbreviation: AAS, anabolic-androgenic steroids.

[a]$n = 39$.

[b]Not determined.

[c]1; not conclusive, 2; no intravenous contrast.

TABLE 8 Pathological coronary CT angiography

	Stenosis degree:	Previous CVD:	Agatston score:	Diseased arteries (n):
1	Mild	Yes	ND[a]	3
2	Moderate	Yes	2872	3
3	Mild	No	ND	1
4	Minimal	No	8	1
5	Minimal	No	63	3
6	Minimal	No	31	3
7	Minimal	No	0	1

Abbreviations: CVD, cardiovascular disease; ND, not determined.

[a]Visually high score.

an age- and sex-matched group of healthy individuals. To the best of our knowledge, no such data exist. Hoffmann et al. have described normal distributions of coronary arterial calcifications in asymptomatic men ≥35 years.[26] They found coronary calcifications in 20.6% of men aged 35–45 years, approximately the same proportion of pathological cardiac CTs in our study. Few studies have examined the prevalence of coronary atherosclerosis in AAS user populations, but a study by Baggish et al.[7] showed increased coronary plaque burden among long-term AAS users. Calcium score was determined in five out of seven pathological coronary CT angiograms in our study. One of them had a calcium score of zero, indicating non-calcified plaques.

The pathophysiological causes of premature CAD in this population are multifactorial, and not fully understood. Different models have been presented by Melchert and Welder.[27] Altered lipid levels dominated by a marked reduction in HDL, may contribute to accelerated atherosclerosis, but cannot explain the full picture. Other hypotheses are the thrombotic and vasospastic models. AAS-induced inflammation as a contributing cause to the development of CAD, is also an issue of interest. Further evaluation with measures of novel inflammatory markers will probably elucidate these hypotheses better.

4.2 | Risk of ventricular arrhythmias

Increased mortality among AAS users has previously been described.[28] Ventricular arrhythmia, either primary or secondary to ischemia, is a possible cause of increased cardiovascular morbidity and mortality among AAS users.[28] Various non-invasive tests have been used for SCD risk prediction in different patient populations; echocardiography, long-term ECG recording, exercise test, heart rate variability measures, QT dispersion, and signal averaged ECG.[29–31] Left ventricular ejection fraction is a widely used variable, but has limited sensitivity and specificity.[32] The effect of one variable alone is modest, but might have complementary value in SCD risk stratification.[33] We performed a comprehensive evaluation of arrhythmic risk among the study participants; to the best of our knowledge no similar studies have been published. We found a small difference in the short-term HRV measure pNN50, but no difference in any of the other ECG tests. Based on these non-invasive measures, no ECG findings indicated an increased risk of ventricular arrhythmias among the long-term AAS users.

4.3 | Exercise capacity

AAS users tended to have lower maximal exercise capacity (W) compared with non-users. We also found a small, non-significant difference measured in METs. This finding

indicates that the AAS users did not have better endurance despite their use of performance-enhancing drugs and higher hemoglobin levels, consistent with previous studies.[34,35] Yet, both our study groups performed worse compared with endurance athletes, where cardiopulmonary exercise data recently have been published.[36] Our study participants did not perform regular endurance training, and therefore, this finding cannot assess whether or not combined AAS use and endurance training have beneficial effects on physical performance. However, our results might suggest that AAS use alone without combined endurance training does not increase cardiovascular performance.

4.4 | Structural left ventricular remodeling

AAS users had significantly thicker left ventricular walls, greater left ventricular mass, and a substantial proportion had concentric hypertrophy. Baggish et al. and Rasmussen et al. have previously described the same myocardial changes in larger cohorts.[7,37]

The findings in the present study possibly indicate that AAS use has an anabolic effect not only on skeletal muscle cells but also on the myocardial cells. Increased afterload caused by strength training might be a contributing mechanism for the left ventricular hypertrophy demonstrated in our study (physiological changes referred to as strength-trained athlete's heart[38]). However, this cannot explain the difference between AAS users and non-users. Despite increased myocardial mass, our AAS users had a slight decrease in LVEF compared with non-users, possibly indicating that AAS use also affects cardiac function. Furthermore, the slight decrease in LVEF might suggest that the anabolic effect on myocardial cells not only differs from the anabolic effect seen in skeletal muscle cells, where AAS exposure results in increased functioning, but that it also differs from the physiological changes seen in strength-trained athlete's heart. The myocardial changes presumably depend on the length of AAS exposure[39] suggesting that long-term AAS exposure can be detrimental and cause loss of myocardial function. Rasmussen et al. demonstrated cardiac systolic dysfunction by a reduction in global longitudinal strain (GLS) years after AAS cessation. Our findings might support the previous findings and indicate a vulnerability in these men's hearts, possibly increasing the risk of serious cardiovascular events and congestive heart failure.

4.5 | Study strengths

One of the main strengths of our study is the broad evaluation of CV health among long-term AAS users, and the number of similar studies are limited. Moreover, the number of AAS users must be considered substantial compared with previous studies. Another main strength is that we have unequivocally verified AAS use as well as non-use by both blood and urine analyses. To the best of our knowledge, this has not been performed in comparable previous studies.

4.6 | Study limitations

The present study has several limitations. Even though we included a substantial number of AAS users, the value of our findings is limited due to some missing data.

The number of non-users was rather small compared with the number of AAS users. In addition, there was a long recruitment period in the study. Most of the participants were recruited between 2005 and 2010. To get a larger control group, we recruited seven non-users in 2016. No participants were recruited between 2010 and 2016.

Another limitation is the lack of comparative data, especially for CCTA, where no data are available. Overall, it would have been a strength to include a third group, consisting of sedentary, age-matched men, to illustrate their physical performances better. The reason for choosing athletes as the control group, was to try to eliminate the cardiac effects of extensive strength training (athlete's heart).

To better evaluate cardiorespiratory endurance and overall functional capacity, a cardiopulmonary exercise test would have been optimal.

We did not differentiate between users on- and off-cycle at the time of examination. This presumably explains the five negative urine samples among the AAS users. There is conflicting evidence about the reversibility of the detrimental effects of AAS. Altered cholesterol levels seem to be reversed within months after drug withdrawal.[40] There is a conceptual possibility of normalized HDL values among users off-cycle at the time of investigation. Structural and functional cardiac changes seem to vary with AAS exposure, and might be reversed short time after drug withdrawal. Both these limitations would lead to less significant differences between the two groups.

A factor making the association between organ damage and AAS exposure per se less clear, is the use of accessory drugs, a trend among most AAS users. In our study, 63% of all the participants confirmed using accessory drugs, and in addition, a substantial proportion of the study participants did not respond. Thus, the number might be higher. Substances commonly used are human growth hormone (hGH), insulin, thyroxine, amphetamine, cocaine,

clenbuterol, and ephedrine. While their individual contributions to possible pathologies remain unclear, the overall real-life usage of AAS with or without ancillary drugs is the overarching factor in this investigation.

Some of the accessory drugs are used with the intention to increase muscle volume and/or reduce the amount of body fluids, a desired effect for many bodybuilders especially in times before competitions. Since we did not differentiate between users on- and off-cycle, there is a possibility that our hematological findings, dominated by increased hemoglobin levels and hematocrit, can in part be explained by hemoconcentration.

We unfortunately used a 35 Hz low-pass filter (muscle noise filter) when recording resting ECG. This reduces the sensitivity for detection of left ventricular hypertrophy, underestimating its prevalence.

5 | PERSPECTIVES

Abuse of AAS among recreational athletes has become a looming health problem, and the unwanted effects have not been thoroughly evaluated. AAS are used in supraphysiological doses and exert a systemic effect on the body, including the cardiovascular system. Despite some uncertainty, the present data suggest that long-term AAS use might increase the risk and prevalence of CAD and induce structural myocardial remodeling. No ECG findings demonstrated an adverse electrical remodeling and thereby an increased risk of ventricular arrhythmias. Conventional coronary risk assessment classify these individuals as low-risk, and they will presumably not be prescribed prophylactic pharmacological therapy. As long as the disease remains undetected and the exposure persists, it will likely progress and ultimately manifest clinically. It is of high importance that clinicians treating this population are aware of the potential detrimental cardiovascular side effects of AAS exposure.

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CONFLICT OF INTEREST

No conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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