



OPEN Impaired vascular function among young users of anabolic–androgenic steroids

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Supraphysiological doses of anabolic–androgenic steroids (AAS) is popular among recreational weightlifters and bodybuilders due to the performance-enhancing properties but is also associated with adverse cardiovascular effects. The knowledge about how AAS affect the vasculature is limited, although results from previous studies suggest alterations in vasoreactivity and morphology. In the present study we investigate the association between long-term use of AAS and vascular function. Hundred and twenty-three males were included in the study, 56 of them current AAS users and 67 weightlifting controls. Vascular function was evaluated by carotid artery reactivity and flow-mediated dilation. AAS users had significantly reduced carotid artery reactivity ($p < 0.001$) and flow-mediated dilation ($p < 0.001$) compared to weightlifting controls. Results from the present study indicate that long-term use of AAS affect the cardiovascular system negatively, measured as reduced carotid artery reactivity and flow-mediated dilation. These findings could partly explain sudden cardiovascular events among young long-term users of AAS.

Keywords Anabolic–androgenic steroids, Flow-mediated dilation, Carotid artery reactivity, Vascular health

Anabolic–androgenic steroids (AAS) consist of the male sex hormone testosterone and its synthetic derivatives^{1,2}. Testosterone was first discovered in 1935, and in 1937 it was first used clinically³. The discovery of the anabolic properties of AAS resulted in AAS use propagating into elite sports in the 1950s⁴. The use of AAS expanded during the next decade before it was banned⁴. It was not until the late 1980s that use gained ground among gym members in the general population and is today primarily used to improve body image and build muscles more easily^{5–7}. Recent estimates suggest that about 2–3% of the population have used AAS at some point^{5,6}, but higher prevalence is seen among men⁶ and subpopulations such as recreational weightlifters, bodybuilders, inmates⁸ and substance use patients⁹.

High-dose AAS use is associated with both adverse medical and psychological outcomes¹⁰, with cardiovascular effects posing a significant health risk^{10–12}. There are numerous case reports and observational studies suggesting an association between AAS use and a variety of cardiovascular complications, including myocardial infarction^{13,14}, cardiac dysfunction^{10–12,15,16}, unfavorable lipid profile^{12,17,18}, increased coronary plaque burden¹⁰ and hypertension¹⁹. Prospective studies also show cardiac dysfunction²⁰, adverse changes in blood pressure, lipid metabolism and erythrocytosis²¹ after administration of AAS for one cycle, median duration of 16 and 13 weeks, respectively. Previous studies have also demonstrated that long-term AAS use is linked to impaired vascular function^{22–24} and arterial stiffening²⁵.

Carotid artery reactivity (CAR%) to cold pressor test (CPT) represents a novel measure for evaluating carotid artery endothelial function. The CPT induces sympathetic activation, that among others results in production of nitric oxide^{26–28} and dilation of healthy arteries²⁹. CAR% tends to decline with advancing age and in the presence of cardiovascular risk factors, exhibiting associations with coronary endothelial function³⁰.

Flow-mediated dilation (FMD) is a widely adopted non-invasive, ultrasound-based modality for the assessment of peripheral artery endothelium-dependent dilation³¹. It serves as a prognostic indicator for future atherosclerotic development and cardiovascular events^{31,32}. Prior investigations has yielded conflicting results regarding the effect of long-term AAS use on FMD, with one study showing no difference between AAS users and non-users³³, while others demonstrating reduced FMD after prolonged AAS use^{22–24}. These studies, however, are limited by small sample sizes.

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In the present study we aimed to assess vascular function through both CAR% and FMD, hypothesizing that prolonged AAS use detrimentally impact vascular health, resulting in diminished CAR% and FMD.

Methods

Ethical approval

All experiments were approved by the Regional Committees for Medical and Health Research Ethics South East Norway (REC) (2013/601), and the research was carried out in accordance with the Declaration of Helsinki. All participants received oral and written information prior to participation and provided written informed consent. The participants were compensated for their participation with a gift certificate equivalent to 500 NOK (approximately 45 USD).

Study population

This study is part of a longitudinal study focusing on brain, medical and mental health consequences of long-term AAS use, conducted by the Anabolic Androgenic Steroid Research Group at Oslo University Hospital, Norway (<https://www.ous-research.no/anabolic-steroids/>). The study population aligns with the one detailed in a prior investigation²⁵.

The participants consist of men engaged in heavy resistance strength training, categorized into two groups: AAS users and a weightlifting control (WLC). AAS users have reported a minimum of 1 year of cumulative AAS use, including recent use within the past 12 months.

Eligibility criteria for the WLC group were being male engaging in heavy resistance training, with no history of AAS use or other prohibited doping substances. To match the AAS users commitment to heavy strength training, we targeted men with bench press capability of 120 kg (~265 pounds) for at least one repetition, with 100 kg (~220 pounds) as the minimum inclusion criteria. Recruitment strategies involved outreach through various internet forums, social media platforms, and local gyms in Oslo.

All participants were tested as described by Bjørnebekk et al.³⁴, encompassing urine samples, questionnaire, and interviews to confirm alleged AAS use. Doping analysis confirmed the use of AAS among AAS users and confirmed no use among WLC, as previously described³⁵. Detailed information on blood and urine samples are described previously by Melsom et al.²⁵.

Preparation

Subjects were instructed to fast for >6 h, refrain from exercise for ≥24 h and abstain from caffeine, tobacco, alcohol and vitamin C ≥18 h prior to testing, according to guidelines for assessing endothelial function³². All factors are known to alter endothelial function³². Before measurements, subjects rested in a supine position for 10 min in a dark, quiet, temperature-controlled room (20 °C) followed by assessment of blood pressure, measured manually with pressure cuff and stethoscope.

Flow-mediated dilation (FMD)

Endothelial function was assessed by the flow-mediated dilation method (FMD method)³². Participants were examined in the supine position after 20 min of rest. A standard blood pressure cuff was positioned around the right arm, two inches below the ante-cubital fossa, and the brachial artery was imaged 5–9 cm above the ante-cubital fossa. A linear-array multifrequency transducer probe 9 MHz (GE, E-95 scanner) was used to acquire images of the brachial artery. To optimize the stability of recordings, the transducer was placed in a fixed position at the brachial artery and stabilized with a custom-made tripod. When an optimal image was found and the probe placed in a fixed position, the cuff was inflated to 230 mmHg for 5 min. Digitized images of the right brachial artery were continuously captured for 190 s, starting 10 s before the cuff deflation, to document the vasodilator response to reactive hyperemia. Semi-automated readings of the digitized images were then used to determine the FMD %:

$$\text{FMD \%} = ((\text{maximum diameter} - \text{diameter 10 s before cuff deflation}) / \text{diameter 10 s before cuff deflation}) \times 100$$
. The results were analyzed offline using the Brachial analyzer software (Medical Imaging Applications LLC, US).

Carotid artery reactivity (CAR%)

Participants were in a supine position for assessment of the left carotid artery. Diameter of the left carotid artery was measured continuously for 30 s before and 90 s during cold pressor test (CPT) with the left hand immersed in ice slush (4 °C). A linear array multifrequency transducer probe 9 MHz (GE E-95 scanner) was used to acquire images of the carotid artery. When an optimal image was found, all parameters were set to optimize the image and the probe was held stable. After 30 s of baseline assessment of the carotid artery, the hand was immersed for 90 s with continuous assessment of the carotid artery.

CAR% responses were measured as the relative change from baseline diameter to peak dilation or constriction during 90 s of immersion in ice slush. Baseline diameter was calculated as the mean of the diameter measured every 10th sec the first 30 s. The diameter of the carotid artery was measured every 10th sec during the CPT. CAR% was then calculated as the relative change from baseline diameter to peak dilation or constriction.

Statistics

Statistical analysis was performed using SigmaPlot 14.0 (Systat Software, Inc., GmbH, Erkrath, Germany). Given the non-normal distribution of the data, the Mann–Whitney U Test was used to test for statistical

differences between groups. Data are presented as median values (25th-75th percentile), unless otherwise stated. A *p*-value < 0.05 was considered statistically significant.

Results

We included 123 male participants, 56 with proven use of AAS and 67 WLC. Demographical data and statistics for the two groups are presented in Table 1. Doping analysis confirmed the use of AAS among AAS users and confirmed no use among WLC, as previously described²⁵. Of the 56 AAS users, 49 of them were currently in an AAS cycle. There were no differences between the two groups with respect to age, height, systolic blood pressure, or training hours per week. Body weight was significantly higher in the AAS group, compared to the WLC. AAS users exhibited significantly elevated maximal strength levels in both bench press and ground lift when compared to WLC. Education was significantly lower among AAS users than WLC.

One AAS user and one WLC was excluded from the CAR% analysis due to loss of data, and one WLC was excluded from the FMD analysis due to loss of data.

Carotid artery reactivity (CAR%)

We observed a significantly reduced CAR% in the AAS group compared to the control group [3.58 (2.78–5.80) %, 6.33 (4.48–8.78) % respectively, *p* < 0.001] (Fig. 1).

Flow-mediated dilation (FMD)

The FMD response was significantly lower in the AAS group compared to the control group [3.99 (2.85–6.81) %, 6.72 (4.63–9.48) % respectively, *p* < 0.001] (Fig. 2). No significant difference was observed in absolute change in flow after cuff release between the AAS group and the WLCs [522.50 (410.50–637.25) mL/min, 474.00 (377.25–578.00) mL/min respectively, *p* = 0.152] (Fig. 3). AAS users demonstrated a significantly greater baseline diameter compared to the WLCs [5.11 (4.51–5.50) mm, 4.54 (4.09–4.97) mm respectively, *p* < 0.001]. Additionally, AAS users exhibited a significantly smaller absolute change in diameter compared to the WLCs [0.21 (0.14–0.33) mm, 0.30 (0.23–0.40) mm respectively, *p* < 0.001].

Discussion

The main findings in this study were that long-term AAS users showed impaired vascular function compared to WLC, evaluated by CAR% and FMD.

To our knowledge, this is the first study to evaluate CAR% among men with a history of long-term AAS use. The finding of reduced CAR% among AAS users indicate diminished vascular function. Reduction in CAR% heightens the susceptibility to acute myocardial infarction, due to the shift from laminar to turbulent blood flow,

	WLC (n = 67)	AAS users (n = 56)	<i>p</i> -value
	Median (25th–75th percentile)	Median (25th–75th percentile)	
Age, years	38 (30–45)	39 (32–49)	0.389
Height, cm	180 (180–190)	180 (180–190)	0.074
Weight, kg	93 (84–100)	100 (94–111)	< 0.001*
BMI, kg/m ²	27.7 (26.2–30.7)	30.7 (28.7–33.1)	< 0.001*
SBP, mmHg	125 (120–130)	130 (120–140)	0.060
DBP, mmHg	80 (75–85)	80 (80–85)	0.022*
MAP, mmHg	93 (90–100)	97 (93–103)	0.013*
AAS debut age, years	-	20 (18–24)	-
Weekly dose of AAS, mg	-	750.0 (415.0–1262.5)	-
Accumulated time of use, years	-	11.0 (6.5–17.5)	-
Education, years	17 (15–19)	15 (13–16)	< 0.001*
Weight training, hours per week	5.9 (3.9–8.0)	5.7 (4.0–9.3)	0.789
Endurance training, hours per week	1.0 (0.2–2.0)	0.7 (0.0–2.0)	0.489
Bench press, kg	140.0 (134.0–159.0)	175.0 (152.5–206.0)	< 0.001*
Ground lift, kg	200.0 (180.0–240.)	240.0 (210.0–275.0)	< 0.001*
	WLC	AAS users	
Alcohol, yes	56	34	0.004*
Alcohol, units per week, median (25th–75th percentile)	2 (0–5)	2 (0–4)	0.406
Smoke, yes	0	4	0.022
†Other tobacco, yes	17	15	0.700

Table 1. Demographical data for the study subjects. AAS, anabolic androgenic steroids; WLC, weightlifting controls; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. *Significant difference between groups. †Other tobacco (e.g. snuff, nicotine patches, E-cigarettes).

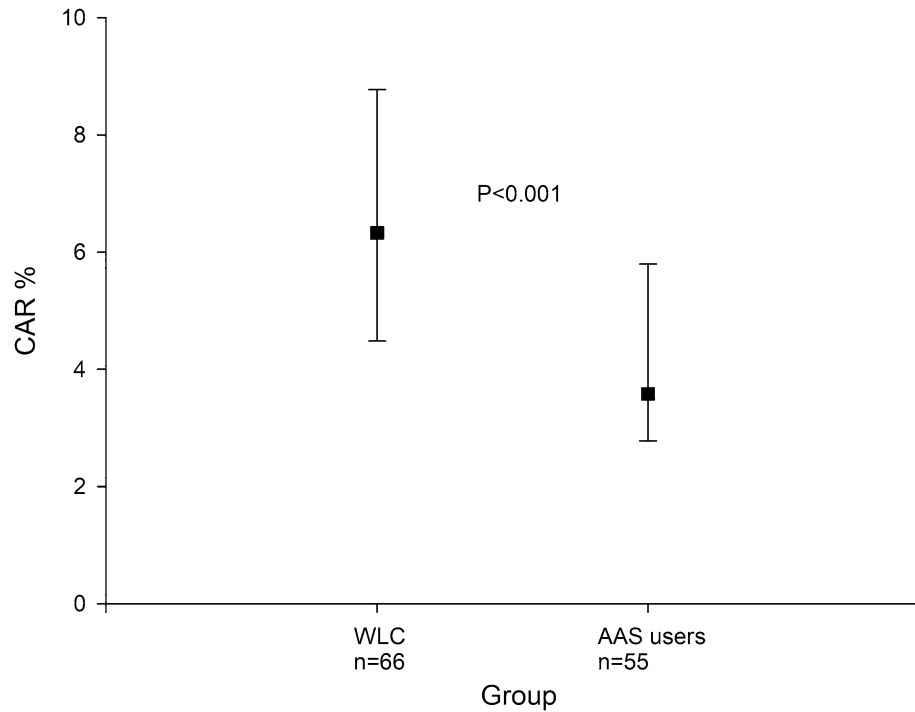


Figure 1. Carotid artery reactivity. The figure shows the relative change in carotid artery reactivity (CAR%) from baseline to peak dilation during 90 s immersion of the hand to ice slush. The CAR% was significantly reduced in the AAS group compared to the control group [3.58 (2.78–5.80) %, 6.33 (4.48–8.78) % respectively, $p < 0.001$].

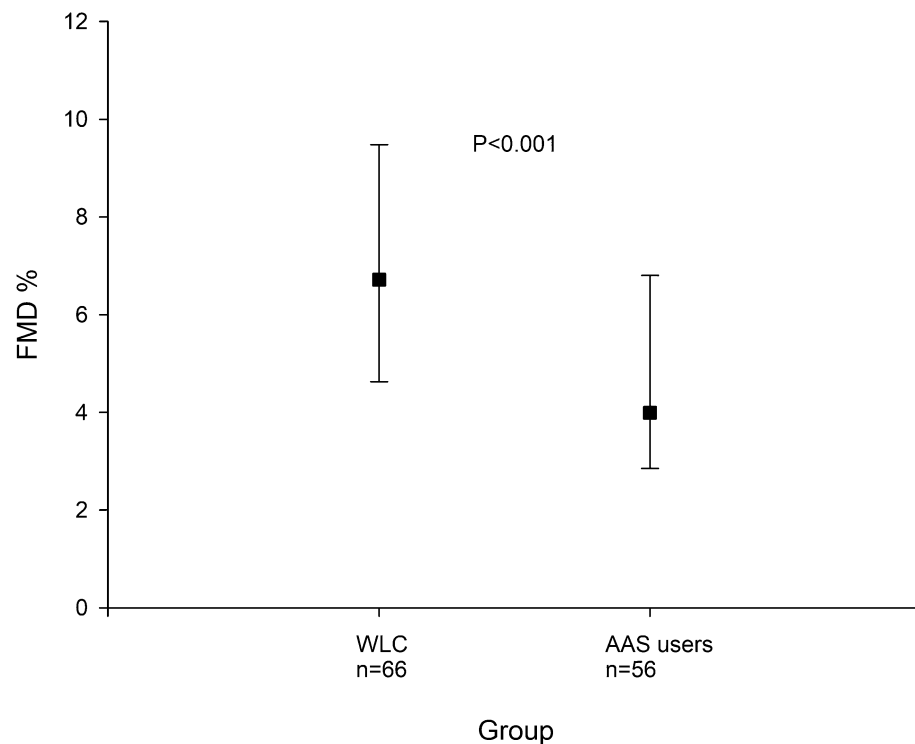


Figure 2. Flow-mediated dilation. The figure shows the relative change (%) in flow-mediated dilation (FMD) from baseline to peak dilation after deflation. The FMD was significantly reduced in the AAS group compared to the control group [3.99 (2.85–6.81) %, 6.72 (4.63–9.48) % respectively, $p < 0.001$].

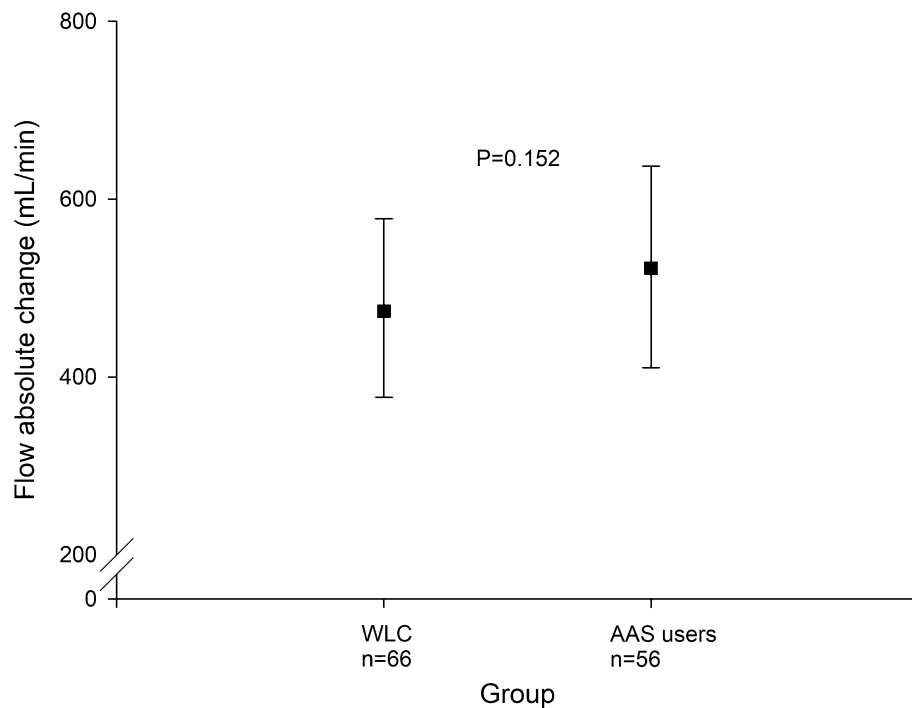


Figure 3. Absolute change in flow. The figure represents the absolute change in flow (mL/min) from baseline (10 s before deflation) to peak flow after deflation. There was no difference in absolute change in flow (mL/min) between the AAS group and the control group [522.50 (410.50–637.25) mL/min, 474.00 (377.25–578.00) mL/min respectively, $p=0.152$].

thereby increasing the likelihood of clot formation³⁶. Dilation of the coronary arteries is an important response in situations with increased oxygen demand, such as physical activity or other situations where sympathetic activity increases. To meet the increased oxygen demand, blood flow increases, leading to arterial dilation. In 1988 Nabel et al. explored how healthy and atherosclerotic coronary arteries respond to an exogenous stimulus that excites the sympathetic activity, and found that healthy coronary arteries dilate in response to this exogenous stimulus³⁷. The vascular responses to CPT involve intricate mechanisms not fully elucidated. However, three key contributors to coronary vasodilation are identified²⁸: increased flow induces shear stress, resulting in flow-mediated dilation contingent on an intact endothelium; epinephrine release activates β_2 -adrenergic receptors on coronary smooth muscle cells, promoting vasodilation; and norepinephrine is suggested to stimulate nitric oxide synthesis via α_2 -adrenergic receptors on coronary artery endothelial cells²⁸. The carotid arteries comprise central vessels with similar properties as the coronary arteries and are recognized surrogate measures of coronary artery function³⁰. Thus, we speculate that AAS use negatively affects the balance between the dilation and constriction during the CPT. The reduced dilation of the carotid and coronary arteries under increased blood flow has profound consequences for blood circulation. When arteries fail to dilate adequately in response to increased blood flow, there is a risk that blood flow velocity accelerates and reaches the critical speed where laminar flow is replaced by turbulent flow, as seen in stenotic arteries. The difference is that the turbulent flow is created due to reduced ability of the artery to dilate and thus the whole artery is too narrow when the blood flow velocity increases. The result is increased risk for turbulent flow and subsequently clot formation, potentially resulting in cardiovascular events like myocardial infarction. This could offer insight into sudden cardiovascular events among young users of AAS, despite the absence of morphological changes in the artery wall^{13,14}.

The diminished CAR% observed in AAS users may also be indicative of accelerated arterial ageing process. Previous studies demonstrate that CAR% is reduced in older individuals compared to younger ones^{30,38}. Individuals at risk for CVD also exhibit reduced CAR% in response to a cold pressor test compared to those without risk factors^{29,30}. CAR% is considered a marker of physiological arterial ageing, as its response diminishes with age³⁸, and reduced CAR% is pathological when found in the younger population. In this context, we might argue that AAS use appears to expedite the ageing process and increase the risk for CVD.

This study also identified a significantly lower FMD response in AAS users compared to the WLC group. The baseline diameter was significantly larger in the AAS group. Notably, FMD represents a relative alteration in diameter, meaning the size of the artery impacts the observed relative change³². This means that a small artery will have a bigger relative change than a bigger artery, when the absolute change in diameter is equal³². If both the baseline diameter and the absolute change in diameter would be bigger in the AAS group compared to the WLC, the reduced FMD could be explained by the bigger baseline diameter in the AAS group. However, in this study, the absolute change in diameter was significantly smaller in the AAS group compared to the WLC, with no difference in absolute change in flow. This suggests comparable flow stimulus for the FMD were applied across

both groups, supporting the notion that attenuated FMD response among AAS users reflects endothelial dysfunction. FMD can be measured in different conduit arteries and are mediated through increased shear stress on the arterial wall due to increased blood flow^{32,39}. The FMD method in large conduit arteries were first introduced in 1992 when Celemajer et al. described reduced arterial dilation in response to increased blood flow in children and adults at higher risk of developing CVD³⁹. Reduced FMD is considered a warning sign for unhealthy vasculature and a predictor for future cardiovascular events⁴⁰ and support our hypothesis that long-term use of AAS causes vascular impairment, posing a risk factor for CVD.

Sader et al. reported significantly higher carotid intima media thickness (cIMT) among AAS-users compared to controls³³, which is in line with results previously published by our group²⁵. This reinforces the notion that AAS negatively impact the vascular system. However, Sader et al. did not find significant differences in FMD between AAS using bodybuilders, non-using bodybuilders, and controls³³, conflicting with results from the present study. The small sample size in the study of Sader et al. might explain the disparities. Moreover, AAS use is associated with increased sympathetic tone^{41–43} and reduced baroreflex sensitivity⁴³. The sympathetic tone is also important in regulating the vascular tone in central arteries^{44,45}. The endothelium and the smooth muscle cells express adreno-receptors, which respond to regional and systemic sympathetic stimuli^{44,45}. While activation of β -receptors induce vasodilation, activation of α -receptors induce constriction⁴⁴. In healthy individuals sympathetic stimulation leads to dilation, whilst in individuals with coronary disease sympathetic activation leads to vasoconstriction⁴⁶. It is suggested that AAS use can increase vascular responsiveness to catecholamines⁴⁷. Thus, an alternative explanation for the reduced FMD found in the present study could be that the AAS user group has an initial dilation of brachial artery, resulting in a relatively lower dilation compared to the WLC. Moreover, Santos et al. found lower baroreflex sensitivity among AAS users compared to non-users and discuss that this could explain the increased sympathetic tone⁴³. Furthermore, they discuss reduced baroreflex sensitivity as a potential consequence of vascular damage, e.g. increased arterial stiffness^{43,48}. Considering existing literature on medical consequences of AAS, reduced FMD most likely reflects endothelial dysfunction. Further, our results from the present study regarding FMD align with those of Ebenbichler et al. and Severo et al.^{22,24}, reporting reduced FMD among AAS users compared to non-users both in phases of AAS use and non-use²², suggesting that reduced FMD reflects endothelial dysfunction rather than a lack of flow stimulus and sympathetically induced vasodilation of the resting diameter.

Limitations

Some limitations should be considered when interpreting the present findings. The cross-sectional study design precludes establishing causality. Also, AAS is legally prohibited in Norway, leading to secrecy around personal use and making it challenging to recruit users. Despite this, the study boasts a relatively large population compared to prior investigations. The diversity in AAS substances used, administration methods, polypharmacy, and duration of use may exert varying effects on the vascular system. Moreover, ethical constraints prevent placebo-controlled studies where specific AAS compounds in high dose are administered over longer time. Consequently, we must study individuals taking AAS at their own initiative. We also cannot rule out the influence of genetic effects or the possibility that AAS use is associated with other lifestyle factors such as diet and drug use that are difficult to control for and might influence our results. Furthermore, our sample mainly comprising men with Scandinavian ethnicity, meaning that the findings may not be generalizable to other ethnicities or female AAS users. While AAS users and WLC align on training hours per week and share a common interest in heavy resistance training, discrepancies in exercise regimens that could differentially affect the cardiovascular system cannot be excluded.

Conclusion

Long-term use of AAS is associated with impaired vascular function, as evaluated by CAR % and FMD. The findings align with our previous study, where morphological changes in the vasculature were observed²⁵. The results suggest that long-term use of AAS negatively affect the cardiovascular system, evident in reduced CAR % and FMD, a pattern also seen in other groups at increased risk for CVD. Therefore, AAS should be considered a significant threat to cardiovascular health, potentially contributing to severe cardiovascular events, such as myocardial infarction and sudden cardiovascular death, observed among young male users of AAS.

Data availability

The raw data cannot be shared publicly due to General Data Protection Regulation (GDPR), and is available from the corresponding author (h.m.tungesvik@medisin.uio.no) on reasonable request.

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Author contributions

HMT recruited participants, collected, analyzed, and evaluated the data. HMT wrote the initial manuscript. AB was the project manager of the study, coordinated recruitment and collection of biometrical data. JH contributed with method training and data interpretation. JH and AB contributed with manuscript writing. JH and HMT contributed to experimental and conceptual planning. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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