Decreased Native T1 Values and Impaired Myocardial Contractility in Anabolic Steroid Users

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ABSTRACT

Anabolic androgenic steroid (AAS) abuse leads to myocardial toxicity. Human studies are conflicting about the myocardial fibrosis in AAS users. We evaluated cardiac tissue characterization, left ventricle (LV) function, and cardiac structure by cardiovascular magnetic resonance (CMR). Twenty strength-trained AAS users (AASU) aged 29 ± 5 yr, 20 strength-trained AAS nonusers (AASNU), and 7 sedentary controls (SC) were enrolled. Native T1 mapping, late-gadolinium enhancement (LGE), extracellular volume (ECV), and myocardial strain were evaluated. AASU showed lower Native T1 values than AASNU (888 ± 162 vs. 1020 ± 179 ms $p = 0.047$). Focal myocardial fibrosis was found in 2 AASU. AASU showed lower LV radial strain (30 ± 8 vs. 38 ± 6 %, $p < 0.01$), LV circumferential strain (−17 ± 3 vs. −20 ± 2 %, $p < 0.01$), and LV global longitudinal strain (−17 ± 3 vs. −20 ± 3 %, $p < 0.01$) than AASNU by CMR. By echocardiography, AASU demonstrated lower 4-chamber longitudinal strain than AASNU (−15 ± g3 vs. −18 ± 2 %, $p = 0.03$). ECV was similar among AASU, AASNU, and SC (28 ± 10 vs. 28 ± 7 vs. 30 ± 7 %, $p = 0.93$). AASU had higher LV mass index than AASNU and SC (85 ± 14 vs. 64 ± 8 vs. 58 ± 5 g/m^2, respectively, $p < 0.01$). AAS abuse may be linked to decreased myocardial native T1 values, impaired myocardial contractility, and focal fibrosis. These alterations may be associated with maladaptive cardiac hypertrophy in young AAS users.

Introduction

Anabolic androgenic steroid (AAS) abuse is a strategy to improve performance, strength, and muscle hypertrophy for athletics or personal appearance purposes [1]. However, AAS abuse has been associated with several impairment on cardiovascular system [2, 3]. Neurovascular alterations [4, 5], decreased high-density lipoprotein (HDL) [6], diminished cholesterol efflux mediated by HDL [7], increased retrograde and oscillatory shear rate in the brachial artery [8], and coronary arterial disease (CAD) have all been reported in AAS users [7, 9].

Long-term AAS abuse seems to cause myocardial dysfunction in older adult men [9]. Previous studies have shown that AAS could be linked to structural changes in the myocardium, left ventricular dysfunction, cardiac hypertrophy, and sudden cardiac death [10, 11].

Cardiovascular magnetic resonance (CMR) is a reference standard to evaluate morphology and cardiac function, and it is widely used to differentiate cardiomyopathies [12]. Moreover, myocardial tissue characterization can be assessed by CMR with late gadolinium enhancement (LGE) [12]. Myocardial fibrosis may be involved in underlying arrhythmogenic mechanisms in patients with hypertrophic cardiomyopathy [13], which may explain the malignant ventricular arrhythmias in young athletes [3].

Pathological changes in the myocardium have been associated with chronic abuse of AAS [14]. Concentric cardiac hypertrophy with focal fibrosis were observed in a small number of investigated cases of sudden cardiac death in AAS users [3]. However, focal myocardial fibrosis [15] and diffuse myocardial fibrosis were not observed in current and former AAS users by myocardial T1 mapping[16]. Thus, the association between AAS abuse and cardiac tissue alterations remains unclear.

The aim of this study was to evaluate cardiac structure using CMR-LGE, myocardial T1 values, and extracellular volume (ECV). Additionally, we evaluated cardiac contractility by CMR and echocardiography in young AAS users.

Materials and Methods

Subjects

Between April 2015 and April 2017, we screened 68 male participants between 18 and 45 years of age (asymptomatic and without previous cardiovascular disease) by email and phone call. Of these, 18 volunteers refused to participate due to lack of time or because of exclusion criteria (see exclusion criteria below). Fifty participants accepted to participate and were allocated as following: 20 AAS users (AASU group), 20 AAS nonusers (AASNU group). Both groups (AASU and AASNU) were recreational weightlifters or amateur bodybuilding athletes who were recruited from gymnasiums. In addition, 10 sedentary men (without regular exercise training and/or sports, < 150 min/week of physical activity such as walking with light/moderate intensity) without cardiovascular disease (hypertension, diabetes, hypercholesterolemia, obesity [body mass index > 30 kg/m^2]) were enrolled as sedentary control group (SC group). Exclusion criteria for all participants were: previous CAD; smoking; alcohol consumption (more than 2 drinks per day); use of diuretics, statins, and/or antihypertensive medications; and kidney disease (creatinine clearance < 60 ml/min/1.72m^2) [17]. All these participants were involved in a study published recently [7]. The study was conducted in accordance with ethical standards of this journal [18].

AASU and AASNU groups had been involved in strength training for at least 2 years. AASU was under the use of AAS by themselves in periodic cycles (periods of on-drug interspersed by periods of off-drug) lasting from 8 to 12 weeks for at least 2 years with 2–4 cycles per year. All AASU were on a cycle over the course of the study. Urine was collected to test the presence of AAS. Moreover, we performed the testosterone/epitestosterone (T/E) ratio.

Two participants of AASU group did not performe the CMR due to claustrophobia. One participant of AASNU group did not perform CMR. Due to the poor image quality of echocardiography, we did not evaluate 1 participant in the AASU group and 4 participants in the AASNU group. Furthermore, 3 participants of SC group showed focal myocardial fibrosis and were excluded of the final analysis (▶ **Fig. 1**).

Cardiovascular magnetic resonance (CMR)

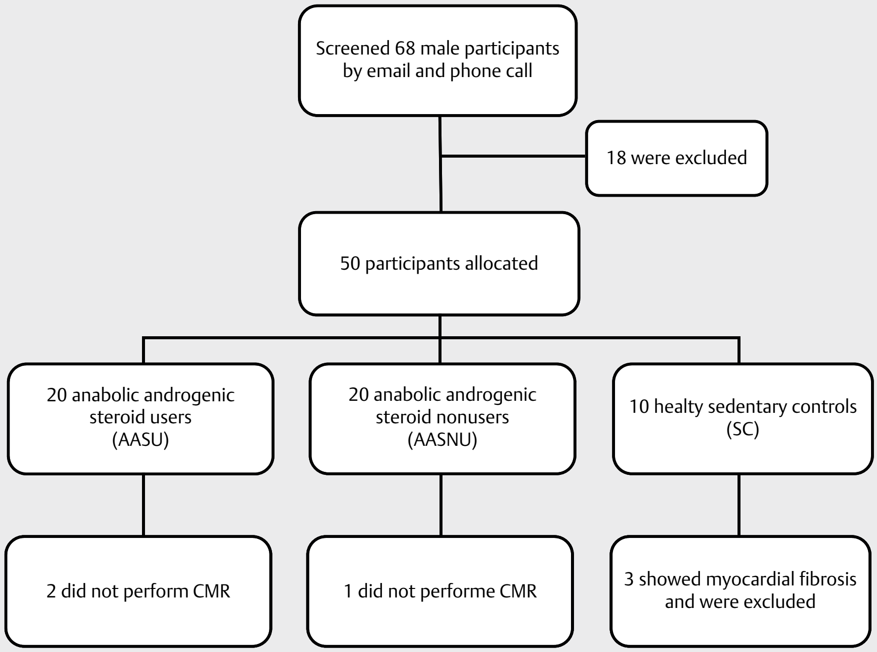
The patients underwent CMR examination on a Vantage-Titan 1.5 T scanner (Canon Medical Systems – formerly Toshiba). For the measurements of myocardial T1 values, LV short-axis images were acquired using a pulse sequence called FFE_125k_tiprep, which is a polarity inversion prepared gradient-echo sequence developed by Canon, specifically for T1 mapping. Hematocrit was measured from a sample of blood collected at CMR session and used to calculate ECV. For the myocardial focal fibrosis quantification, we used a 5 SD threshold above the mean intensity of normal myocardium to define pixels with LGE. Myocardial strain of the left ventricle was measured by feature tracking technique (FTI).

The acquired images were analyzed offline using specific software and tool (CVi42, Circle, Cardiovascular Imaging Inc., Calgary, Canada). This package has the option of obtaining T1 values from ROIs placed on the myocardium and manually corrected to obtain the best exponential curve or generating a parametric map, where T1 values were calculated in pixel-by-pixel base. T1 mapping values were measured as mid ventricular slice (Mid Native T1), only to avoid motion and partial volume effect more prevalent in apical and basal slices [19]. Detailed CMR method is described in the **Supplementary material**.

The analyses were performed by 2 blinded observers (C.E.R, 20 years of experience; and R.A.F, 3 years of experience). Discrepancies were solved by consensus between the 2 experienced observers.

Transthoracic echocardiography

The images were collected by the Vivid E9 (GE Healthcare; Oslo, Norway). The patients underwent 2-dimensional echocardiography. Specific speckle-tracking software that tracks natural acoustic markers or “kernals” facilitated the estimation of strain in all segments. Cine loops of LV motion were captured for offline analysis (Echopac; GE Healthcare, Oslo, Norway). Detailed transthoracic echocardiography method is described in the **Supplementary material**.



▶ **Fig. 1** Flow chart of the study.

Body composition

Body composition was assessed by dual-energy X-ray absorptiometry (DXA), (Lunar iDXA; GE Medical Systems Lunar, Madison, USA). The participants were positioned in supine position, feet strapped together, and hands placed flat on the table adjacent to the side of the body. DXA scaned the whole-body and color mapping to set thresholds on fat %, color coding to code bone, lean tissue and fat tissue were used. DXA radiation is very low, ranging from 1 to 6 μSv, which is considered negligible when compared to natural background radiation (2.4 mSv) [20]. DXA was used to exclude possible bias of body mass index (BMI) among the participants. DXA measurements were performed by the same experienced technician.

Doping urine test

Doping urine test was performed by ultra-performance liquid chromatography with tandem mass spectrometry detection (UPLC-MS/MS). In addition, the testosterone/epitestosterone (T/E) concentration ratio in the urine was determined as previously reported [21]. A T/E ratio greater than 6 indicates exogenous testosterone use [21]. In addition, cocaine, tetrahyocannabinol (THC), amphetamine/methamphetamine, methylenedioxymethamphetamine (MDMA), and 3,4–methylenedioxyamphetamine (MDA) were tested in the urine by gas chromatography-mass spectrometry (GC-MS) analysis as previously described [22].

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median (interquartile range – IQR – 25–75 %). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the variables studied. The parametric data were obtained by 1-way ANOVA analysis of variance. When a significant difference was found, the Bonferroni post-hoc comparison test was used. Kruskal Wallis and Dunn's multiple comparison tests were used for nonparametric data. The chi-square test was used for categorical variables. The Statistical Package for the Social Sciences (SPSS) version 23 was used to perform all the statistical analyses.

Results

Physical characteristics, cumulative lifetime duration of strength training, duration of AAS use in years, and the most AAS used are described in ▶ **Table 1**. Within the AASU group, 20 %, 40 %, 35 % and 5 % of them were using 2, 3, 4, and 5 different types of AAS, respectively. Testosterone (enanthate, propionate, undecylate, and cypionate), nanolone, boldenone, trenbolone, and stanozolol were the most common types of AAS found in AASU. The testosterone/epitestosterone (T/E) ratio was higher in AASU when compared with AASNU and SC ($p < 0.05$). AASU had higher weight, body mass index, and lean mass when compared with AASNU and SC ($p < 0.05$). Fat was lower in AASU when compared with AASNU and SC ($p < 0.05$). No significant difference was found among AASU, AASNU, and SC in age and height ($p > 0.05$). Both AASU and AASNU groups had similar lifetime years of strength training ($p > 0.05$).

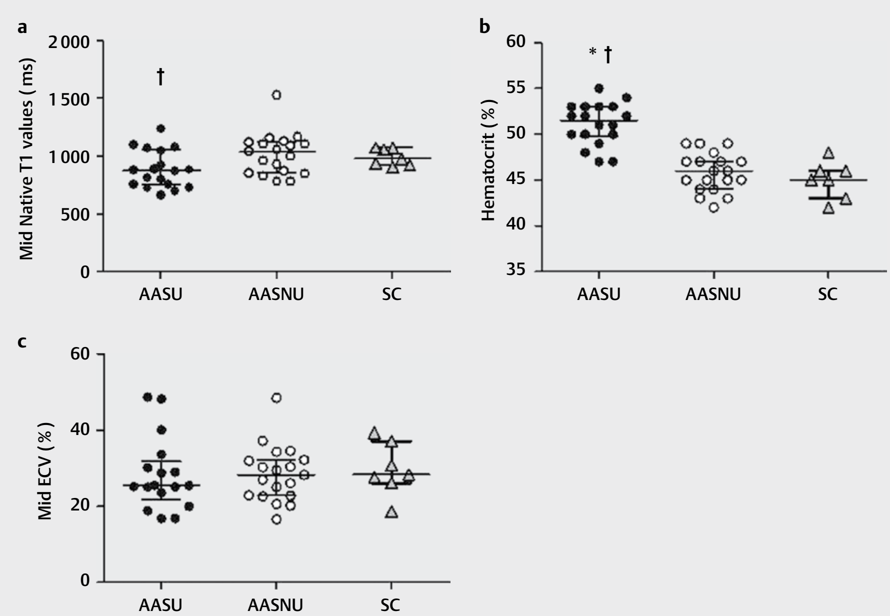
In addition, the drug test assessment was positive for MDMA, amphetamine, and tetraiocanabinol in 7 participants in the AASU group, and positive in 3 participants in the AASNU group ($p = 0.06$).

CMR parameters are shown in ▶ **Fig. 2**. The AASU showed decreased Native T1 values (888 ± 162 vs. 1020 ± 179 ms, $p = 0.047$) when compared with AASNU (▶ **Fig. 2a**). Hematocrit was higher in the AASU group when compared with AASNU and SC groups (51 ± 2

▶ **Table 1** Physical characteristics in anabolic androgenic steroid users (AASU), anabolic androgenic steroid nonusers (AASNU), and sedentary control (SC).

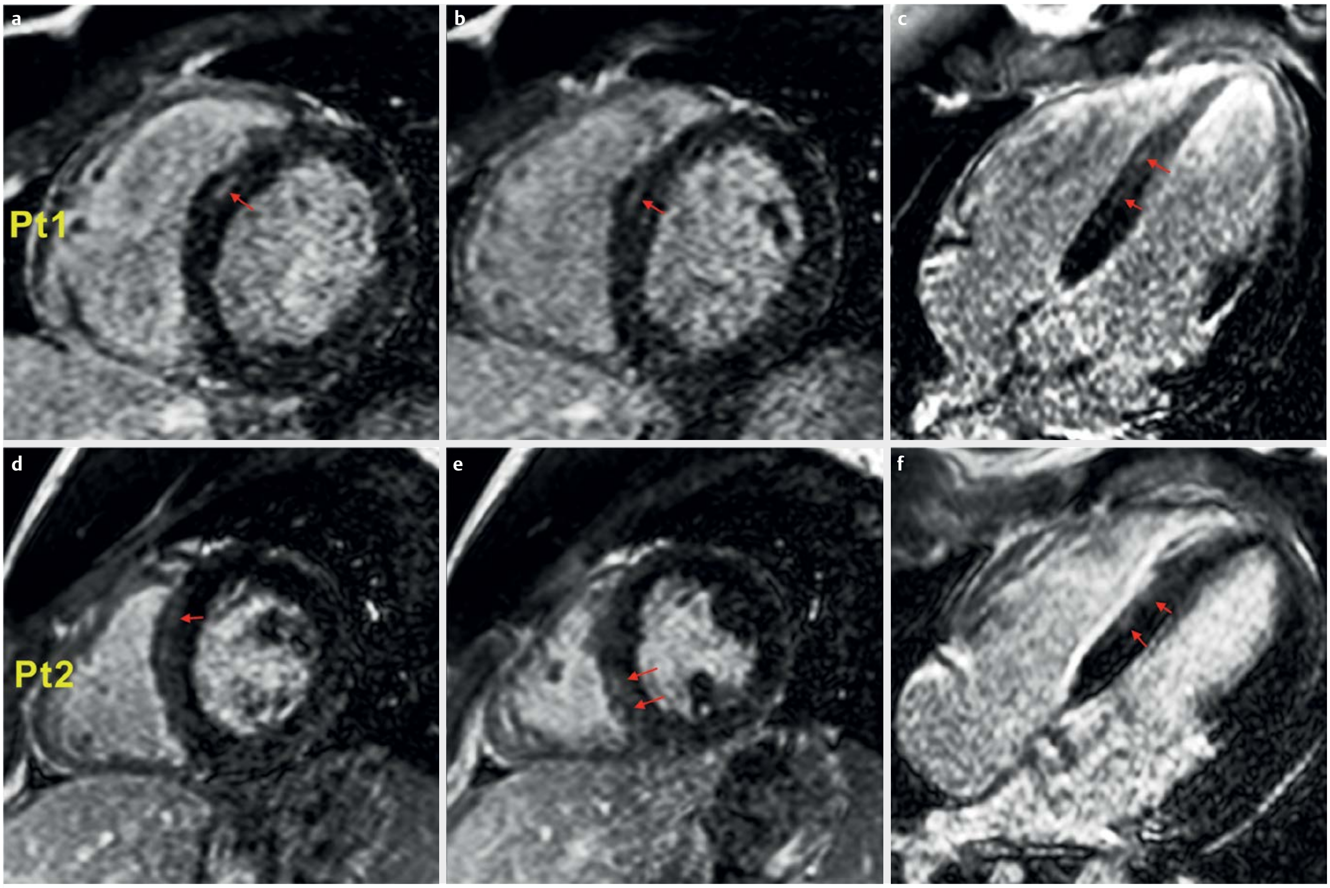
Variables	AASU (n = 20)	AASNU (n = 20)	SC (n = 7)	p
Physical characteristics				
Age (years)	29 ± 5	29 ± 5	29 ± 3	0.964
Weight (kg)	97.4 (90.1–104.9) * †	82.0 (74.0–88.0)	74.8 (70.0–87.5)	0.003
Height (m)	1.78 ± 0.04	1.80 ± 0.09	1.75 ± 0.09	0.343
BMI (kg/m²)	31 ± 3 * †	25 ± 2	26 ± 3	< 0.001
Lean Mass (kg)	82 ± 9 * †	63 ± 7 *	53 ± 8	< 0.001
Fat (kg)	12 (9–15) * †	15 (11–18) *	19 (15–27)	< 0.001
Fat percentage (%)	13 ± 6 * †	19 ± 4 *	28 ± 7	0.005
Strength training (years)	12 ± 5	10 ± 4	-	0.435
Types of AAS, n % (weekly dose)				
Testosterone ††	85 % (575 ± 220 mg)	-	-	-
Nandrolone	20 % (630 ± 125 mg)	-	-	-
Boldenone	75 % (500 ± 100 mg)	-	-	-
Trenbolone	45 % (480 ± 200 mg)	-	-	-
Stanozolol	65 % (350 ± 180 mg)	-	-	-
Durationof AAS use (years)	8 ± 6	-	-	-
T/E ratio	41.0 (25.0–67.5) * †	1.0 (0.2–1.7)	1.0 (0.7–2.7)	< 0.001

Data are presented as mean ± SD or median ± IQR (25 %–75 %; IQR = interquartile range). **BMI** = body mass index. **n** = individuals. **T/E** = testosterone/epitestosterone.**††**Represents all testosterone derivatives (enanthate, propionate, undecylate, and cypionate). * = p < 0.05 vs. SC; † = p < 0.05 vs. AASNU.



▶ **Fig. 2** Native T1 values (2 A), Hematocrit (2B), and ECV (2 C) in AASU, AASNU and SC groups. * = *P* < 0.05 vs.. SC; † = *P* < 0.05 vs. AASNU.

vs. 46 ± 2 vs. 45 ± 2 %, p < 0.001, ▶ **Fig. 2b**). No significant difference in mid ECV was found between groups (AASU: 28 ± 10 vs. AASNU: 28 ± 7 vs. SC: 29 ± 7 %, p = 0.931, ▶ **Fig. 2c**). Focal myocardial fibrosis was found in 2 AASU (11 %). Participant 1: 27 yr (12 years of cumulative AAS use) with late gadolinium enhancement of nonischemic pattern, a linear mid-wall LGE in anteroseptal segment (red arrows). The total estimated LV scar mass was 1.2 g (0.7 %) (▶ **Fig. 3 a, b, c**). Participant 2: 29 ys (6 years of cumulative AAS use) with late gadolinium enhancement of nonischemic pattern, a heterogenous and patchy LGE in anteroseptal and inferoseptal segments (red arrows). The total estimated LV scar mass was 1.3 g (0.6 %) (▶ **Fig. 3 d, e, f**). In contrast, none of the participants in the AASNU group had myocardial fibrosis. Representative measurements of T1 mapping are in the **Supplementary Fig. 1**.



▶ **Fig. 3** Two examples of AASU with small areas of LGE interpreted as focal myocardial fibrosis on top and bottom rows. Panels A/B (Participant - Pt1) and D/E (Participant - Pt2) depict 2 adjacent short axis views of mid to basal portion of LV and panels C/F show LV 4-chamber views of both patients. Red arrows indicate focal LGE areas seen in 2 adjacent short-axis views and confirmed in a perpendicular long-axis 4-chamber view for both patients.

Left ventricular systolic function and cardiac structures variables obtained by CMR among groups are demonstrated in the ▶ **Table 2**. AASU showed decreased LV mid radial strain, LV mid circumferential strain, and LV global longitudinal strain when compared with AASNU ($p < 0.05$). 4-chamber longitudinal strain was lower in AASU when compared with AASNU and SC ($p < 0.05$). Additionally, AASU had higher LV volume at end-systolic index, LV mass index, interventricular septum, LV posterior wall thickness, LV diameter at end-systolic and LV diameter at end-diastolic when compared with AASNU and SC ($p < 0.05$). The AASU had higher LV volume at end-diastolic index and RA volume index when compared with SC ($p < 0.05$); and higher RV volume at end-systolic index when compared with AASNU ($p > 0.05$). However, no statistical difference was found among groups for LV ejection fraction, RV volume at end-diastolic index, aortic root, LA volume index, LA diameter, and RA diameter ($p > 0.05$).

By echocardiography (▶ **Table 3**), differently from CMR, the AASU group showed decresead 4-chamber longitudinal strain when compared with SC ($p < 0.05$). Additionally, AASU showed decreased E/A ratio and mitral annulus velocity average when compared with AASNU ($p < 0.05$). No difference was found among groups for mitral valve peak E velocity (peak early), mitral valve peak A velocity (peak late), and and E/e' ($p > 0.05$).

Discussion

The new findings of the present study are that AAS users showed (1) decreased native T1 values, (2) focal myocardial fibrosis in 11 % of them, and (3) impaired myocardial contractility.

Myocardial T1 mapping has clinical application and may be used to differentiate physiologic adaptation induced by physical training and pathological hypertrophy [12, 23]. Native T1 values are a composite signal of myocytes and ECV [12]. Increased T1 values are associated with acute myocardial infarction, fibrosis, and cardiomyopathy, whereas decreased native T1 values are associated with both lipid and iron overload [12]. Exercise training can also lead to cardiac remodeling and it is associated with fitness level [24]. McDiarmid et al., using a 3-Tesla Achieva TX system, showed decreased native T1 values in endurance athletes (approximately 1178 ms) compared with untrained individuals (approximately 1202 ms) [24]. Tahir et al., using a 1.5-T Achieva scanner, also observed decreased T1 values in male triathletes (approximately 990 ms) compared with male controls (approximately 1014 ms) and female triathletes (approximately 1015 ms) compared with female controls (approximately 1059 ms) [23]. In atheletes, decreased T1 values have been associated with increased myocyte mass rather than extracellular mass [24]. Interestingly, McDiarmid showed that native T1 values are significantly lower in endurance athletes when

▶ **Table 2** Native T1 values, hematocrit, ECV, left ventricular systolic function and cardiac structures variables obtained by CMR in anabolic androgenic steroid users (AASU), anabolic androgenic steroid nonusers (AASNU), and sedentary control (SC).

Variables	AASU (n = 18)	AASNU (n = 19)	SC (n = 7)	*p*
Mid Native T1 values (ms)	888 ± 162 †	1020 ± 179	994 ± 73	0.047
Hematocrit (%)	51 ± 2 *†	46 ± 2	45 ± 2	< 0.001
Mid ECV (%)	28 ± 10	28 ± 7	29 ± 7	0.931
Left ventricular systolic function				
LV mid radial strain (%)	30 ± 8†	38 ± 6 *	30 ± 3	0.003
LV mid circumferential strain (%)	−17 ± 3†	−20 ± 2	−18 ± 1	0.003
4-chamber longitudinal strain (%)	−16 ± 3 * †	−20 ± 4	−19 ± 2	0.020
LV global longitudinal strain (%)	−17 ± 3†	−20 ± 3	−18 ± 1	0.006
LV ejection fraction(%)	60 ± 8	65 ± 8	61 ± 3	0.096
Cardiac structures				
LV volume at end-diastolic index (ml/m²)	92 ± 12 *	83 ± 13	78 ± 6	0.014
LV volume atend-systolic index (ml/m²)	34 (32–48) * †	26 (22–32)	30 (28–31)	0.002
LV mass index (g/m²)	85 ± 14 * †	64 ± 8	58 ± 5	< 0.001
RV volume at end-diastolic index (ml/m²)	91 ± 12	83 ± 14	77 ± 13	0.054
RV volume atend-systolic index (ml/m²)	46 ± 13 †	35 ± 7	38 ± 4	0.004
RV ejection fraction (%)	53 ± 9	58 ± 6	50 ± 5	0.073
Interventricular septum (mm)	10.0 (9.0–11.2) * †	8.0 (8.0–9.0)	7.0 (6.0–9.0)	0.002
LV posterior wall thickness (cm)	1.0 (0.8–1.1) * †	0.8 (0.7–0.8)	0.7 (0.6–0.8)	< 0.001
LV diameterat end-systolic (cm)	4.1 ± 0.6 * †	3.5 ± 0.4	3.5 ± 0.4	0.001
LV diameterat end-diastolic (cm)	5.5 (5.3–6.3) *†	5.3 (5.0–5.7)	5.2 (5.0–5.7)	0.024
Aortic root (cm)	3.1 (2.8–3.3)	2.8 (2.7–3.2)	3.0 (2.8–3.3)	0.143
LA volume índex (ml/m²)	82 ± 20	72 ± 15	68 ± 18	0.139
LA diameter (cm)	2.9 (2.6–3.1)	2.8 (2.6–3.1)	2.4 (2.3–2.8)	0.947
RA volume índex (ml/m²)	26 (23–27) *	23 (21–27)	20 (19–24)	0.007
RA diameter (cm)	5.2 ± 0.5	5.0 ± 0.5	4.9 ± 0.4	0.297

Data are presented as mean ± SD or median (25 %–75 %; IQR = interquartile range).**AASU** = anabolic androgenic steroids users; **AASNU** = anabolic androgenic steroids nonuser; **SC** = sedentary control; **LV** = left ventricle; **RV** = right ventricle; **LA** = left atrium; **RA** = right atrium. * = p < 0.05 vs. SC and † = p < 0.05 vs. AASNU.

▶ **Table 3** Left ventricular systolic function and left ventricular diastolic function by echocardiography in anabolic androgenic steroid users (AASU), anabolic androgenic steroid nonusers (AASNU), and sedentary control (SC).

	AASU n = 17	AASNU n = 16	SC n = 7	*p*
Left ventricular systolic function				
LV mid radial strain (%)	30 ± 7	25 ± 12	31 ± 12	0.453
LV mid circumferential strain (%)	−22 ± 4	−25 ± 6	−23 ± 5	0.188
4-chamber longitudinal strain (%)	−15 ± 3 †	−18 ± 2	−17 ± 1	0.024
LV Global longitudinal strain (%)	−17 ± 2	−19 ± 2	−18 ± 4	0.094
LV Ejection fraction (%)	56 ± 4	58 ± 3	59 ± 5	0.162
Left ventricular diastolic function				
Mitralvalve peak E velocity (cm/s)	75 ± 13	78 ± 14	77 ± 11	0.813
Mitral valve peak A velocity (cm/s)	56 ± 13	56 ± 33	46 ± 8	0.689
E/A ratio	1.4 (1.3–1.5)†	1.6 (1.4–1.8)	1.4 (1.1–2.3)	0.024
Mitral annulus velocity average(cm/s)	12 ± 2†	15 ± 2	14 ± 3	0.004
E/e’ ratio	6.3 ± 1.4	5.3 ± 1.2	5.7 ± 1.5	0.147

Data are presented as mean ± SD or median (25 %–75 %; IQR = interquartile range). **AASU** = anabolic androgenic steroids users; **AASNU** = anabolic androgenic steroids nonuser; **SC** = sedentary control. **LV** = left ventricle**.** * = vs. SC; † = vs. AASNU.

compared with sedentary individuals; however, native T1 value is not different between athletes regardless of the level of cardiorespiratory fitness [24]. In our study, we evaluated strength-trained individuals and we found decreased T1 values (approximately 888 ms) only in those athletes under AAS abuse when compared with AAS nonusers. However, the ECV was similar between groups.

Increased ECV is observed in LV hypertrophic cardiomyopathy due to extracellular matrix expansion and myocardial disarray. On the other hand, decreased ECV is observed in endurance athletes with higher wall thickness due to myocardial hypertrophy [25]. Aerobic training practioners (runners, triathletes, and cyclists) have lower ECV than those with hypertrophic cardiomyopathy [25]. These findings point out that myocardial hypertrophy in endurance athletes is mediated by cellular hypertrophy rather than cellular disarray and extracellular matrix expansion.

The question that emerges from our results is why AAS abusers have decreased T1 values with normal ECV. Our study was not designed to answer this question. One possible mechanism could be explained by the increased myofibril hypertrophy inside the myocyte, leading to decreased intracellular water content and lower T1 relaxation times [26]. Moreover, AAS abuse could trigger greater LV hypertrophy, which seems to be related to cumulative lifetime of use and type of AAS abuse [27, 28]. In fact, Baggish et al. reported higher LV mass in AAS users when compared with nonusers [9], which is in line with our findings. However, our study is an observational, cross-sectional study and future longitudinal studies are needed to evaluate the potential causality between AAS abuse and T1 values.

LGE is the reference standard for noninvasive imaging of focal myocardial fibrosis [12]. Focal myocardial fibrosis has been associated with long-term of intense endurance training in veteran male athletes (aged 50–72 years) [29, 30]. However, the mechanism involved in this alteration is not completely understood. For instance, evidence for genetic predisposition, myocarditis, pulmonary artery pressure overload, and intense exercise-induced heart micro-injury have been associated with this pathologic alteration [31]. Moreover, prolonged endurance training may trigger cardiac injury with consequent myocardial fibrosis [32]. Mohlenkamp and collaborators reported LGE in 12 % of veteran runners associated with subclinical coronary events in some athletes [33]. Wilson and collaborators reported LGE in 50 % of elite veteran athletes but not in young athletes or older non-athletes [29].

Our study shed light on a possible relationship between AAS abuse and focal myocardial fibrosis in young strength-trained athletes. Experimental study with histological analysis of the myocardium showed that AAS causes myocardial hypertrophy, myocardial fibrosis, and activation of apoptosis [34]. Evidence also exists of interstitial fibrosis mediated by the renin angiotensin system in rats with AAS administration [35]. Increased cardiac angiotensin II concentration contributes to the hyperplasia of cardiac fibroblasts, which could be linked to development of cardiac fibrosis [36]. Furthermore, hemodynamic alterations and adverse structural remodeling could be involved in myocardial fibrosis [35]. In humans, Montisci et al. reported concentric cardiac hypertrophy with focal fibrosis associated with AAS abuse in 1 fatal case [37]. However, recent studies did not show myocardial fibrosis in young AAS users [15, 16] and former AAS users [16]. In our study, we found focal myocardial fibrosis in 2 young asymptomatic individuals in the AASU group. The controversy among studies is uncertain and someone could raise some possible explanations for the different findings. First, our AASU participants had a mean of 8 years of cumulative use of AAS, which is more than previously reported [16]. Second, approximately 60 % of the current and former AAS abusers were concomitantly involved in aerobic training [16], and our participantes were only involved in strengh training. Third, the type and dosage of AAS concomitantly with polypharmacy were different across studies.

Previous studies have reported associations between AAS abuse and LV systolic and diastolic dysfunction [38–40]. Rasmussen and collaborators assessed myocardial function and structure using advanced echocardiography (speckle tracking), and they found decreased LV global longitudinal strain (GLS) in current and former AAS abusers compared with nonusers [16]. GLS is a new method for assessing LV function, and it is an independent marker of adverse cardiovascular outcomes such as heart failure [41]. In our study, we also found decreased GLS in AASU compared with the AASNU. However, the GLS was only significantly different by CMR (feature tracking technique), which is the reference standard to evaluate cardiac function. Moreover, mid radial strain, mid circumferencial strain, and 4-chamber longitudinal strain were lower in AASU compared with AASNU. Differently from previous studies [16, 42], we did not observe significant alterations in GLS and circumferential strain when evaluated by echocardiography (speckle tracking). By speckle tracking, we found a decreased 4-chamber longitudinal strain in the AASU compared with AASNU. Diastolic dysfunction in AAS abusers was reported in previous studies [9, 15, 16]. We also found diastolic alteration in AAS abusers as demonstrated by decreased E/A ratio and mitral annulus velocity average. Impairment in E/A ratio was reported in endurance athletes [43]. Tahir and collaborators showed decreased post-race diastolic volume in triathletes. Increased heart rate and the higher atrial contraction to facilitate LV filling might be a compensatory mechanism for increased LV stiffness [43]. This alteration has an interesting clinical application because diastolic dysfunction has been associated with early stages of hypertension, lower functional capacity, and development of heart failure [44, 45]. Futhermore, diastolic functional parameters by echocardiography or CMR can help to characterize the physiological or pathological adaptation, and there is evidence that assessment of global longitudinal strain during exercise may be an interesting tool in the future [46].

Perspective

The illicit use of AAS among young male is a widespread problem worldwide. The abuse of AAS may lead to myocardial toxicity even in younger men. Our study suggests that young individuals under AAS abuse have decreased native T1 values, impaired myocardial contractility, and focal myocardial fibrosis. Therefore, AAS abuse may be associated with maladaptive cardiac hypertrophy in young AAS users. These findings are clinically relevant because suggest that young AAS users may be at risk of early development of cardiac dysfunction. Future studies with a larger sample size and longer follow-up are needed to determine the risk of AAS abuse in this population.

Study Limitations

We recognize limitations in our study. We studied a small number of strength-trained individuals. We did not evaluate the hours per week of strength training between AASU and AASNU, which could influence LV function and structure. Polypharmacy among AASU is often associated with AAS use [47]. Therefore, we assessed several drugs as described previously; however, we did not evaluate other non-AAS substances, such as heroin, and clenbuterol, which could also lead to adverse effects. We used a novel pulse sequence for T1 mapping and the values cannot be compared directly with other pulse sequences. The intrinsic measurement errors of this pulse sequence compared with conventional inversion-recovery spin-echo for T1 measurements were evaluated in phantom studies and estimated a low mean measurement error of 7.4 ± 3.8 % [48, 49].

Conclusion

This study indicates that AAS abuse may be linked to decreased native T1 values, impaired myocardial contractility, and focal myocardial fibrosis. Myocardial structural and functional alterations may be associated with maladaptive cardiac hypertrophy in young AAS users.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Forbes GB. The effect of anabolic steroids on lean body mass: the dose response curve. Metabolism 1985; 34: 571–573

[2] Santos D, Sayegh ALC, Armani R et al. Resting spontaneous baroreflex sensitivity and cardiac autonomic control in anabolic anogenic steroid users. Clinics (Sao Paulo) 2018; 73: e226

[3] Montisci M, El Mazloum R, Cecchetto G et al. Anabolic anogenic steroids abuse and cardiac death in athletes: Morphological and toxicological findings in four fatal cases. Forensic Sci Int 2012; 217: e13–e18

[4] Alves MJ, Dos Santos, Dias RG et al. Abnormal neurovascular control in anabolic anogenic steroids users. Med Sci Sports Exerc 2010; 42: 865–871

[5] Porello RA, Dos Santos, Souza FR et al. Neurovascular response during exercise and mental stress in anabolic steroid users. Med Sci Sports Exerc 2018; 50: 596–602

[6] Morikawa AT, Maranhao RC, Alves MJ et al. Effects of anabolic anogenic steroids on chylomicron metabolism. Steroids 2012; 77: 1321–1326

[7] Souza FR, Dos Santos, Porello RA et al. Diminished cholesterol efflux mediated by HDL and coronary artery disease in young male anabolic anogenic steroid users. Atherosclerosis 2019; 283: 100–105

[8] de Souza FR, Sales ARK, Dos Santos et al. Retrograde and oscillatory shear rate in young anabolic anogenic steroid users. Scand J Med Sci Sports 2019; 29: 422–429

[9] Baggish AL, Weiner RB, Kanayama G et al. Cardiovascular toxicity of illicit anabolic-anogenic steroid use. Circulation 2017; 135: 1991–2002

[10] Angell P, Chester N, Green D et al. Anabolic steroids and cardiovascular risk. Sports Med 2012; 42: 119–134

[11] Hoffman JR, Ratamess NA. Medical issues associated with anabolic steroid use: are they exaggerated? J Sports Sci Med 2006; 5: 182–193

[12] Haaf P, Garg P. Messroghli et al. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: A comprehensive review. J Cardiovasc Magn Reson 2016; 18: 89

[13] Olivotto I, Maron MS, Autore C et al. Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2008; 52: 559–566

[14] Lusetti M, Licata M, Silingardi E et al. Pathological changes in anabolic anogenic steroid users. J Forensic Leg Med 2015; 33: 101–104

[15] Angell PJ, Ismail TF, Jabbour A et al. Ventricular structure, function, and focal fibrosis in anabolic steroid users: A C study. Eur J Appl Physiol 2014; 114: 921–928

[16] Rasmussen JJ, Schou M, Madsen PL et al. Cardiac systolic dysfunction in past illicit users of anabolic anogenic steroids. Am Heart J 2018; 203: 49–56

[17] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41

[18] Harriss DJ, MacSween A, Atkinson G. Ethical standards in sport and exercise science research: 2020 update. Int J Sports Med 2019; 40: 813–817

[19] Rogers T, Dabir D, Mahmoud I et al. Standardization of T1 measurements with MOLLI in differentiation between health and disease--the ConSept study. J Cardiovasc Magn Reson 2013; 15: 78

[20] Bandirali M, Lanza E, Messina C et al. Dose absorption in lumbar and femoral dual energy X-ray absorptiometry examinations using three different scan modalities: an anthropomorphic phantom study. J Clin Densitom 2013; 16: 279–282

[21] van de Kerkhof DH, de Boer D, Thijssen JH et al. Evaluation of testosterone/epitestosterone ratio influential factors as determined in doping analysis. J Anal Toxicol 2000; 24: 102–115

[22] Mantovani CC, Silva JPE, Forster G et al. Simultaneous accelerated solvent extraction and hyolysis of 11-nor-Delta(9)-tetrahyocannabinol-9-carboxylic acid glucuronide in meconium samples for gas chromatography-mass spectrometry analysis. J Chromatogr B Analyt Technol Biomed Life Sci 2018; 1074-1075: 1–7

[23] Tahir E, Starekova J, Muellerleile K et al. Myocardial fibrosis in competitive triathletes detected by contrast-enhanced C correlates with exercise-induced hypertension and competition history. JACC Cardiovasc Imaging 2018; 11: 1260–1270

[24] McDiarmid AK, Swoboda PP, Erhayiem B et al. Athletic cardiac adaptation in males is a consequence of elevated myocyte mass. Circ Cardiovasc Imaging 2016; 9: e003579

[25] Swoboda PP, McDiarmid AK, Erhayiem B et al. Assessing Myocardial Extracellular Volume by T1 Mapping to Distinguish Hypertrophic Cardiomyopathy From Athlete's Heart. J Am Coll Cardiol 2016; 67: 2189–2190

[26] Robinson AA, Chow K, Salerno M. Myocardial T1 and ECV measurement: Underlying concepts and technical considerations. JACC Cardiovasc Imaging 2019; 12: 2332–2344

[27] Urhausen A, Albers T, Kindermann W. Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? Heart 2004; 90: 496–501

[28] Payne JR, Kotwinski PJ, Montgomery HE. Cardiac effects of anabolic steroids. Heart 2004; 90: 473–475

[29] Wilson M, O'Hanlon R, Prasad S et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. J Appl Physiol (1985) 2011; 110: 1622–1626

[30] Breuckmann F, Mohlenkamp S, Nassenstein K et al. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. Radiology 2009; 251: 50–57

[31] van de Schoor FR, Aengevaeren VL, Hopman MT et al. Myocardial fibrosis in athletes. Mayo Clin Proc 2016; 91: 1617–1631

[32] La Gerche A, Burns AT, Mooney DJ et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. Eur Heart J 2012; 33: 998–1006

[33] Mohlenkamp S, Lehmann N, Breuckmann F et al. Running: The risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. Eur Heart J 2008; 29: 1903–1910

[34] Papamitsou T, Barlagiannis D, Papaliagkas V et al. Testosterone-induced hypertrophy, fibrosis and apoptosis of cardiac cells--an ultrastructural and immunohistochemical study. Med Sci Monit 2011; 17: BR266–BR273

[35] Rocha FL, Carmo EC, Roque FR et al. Anabolic steroids induce cardiac renin-angiotensin system and impair the beneficial effects of aerobic training in rats. Am J Physiol Heart Circ Physiol 2007; 293: H3575–H3583

[36] Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991; 83: 1849–1865

[37] Montisci M, El Mazloum R, Cecchetto G et al. Anabolic anogenic steroids abuse and cardiac death in athletes: Morphological and toxicological findings in four fatal cases. Forensic Sci Int 2012; 217: e13–e18

[38] Luijkx T, Velthuis BK, Backx FJ et al. Anabolic androgenic steroid use is associated with ventricular dysfunction on cardiac MRI in strength trained athletes. Int J Cardiol 2013; 167: 664–668

[39] Angell PJ, Chester N, Green DJ et al. Anabolic steroid use and longitudinal, radial, and circumferential cardiac motion. Med Sci Sports Exerc 2012; 44: 583–590

[40] Baggish AL, Weiner RB, Kanayama G et al. Long-term anabolic-anogenic steroid use is associated with left ventricular dysfunction. Circ Heart Fail 2010; 3: 472–476

[41] Biering-Sorensen T, Biering-Sorensen SR, Olsen FJ et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: The Copenhagen City Heart Study. Circ Cardiovasc Imaging 2017; 10: e005521. doi: 10.1161/CIRCIMAGING.116.005521

[42] D'Anea A, Radmilovic J, Caselli S et al. Left atrial myocardial dysfunction after chronic abuse of anabolic anogenic steroids: A speckle tracking echocardiography analysis. Int J Cardiovasc Imaging 2018; 34: 1549–1559

[43] Tahir E, Scherz B, Starekova J et al. Acute impact of an endurance race on cardiac function and biomarkers of myocardial injury in triathletes with and without myocardial fibrosis. Eur J Prev Cardiol 2020; 27: 94–104

[44] Kane GC, Karon BL, Mahoney DW et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA 2011; 306: 856–863

[45] Kosmala W, Jellis CL, Marwick TH. Exercise limitation associated with asymptomatic left ventricular impairment: Analogy with stage B heart failure. J Am Coll Cardiol 2015; 65: 257–266

[46] Augustine DX, Howard L. Left ventricular hypertrophy in athletes: Differentiating physiology from pathology. Curr Treat Options Cardiovasc Med 2018; 20: 96

[47] Sagoe D, McVeigh J, Bjornebekk A et al. Polypharmacy among anabolic-anogenic steroid users: a descriptive metasynthesis. Subst Abuse Treat Prev Policy 2015; 10: 12

[48] Kuhara S, Ishikawa H, Kanazawa T. Polarity-corrected TI prep tool for delayed-enhancement imaging and T1 mapping. Proc Intl Soc Mag Reson Med 2014; abstract 2447

[49] Ishikawa H, Seino S, Takasumi H et al. The measurement precision and accuracy of t1 mapping using polarity corrected (PC) ti prep tool. Nihon Hoshasen Gijutsu Gakkai Zasshi 2018; 74: 13–21