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Left ventricular dyssynchrony and post-systolic shortening in young bodybuilders using anabolic-androgenic steroids

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Abstract

Left ventricular (LV) remodeling, characterized by increased LV hypertrophy and depressed systolic and diastolic function, is observed in strength-trained athletes who use anabolic-androgenic steroids (AAS). Previous studies suggested a pathological remodeling with an increase in cardiac fibrosis in these athletes, which could promote intraventricular dyssynchrony. In this context, this study evaluated LV dyssynchrony in strength-trained athletes using AAS, hypothesizing that the use of AAS would lead to an increase in post-systolic shortening. Forty-four male subjects (aged 20–40 yr) were divided into three age-matched groups: strength-trained athletes using (users, $n = 14$) or not (nonusers, $n = 15$) AAS and healthy sedentary men (controls, $n = 15$). After completing a survey, each participant was assessed with two-dimensional (2D)-strain echocardiography. LV dyssynchrony was quantified using the standard deviation (SD) of the time to peak for longitudinal strain of the 18 LV-segments (from the apical 4, 3, and 2 chambers views), the longitudinal strain delay index (LSDI), and the segmental post-systolic index (PSI). Users showed mean AAS dosages of 564 ± 288 mg·wk⁻¹ with a mean protocol duration of 12 ± 6 wk and a history of use of 4.7 ± 1.8 yr. They exhibited a greater LV mass index and depressed systolic and diastolic function when compared with both nonusers and controls. The decrease in LV strain in users was predominantly observed at the interventricular septum level ($-16.9\% \pm 2.5\%$ vs. $-19.2\% \pm 1.8\%$ and $-19.0\% \pm 1.6\%$ in users, nonusers, and controls, respectively, $P < 0.01$). Users showed higher SD than controls (43 ± 8 ms vs. 32 ± 5 ms, respectively, $P < 0.01$). The LSDI was significantly higher in users compared with both nonusers and controls (-23.4 ± 9.5 vs. -15.9 ± 9.3 and -9.8 ± 3.9 , respectively, $P < 0.01$). PSI, calculated on the basal inferoseptal, basal anteroseptal, and basal inferolateral segments, were also greater in users compared with the two other groups. Our results reported an increase in LV dyssynchrony in young AAS users that brought new evidences of a pathologic cardiac remodeling in this specific population.

NEW & NOTEWORTHY Illicit androgenic anabolic steroids (AAS) use is widespread, but data on LV dyssynchrony are lacking, although it could be increased by a higher prevalence of myocardial fibrosis reported in this population. In AAS users, the decrease in LV strain was predominantly observed in interventricular segments. All dyssynchrony indices were higher in AAS users and several segments exhibited post-systolic shortening. These results showed an association between AAS consumption, LV remodeling, and dyssynchrony.

anabolic-androgenic steroids; cardiac hypertrophy; dyssynchrony; post-systolic shortening

INTRODUCTION

Previous research has suggested that there is an association between the use of anabolic-androgenic steroids (AAS) and cardiovascular events in strength-trained athletes, with a pathophysiological link first proposed by early case reports detailing sudden cardiac death or ischemic stroke in that specific athletic population (1, 2). Strength-trained athletes using AAS exhibit greater left ventricular (LV) muscle mass (3–5), induced by exacerbated concentric hypertrophy (2). Both postmortem

and ultrasonic myocardial backscatter-based studies have provided evidence that this form of cardiac remodeling is associated with an increase in myocardial fibrosis, predominantly localized to the interventricular septum (1, 2, 5–7).

Myocardial fibrosis has adverse effects on myocyte excitability, cell-to-cell coupling, and the regulation of intercellular calcium, all of which are potential mechanisms that could increase the risk of LV dyssynchrony (8, 9). This condition, in which there is a lack of synchronicity in the contraction of the LV walls, results in myocardial inefficiency and is

associated with poor prognoses in patients with heart failure (10). LV dyssynchrony increases the occurrence of post-systolic shortening (PSS), which is defined as myocardial shortening that occurs after end-systole and, thus, does not contribute to ejection of the blood (11). Persistent PSS has also been observed after brief ischemia and, thus, could be a marker of regional myocardial dysfunction (12, 13). However, to our knowledge, no study has aimed to evaluate LV dyssynchrony and PSS in strength-trained athletes using AAS, despite their importance in the evaluation of LV function.

Recent advances in echocardiography have provided the possibility to assess regional LV strain. Although there are several parameters for quantifying PSS, the post-systolic index (PSI), which provides the ratio of the amplitude of PSS to total shortening, is the most widely used (14, 15). In this context, the aim of the present study was to evaluate if cardiac remodeling in strength-trained athletes using AAS is associated with an increase in LV dyssynchrony and an increase in the occurrence of PSS. We hypothesized that 1) the abuse of AAS leads to an increase in LV dyssynchrony and 2) strains are delayed and the occurrence of PSS are increased predominantly at the intraventricular septal segments of the myocardium.

METHODS

Study Population

Fourteen strength-trained athletes actively using AAS for >2 yr (users), 15 strength-trained athletes who had never taken AAS (nonusers), and 15 age-matched healthy sedentary controls were prospectively included. All participants were male and aged 18–40 yr. The inclusion criteria for the strength-trained athletes, both users and nonusers, was a training history of at least 7 h of training per week for a minimum of 5 yr. To be included in this study, users needed to self-report a documented history of AAS use for at least three courses of 2 wk in the last 2 years. Nonusers had a self-reported history of never taking AAS.

Exclusion criteria were coronary artery disease, congestive heart failure, moderate or severe valvular heart disease, congenital heart disease, treatment for hypertension, respiratory or metabolic disorders, or active cigarette smoking in the past 10 years. Before taking part in the study, each part of the protocol was described in detail to each of the participants. Indeed, written informed consent was obtained from each participant. The protocol of the study was approved by the French Ethic Committee in Sports Science (CERSTAPS n°2018-04-10-28).

Medical Survey and Examination

Each participant was asked about their medical and training history (e.g., years of training, the average number per week, and the average duration of each session). All participants were systematically asked about doping or performance-enhancing drugs in a confidential manner. If a participant reported partaking in doping or the use of performance-enhancing drugs, the type of drug (e.g., testosterone, nandrolone decanoate, decabalone, trenbolone), dosage (mg per week for each molecule), number of courses, and duration (number of weeks for each courses and years of AAS

consumption) of use were assessed. All participants underwent blood pressure measurements. Systemic vascular resistances (SVRs) were calculated using Poiseuille's law. Their body mass index was also calculated.

Echocardiographic Recordings

Echocardiography assessments were performed using the Vivid Q system (GE Healthcare, Horten, Norway) with a 3.5-MHz transducer (M4S probe), as the participant remained in a left lateral decubitus position. Cine loops were recorded in parasternal short-axis (at the basal and apical levels), parasternal long-axis and apical (4, 3, and 2 chambers) views; and were saved for blinded offline analyses (EchoPAC, BT113 version, GE Healthcare). Special care was taken to avoid oblique views from the midlevel short-axis images and to obtain images with the most circular geometry possible. Grayscale images were saved at a frame rate of 80–90 frames/s and color tissue velocity images at a frame rate of 120–140 frames/s. All measurements were averaged over three to five cardiac cycles. Two-dimensional echocardiographic measurements were performed in accordance with guidelines from the American Society of Echocardiography (16).

Echocardiographic Analysis

Left ventricular morphology and function.

LV diameters, volumes, wall thickness and mass were assessed in accordance with current guidelines (16). LV mass was indexed to body surface area. LV global diastolic function was assessed using the peak early (*E*) and atrial (*A*) transmitral flow velocities. LV global systolic function was assessed using the ejection fraction (EF) based on the Simpsons biplane method and by using stroke volume and cardiac output from a five-chamber view. Tissue Doppler imaging velocities (peak *E'*, *A'*, and *S'*) were assessed at the mitral annular level in the apical four-chamber view. Peak *E'* average from septum and lateral walls (E'_{mean}) was used as index of LV relaxation (17).

Left ventricular strain.

From an end-systolic single frame, a region of interest was traced over the endocardial cavity interface by a point-and-click approach. An automated tracking algorithm then followed the endocardium from this single frame throughout the cardiac cycle. Further adjustment of the region of interest was performed to ensure that all of the myocardial regions were included. This allowed for the acoustic markers (i.e., the so-called speckles), equally distributed in the region of interest, to be followed throughout the entire cardiac cycle. The distance between the speckles was measured as a function of time from which parameters of myocardial deformation could be calculated. Cine loops were recorded for offline analysis. EchoPAC data were exported as “.txt files” to be processed with a specific toolbox (Scilab version 4.1; Consortium Scilab, INRIA-ENPC, Paris, France). Data were normalized to the percentage of systolic duration to avoid differences in heart rate and cine loop frame rates, and the peaks were automatically determined.

Longitudinal strain (LS) and circumferential strain (CS) were obtained as previously detailed by our group (18, 19), using apical (4, 3, and 2 chambers) and parasternal short-

axis (at the basal and apical level) views, respectively. Global LS and diastolic longitudinal strain rates (LSr diastolic) were used as index of LV contractility and relaxation, respectively (20).

Left ventricular segmental strain and dyssynchrony.

The myocardium was automatically divided into six segments (for each echocardiographic view) that were color coded as previously described and displayed as six segmental time-strain curves for LS and CS (21). On the apical four-chambers (A4C) view, peak strain was averaged over segments one, two, and three to evaluate the septum, and over segments four, five, and six to evaluate the lateral wall. On the parasternal short-axis views (at the basal and apical level), peak strain was averaged over segments one and two, five and six to evaluate the septum, and over segments three and four to evaluate the lateral wall. For each segment, the time to peak (TTP, ms) strain and strain at aortic valve closure (%) were determined. Parameters for LV dyssynchrony were assessed as follows: the maximum delay was calculated as a difference between the TTP strain for the earliest and the most delayed segment (from the apical four and two chamber views) (22). The standard deviations (SD) of the TTP for the segmental strain was calculated over six segments (A4C view, SD_{6S}), 12 segments [A4C and apical two-chambers (A2C) views, SD_{12S}], and 18 segments [A4C, A2C and apical three-chambers (A3C) views, SD_{18S}]. The maximum delay and SD were then indexed to the systolic duration. For each segment, the post-systolic index (PSI) was defined as follows (14):

$$\text{PSI} = \frac{\text{peak strain} - \text{strain at aortic valve closure}}{\text{peak strain}} \times 100$$

Finally, the longitudinal strain delay index (LSDI) was also calculated (23). The LSDI represents the sum of the differences between peak strain and the strain value at the closure of the aortic valve for each segment, resulting in LSDI_{6S} (A4C view), LSDI_{12S} (A4C and A2C views), and LSDI_{18S} (A4C, A2C, and A3C views):

$$\text{LSDI} = \sum_1^n (\text{strain peak} - \text{strain at aortic valve closure})$$

Statistical Analysis

Statistical analyses were performed using MedCalc (version 19.1) software. All values were expressed as means \pm SD. The normality of the distribution was checked by the kurtosis and skewness coefficient and the homogeneity of the variances by the Bartlett test. A one-way analysis of variance (ANOVA) and the Tukey post hoc test was used to compare groups where appropriate. Single linear regression analyses were performed to assess the association between LV mass, global LS, and dyssynchrony parameters.

RESULTS

Anthropometric data are presented in Table 1. There was no difference in body mass and body surface area between users and nonusers. However, body mass index and body surface area were higher in both users and nonusers when compared with controls. Users and nonusers had a higher

Table 1. Anthropometric data of the study populations

| | Ctrl | Nonusers | Users |
|-----------------------------------|-----------------|-------------------|--------------------|
| <i>n</i> | 15 | 15 | 14 |
| Age, yr | 31.1 \pm 8.2 | 27.2 \pm 4.5 | 32.0 \pm 8.5 |
| Body height, cm | 175.8 \pm 5.7 | 178.6 \pm 6.2 | 178.7 \pm 7.9 |
| Body mass, kg | 71.7 \pm 8.7 | 87.4 \pm 11.1** | 92.9 \pm 11.3*** |
| Body surface area, m ² | 1.86 \pm 0.11 | 2.05 \pm 0.11** | 2.1 \pm 0.21*** |
| Systolic blood pressure, mmHg | 114 \pm 7 | 130 \pm 11*** | 124 \pm 9** |
| Diastolic blood pressure, mmHg | 74 \pm 6 | 71 \pm 8 | 74 \pm 8 |
| Heart rate, bpm | 62 \pm 9 | 67 \pm 14 | 67 \pm 10 |
| Systemic vascular resistances, AU | 19.6 \pm 3.0 | 17.6 \pm 2.9 | 16.8 \pm 1.7** |

Values are means \pm SD; *n*, number of subjects. AU, arbitrary unit; Ctrl, control. Statistics were made using an ANOVA with a Tukey post hoc test. Significantly different from Ctrl (***P* < 0.01; ****P* < 0.001).

resting systolic blood pressure than controls. SVR were significantly lower in users compared with controls. Users and nonusers reported similar weekly training volumes (8.8 \pm 0.4 vs. 8.9 \pm 1.7 training hours per week, respectively), but training experience was greater in users than in nonusers (11.8 \pm 0.4 yr of training vs. 8.6 \pm 2.3 yr of training, respectively, *P* < 0.05). The medical survey revealed that users were taking 3.5 \pm 1 AAS simultaneously (range: [2–5] AAS): testosterone (*n* = 14 out of 14), nandrolone decanoate (*n* = 11 out of 14), decabolone (*n* = 10 out of 14), trenbolone (*n* = 8 out of 14), masterone (*n* = 5 out of 14), and boldenone (*n* = 3 out of 14). They used mean AAS dosages of 564 \pm 288 mg·wk⁻¹ (range: [250–1,000] mg·wk⁻¹) mainly administered via intramuscular injections with a mean protocol duration of 12 \pm 6 wk and a history of use of 4.7 \pm 1.8 yr (range: [4–8] yr). All subjects were ON-drugs and their last AAS intake was <24 h.

Left Ventricular Morphology and Function

Left ventricular morphology and function are presented in Table 2. Left ventricular wall thickness and mass were higher in both users and nonusers than in controls. Compared with nonusers, users had a significantly thicker interventricular septum, greater LV mass (absolute or indexed values), and greater end-systolic volume. Users exhibited a lower E-wave velocity, E' mean velocity, and LSr diastolic than nonusers and controls, and a lower E/A ratio than nonusers. Assessments of LV systolic function revealed that despite similar stroke volume or cardiac output (indexed to body surface area) between groups, users presented with a lower ejection fraction compared with nonusers and lower global LS compared with both nonusers and controls.

Left Ventricular Regional Strain

Regional LS (Fig. 1) was lower on the interventricular septum segments in users than in both nonusers and controls. The TTP strain was similar between groups, except on segment 18 (basal anteroseptal, A3C view) where it was higher in users (127% \pm 20% vs. 115% \pm 21% in nonusers and 105% \pm 9% in controls, *P* < 0.01). Regional CS at the basal level (Fig. 2A) was significantly lower on the interventricular septum segments in users than in nonusers and controls. However, regional CS at the apical level (Fig. 2B) was significantly lower on all segments in users than in nonusers and controls.

Table 2. Left ventricular morphology and function

| | Ctrl | Nonusers | Users |
|--|-------------|--------------|-----------------|
| <i>n</i> | 15 | 15 | 14 |
| IVST, cm | 0.94 ± 0.10 | 1.10 ± 0.20* | 1.30 ± 0.30***# |
| PWT, cm | 0.7 ± 0.1 | 1.0 ± 0.2*** | 1.2 ± 0.2*** |
| LVM, g | 155 ± 30 | 237 ± 46*** | 299 ± 73*** ## |
| LVMi, g·m ⁻² | 83 ± 17 | 116 ± 18*** | 142 ± 31*** ## |
| RWT | 0.33 ± 0.04 | 0.39 ± 0.06* | 0.43 ± 0.08** |
| LV end-diastolic volume, mL | 96 ± 16 | 123 ± 17** | 137 ± 23** |
| LV end-systolic volume, mL | 37 ± 8 | 45 ± 8* | 56 ± 11*** ## |
| LV diastolic function | | | |
| E wave, cm·s ⁻¹ | 69 ± 12 | 79 ± 9* | 60 ± 11***## |
| A wave, cm·s ⁻¹ | 41 ± 5 | 44 ± 7 | 41 ± 7 |
| E/A | 1.7 ± 0.3 | 1.8 ± 0.3 | 1.5 ± 0.3## |
| E' mean, cm·s ⁻¹ | 13.4 ± 1.9 | 13.8 ± 2.1 | 11.0 ± 2.4***## |
| A' mean, cm·s ⁻¹ | 6.9 ± 1.3 | 7.5 ± 1.3 | 7.9 ± 1.4 |
| LSr Diastolic, cm·s ⁻¹ | 1.55 ± 0.3 | 1.63 ± 0.2 | 1.30 ± 0.3***## |
| LV systolic function | | | |
| Stroke volume, mL·m ⁻² | 39.6 ± 4.1 | 38.9 ± 5.1 | 42.7 ± 7.5 |
| Cardiac output, L·min ⁻¹ ·m ⁻² | 2.4 ± 0.4 | 2.6 ± 0.5 | 2.8 ± 0.8 |
| EF, % | 61 ± 4 | 63 ± 5 | 58 ± 6## |
| S' mean, cm·s ⁻¹ | 9.2 ± 1.0 | 9.5 ± 1.5 | 8.8 ± 1.8 |
| GLS, % | 18.5 ± 1.9 | 18.9 ± 1.8 | 16.6 ± 2.6***## |

Values are means ± SD; *n*, number of subjects. Ctrl, control; EF, ejection fraction; GLS, global longitudinal strain; IVST, interventricular septum thickness; LV, left ventricular; LVM, left ventricular mass; LVMi, left ventricular mass index; LSr Diastolic, diastolic longitudinal strain rates; PWT, posterior wall thickness; RWT, relative wall thickness. Statistics were made using an ANOVA with a Tukey post hoc test. Significantly different from Ctrl (**P* < 0.05; ***P* < 0.01; ****P* < 0.001). #Significantly different from nonusers (#*P* < 0.05; ##*P* < 0.01; ###*P* < 0.001).

All regional LS and CS results were similar across global, sub-endocardial, and subepicardial layers.

Left Ventricular Dyssynchrony

Parameters of LV dyssynchrony are presented in Table 3. Users exhibited higher values of maximum delay, SD_{6S}, SD_{12S}, LSDI_{6S}, LSDI_{12S}, and LSDI_{18S} when compared with controls. Interestingly, we observed higher maximum delay and SD in users compared with controls even when values

were indexed to systolic duration. The segmental PSI are presented in Fig. 3. In the three groups, the PSI was higher on the basal segments. Interestingly, the PSI was significantly higher in users than in controls on segment 1 (basal inferoseptal, A4C view) and segment 13 (basal inferolateral, A2C view). It was also higher in users than in nonusers and controls on segment 18 (basal anteroseptal, A3C view). Patterns of strain during the cardiac cycle in segments 1, 13, and 18 are presented in Fig. 4, highlighting that post-systolic shortening was higher in AAS users than in nonusers and controls.

There were significant correlations between LSDI_{12S}, SD_{12S}, and LV mass (Fig. 4, A and B, respectively); and between SD_{6S} and global LS (Fig. 4C). There was also a significant correlation between LSDI_{12S} and the ejection fraction (*R*² = 0.21; *P* < 0.001) (Fig. 5).

DISCUSSION

Using a segmental 2D-strain analysis, this study evaluated strength-trained athletes using AAS to determine if the AAS-mediated decrease in LV strain is localized to the interventricular septum. This study also investigated whether the use of AAS is associated with an increase in LV dyssynchrony and an increase in the occurrence of PSS in strength-trained athletes. Findings suggest that 1) the decrease in LV strain in users was amplified in the septal segments of the heart, with similar observations made on the subendocardial and subepicardial layers; 2) LV dyssynchrony, which was correlated with LV mass and ejection fraction, was higher in users than in nonusers and controls; and 3) the PSI was higher in users, especially on the three basal segments.

As expected, strength-trained users and nonusers from our study exhibited LV hypertrophy with higher left ventricular mass index (LVMi) and higher relative wall thickness than controls, on account very likely of regular pressure overload related to weight lifting. Interestingly, LV hypertrophy was exacerbated in users, since 78% of them (11 out of 14) exhibited an LVMi exceeding the cutoff value of 115 g·m⁻² (16) compared with 40% in nonusers (6 out of 15). In AAS-

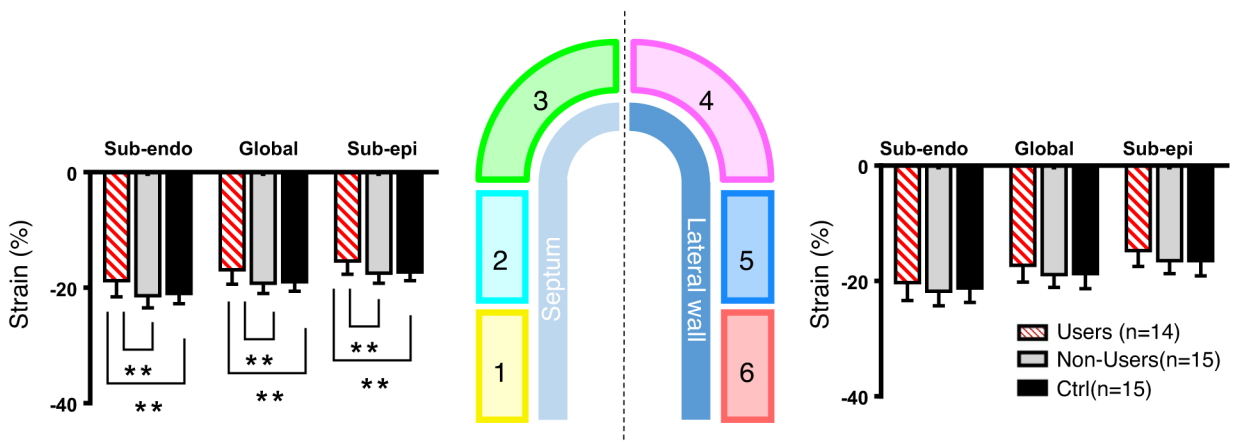


Figure 1. Left ventricular longitudinal strain with differentiation between global, subendocardial (Sub-endo), and subepicardial (Sub-epi) layers. One-way ANOVA was used to compare the three groups and then Tukey post hoc test. **Significantly different (*P* < 0.01). Ctrl, controls; endo, endocard; epi, epicard.

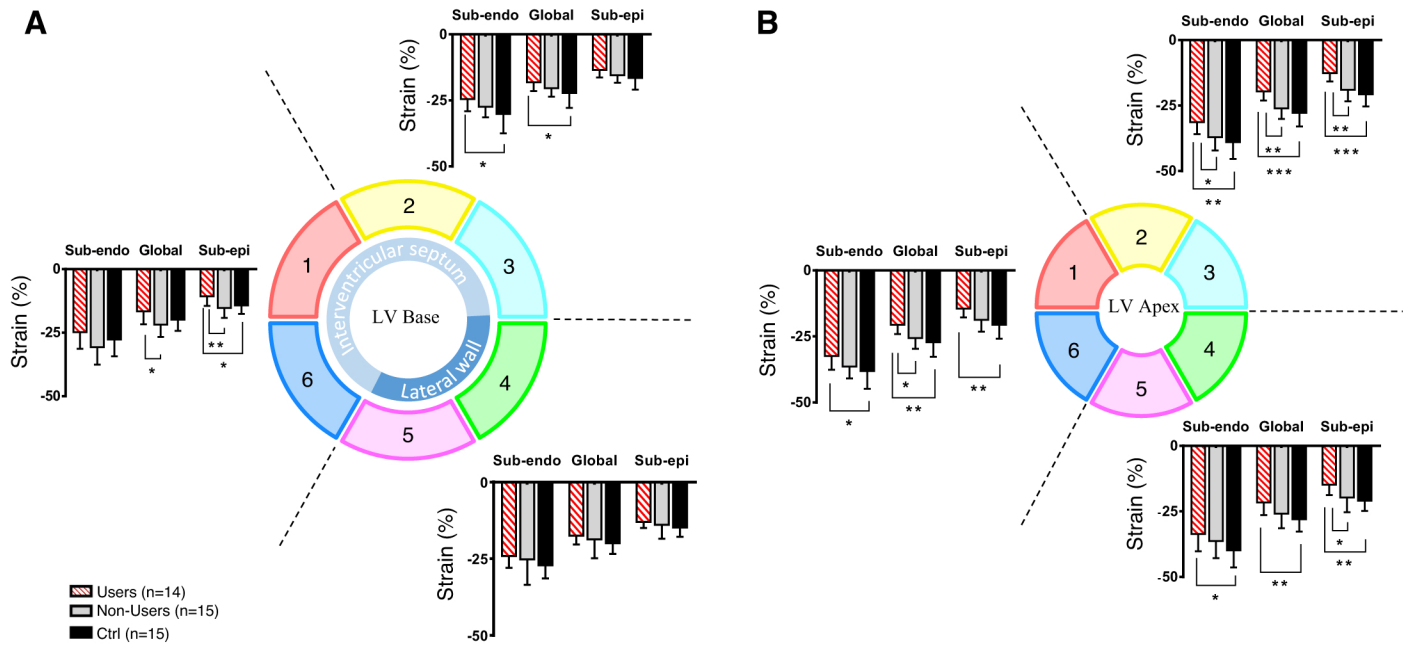


Figure 2. Left ventricular circumferential strain with differentiation between global, subendocardial (Sub-endo), and subepicardial (Sub-epi) layers at the base (A) and the apex (B). One-way ANOVA was used to compare the three groups and then Tukey post hoc test. Significantly different ($*P < 0.05$; $**P < 0.01$; $***P < 0.001$). Ctrl, controls; endo, endocard; epi, epicard; LV, left ventricular.

free strength-trained athletes, a major LV hypertrophy, sometimes exceeding cutoff values, was also previously reported [for review, see Haykowsky et al. (24)], but values remained significantly lower than those reported in AAS users.

The Decrease in Left Ventricular Strain Was Most Evident at the Septum in Users

Previous studies recently observed a drop in LV function with a decrease in LV longitudinal and circumferential strain in the hypertrophied hearts of strength-trained athletes reporting the regular use of AAS (4, 5). In this present study, we assessed regional myocardial strain to distinguish septal

and basal regions. In users, the decrease in LS was observed mainly at the septal segments. Interestingly, similar findings were obtained when assessing the basal CS, with a more evident decrease in the septal segments compared with the lateral ones. Considered altogether, these results strongly support that LV strain of the septal regions are decreased to a greater extent when compared with other regions in users of AAS.

In addition, since active fibrosis inside the myocardium of bodybuilders after sudden cardiac death seems to be mainly located in the subendocardium regions (2, 25), this study evaluated if the subendocardial and subepicardial regions were affected differently by the use of AAS. However, for the assessments of both regional LS and CS, the findings were strictly similar at the subendocardial and subepicardial layers compared with the global myocardium.

Table 3. Parameters of left ventricular dyssynchrony

| | Ctrl | Nonusers | Users |
|--|------------|-------------|----------------|
| <i>n</i> | 15 | 15 | 14 |
| Indexes of LV dyssynchrony | | | |
| Maximum delay, ms | 90 ± 25 | 94 ± 28 | 106 ± 32* |
| Maximum delay, % of systolic duration | 28.1 ± 3.9 | 34.2 ± 7.0 | 36.0 ± 8.0 * |
| SD _{6S} , ms | 34 ± 4 | 36 ± 9 | 42 ± 8** |
| SD _{6S} , % of systolic duration | 9.4 ± 1.0 | 10.6 ± 2.3 | 11.8 ± 2.8** |
| SD _{12S} , ms | 32 ± 5 | 36 ± 9 | 43 ± 8** |
| SD _{12S} , % of systolic duration | 9.0 ± 1.3 | 11.8 ± 2.9 | 12.5 ± 2.6* |
| SD _{18S} , ms | 37 ± 8 | 41 ± 12 | 46 ± 9 |
| SD _{18S} , % of systolic duration | 10.3 ± 2.6 | 11.8 ± 3.3 | 13.1 ± 2.8* |
| Longitudinal strain delay index | | | |
| LSDI _{6S} | -4.0 ± 2.2 | -4.9 ± 2.7 | -6.7 ± 3.1 * |
| LSDI _{12S} | -7.0 ± 3.1 | -9.9 ± 5.3 | -14.0 ± 5.2*** |
| LSDI _{18S} | -9.8 ± 3.9 | -15.9 ± 9.3 | -23.4 ± 9.5**# |

Values are means ± SD; *n*, number of subjects. A2C, apical 2 chambers; A4C, apical 4 chambers; LSDI, longitudinal strain delay index; LV, left ventricular; S, segment; SD, standard deviation. Statistics were made using an ANOVA with a Tukey post hoc test. Significantly different from Ctrl ($*P < 0.05$; $**P < 0.01$; $***P < 0.001$). #Significantly different from nonusers ($P < 0.05$).

Left Ventricular Dyssynchrony Is Higher in Users

In a structurally normal heart, the concept of nonuniformity in contractions due to its complex myocardial fiber spatial orientation and geometric architecture has been largely described (26). In pathological remodeling of the myocardium, slower intramyocardial conduction could result in regional delays in electrical activation and, thus, increase LV dyssynchrony (27, 28). In this present study, we observed that the SD_{6S}, SD_{12S}, and the maximum delay were higher in users compared with controls. Interestingly, nonusers exhibited higher values compared with controls, despite the difference did not reached statistical significance. These results underlined that strength training itself could induce an increase of mechanical dispersion, maybe linked to their LV hypertrophy. However, in users, the significant and major increase of all these parameters strongly supports the hypothesis that the regular consumption of AAS promotes and exacerbates LV dyssynchrony that could be considered as

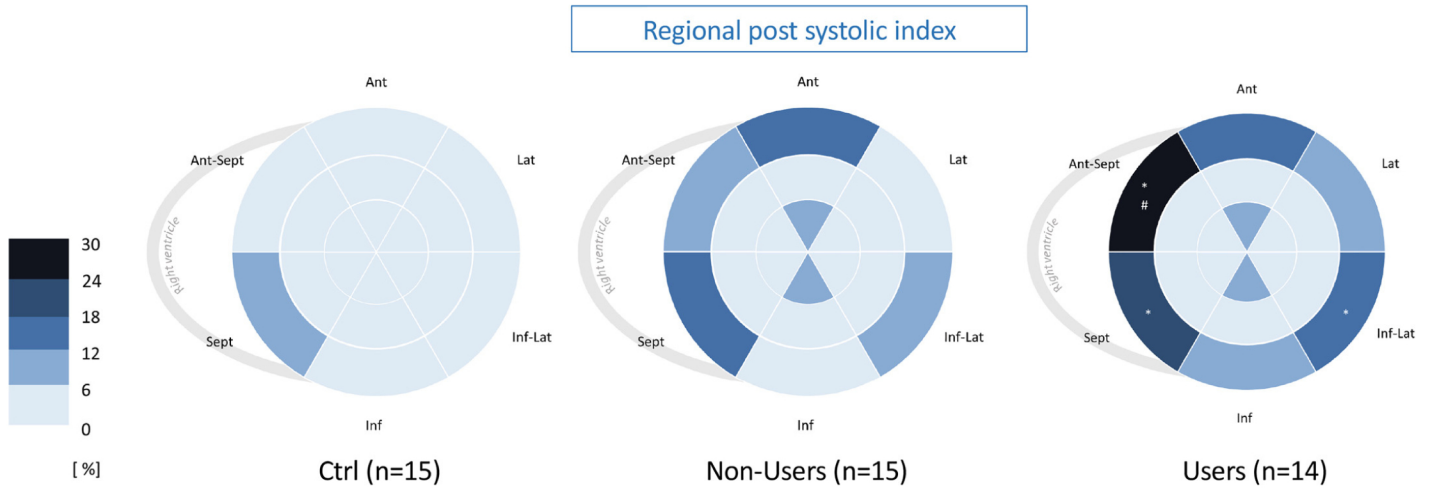


Figure 3. The distribution of the post-systolic index over the left ventricle. Color-coded bull's eye maps for average post-systolic index using an 18-segment model. Septum (Sept) and lateral (Lat) represents the data obtained on the apical 4C view, the inferior (Inf) and anterior (Ant) with the apical 2C view, and the anteroseptal (Ant-Sept) and infero-lateral (Inf-Lat) with the 3C view. Segments localized in the outer layer of the bull's eye represent basal segments, segments in the middle layer of the bull's eye represents midwall segments, and segments in the inner layer represents apical segments. One-way ANOVA was used to compare the three groups and then Tukey post hoc test. *Significantly different from Ctrl ($P < 0.05$). #Significantly different from nonusers ($P < 0.05$). 2C, two chambers; 3C, three chambers; 4C, four chambers.

another evidence of a pathological remodeling. To the best of our knowledge, this is the first study to assess LV dyssynchrony in strength-trained athletes using AAS. The increase in LV dyssynchrony was observed in other forms of cardiac hypertrophies, such as hypertrophic cardiomyopathy and hypertension-induced hypertrophy, but with values higher than those observed in this study's users' group (e.g., for SD_{18S} : 37 ± 8 ms in this study's controls; 46 ± 9 ms in this study's users vs. 69 ± 30 ms in patients with hypertrophic cardiomyopathy) (29).

This increase in LV dyssynchrony might partly be explained by an increase in fibrosis in the hypertrophied heart of the AAS users. Indeed, previous ultrasonic myocardial backscatter (7), postmortem (2), or experimental (30, 31) studies demonstrated that the long-term use of AAS leads to an increase in fibrosis inside the myocardium, a finding not observed in strength-trained athletes who did not report any use of AAS (4). Cardiac fibrosis causes an alteration in the electrophysiology of the myocardium that may predispose those with cardiac fibrosis to the reentry mechanism (32). Indeed, the increase in fibrosis can lead to myocardial

electrical conduction disturbances, with the electrical signals that stimulate the myocardium to contract being impaired by a need to bypass areas of fibrosis (33), a mechanism which has been shown to be linked to arrhythmias.

Left Ventricular Post-Systolic Index and Wasted Energy Is Higher in Users

The assessment of LV dyssynchrony by time-delay indexes alone is inherently limited due to a lack of consideration for residual myocardial contractions. In this present study, we used the LSDI (23) and the segmental PSI (13), both indexes that overcome these limitations by estimating the energy wasted in the myocardial post-systolic contractions across all LV segments. Our results highlighted that $LSDI_{6S}$, $LSDI_{12S}$, and $LSDI_{18S}$ were higher in users than in nonusers and controls. Interestingly, $LSDI_{12S}$ was correlated to LV mass and inversely correlated with ejection fraction, suggesting that the increase in "wasted energy" due to post-systolic contractions could be one potential mechanism responsible for the decrease in ejection in the users who participated in this study.

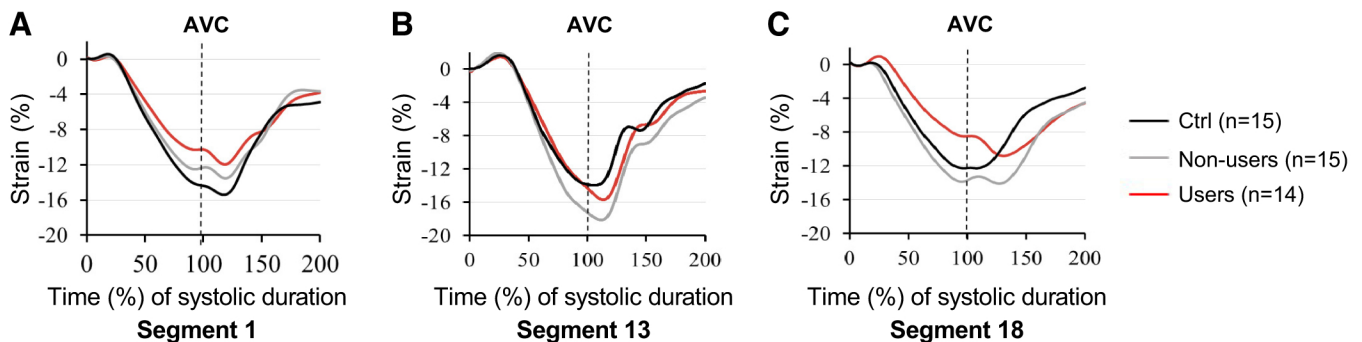


Figure 4. Patterns of LV longitudinal strain during the cardiac cycle obtained on segments 1 (A), 13 (B), and 18 (C). The curve of each group was averaged from the data of all subjects. In the users group, the strain curve continued to decrease after end-systole, highlighting an increase in their PSI. AVC, aortic valve closure; Ctrl, controls; LV, left ventricular; PSI, post-systolic index.

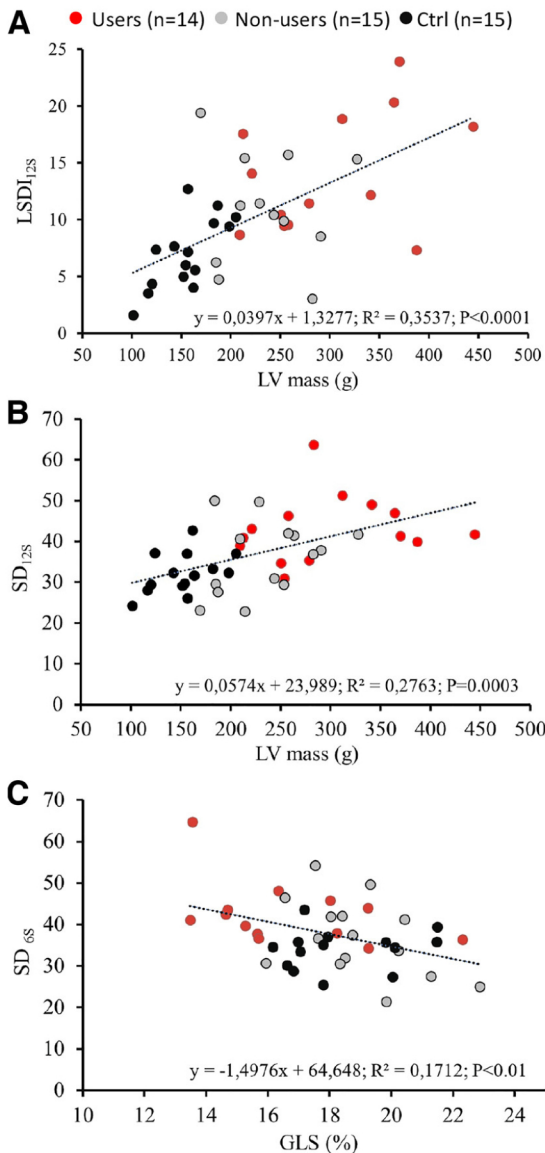


Figure 5. Correlation between left ventricle mass (LVM) and longitudinal strain delay index 12 segments ($LSDI_{12S}$; **A**) and standard deviation of the time to peak strain in the 12 segments of both apical two and four chambers views (SD_{12S} ; **B**), and between global longitudinal strain (GLS) and standard deviation of time to peak strain evaluated on apical four chambers view (SD_{6S} ; **C**). We used single linear regression. Ctrl, controls; SD, standard deviation.

Post-systolic shortening that occurs after aortic valve closure and, therefore, does not contribute to the ejection of the blood (15), is present to a small extent in the normal myocardium (13), but with a higher occurrence in pathological states such as ischemic or scarred myocardium (13). In the present study, we assessed the segmental PSI on an 18-segment model (15, 16). Interestingly, the PSI was significantly increased on segments 1 (basal inferoseptal), 13 (basal inferolateral), and 18 (basal anteroseptal) in users when compared with nonusers and controls. Of note, the higher PSI observed in users was detected in the septal segments in which peak strain were also decreased.

The underlying mechanisms that may explain these substantial regional alterations remain unknown. Previous studies reported that myocardial fibrosis could be observed in

some athletes, especially at the inferior insertion point (34). Its prevalence has been correlated with training load and intensity (35), which may reflect the time of pressure overload present in the right ventricle during effort, increasing tension at the insertion points (34). During strength-training, blood pressures increases dramatically by up to 300–400 mmHg (36). In users who participated in this study, increases in blood pressure during effort was probably higher compared with nonusers due to both the heavier weights being lifted and the systematic use of a brief Valsalva maneuver (36), which could induce a substantial increase in tension at their insertion points. However, this explanation is purely speculative. Another explanation could be that these specific zones could have a higher number of androgen receptors, favoring pathologic hypertrophic pathways and fibrosis, but this also remains speculative and will need further investigation.

Study Limitations

The study population was relatively small. However, there were still significant differences for many parameters. Moreover, the users were compared not only with strength-trained nonusers, but also with nontraining controls to differentiate the effects of strength training itself from the effects of AAS. Inevitably, and for ethical reasons, blood or urine collection was not possible and information about the use of AAS was self-reported and the type of drugs and dosages differed between athletes. However, we collected accurate information about AAS consumption (type of molecule, doses, years of consumption, etc.) to provide information about long-term AAS misuse which is a key point for cardiac remodeling. The risk of hiding misuse in the nonusers group exists, but the inclusion of a group of strength-trained nonusers is essential for differentiating both the effects of AAS and strength-training itself. The layer-specific analysis of LV strains by echocardiography is limited by the low width of the region of interest. However, accuracy of this method appeared similar to that obtained with strain-encoded cardiovascular magnetic resonance (37). Finally, the populations of users and nonusers were characterized by their training volume and training experience only since we did not ask for their muscular performances.

Conclusions

The findings of this study strongly support that the decrease in LV strain in strength-trained athletes who regularly use AAS was amplified at the septal segments of the myocardium. This was associated with an increase in LV dyssynchrony and in the PSI, especially at the basal septal segments. A greater number of segments with post-systolic shortening was observed in the users of AAS, probably resulting in an increase in wasted energy after the end of blood ejection, which could contribute, at least in part, to the decrease in their LV systolic function. However, further studies will be needed to assess the link between regional hypertrophy, the presence of fibrosis, and LV dyssynchrony in this specific population.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.G., I.S., O.I., and S.N. conceived and designed research; A.G. and S.N. performed experiments; A.G., T.R., O.I., P.O., and S.N. analyzed data; A.G., I.S., P.O., and S.N. interpreted results of experiments; A.G. and S.N. prepared figures; A.G. and S.N. drafted manuscript; A.G. and S.N. edited and revised manuscript; A.G., I.S., T.R., O.I., P.O., and S.N. approved final version of manuscript.

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