

Systolic Subclinical Dysfunction in Anabolic Steroid Users: A Real Life Study

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Abstract

Background: Considering the uncertainty regarding the cardiovascular safety of anabolic steroid use, we believe that the use of advanced echocardiography techniques, such as speckle tracking, may contribute more objectively to the analysis of cardiotoxicity induced by these substances.

Objectives: To compare, through speckle tracking, the echocardiograms of bodybuilders who abuse anabolic steroids with those who do not use these substances.

Methodology: This work is a retrospective, observational study that analyzed echocardiograms performed on bodybuilders followed up in an outpatient sports cardiology service, comparing the results between individuals who use and those who have never used anabolic steroids. Continuous data was compared, using unpaired, two-tailed, Student's T test, with a p-value < 0.05 considered to be significant.

Results: The final sample of this study included 22 bodybuilders, 14 of whom were anabolic steroid users (UAS) and 8 non-users of anabolic steroids (NUAS). All 22 participants had a left ventricular ejection fraction (LVEF) > 50% (UAS = 55±4 vs. NUAS = 63±1%; p < 0.001). All 14 steroid users showed abnormal global longitudinal strain (GLS), while all 8 non-users presented normal values for this variable (UAS = 13±2 vs. NUAS = 20±2; p < 0.01).

Conclusion: Bodybuilders who use anabolic steroids, despite having normal values for conventional echocardiography parameters, show a reduction in GLS of the left ventricle. The use of speckle-tracking echocardiography represents an important tool in the analysis of myocardial injury in UAS, offering the possibility of early detection of systolic dysfunction in these individuals.

Keywords: Anabolic Androgenic Steroids; Echocardiography; Resistance Training.

Introduction

Testosterone is the primary human endogenous androgen. German researchers developed the first synthetic testosterone in 1935, aiming to treat depressive disorders.¹ The Cold War stimulated the use of anabolic androgenic steroids (AAS), with the goal of enhancing sports performance, and the first report of doping with testosterone analogs in the Olympics dates back to 1954, involving Russian Olympic weightlifters.² Since the 1980s, AAS usage has expanded beyond elite athletes, and its use for aesthetic purposes has increased in the general population.³ Some studies suggest that the lifetime prevalence of AAS use may be between 1% and 5% of the global male population.³

Testosterone levels in men decrease with aging, and this reduction has been associated with increased atherosclerotic processes and cardiovascular risk.⁴⁻⁶ In response, numerous studies have been conducted to evaluate the cardiovascular benefits of testosterone replacement therapy in hypogonadal patients. However, the results are conflicting. Meta-analyses show that testosterone replacement therapy has not been able to prevent major cardiovascular outcomes, such as death and myocardial infarction in men with hypogonadism.^{7,8}

Since 2010, several studies have been published, revealing the possible cardiovascular adverse effects of testosterone replacement therapy. Basaria et al. published a series of studies confirming a higher incidence of acute myocardial infarction in elderly individuals who received exogenous testosterone gel administration, as compared to those who received a placebo.^{9,10} Recently, Lincoff et al.¹¹ published a prospective study where 5,246 hypogonadal men with high cardiovascular risk or established cardiovascular disease were randomized to receive testosterone gel replacement or placebo. After a mean follow-up of 33 months, there was no increase in the number of major cardiac events. However, there was an increased incidence of atrial fibrillation, thrombosis, and worsening renal function in

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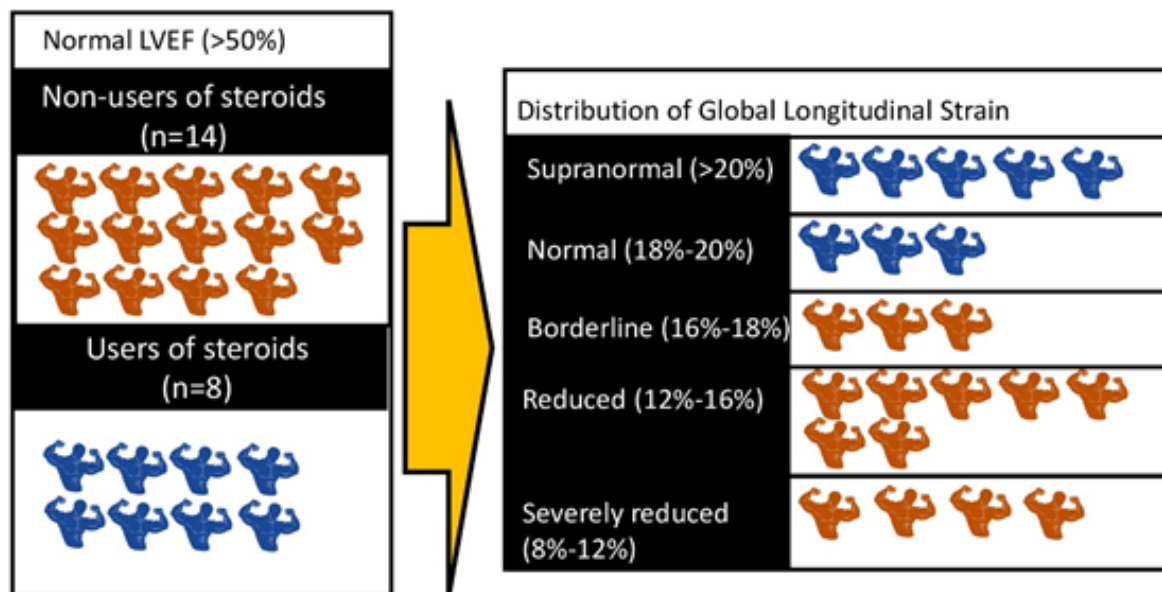
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Central Illustration: Systolic Subclinical Dysfunction in Anabolic Steroid Users: A Real Life Study



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Distribution of the LVEF and global systolic strain of left ventricle in bodybuilders who are users and non-users of steroids
LVEF: Left ventricular ejection fraction

patients who received testosterone replacement. These studies were criticized for including a population already at high cardiovascular risk and for their low reproducibility.

So far, the cardiovascular safety of testosterone use remains controversial. This uncertainty is justified by the heterogeneity of studies regarding population, preparations, and studied dosages. While little is known about the cardiovascular effects of therapeutic testosterone replacement in men with hypogonadism, uncertainties are even greater when it comes to the cardiovascular adverse effects of testosterone abuse and its analogs for aesthetic and performance purposes.

Most of these studies involved few individuals in retrospective analyses. Windfeld-Mathiasen et al.¹² recently published a cohort study where doping-sanctioned men (1,189 individuals) and control individuals (59,450 individuals) were followed for a mean period of 11 years. In this study, the relative risk of death was 2.81 times higher in individuals with a history of doping punishment, with cancer and cardiovascular disease being the main causes of non-violent death in this group.

In the last decade, some reports have been published regarding the direct toxicity of testosterone on the myocardium.¹³⁻¹⁶ Baggish et al.¹⁶ evaluated 140 young bodybuilders, 86 of whom were users of anabolic-androgenic steroids (AAS) for at least two years, and observed differences in echocardiographic measurements

when comparing data from users and non-users of AAS. However, few of the studied patients showed echocardiographic parameters outside the normal range.

Indeed, despite its value and availability in clinical practice, two-dimensional echocardiography presents important limitations, especially regarding inter-observer variability in the assessment of global and segmental ventricular function.¹⁷ Speckle tracking technique is relatively operator-independent, with a much lower inter-observer variability rate than traditional two-dimensional echocardiography.¹⁸ In this context, this advanced echocardiography technique may assist in the early identification of myocardial pathologies induced by the use of AAS.

Our hypothesis is that the use of advanced echocardiographic techniques, such as speckle tracking, may be able to identify cardiotoxicity in AAS users whose routine echocardiographic analyses are normal.

Methods

Study Design

This was a retrospective, observational study that analyzed echocardiograms performed on male bodybuilders followed up in an outpatient cardiology service, specifically in a private sports cardiology clinic.

Inclusion and Exclusion Criteria

To be included in the study, individuals had to be over 18 years of age, been practicing bodybuilding for at least 5 years (strength training 5-6 times/week), have no known chronic diseases, be non-smokers, and not use regular medications except for anabolic steroids — anabolic steroid users (UAS) group, use for at least three years — or never have used steroids (NUAS group). Patients who claimed growth hormone use were not included in the study. All individuals included in the study were asymptomatic and sought medical care for sports cardiology follow-up, seeking guidance on performance and quality of life. Additionally, none of them presented clinical signs compatible with heart failure (pulmonary crackles, presence of third heart sound on auscultation, pathological jugular vein distension, hepatojugular reflux, or lower limb edema), as recorded in their medical charts.

All participants included in the study had a two-dimensional echocardiogram with all values within normal limits. Patients who had not undergone an echocardiogram during their first consultation and individuals with symptoms or clinical signs of heart failure were excluded from the study.

Demographic data, including age, sex, ethnicity, weight, height, and clinical data, were collected from medical records. It is important to emphasize that this retrospective study did not interfere in the medical management adopted during outpatient follow-up and considered that all care provided was in accordance with current best practices.

Echocardiographic Analysis

All included patients underwent echocardiographic analysis in M-mode, two-dimensional, and with speckle tracking analysis (System - Vivid IQ – GE using adult Sectorial 3Sc-RS GE transducer, Healthcare), together with a subsequent study of myocardial deformation in an offline analysis platform (EchoPAC Software Only v202, GE Medical Systems) requested by the attending physician at their first outpatient sports cardiology consultation. Image acquisition in the service follows the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging,¹⁹ additionally all examinations included in this study were performed by the same observer, who was blinded to the patients' history of anabolic steroid use. Deformation analyses by speckle tracking technique were performed after image acquisition of the apical long-axis in four, two, and three chambers for longitudinal deformations, as well as in apical, medial, and basal short-axis images for circumferential, radial deformations, and twist. Peak systolic deformation was defined as the point of maximum systolic shortening for longitudinal and circumferential deformation and maximum systolic thickening for radial deformation, respectively. Aortic valve closure was used as a reference point to define the end of the systole.

Subclinical systolic dysfunction was defined as the occurrence of a global longitudinal strain (GLS) of the left ventricle $\leq 16\%$ in patients with preserved ejection fraction ($\geq 50\%$).

Myocardial work indexes were calculated (EchoPAC Software Only v202, GE Medical Systems) by combining systolic blood pressure measurement and echocardiographic

data from strain curves.^{20,21} In this approach, systolic blood pressure measured with a sphygmomanometer is assumed to be equal to peak systolic left ventricle pressure. Opening and closing times of the aortic and mitral valves are identified by electrocardiographic triggered echocardiogram in the apical 3-chamber view. Next, the left-ventricle pressure-strain curve is constructed and left ventricle work is calculated as a product of the segmental shortening rate and the instantaneous left ventricle pressure, enabling the calculation of the following indexes: Global work index (GWI), Global constructive work (GCW), Global wasted work (GWW), and Global work efficiency (GWE).^{20,21}

Statistical Analysis

Echocardiographic, clinical, and epidemiological variables were analyzed for normality of distribution using the Shapiro-Wilk method. Since all data presented a normal distribution, continuous variables were reported as mean \pm standard deviation, and comparisons between groups (users and non-users) were made using the unpaired, two-tailed, Student's t-test. A two-tailed p-value < 0.05 was considered significant.

The interquartile range (IQR) method was used to detect outliers. Values below the lower limit [quartile 1 – $(1.5 \times \text{IQR})$] or above the upper limit [quartile 3 – $(1.5 \times \text{IQR})$] was analyzed by the authors to consider data exclusion. However, no outliers were found.

A sample size calculation was performed, considering a difference of 3 points between the mean GLS of the left ventricle (the primary continuous variable), a statistical power of 80%, and a recruitment ratio of 2 steroid users for every non-user (independent samples), with an alpha error of 0.05. The sample size obtained was 15, with 10 steroid users and 5 non-users.

All statistical analyses were performed using STATA 14.2 software (StataCorp, Texas, USA).

Ethics

This study was submitted and approved by the institutional ethics committee (protocol CAAE: 68615323.1.0000.8044), and because it was a retrospective study, a waiver of informed consent was granted.

Results

The volunteers had similar age and anthropometric characteristics, as summarized in Table 1. All volunteers denied hypertension and smoking, and were unaware of

Table 1 – Demographic parameters of bodybuilders

Variables	Non-users of steroids	Users of steroids	p-value
Age (years)	40 \pm 3	38 \pm 9	0.57
Weight (Kg)	97 \pm 12	103 \pm 16	0.36
Height (cm)	178 \pm 5	180 \pm 8	0.38

any comorbidities. Non-users of anabolic steroids (NUAS) denied regular use of medications and hormones, while UAS denied the use of any medications other than AAS. All participants had used AAS intramuscularly for more than two years.

According to the analyzed echocardiographic parameters (Table 2), UAS showed higher left ventricular (LV) mass and left atrial volume compared to NUAS. Although UAS had a lower left ventricular ejection fraction (LVEF), none of them had LVEF < 50%.

However, despite LVEF > 50%, all UAS, when compared to NUAS, showed reduced GLS of the left ventricle (GLS-LV) and longitudinal strain of the right ventricle (Table 3). All UAS (n=14) had GLS-LV < 18%, 11 of which (78%) showed reduced GLS-LV (< 16%), indicating LV dysfunction (Central Illustration).

Regarding myocardial work, UAS showed lower GCW, higher global deconstructive work, lower global efficiency work, and lower myocardial torsion (Table 3).

Discussion

The use of AAS for aesthetic and performance enhancement purposes is increasing worldwide. In Brazil, it is estimated that about 3% of the population has used or currently uses these substances.²² This study demonstrates

that even with normal conventional echocardiographic parameters, AAS users exhibit systolic dysfunction that can be identified using advanced techniques, such as speckle tracking and myocardial work analysis.

GLS of the left ventricle has proven to be an independent predictor of adverse outcomes that are better than LVEF.^{18,21} All AAS users in this sample presented below normal GLS-LV values, 78% of whom actually showed systolic dysfunction despite normal LVEF.²³

Baggish et al.²⁴ detected reduced GLS of the left ventricle in AAS users. However, this study mostly included patients with LVEF < 50%, where GLS-LV analysis adds little to the detection of ventricular dysfunction. D'Andrea et al.²⁵ analyzed echocardiograms of 45 elite bodybuilders, of whom 20 reported prolonged AAS use (users), 25 practiced bodybuilding without AAS (non-users), and 25 were controls. In AAS users, as compared to non-users, the longitudinal strain was notably reduced, indicating subclinical systolic dysfunction. However, in this study, AAS users had higher blood pressure than non-users, which may have influenced the results, since increases in systolic blood pressure are known to reduce GLS-LV.²³ In our study, none of the included individuals were hypertensive. Furthermore, we performed myocardial work analysis, confirming the presence of subclinical systolic dysfunction in AAS users.

Table 2 – Usual echocardiographic parameters of bodybuilders

Variables	Non-users of steroids	Users of steroids	p-value
Left atrium volume (mL/m ²)	32±2	35 ± 5	0.02
LVEF (%)	63 ± 1	55 ± 4	p < 0.001
LV end-systolic diameter (mm/m ²)	14.4 ± 1	15,7 ± 2	0.045
LV end-diastolic diameter (mm/m ²)	22.7 ± 1	23,8 ± 2	0.07
LV free wall thickness (mm)	10 ± 0.8	10,8 ± 1.3	0.12
LV mass indexed (g/m ²)	101 ± 11	131 ± 27	0.007
Interventricular septal thickness (mm)	10 ± 0.5	11 ± 1.3	0,099

LVEF: left ventricular ejection fraction; LV: left ventricular.

Table 3 – Advanced echocardiographic parameters of bodybuilders

Variables	Non-users of steroids	Users of steroids	p-value
Left ventricle GLS (%)	20 ± 2	13 ± 2	p<0.01
Right ventricle GLS (%)	24 ± 1	21 ± 1	p<0.01
GCW (%)	2305.2 ± 132	1722.4 ± 313	p<0.001
Global wasted work (%)	49.1 ± 9.1	114.7 ± 41.5	p<0.001
Global Work Efficiency (%)	96.5 ± 1.1	92.3 ± 1.8	p<0.001
Myocardial twist (°)	12.1 ± 2.3	8.6 ± 4.3	P=0.047

GLS: global longitudinal strain; GCW: global constructive work.

It is important to note that we found no previous study using both myocardial work analysis and speckle tracking echocardiography to analyze and detect early systolic dysfunction in bodybuilders using AAS. Myocardial work analysis is a recent technique that incorporates LV afterload data into GLS analysis. Besides correlating with myocardial oxygen consumption, myocardial work allows analysis of LV efficiency, proving to be a highly effective technique for ventricular performance analysis.²⁶ The lower values of GCW, myocardial efficiency, and myocardial torsion, as well as the higher global deconstructive work found in AAS users, support ventricular dysfunction related to steroid abuse in the studied population.

Although with a different objective than the present article, Grandperrin et al.²⁷ analyzed the myocardial work of 24 asymptomatic strength athletes using steroids, 22 athletes diagnosed with hypertrophic cardiomyopathy, and 20 healthy control athletes. Their findings did not indicate a difference in constructive and deconstructive work when comparing the UAS and NUAS groups, which differs from our study. These points of divergence may be related to variations in the studied population, as well as in the characteristics of the type and duration of steroid use. However, regarding global efficiency, the group of steroid-using athletes showed lower myocardial efficiency when compared to the controls, corroborating our findings.

Angell et al.²⁸ used cardiac magnetic resonance imaging and speckle-tracking echocardiography to document the impact of AAS abuse on the cardiac structure and function of bodybuilders. In their results, UAS, when compared to NUAS, showed a greater mean LV wall thickness, LV end-diastolic volume, and LV mass, even after covariate analysis, which aligns with our data. Additionally, the analysis of the GLS of the LV also supported our findings, showing a reduction in the group of athletes using anabolic steroids, indicating systolic dysfunction.

The indiscriminate use of AAS is a public health problem in our country and worldwide. It is not uncommon for some professionals to present studies where relatively low doses of AAS were used for a short period of time, using the absence of pathological variation in two-dimensional echocardiograms to justify the safety of this practice. In one of these studies, Chung et al.²⁹ compared the two-dimensional echocardiograms of 30 healthy men who received testosterone (200 mg/week, intramuscular), nandrolone decanoate (200 mg/week, intramuscular), or placebo for 4 weeks, and found no adverse or beneficial effects from these medications. The analysis of our data, together with data from other studies that examined advanced echocardiographic techniques,^{16,23,24} emphasizes the need for these techniques to identify early myocardial injury caused by steroids. We highlight that these findings imply a worse prognosis³⁰ and may assist physicians in the difficult task of convincing AAS users to discontinue this practice.³¹

Limitations

The study sample, consisting of 22 participants, although relatively small, demonstrated a statistical power

of over 90%. The representativeness of the sample may be questionable, as participants were recruited from a private outpatient sports cardiology service, which may not reflect the general population of steroid users.

Additionally, the retrospective and observational nature of the study may introduce selection biases and limitations in data collection, making it challenging to assess the direct causality between steroid use and early ventricular dysfunction. In this regard, it is important to clarify that the definition of subclinical systolic dysfunction was not based on worsening GLS of the left ventricle (LV), but rather on values below the normal range for this variable in patients with preserved LVEF. Various clinical studies and the updated position of the Brazilian Society of Cardiology regarding the use of myocardial strain³² support this definition, especially when the detection of strain alteration occurs without a prior examination (with normal values) having been performed.

Finally, the cross-sectional design of the study prevents definitive causal determinations between anabolic steroid use and early ventricular dysfunction, allowing only for the identification of associations. Nevertheless, it is important to note that studies aiming to analyse the toxic effects of substance abuse are ethically forbidden to follow a prospective pre- and post-design.

Conclusion

The presence of normal conventional echocardiographic parameters on two-dimensional echocardiography does not exclude the presence of subclinical ventricular dysfunction in UAS. The use of specific techniques, such as speckle tracking and myocardial work, not only provides greater accuracy, but also allows for the early identification of myocardial injury. This directly impacts the prognosis of these patients, providing clinicians with an important tool to persuade this population to discontinue the use of these substances. Future studies should analyze the effects of different steroids and dosages, in an attempt to improve knowledge on the subject and raise awareness about the harmful effects of this increasingly common and trivialized practice.

Author Contributions

Conception and design of the research: Castro RRT, Campos M, Silveira Neto JG; acquisition of data: Castro RRT, Campos M, Mello L, Silveira Neto JG; analysis and interpretation of the data: Castro RRT, Campos M, Silveira Neto JG; statistical analysis and critical revision of the manuscript for intellectual content: Castro RRT, Silveira Neto JG; obtaining financing: Castro RRT; writing of the manuscript: Castro RRT, Campos M, Mello L.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Universidade Iguacu under the protocol number 68615323.1.0000.8044. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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