Comparison of Left Atrial Function in Long-term Anabolic-androgenic Steroid Users Versus Non-user Bodybuilders By Using Two Dimensional Speckle Tracking Echocardiography

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ABSTRACT

Introduction: Long-term illicit use of supraphysiologic doses of Anabolic-Androgenic Steroid (AAS) may cause pathological left ventricular hypertrophy (LVH), diastolic dysfunction, left atrial (LA) hypertrophy, increased myocardial stiffness and myocardial fibrosis. Therefore, distinguishing AAS user athlete's from the nonpathological "athlete's heart" is critically important. The aim of this study was to evaluate LA myocardial function using 2D-STE method in both AAS user and drug-free bodybuilders, and assess its potential role in the differential diagnosis between these two entities.

Materials and Method: We selected a population of 33 competitive bodybuilders, including 15 actively using AAS for > 2 years (users) and 18 who had never used AAS(non-users), all men.

Results: AAS using athletes had significantly lower global left atrium starin reservoir (GLAS-R), global LA strain during early diastole (GLAS-E) (38.2 ± 8.4 vs 48.6 ± 11.9, P < 0.01; 24.4 ± 8.6 vs 37.1 ± 12.8, P <0.01; respectively), global left atrium starin rate reservoir (GLASR-R), global LA strain rate during early diastole (GLASR-E) (1.8 ± 0.3 vs 2.2 ± 0.4, P <0.01; -1.4 ± 0.2 vs -1.8 ± 0.3, P < 0.01; respectively) compared to non-user athletes. The uni-variate correlation analysis demonstrated that the GLAS-R, GLAS-E, GLASR-R and GLASR-E had a good inverse correlation with E/Em (r: -0.34, P = 0.04; r: -0.35, P=0.04; r: −0.35,P= 0.04 and r: −0.35,P= 0.04, respectively).

Conclusion: The present study confirms that LA strain and strain rate are impaired in AAS using athletes compared to non-using athletes and provide valuable additional information to that obtained by conventional echocardiography in the differential diagnosis between pathologic and physiologic LVH.

Keywords: Anabolic-Androgenic Steroid, Bodybuilder Athletes, Left atrial function, Speckle Tracking, Left atrial strain

Uzun Dönem Anabolik-androjenik Steriod Kullanan ve Kullanmayan Vücut Geliştiricilerde Sol Atrial Fonksiyonların İki Boyutlu Benekli İşaretleme Ekokardiyografik Yöntemi ile Karşılaştırılması

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ÖZET

Giriş: Uzun dönem ve yüksek dozda anabolik-androjenik steriod (AAS) kullanımı sol ventirkül patalojik hipertrofisine (SVH), diyastolik disfonksiyona, sol atrium (SA) hipertrofisine, miyokard sertlik ve fibrosisinde artmaya neden olur. Bundan dolayı, AAS kullanan sporcuların patalojik olmayan ‘’sporcu kalbi’’inden ayrımı kritik öneme sahiptir. Bu çalışmanın amacı SA miyokard fonksiyonlarının iki boyutlu benekli ekokardiyografik yöntem ile AAS kullanan ve kullanmayan vücut geliştiricilerde değerlendirilmesi ve bu yöntemin bu iki durumun ayrımında kullanılmasıdır.

Hastalar ve Metod: Çalışmamıza 15’i aktif olarak AAS kullanan (>2 yıl) ve 18’i hiç AAS kullanmayan hepsi erkek olan toplam 33 yarışımcı vücut geliştirici alındı.

Bulgular: AAS kullanan atletlerin global SA strain reservoir(GLAS-R), global SA erken diyastol strain (GLAS-E) (38.2 ± 8.4 vs 48.6 ± 11.9, P < 0.01; 24.4 ± 8.6 vs 37.1 ± 12.8, P <0.01; sırasıyla), global SA strain rate reservoir (GLASR-R), global SA erken diyastol strain rate (GLAS-E)(1.8 ± 0.3 vs 2.2 ± 0.4, P <0.01; -1.4 ± 0.2 vs -1.8 ± 0.3, P < 0.01; sırasıyla) değerlerinin kullanmayan sporculara göre önemli ölçüde azaldığı görüldü. Univaryant korelasyon analizi GLAS-R, GLAS-E, GlASR-R ve GLASR-E değerlerinin E/Em (r: -0.34, P = 0.04; r: -0.35, P=0.04; r: −0.35,P= 0.04 and r: −0.35,P= 0.04,sırasıyla) ile ters korelasyon olduğunu gösterdi.

Sonuç: Bu çalışma SA strain ve strain rate değerlerinin AAS kullanan sporcularda kullanmayan sporculara göre azaldığı ayrıca patolojik ve fizyolojik SVH ayırıcı tanısında konvansiyonel ekokardiyografi ile elde edilen bulgulara ek değerli bilgiler sağladığı doğrulanmıştır.

Anahtar Kelimeler: Anabolik-Androjenik Steroid, Vücut geliştirici sporcular, sol atrial fonksiyon, benekli işaretleme, sol atrial strain

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Introduction

Self-administration of high doses of anabolic androgenic steroids (AAS) is a widespread practice among athletes to increase lean body mass and muscular strength. Long-term illicit use of supraphysiologic doses of AAS may cause several adverse cardiovascular effects.[1, 2, 3, 4] There are several case reports of sudden death (SD) in athletes which indicate an association between chronic AAS abuse and increased risk of arrhythmias and sudden cardiac death.[5, 6] It has been reported that cardiovascular morbidity and mortality have significantly increased in long term AAS using bodybuilders than non-users.[5] Furthermore, recent studies have found pathological left ventricular (LV) hypertrophy, diastolic dysfunction (impaired relaxation and reduced compliance of LV), increased LV mass, left atrial (LA) hypertrophy, subclinical systolic impairment, increased myocardial stiffness and myocardial fibrosis in long-term AAS users.[4, 7-9] These conditions are independent risk factors for cardiovascular morbidity and mortality. Therefore, distinguishing AAS user athlete's from the nonpathological "athlete's heart" is critically important. Echocardiography plays a key role in differential diagnosis, but significant overlap exists between both conditions and its differentiation remains challenging.

LA volume and function are useful barometers of LV diastolic function and predictors of cardiovascular outcomes.[10] Changes in LA size or phasic function may indicate the presence and the severity of heart disease. [11, 12] Pathological LVH is associated with LA dilatation and dysfunction. Echocardiographic assessment of LA myocardial function might contribute to differentiate between pathological and physiological LVH.[13] Recently, two-dimensional S and SR echocardiographic imaging based on 2D-STE have been proposed as a method for assessment of LA function. 2D-STE is a novel non-Doppler-based method for the angle-independent and objective quantification of myocardial deformation from bidimensional datasets in contrast to Doppler-derived indexes, speckle tracking has the advantage of being angle independent and being less affected by reverberations, side lobes and drop out artifacts.[14] This analysis may allow a more direct assessment of LA endocardial contractility, and passive deformation has been recently proposed. The feasibility and reproducibility of 2D-STE for the study of LA mechanics have been recently validated. Abnormalities in LA S and SR have been shown by 2D-STE in some pathophysiologic conditions, including systolic and diastolic heart failure, atrial fibrillation, stroke, heart valve disease and hypertrophic cardiomyopathy.[14,15]

The LA function contributes to LV filling by means of its three components: a reservoir component, which receives blood from the pulmonary veins during ventricular systole; a passive conduit component during

early diastole and diastasis; and a pump component, with active contraction during late diastole. LV dysfunction that arises in pathologies that affect the structure and function of the LV affects LA functions; also, LA functions can be affected related to the negative impact of these pathologies on the structure of the LA.[15]

Although LV systolic and diastolic functions have been examined in various echocardiographic researches, no research has been conducted to examine LA functions between AAS user and non-user athletes using the 2D-STE method. The aim of this study was to evaluate LA myocardial function using 2D-STE method in both AAS user and drug-free bodybuilders, and assess its potential role in the differential diagnosis between these two entities.

Methods

Study Population

We selected a population of 33 competitive bodybuilders, including 15 actively taking AAS for $\geq$ 2 years (users) and 18 who had never used AAS (non-users), all men. The protocol of this cross-sectional study was approved by the institutional review board of Kartal Kosuyolu Heart and Training Hospital and performed in accordance with the guidelines proposed in the Helsinki Declaration. Written informed consent was obtained from all the participants. Patients with coronary artery disease, chronic renal failure, chronic liver disorders, chronic lung disease, moderate or severe valvular heart disease, diabetes mellitus, congenital heart disease, left ventricular systolic dysfunction on echocardiography (EF<50%), recent acute coronary syndrome, anemia, obstructive sleep apnea, secondary hypertension, hematological disorders, known malignancy, thyroid dysfunction, hypercholesterolemia, electrolyte imbalance and bundle branch block, atrio-ventricular conduction abnormalities on ECG were excluded from the study. All the patients were in sinus rhythm and none of them was taking medications such as anti-arrhythmics, tricyclic antidepressants, anti-histaminics and antipsychotics.

Training Protocols. All participants had trained intensively for >10-15 h/wk for >5 years. AAS users and non users had started bodybuilding at approximately the same age (21.47 $\pm$ 3.24 vs 22.34 $\pm$ 3.68 years, respectively, p=non significant) and training protocols (anaerobic isometric static exercises and aerobic exercises) were not different between the groups. Maximum self-reported one-repetition squat results were significantly greater among AAS users (142.6 $\pm$ 19.0 vs 120.6 $\pm$ 21.6 kg, P <0 .001) (Table.1).

AAS Abuse: A self-reported clinical history of each participant including type and timing of AAS use and other performance-enhancing drugs was carefully noted. The orally self-administered drugs were oxymetholone and stanozolol, and the injectable steroids were nandrolone, stanozolol, and testosterone propionate. The mean duration of AAS use was 5.73 ± 3 years. The mean weekly dosage of AAS was 1085.5 ± 354 mg.

Physical Examination and Laboratory Tests: All subjects were examined on an empty stomach. Height, weight, body mass index, body surface area (BSA), body fat mass, heart rate, and blood pressure were measured. Venous blood samples were drawn from each subject, always in the afternoon between 1 and 2 PM, to evaluate serum hormone levels (testosterone, luteinizing hormone, follicle-stimulating hormone, insulin, T3, and T4), hematology (hematocrit, hemoglobin), and blood lipids (total cholesterol, high-density lipoprotein). The subjects' bodyweight and height were measured and the body mass index (BMI) was calculated as body weight divided by squared height (kg⁄m2).

Echocardiographic Measurements

Echocardiography was performed in left lateral decubitus position with an ultrasound machine GE-Vingmed Vivid 7 system (Vivid system 7, GE-Vingmed Ultrasound AS, Horten, Norway) and 3S-RS (3.5 MHz) probe. Examinations were performed by a cardiologist who was blinded to the clinical details of each subject. Single-lead ECG was recorded continuously during the echocardiographic examination. Two-dimensional, M-mode and tissue Doppler images were acquired from the parasternal long and short axis and apical four-chamber views at end-expiratory apnea, and were transferred to a customized dedicated software package (EchoPAC, General Electric Vingmed Ultrasound) for off-line analysis of stored data. All measurements were averaged from three cardiac cycles. 2D echocardiographic measurements were performed according to standards outlined by the American Society of Echocardiography.[16]

Left Ventricular Assessment

LV dimensions and wall thickness were obtained from the parasternal long axis with an M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the ventricle. LV end-diastolic diameter (LVEDD) and end-systolic (LVESD) diameter, thickness of the interventricular septum (IVS), and posterior wall of the left ventricle (PW) were measured. LV ejection fraction was calculated according to the Simpson method[16). For determination of left ventricular mass (LVM), the Devereux formula was used: LVM (g), 1.04 [(LVID + PWT + IVST)3 − LVID3] − 14 (LVID indicates LV internal dimension; PWT, PW thickness; IVST, IVS thickness). Left ventricular mass index was calculated by dividing LVM by body surface area

(BSA). LV hypertrophy was defined as an LV mass index>115 g/m2 in men, as recommended by the American Society of Echocardiography and the European Association of Echocardiography.[16] Mitral inflow velocities were evaluated by pulsed-wave Doppler echocardiography with the sample volume placed at the tip of the mitral leaflets from the apical four-chamber view. Diastolic peak early (E) and peak late (A) transmittal flow velocity, peak E to peak A velocities (E/A), deceleration time of peak E velocity (EDT) and isovolumetric relaxation time (IVRT) were measured.[17]

The tissue Doppler imaging (TDI) was performed in the apical four-chamber view using a 5-mm pulsed Doppler sample volume with as minimum optimal gain as possible to obtain the best signal-to-noise ratio. Care was taken to align the echo image so that the annular motion was parallel to the TDI cursor. Spectral pulsed-wave Doppler signal filters were adjusted until a Nyquist limit of 15–20 cm/s was reached. The monitor sweep speed was set at 50– 100 mm/s to optimize the spectral display of myocardial velocities. In apical 4- chamber view, the pulsed Doppler sample volume was subsequently placed at the level of LV lateral mitral annulus, septal mitral annulus, and right ventricular (RV) tricuspid annulus. The myocardial peak systolic (Sm), and early diastolic (Em) velocity, and late diastolic (Am) velocity were obtained from the septum, the lateral wall of the left ventricle and the annulus of the right ventricle. The Sm global, Em global and Am global velocities were derived by averaging the velocities from the 2 mitral annular sites. Global Em/Am ratio and E/Em ratio were calculated.[18]

Left Atrium Assessment

All volumes were calculated from the apical four- and two-chamber views using the Simpson biplane method of discs.[19] Left atrial length was defined as the longest line that could be drawn between the posterior LA wall and the mid-portion of the mitral valve, and was similar in the four-chamber and two-chamber views, which are perpendicular to each other. Maximum LA volume was measured just before mitral valve opening. Minimum LA volume was measured at mitral valve closure. All volumes were indexed to body surface area. LA volume at onset of atrial systole was considered the volume corresponding to the onset of the P wave in the simultaneously recorded ECG. All LA volume values were corrected for BSA. Left atrial systolic (active emptying) function was assessed using (1) LA active emptying volume = LA volume at onset of atrial systole - LA minimal volume and (2) LA active emptying fraction = LA active emptying volume/LA volume at onset of atrial systole.[20, 21]

To analyze 2D speckle tracking imaging, we obtained 2D gray scale harmonic images from the apical four- and two-chamber views focused on the left atrium. All images were obtained at a frame rate of 40–90 frames/sec without dual focus. Three consecutive cardiac cycles were saved in digital format for offline analysis using dedicated software (EchoPAC version 8.0.0; GE Vingmed). The software is based on real time tracking of natural acoustic markers, which allows the derivation of 2D strain and strain rate by comparing the relative displacement of speckles throughout the cardiac cycle. To determine the LA longitudinal strain and strain rate, the endocardial border of the left atrium was traced manually and tracked by the software. The software divided each LA wall arbitrarily into 3 segments: annular, mid, and basal segments. In the case of unsatisfactory tracking, the operator could repeat the imaging or change software parameters such as the region of interest width and the smoothing functions. When more than 2 inadequately traced segments were found among 6 segments in each apical view even after the repeated tracing, the image was excluded from the analysis. Inadequately traced segments were automatically excluded from analysis. Finally, the software calculated average SR for six segments for each apical view and the LA S-SR values for each view were the averages of the values obtained for the LA segments of each view. The final Global LA-S and -SR values were the averages of the values obtained for each apical view.[22, 23]

LA strain during systole (LAS-S) was obtained at the time of aortic valve closure, strain during late diastole (LAS-A) was obtained at the onset of the P wave on electrocardiography, peak systolic strain rate (LASR-S), peak early diastolic strain rate (LASR-E) and peak late diastolic strain rate (LASR-A) were obtained for the entire traced contour of the left atrium. LA strain during early diastole (LAS-E) was defined as (LAS-S) – (LAS-A). LAS-S and LASR-S left atrium reservoir, LAS-E and LASR-E left atrium conduit, LAS-A and LASR-A values are related to pump functions of the left atrium.[23] (Figure.1)

Statistical analysis

The SPSS 15.0 statistical program (SPSS Inc., Chicago, Ill.) was used for the statistical study. All values are given as mean ± standard deviation. Mean values of continuous variables were compared between groups using the Student t test or Mann–Whitney U test, according to whether normally distributed or not, as tested by the Kolmogorov– Smirnov test. The Chi-square test was used to assess differences between categorical variables. Spearman's correlation coefficients were used to assess the strength of relationship between continuous variables. A P value of < 0.05 was considered significant.

Results

Clinical characteristics of the study population

The characteristics of the subjects are listed in Table 2. No differences between groups emerged in age, height, weight, BSA, blood pressure, or heart rate. However, AAS users had higher body mass indexes compared with AAS non users.

Echocardiographic analysis

Table 3 shows the details of the echocardiographic analysis. LV mass index, interventricular septal thickness, LV posterior wall thickness, and relative diastolic wall thickness were significantly greater in AAS users than in nonusers (P< 0.01). No significant differences were found in LV end-systolic, end- diastolic dimensions and LV ejection fraction among the groups.

Transmitral Doppler echocardiography data of LV diastolic function are listed in Table 3. No significant differences were found in peak E and peak A between AAS user and nonusers. However, drug-using bodybuilders exhibited longer isovolumetric relaxation times and lower ratio of E/A than their drug-free counterparts.

When comparing the diastolic functions obtained by measuring the TDI velocities, lateral and septal E_m were significantly lower in AAS users than in nonusers (11.6 $\pm$1.2 vs. 16.2 $\pm$ 1.5, P < 0.01; 10.1 ± 1.3 vs. 12.1 ± 1.5, P < 0.01; respectively), whereas, lateral and septal A_m were not a significant difference in AAS users than in nonusers (9.4 $\pm$ 1.3 vs 9.9 $\pm$ 1.2, P > 0.05; 9.5 ± 0.7 vs 9.4 ± 1.2, P > 0.05; respectively). Global E/E_m and E_m/A_m were significantly different in ASS users than in nonusers (7.3 $\pm$ 1.5 vs 5.8 $\pm$ 0.9, P < 0.01; 1.6 $\pm$ 0.1 vs 1.5 $\pm$ 0.2, P < 0.01; respectively). In addition, S_m was significantly lower in AAS users than in nonusers (6.23 $\pm$ 0.63 vs. 7.04 + 1.16, P < 0.01).

LA active emptying volume and active emptying fraction were increased in AAS user athletes than in nonusers (4.6 ± 1.0 vs 3.07 ± 1.1, P < 0.001; 33.1 ± 8.1 vs 25.8 ± 9.1, P<0.001: respectively), but LA volume index was not different between these groups. With respect to the LA strain and strain rate, AAS using athletes had significantly lower Global LAS-R, Global LAS-E (38.2 ± 8.4 vs 48.6 ± 11.9, P < 0.01; 24.4 ± 8.6 vs 37.1 ± 12.8, P <0.01; respectively), Global LASR-R, Global LASR-E (1.8 ± 0.3 vs 2.2 ± 0.4, P <0.01; -1.4 ± 0.2 vs -1.8 ± 0.3, P < 0.01; respectively) compared to non-user athletes. Global LAS-A and Global LASR-A was also increased in AAS user athletes (Table.4).

The univariate correlation analysis demonstrated that the Global LAS-R, Global LAS-E, Global LASR-R and

Global LASR-E had a good inverse correlation with E/Em (r: -0.34, P = 0.04; r: -0.35, P=0.04; r: −0.35, P= 0.04 and r: −0.35, P= 0.04, respectively). There were also negative correlation between Global LAS-R, Global LAS-E, Global LASR-R, Global LASR-E and LV mass index (r: −0.38, P=0.02; r: −0.39, P= 0.02; r: −0.37, p=0.03 and r: −0.40, p=0.02, respectively). LA strain and strain rate parameters all had a positive correlation with both Em and Sm (Table.5).

Intra- and interobserver variability coefficients were calculated using images independently recorded in 2 different occasions by the same investigator or by 2 different observers. When the reproducibility was separately considered in the 2 apical views, inter-observer variability coefficients were 5.4% and 5.9% for four- and two-chamber average Global LAS-R, 6 % and 6.1% for Global LASR-R, 6.1% and 6% for Global LASR-E, 5.4% and 5.1% for Global LASR-A, respectively. Corresponding intra-observer variability coefficients were 4.7% and 5.1% for Global LAS-R, 5.4% and 5.6% for Global LAS-R, 5.4% and 5.2% for Global LASR-E, and 4.4% and 4.3% for Global LASR-A.

Discussion

The principal finding of this study is that assessment of LA strain and strain rate by 2D speckle tracking provides additional information to that obtained with standard echocardiography in the differential diagnosis between AAS using bodybuilders compared with non-AAS users. Furthermore, LA reservoir, conduit and pump function are impaired in AAS user athletes.

Haemodynamic overload due to long-term training usually involves both left and right ventricles, inducing changes in cardiac structure such as increases in internal cavity diameters, wall thickness and mass, usually described as ‘‘athlete’s heart’’.[24-26] This is thought to be a physiologic and benign response to exercise conditioning, without the adverse prognostic implications of HCM or hypertensive LV hypertrophy. The physiologic hypertrophy that occurs in athletes is associated with increased ventricular mass, normal organization of cardiac structure, and no increase in collagen content. On the other side, the hypertrophy observed in AAS using bodybuilders is characterized by myofibrillar disarray and collagen accumulation, eventually leading to systolic and diastolic dysfunction.[27, 28]

Echocardiography plays a key role in the early differential diagnosis between these two entities. Echocardiographic studies show that concentric LVH is a common morphologic change of the heart in both long-term use of supraphysiologic doses of AAS users and non-user bodybuilder athletes. There are some studies related to the differences between pathologic and physiologic adaptative LVH in AAS using and non-

using athletes.[7, 8] In contrast to the physiological LVH caused by endurance training, LVH in pathological conditions like systemic hypertension and hypertrophic cardiomyopathy is characterized by impaired diastolic function.[29-31] In addition, pathologic LVH with impaired diastolic function which is induced by long-term illicit use of supraphysiologic doses of AAS has also been described.[9, 32, 33] In our study, we found that E/Em ratio was significantly higher in AAS users than in nonusers. In addition, the Em/Am ratio was significantly lower in AAS users than in nonusers. Also we found that IVRT is prolonged in AAS using group, indicating the impairment of diastolic function.

Although standard Doppler echocardiography has been widely used to distinguish athlete's heart from pathological left ventricular hypertrophy, recent studies indicate that Doppler tissue imaging techniques, in particular PWTDI, are also useful in assessing myocardial systolic and diastolic function and differentiating pathologic ventricular hypertrophy from the physiologic one.[7, 34, 35] Shan et al, comparing Doppler tissue imaging and histologic findings in patients affected by coronary artery disease, demonstrated that Sm and Em are strongly dependent on the number of myocytes, myocardial b-adrenergic receptor density, and the amount of interstitial fibrosis.[36] D'Andrea et al and other studies observed lower myocardial early diastolic peak velocities of the interventricular septum and the lateral LV wall in AAS users when compared to AAS free athletes.[7, 8] Confirming previous findings, we observed low Sm velocity and low early diastolic peak velocities (Em) at the interventricular septum and the lateral LV wall which indicate pathologic LVH in AAS users.

LA function is an integral part of cardiac function that is often neglected. In recent years, LA strain and strain rate analysis by two-dimensional (2D) speckle tracking has emerged as a novel method to evaluate LA function. This analysis may allow a more direct assessment of LA endocardial contractility, and passive deformation has been recently proposed. The feasibility and reproducibility of 2D-STE for the study of LA mechanics have been recently validated. Abnormalities in LA-S and SR have been shown by STE in some pathophysiologic conditions, including systolic and diastolic heart failure, atrial fibrillation, stroke, and heart valve disease.[37, 38] In addition, some authors have recently applied 2D strain echocardiography analysis to characterize LA myocardial function in patients with either physiological or pathological LVH.[39] It is known that hypertensive LVH shares many features with HCM and it has been suggested that evaluation of LA function may be relevant in the diagnosis of pathologic LVH and in this sense LA-S and SR showed an acceptable reproducibility to assess LA function similar to other reports.[13, 40] D'Andrea et al. found that LA myocardial deformation assessed by 2D speckle tracking is impaired in patients with LVH due to

hypertension compared with elite athletes and control subjects.[13] In another study by Sun et al. demonstrated that all components of LA-SR in the hypertensive group were significantly lower compared with athletes and normal controls.[41] Previous study showed that LA-S and SR were significantly lowered in patients with HCM compared to highly trained athletes and healthy controls and provided valuable additional information to that obtained by conventional echocardiography in the differential diagnosis between pathologic and physiologic LVH.[28] Moreover, recent studies have found pathological LVH in long-term AAS user athletes. Although conventional echocardiography has been widely used to distinguish pathologic and physiologic LVH between AAS user and non-user athletes, no research has been conducted to examine LA functions using the 2D-STE method between these groups. Thus, in the current study we evaluate LA myocardial function using 2D-STE method in both AAS user and drug-free bodybuilders to distinguish pathologic and physiologic LVH. In our study, in AAS user athletes group, Global LAS-A, Global LASR-A and indexes of LA booster pump function (LA active emptying fraction) were increased, whereas Global LA S/SR parameters which are related with LA reservoir, conduit functions were significantly impaired compared with non-user athletes group. In addition, we found a correlation between Global LA S/SR reservoir and conduit functions with LV mass index, E/Em, Sm and Em (Table.5). There was no correlation between Global LAS-A, Global LASR-A with LV mass index, E/Em, Sm and Em (Table.5). Thus, we observed that Global LA-S and SR parameters give easy tool to differentiate pathologic and physiologic LVH between AAS user and non-user athletes. Global LA reservoir, conduit and pump functions in AAS user athletes are impaired, even in the absence of LA enlargement.

There are several possible explanations for impaired Global LA-S and SR parameters in athletes with AAS users. An impaired diastolic function of the LV may be an early symptom of pathological hypertrophy and is helpful to differentiate between pathologic and physiologic LVH. The diastolic function may be restricted in AAS users, which has been described by our working group and others.[7, 8, 42] In our study, we described diastolic dysfunction in AAS using athletes. It is known that LA functions reflect the severity of diastolic dysfunction. 2DSTE is a new modality that is capable of measuring phasic changes in LA strain.[40, 43] It is known that LA reservoir and conduit function progressively declines at the advanced stages of diastolic dysfunction. This was associated with an initial augmentation of LA booster function in mild diastolic dysfunction to maintain total LA emptying volumes.[44] We found that Global LASR-A increased and Global LASR-E/R decreased with the development of LV diastolic dysfunction. The correlation of E/E_m parameter

with the Global LASR-E and Global LASR-R parameters suggests that the left ventricular diastolic dysfunction in AAS using athletes should have an impact on left atrial strain rate in early stage.

The other possible mechanism for impaired LA strain and strain rate parameters in AAS using athletes is LA myocardial fibrosis. Probably adverse effects of AAS on the cardiovascular system are also due to direct toxicity on myocardial structure with increased collagen deposition, fibrosis, and altered microcirculation with intimal hyperplasia of the intramural coronary arteries resulting in chronic ischemic damage.[45] As the cause of these alterations may directly affect the atrium and ventricle, causing inhomogeneous myocardial hypertrophy, focal myocyte damage with myofibrillar loss, and interstitial fibrosis heterogeneity in AAS user athlets.[45, 46] It is well known that LV interstitial fibrosis as a consequence of long term AAS using in athletes, affects primarily the subendocardial systolic and diastolic function of the left ventricle.[7, 13, 47] In this regard, previous studies hypothesized that in long term AAS using athletes, the same fibrotic processes that affect the subendocardial layer of the left ventricle could also alter the subendocardial fibers of the left atrium.[45, 46] Several and recent studies suggest that the degree of elevated LV filling pressures may not fully explain LA failure and that LA myocardial fibrosis may play a role in the systolic and diastolic dysfunction of the left atrium. Systolic and diastolic myocardial functions of the left atrium are disrupted as a result of the fibrosis that occurs in the left atrium.[48] In pathologies that affect the left atrial structure and functions, the severity of the left atrial fibrosis evaluated with the magnetic resonance imaging as well as the correlation between the left atrium longitudinal strain and strain rate values proves the relationship between involved parameters and left atrial fibrosis.[22] The extent of atrial fibrosis detected with late gadolinium enhancement by magnetic resonance correlates with this reduction in atrial S and SR measured with speckle tracking.[49] Also, several studies suggest that LA myocardial fibrosis play a role in the impairment of LA pump, conduit and reservoir functions in different cardiovascular diseases.[49, 50] Suman et al found that LA-S and SR (reservoir, conduit) were decreased in atrial fibrillation patients. In addition they suggested that LA wall fibrosis by delayed-enhancement MRI is inversely related to LA-S and SR, and these are related to the AF burden.[50] Hence, we believe that as a result of fibrosis that occurs in the LA due to long-term illicit use of supraphysiologic doses of AAS, might be one of the reasons for the impairment of LA S/SR reservoir and conduit functions in AAS using bodybuilders.

Consequently, as described different cardiovascular diseases, we hypothesized that; LA myocardial fibrotic alterations, together with chronically elevated LV filling pressures (LV diastolic dysfunction), would leads to the decrease of LA reservoir and conduit function and to the increase of LA pump function (Frank-Starling

law) in the long term AAS using athletes.

Study limitations

The important limitation of our study is the small sample size, which makes necessary to assess the reproducibility of these results in larger scale studies. Our sample might not be representative of the overall population of long-term AAS users or weightlifters. The cross-sectional nature of this exploratory study does not permit to draw definitive conclusions about the long-term clinical implications of our findings.

We were dealing with young individuals. The impact of AAS in older individuals is unknown. The same idea can be used for gender. There is no guarantee that the effects of AAS on LA functions in women will be similar to those found in men. The information about the intake of steroids was self reported, but it is difficult to assess this in an objective manner. In addition, training-related influences are also improbable as an explanation for the differences between the AAS users and non-users in our study, as the training protocol was the same for all the athletes.

Cardiac MRI could not be performed. Therefore, LA remodeling and fibrosis could not be directly evaluated. The absence of studies in which LA deformation parameters obtained by

2D-STE were compared with sonomicrometry or tagged magnetic resonance imaging can be an another limitation. However, LV deformation parameters by 2D-STE is in good agreement with that obtained by sonomicrometry and by tagged magnetic resonance imaging.[51]

Finally, because a dedicated software for LA strain analysis has not been released yet, we used the current software for LV analysis to study the LA pattern strain. Future evolutions in this regard may be useful to improve tracking quality of LA myocardial deformation, and to provide a better instrument for the study of LA function.

Conclusion

The present study confirms that in AAS users, 2D-STE is effective and reliable noninvasive diagnostic tools for detecting early abnormalities of LA myocardial functions. In addition, this study shows that LA strain and strain rate are impaired in AAS using athletes compared to non-using athletes and provide valuable additional information to that obtained by conventional echocardiography in the differential diagnosis between pathologic and physiologic LVH.

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Table 1. Training programs of the AAS User and Non-User Bodybuilders

	AAS non-users (n=18)	AAS users (n=15)	P value
Sessions per week	3.92 ± 0.86	3.67 ±0.84	NS
Years	8.64±2.11	9.03 ± 1.94	NS
Starting age	22.34 ± 3.68	21.61 ± 3.04	NS
Anaerobic exercise (h/wk)	4.73 ± 2.02	4.94 ± 1.82	NS
Aerobic exercise (h/wk)	3.11 ± 3.03	1.94 ± 1.82	NS
Maximal weight (kg)	120.67 ± 21.61	142.67 ± 19.09	<0.05

NS = nonsignificant.

Table 2. Clinical Characteristics of AAS User and Non-User Bodybuilders

Clinical variables	AAS non-users (n=18)	AAS users (n=15)	P value
Age (year)	33.8 ± 4.1	32.5 ± 6.6	NS
Height (cm)	180.4 ± 6.9	179.9 ± 7.3	NS
Weight (kg)	87.4 ± 10.3	90.8 ± 6.3	NS
BMI (kg/m^2)	26.3 ± 3.2	29.1 ± 4.4	<0.05
BSA (m^2)	2.08 ± 0,14	2.1 ± 0,14	NS
Blood pressure (mmHg)	120 ± 13.37 / 80.37 ± 6.49	118.51 ± 9.88 / 78.51 ± 6.9	NS
Heart rate (beats/min)	68.74 ± 10.45	72.22 ± 13.40	NS

NS = nonsignificant.

Table 3. Comparison of the Echocardiographic Parameters of the Subjects Both AAS User and Non-User Bodybuilders

	AAS non-users (n=18)	AAS users (n=15)	P value
2-D Echocardiographic parameters			
LV end-systolic diameter (mm)	31.9 ± 4.4	33.2 ± 3.2	NS
LV end-diastolic diameter (mm)	49.7 ± 1.9	51.2 ± 3.1	NS
Septal wall thickness (mm)	11.5 ± 1.2	12.4 ± 1.3	<0.01
Posterior wall thickness (mm)	9.8 ± 0.9	11.3 ± 0.7	<0.01
RWT	0.39 ± 0.03	0,44 ± 0,02	<0.01
LV mass index (g/ m^2)	90.9 ± 10.8	113.6 ± 13.6	<0.01
LV ejection fraction (%)	61.37 ± 1.6	60.87 ± 2.3	NS
Doppler parameters			
Peak E velocity (cm/s)	79.8 ± 9.4	77.6 ± 11.6	NS
Peak A velocity (cm/s)	55.7 ± 8.9	50.7 ± 6.8	NS
E/A ratio	1.47 ± 0.3	1.54 ± 0.2	NS
IVRT (ms)	80.7 ± 5.8	83.58 ± 11.7	<0.01
S m (cm/s)	7.04 ± 1.16	6.23 ± 0.63	<0.01
E_m septal (cm/s)	12.1 ± 1.5	10.1 ± 1.3	<0.01
A_m septal (cm/s)	9.4 ± 1.2	9.5 ± 0.7	NS
E/E_m septal (cm/s)	6,7 ± 1,2	7,8 ± 1,7	<0,01
E_m/A_m septal (cm/s)	1.29 ± 0.2	1.06 ± 0.2	<0.01
E m lateral (cm/s)	16.2 ± 1.5	11.6±1.2	<0.01
A m lateral (cm/s)	9.9 ± 1.2	9.4 ± 1.3	NS
E/E_m lateral (cm/s)	4.9 ± 0.8	6.8 ± 1.3	<0.01
E_m/A_m lateral (cm/s)	1.6 ± 0.3	1.2 ± 0.2	<0.01
E/E_m global (cm/s)	5.8 ± 0.9	7.3 ± 1.5	<0.01
E_m/A_m global (cm/s)	1.5 ± 0.2	1.6 ± 0.1	<0.01

NS= nonsignificant.

Tablo 4: Left atrial standard echo and two-dimensional strain baseline measurements in the overall study population

	AAS non-users (n=18)	AAS users (n=15)	P value
LA dimension (mm)	33.1 ± 0.3	34.2 ± 0.2	NS
LA volume index (mL/m^2)	26.2 ± 2.3	27.6 ± 2.4	NS
LA active emptying volume (cm^2/m^2)	3.07 ± 1.1	4.6 ± 1.0	<0.01
LA active emptying fraction (%)	25.8 ± 9.1	33.1 ± 8.1	0.02
GLAS-R (%)	48.6 ± 11.9	38.2 ± 8.4	<0.01
GLAS-E (%)	37.1 ± 12.8	24.4 ± 8.6	<0.01
GLAS-A (%)	11.5 ± 2.4	13.8 ± 2.2	<0.01
GLASR-R (1/s)	2.2 ± 0.4	1.8 ± 0.3	<0.01
GLASR-E (1/s)	-1.8 ± 0.3	-1.4 ± 0.2	<0.01
GLASR-A (1/s)	-1.4 ± 0.2	-1.6 ± 0.2	0.02

NS= nonsignificant.

Table 5. Spearman's Correlation Analysis (R and P Values) between LA Strain/Strain Rate and Echocardiographic Parameters

	E/E_m global (cm/s)		**LV mass index (g/m^2)**		**S m**		**E m (cm/s)**	
	R (Coefficient)	P Value	R (Coefficient)	P Value	R (Coefficient)	P Value	R (Coefficient	P Value
GLAS-R (%)	-0.34	**0.04**	−0.38	**0.02**	0.44	**0.01**	0.43	**0.01**
GLAS-E (%)	-0.35	**0.04**	−0.39	**0.02**	0.40	**0.02**	0.42	**0.01**
GLAS-A (%)	0.09	0.60	0.16	0.37	-0.13	0.46	-0.08	0.64
GLASR-R (%)	−0.35	**0.04**	−0.37	**0.03**	0.41	**0.01**	0.42	**0.01**
GLASR-E (%)	−0.35	**0.04**	−0.40	**0.02**	0.39	**0.02**	-0.41	**0.01**
GLASR-A (%)	−0.18	0.31	-0.27	0.11	0.21	0.22	0.16	0.37

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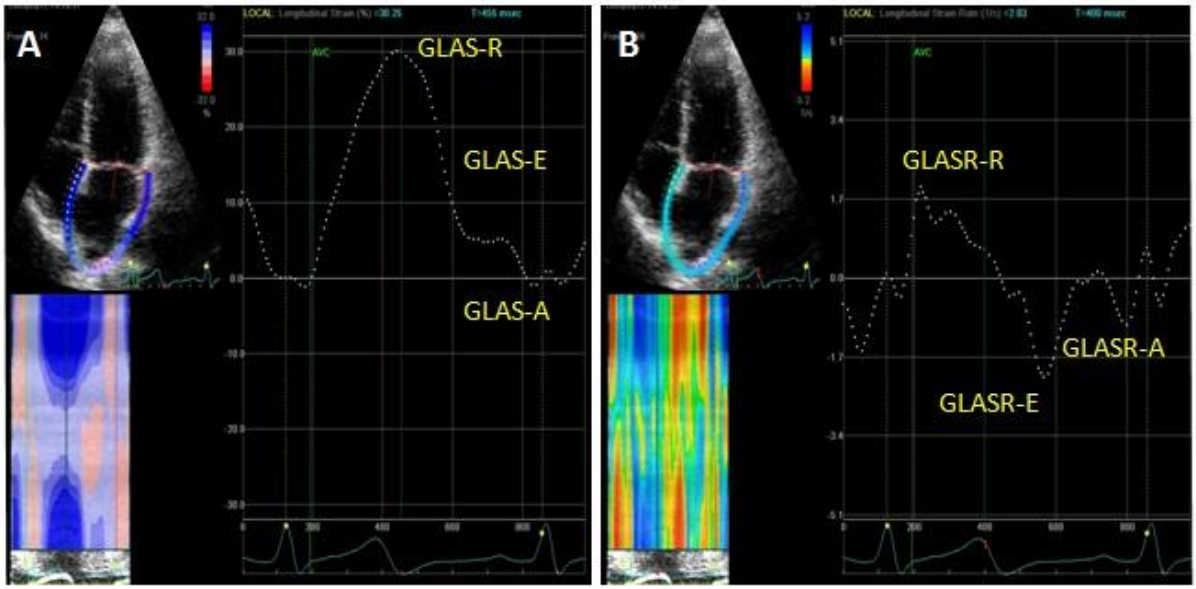
Figure.1: Left atrial strain and strain rate in speckle tracking echocardiography



Supplementary File:

Figure 1 A: Left atrial global strain reservoir (GLAS-R), global strain early diastole (GLAS-E) and global strain late diastole (GLAS-A)

Figure 1B: Left atrial global strain rate reservoir (GLASR-R), global strain rate early diastole (GLASR-E) and global strain rate late diastole (GLASR-A)