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Acute cardiovascular responses to resistance exercise in anabolic steroids users:

A preliminary investigation

Running Title: CV response to resistance exercise in AS users

Key Words: Anabolic Steroids, Resistance Training, Cardiovascular, Cardiac

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ACUTE CARDIOVASCULAR RESPONSES TO RESISTANCE EXERCISE

IN ANABOLIC STEROIDS USERS:

A PRELIMINARY INVESTIGATION

Abstract

Objectives Anabolic steroid (AS) use has increased in recent years, but the cardiovascular consequences for users is not fully understood. *Equipment and Methods* Resistance trained males (AS=7, age=29±5; NAS=6, age=25±1 yrs) undertook a resistance exercise session with echocardiographic measures and cardiac biomarkers taken pre and post exercise (cTnI, NT-proBNP). *Results* A significant decrease in early diastolic tissue velocity (E') (AS= 13±1 vs 11±3, NAS=13±2 vs 12±1 cm.s⁻¹), late diastolic tissue velocity (A') (AS=9±2 vs 8±1, NAS= 8±1 vs 8±1 cm.s⁻¹), E':A' (AS=1.63 vs 1.21, NAS= 1.71 vs 1.62) and E:A (AS=1.61 vs 1.19, NAS=1.63 vs 1.29) with an increase in late diastolic filling velocity (A) (AS=53±8 vs 65±11, NAS= 51±3 vs 57±9 cm.s⁻¹) were seen in both groups post-exercise. A significant decrease in left ventricular end-systolic volume (LVESV) (AS=48±16 vs 45±12, NAS=51±9 vs 43±11 ml) was seen post-exercise with maintenance of ejection fraction (EF). There was a significant group effect on diastolic blood pressure (BP) (AS=74±11 vs 66±7, NAS=68±6 vs 58±2 mmHg) and basal systolic rotation rate (AS=-61.69±18.38 vs -86.65±17.99, NAS= -63.69±14.72 vs -56.50±2.15 .s⁻¹). *Conclusion* Despite significant reductions in diastolic measures, with maintenance of systolic function, there was no altered cardiovascular response in the AS users following resistance exercise.

Keywords: Anabolic Steroids, Resistance Training, Cardiovascular, Cardiac

RÉPONSES CARDIOVASCULAIRES AIGUES À L'EXERCICE DE RÉSISTANCE CHEZ LES UTILISATEURS DE STÉROÏDES

ANABOLIQUES:

UNE ENQUÊTE PRÉLIMINAIRE

Objectifs L'utilisation de stéroïdes anabolisants (AS) a augmenté ces dernières années, mais les conséquences cardiovasculaires pour les utilisateurs ne sont pas entièrement comprises. *Matériel et méthodes* Les mâles entraînés en résistance (AS = 7, âge = 29 ± 5, NAS = 6, âge = 25 ± 1 ans) ont effectué une séance d'exercices de résistance avec des mesures échocardiographiques et des biomarqueurs cardiaques pré et post exercice (cTnI, NT-proBNP). *Résultats* Diminution significative de la vélocité tissulaire diastolique précoce (E') (AS = 13 ± 1 vs 11 ± 3, NAS = 13 ± 2 vs 12 ± 1 cm.s⁻¹), vélocité tissulaire diastolique tardive (A') (AS = 9 ± 2 contre 8 ± 1, NAS = 8 ± 1 contre 8 ± 1 cm.s⁻¹), E': A' (AS = 1,63 vs 1,21, NAS = 1,71 vs 1,62) et E: A (AS = 1,61 vs 1,19, NAS = 1,63 vs 1,29) avec une augmentation de la vitesse de remplissage diastolique tardif (A) (AS = 53 ± 8 vs 65 ± 11, NAS = 51 ± 3 vs 57 ± 9 cm.s⁻¹) ont été observés dans les deux groupes après l'exercice. Une diminution significative du volume télésystolique ventriculaire gauche (LVESV) (AS = 48 ± 16 vs 45 ± 12, NAS = 51 ± 9 vs 43 ± 11 ml) a été observée post-exercice avec maintien de la fraction d'éjection (EF). Il y avait un effet de groupe significatif sur la tension artérielle diastolique (AS = 74 ± 11 vs 66 ± 7, NAS = 68 ± 6 vs 58 ± 2 mmHg) et le taux de rotation systolique basale (AS = -61.69 ± 18.38 vs -86.65 ± 17.99, NAS = -63,69 ± 14,72 contre -56,50 ± 2,15 .s⁻¹). *Conclusion* Malgré des réductions significatives des mesures diastoliques, avec le maintien de la fonction systolique, il n'y a pas eu de réponse cardiovasculaire altérée chez les utilisateurs de SA après un exercice de résistance.

Mots-clés: Stéroïdes anabolisants, Entraînement en résistance, Cardiovasculaire,
Cardiaque

Introduction

Anabolic steroid (AS) use has increased in recent years [1] despite its association with a number of adverse cardiovascular outcomes [2]. Whilst these negative consequences of AS use have largely been inferred from case reports, cross-sectional cohort studies have demonstrated negative side-effects associated with regular AS use such as left ventricular hypertrophy, ECG changes and altered lipid profiles [3].

Transient increase in cardiovascular risk is associated with acute bouts of exercise, so some of the negative consequences associated with AS use may imply an increased risk following exercise in AS users [4]. There is, however, a paucity of data examining the cardiac response to acute exercise in AS users. To date only two studies have assessed cardiac function and/or biomarker responses to acute resistance exercise. Stephenson et al. [5] suggested that cardiac function was unaltered during recovery from resistance exercise, but the training intensity was only moderate and cardiac indices were load-dependent. Stephenson et al [5] also reported no elevation of cTnT immediately following or 24 hours post resistance exercise. Carranza-Garcia et al [6] reported a drop in cTnI at 5 minutes and 1 hour after a heavy resistance training session compared to pre training but this returned to pre training levels by 24 hours post exercise. They also noted a significant increase in NT-proBNP at 24 hours post exercise. Neither of these studies assessed resistance-trained athletes with a history of AS use

Measures of strain and strain rate at both the regional and global level may provide a more accurate representation of overall cardiac tissue contraction. However currently, the response of global and regional cardiac function as well as biomarkers to high intensity resistance exercise has not been described in AS users. The aim of this study

was to assess cardiac function and biomarker responses to a high intensity whole-body resistance exercise session in age matched AS users and non-AS users (NAS).

Methods

Subjects

Strength trained individuals (AS n=7, age=29 ± 5yr; NAS n=6, age= 25 ± 1 yrs.) were recruited through local gyms, personal contacts and local syringe exchange programmes. Inclusion criteria were; participants aged between 18 and 50 years of age; a minimum of 2 years resistance training, with 3-4 training sessions per week. Exclusion criteria for the study were the presence of known respiratory, cardiovascular or musculoskeletal disease. Specific inclusion criteria for the AS using group included a documented self-report history of AS use for at least 2 years (including on and off-cycles). Inclusion criteria for NAS included self-reported history of never taking AS. The study was granted ethical approval by the Liverpool John Moores Ethics committee and participants provided written informed consent. Training history included data on years of training, the average number and length of sessions per week, as well as self-reported one repetition maximums for the bench press and squat. Those in the AS group provided a detailed history of AS use including names, dosage and cycling information and none of the participants self-reported co-abuse of any other illicit substances. For simplicity, we provide a list of exemplar AS used but note that all subjects used multiple AS in various stacking procedures with varied periods of abstinence or “off-cycles”. The types of AS currently being used by the AS participants included testosterone products such as “Sustanon”, “Deca Durabolin”, “Boldebolin” and “Proviron” with the mean AS dose 1642 ± 570 mg/week (range 1000-2500 mg/week) and the mean cycle per AS of 8±5 weeks (range 2-16 weeks).

Research Design

A between groups analysis was utilised to compare AS with NAS users and repeated measures were observed before and after a single high intensity training session. Measurements of cardiac function, blood pressure and biomarkers of cardiac cell damage and stress were taken at rest and following the exercise session. The exercise protocol consisted of a warm-up on the stationary bike for 10 minutes, followed by the full body resistance exercise routine. The exercises were performed for 8-12 reps for 3 sets with one-minute rest between each set. Each participant had a 1 RM assessed *a-priori* and resistance was then assigned for each activity. The total resistance exercise session duration was c. 70 minutes and repeat assessment of cardiac function, blood pressure and biomarkers were made at 15 min of recovery.

Data Collection Protocols

Height and body mass was measured using standard scales. Duplicate brachial artery blood pressures were recorded from the left arm via an automated blood pressure monitor (Dinamap; GE Pro 300V2, GE Healthcare). Resting heart rate as well as global and segmental cardiac functions were assessed using ultrasound echocardiography (Vivid Q, GE Healthcare, Oslo, Norway) with images captured for offline analysis (Echopac, GE Healthcare, Oslo, Norway). A single experienced echocardiographer performed all imaging with the participant in the left lateral decubitus position. Parasternal long-axis views were used to collect M-mode images at the mitral valve leaflets with chamber dimensions assessed following American

Society of Echocardiography guidelines [7]. Apical 2- and 4-chamber views were used to assess left ventricular volumes and estimations of stroke volume and ejection fraction (Simpsons' bi-plane method). Left-ventricular mass was calculated using American Society of Echocardiography guidelines and was scaled to body surface area [7, 8]. Colour Doppler guided Doppler-flow and tissue-Doppler imaging were used to assess peak flow and myocardial wall velocities at peak; systole (S, S') early diastole (E, E') and late diastole (A, A'). This also allowed the production of the E/E' ratio that has been shown to estimate left atrial pressure [9].

Global and segmental strain (ϵ) and strain rate (SR) were obtained from parasternal short-axis view at the basal level (below mitral valve) as well as from the apical 4-chamber view. Images were captured for off-line analysis with speckle-tracking software used to track acoustic markers or "kernels" facilitating the estimation of ϵ and SR in six wall segments. In the short-axis view the LV was split into septal, anteroseptal, inferior, posterior, anterior and lateral wall segments. Radial (R) and circumferential (C) and rotational scores were averaged across segments to provide global measures of ϵ , SR, rotation (Rot) and rotation rate (RotR) data. In the long-axis view the LV was split into basal, mid-wall and apical wall segments for the septal and lateral walls. These scores were also averaged to provide global measures of longitudinal ϵ and SR. SR data were recorded during systole (SSR) and early diastole (ESR). Image optimisation was performed including maintaining frame rate between 40-90 fps. Data reflect the average of 3-5 continuous cardiac cycles.

Venous blood (5 ml) was collected from the brachial antecubital vein directly into serum gel (serum) vacutainers (BD, Oxford, UK). Blood was allowed to clot (~45 min), centrifuged for 10 min at 3000 rpm and stored at -80°C for later analysis. cTnI was determined using the TnI-Ultra assay for Advia Centaur XP immunoassay system (Siemens Medical Solutions Diagnostics, Frimley, Surrey). Assay detection limit was 0.006 ug/L with a linear calibration range up to 50 ug/L [10]. Assay precision in our laboratory was estimated as 10% CV at 0.045 ug/L [11]. NT-proBNP was determined using the NT-proBNP assay for Immulite 2500 (Siemens Medical Solutions Diagnostics, Frimley, Surrey). The assay detection limit was 20 pg/ml with a linear calibration range up to 35,000 pg/ml [12].

Data analysis

Statistical analysis of data was performed using statistical software package SPSS Version 22 (SPSS inc, Chicago, Il). All data were subjected to tests of normality using shapiro-wilks with all data considered normally distributed ($p > 0.05$). Anthropometric and training data were analysed using between groups T-tests. Pre and post exercise measures of blood pressures, heart rate and cardiac structure and function were assessed using a two-way mixed design analysis of variance (2-Way ANOVA) checking for significant effect of exercise or group. Data are presented as mean \pm SD with 95% confidence intervals of the mean difference. A significance level of $p < 0.05$ was set.

Results

Body Composition and Performance

There was no significant between group differences for age, height, weight or BSA. The number of training sessions per week, average session length and 1RM data for both bench press and squat were also similar between groups (Table 1).

[Table 1 near here]

Resting CV Structure & Function

LVPW thickness (AS=11 ± 1 vs NAS=8 ± 1 mm, p=0.002, 95% CI= 1.37, 4.46), and IVS (AS=11 ± 1 vs NAS=10 ± 1 mm, p=0.029, 95% CI= 0.19, 2.76) were greater in AS which underpinned a higher LVM in AS users (AS=216 ± 47 vs NAS=158 ± 27 g, p=0.019, 95% CI= 11, 99). However, once LVM was scaled for BSA there was no significant difference between groups (AS= 64.3 ± 4.4, NAS= 61.35 ± 1.2 g/m², p=0.143, 95% CI= 0.46, 18.4). At baseline, there was no difference in LVEDV between groups as well as no significant difference in resting HR (Table 2). Systolic and diastolic blood pressure at rest was also similar between groups (Table 2). There was also no significant difference in measures of systolic and diastolic function, including Doppler and Tissue Doppler measures, between groups (p>0.05, Table 3).

[Table 2 near here]

Cardiac Functional Changes with Exercise

There was no significant effect of exercise (p=0.089) on LVEDV in either group. Heart rates increased in both groups, in a similar fashion, following exercise. Whilst there

was no significant effect of exercise or group on systolic BP, there was a significant decrease in diastolic BP following exercise ($p=0.001$).

Whilst there was no significant effect of exercise or group on EF or SV, there was a decrease in LVESV following exercise ($p=0.012$, 95% CI= 1.59, 10.46) with no significant interaction of group and exercise. There was an increase in A ($p=0.023$, 95% CI= -0.16, -0.01) and therefore E:A ($p=0.000$, 95% CI= 1.50, 1.70) following exercise with no significant effect of group. Whilst no effect of exercise or group were seen in S' there was a decrease in E' after exercise ($p=0.041$, 95% CI= 0.01, 0.02) and thus E':A' ($p=0.049$, 95% CI= 0.001, 0.310) with no group effect (Table 3). There was an increase in SrLa ($p=0.032$, 95% CI= -0.31, -0.02) post exercise with a significant interaction between group and exercise ($p=0.039$; Table 4). There was an increase in SrRs ($p=0.005$, 95% CI= -1.19, -0.31) and RotRa ($p=0.04$, 95% CI= -26.81, -0.88) following exercise but there was no effect of group. In addition, there was a group effect in RotRs ($p=0.009$, 95% CI= -23.44, -4.71) with an increase seen in the AS group and a decrease in the NAS group post-exercise.

[Tables 3 & 4 near here]

Cardiac biomarkers

There was no significant difference between groups in cTnI pre or post exercise (AS= 0.024 ± 0.008 to 0.023 ± 0.001 , NAS= 0.02 ± 0 to 0.02 ± 0 $\mu\text{g/L}$). However, cTnI did increase post-exercise in a single AS participant with elevated values at both pre- and

post-exercise blood draws (AS, 0.036 and 0.033 mg/L respectively). There was also no significant effect of exercise, group or interaction between group and exercise on NT-proBNP (AS= 33.28 ± 15.85 to 30.45 ± 9.32 , NAS= 24.38 ± 8.92 to 22.12 ± 3.28 pg/ml).

Discussion

This study offers a novel insight into the acute effects of resistance exercise in AS users and builds on previous work examining the cardiovascular consequences of AS use [13-15]. The key findings of the current study are the observation of a reduction in several indices of diastolic function (E' , $E':A'$ and $E:A$) post-exercise was not mediated by AS use and that an acute bout of resistance exercise did not produce wholesale changes in biomarkers of cardiac damage. There was also no significant effect of exercise or AS use on $E:E'$, however changes to diastolic driving forces and active relaxation can occur independently of each other. . Despite previous findings demonstrating an increased CV risk in AS users, the present data suggests that a single bout of resistance exercise doesn't exacerbate exercise effects on cardiac function or biomarkers in AS users.

The AS group had a significantly elevated HR at rest and, as expected, there was a significant increase in heart rate in both groups following exercise with no significant difference in HR response between groups. The increased resting HR in AS users would suggest a lack of aerobic training in AS users [13] although the similar HR response to exercise in both groups suggests that the ability to deal with increasing

energy and CV demands are similar in both groups. There was no significant difference between the two groups in resting BP but there was a post-exercise decrease in diastolic blood pressure following exercise that was greater in the NAS participants. This post-exercise hypotension regularly occurs as a result of exercise but between group differences could reflect differences in vascular function [16]. Previous findings have suggested a decreased vascular response in AS users with direct endothelial damage could be a possible mechanism for the reduced post-exercise hypotension in the AS users in this study [17-19].

Cardiac dimensions are often reported as higher in AS users compared to matched controls but in the present study there was no significant differences between groups in EDV or ESV [15, 20]. There were greater LV and inter-ventricular wall thicknesses in the AS group which resulted in a greater LVM. However, once LVM was scaled for body-surface area there was no significant difference between the AS non-AS users. There was also an absence of any differences in resting functional measure between the two groups. Of particular note was the lack of reduced diastolic measures at rest in AS users which also contradicts previous findings, however, as with much of the data in this area there is substantial contradictions [21, 22]. The significant variation in findings in AS users suggests that the effects of AS in users may be more nuanced than simply using AS equating to a decrease in function or alterations in overall structure.

Despite a significant decrease in ESV in both groups following the exercise bout EF was maintained due to smaller changes in EDV. Stephenson et al [5] reported a reduced LVIDD, considered a surrogate of EDV and preload, immediately following

an acute resistance exercise bout with a reduced SV but a maintenance of EF. Although no significant reduction in EDV was observed in the present study, the trend towards a decrease in both groups would suggest a slight reduction in preload post exercise. Whilst there was much similarity in the cardiac response to the exercise bout in both groups there was a significant difference between group in rotation rate during systole with an increase seen in the AS group and a decrease in the NAS group. With the maintenance of systolic output, it could be suggested that in the AS group there was a compensatory increase in myocardial contraction to maintain cardiac output. This would indicate a maintenance of LV contractility in both groups subsequent to resistance exercise. A lack of systolic “cardiac fatigue” is also supported by no change in systolic tissue velocities and ϵ post-exercise and whilst this was also reported by Stephenson et al. (2015) this is the first study to examine these effects in AS users. Once again it is also worth noting that the total exercise volume may not be substantial enough to produce a noticeable systolic cardiac fatigue (Oxborough et al. 2012).

Post-exercise there was evidence of changes in LV diastolic function with reductions in E:A and E':A' in both groups. Increases in late diastolic filling as well as decreases in both E and E' were observed. This suggests that both early diastolic filling (active relaxation and suction) and atrial contraction (atrial contractility and ventricular compliance) may be altered with such exercise which is in agreement with previous findings [5]. Whilst previous data have suggested a reduction in diastolic function in AS users [13], the lack of significant difference may be in part due to the limited sample size used in the present study . The current study found an increase in longitudinal and radial strain rate in late diastole and systole respectively. In addition,

rotation rate in late diastole was also elevated post exercise suggesting the increase in late atrial filling was facilitated by an increased LV compliance. It is worth noting that isolated changes in diastolic function after acute exercise have been reported after shorter duration/volume endurance exercise studies [23] and may reflect the fact that early diastolic function is largely dependent on a small mass of longitudinally aligned sub-endocardial LV cardio-myocytes. A smaller mass of myocytes may be more prone to fatigue after exercise imposition [24]. Interestingly, Shave et al [25] suggested, in a meta-analysis, that diastolic functional changes after acute exercise bouts were not as influenced by exercise duration (total cardiac work) as systolic function. Previous findings have indicated a reduced diastolic function in AS users however this hasn't been demonstrated in the present study. Previously observed reductions in diastolic function may be associated with supraphysiological levels of circulating serum testosterone [13]. However, previous findings have demonstrated a reduction in diastolic function with lower circulating levels of testosterone [26]. Together, this may suggest that testosterone levels outside of physiological levels could have a negative impact on cardiac diastolic function.

The mechanisms that underpin a depression in diastolic function following a single resistance exercise bout are currently unclear, however a number of ideas have been proposed. A depression caused by ischemia has been suggested by many [27] yet there was no evidence of ischemia in the present study. Desensitisation or down-regulation of Beta-adrenergic cardiac receptors has also been proposed as a possible mechanism for reduced chronotropic or inotropic drive post prolonged exercise [28]. This has been seen following exercise significantly longer in duration than that used in the present study where catecholamine's would be chronically elevated for hours. In

addition, an increase in collagen cross-links between myocytes has also been suggested as a possible mechanism for reductions in diastolic function [17, 29]. Much of this remains as speculation with further work required to fully elucidate the mechanism(s) responsible for post-exercise depressions in cardiac function.

Whilst ε and SR data is increasingly being used as a method for quantifying regional myocardial function in both clinical and research settings, its application in AS users still remains limited. The narrow data set available for many ε and strain rate parameters in AS users and the lack of consistency can make comparison difficult however the inclusion of these parameters may give a better representation of actual tissue contraction. Nonetheless, previous findings have suggested a decrease in radial ε in AS users however the present findings do not suggest that this was the case for the present cohort and that this difference is not borne out by a bout of resistance exercise [13, 14].

The appearance of biomarkers of cardiac cell damage (cTnI) or stress (NT-proBNP) in the present study were limited, small and likely of little clinical significance [30]. Elevated cTnI was observed in one AS participant at rest and post-exercise. Data from previous studies have suggested that endurance exercise trials and short high-intensity running can elicit an acute release of cTnI. The exercise protocol used in the present study reflects the intermittent nature of resistance training and it may be that it provides insufficient cardiac stress to activate processes that lead to the appearance of markers of cardiac damage [24]. Although baseline measures of NT-proBNP were slightly elevated in the AS group at baseline, the changes following exercise were

small and similar between the two groups. Once again, this suggests that the workload of the exercise protocol may be of insufficient intensity, duration or total work to induce cardiac stress.

As with any study in to the effects of AS use there are inherent limitations. The heterogeneity of subjects including variations in age, training status and diet can complicate the interpretation of findings. Further, the inter and intra-individual differences in AS dose and history as well as variations in 'stacks', 'cycles' and post-cycle therapies can complicate data interpretation in this group. Whilst many AS users have been using AS for much longer than the 2 year minimum for inclusion within the study, recruitment of any AS users is problematic and so only recruiting from those with significantly longer AS usage would have limited participation even more. However, the relatively small population of AS users and the clandestine nature of the group make recruitment difficult. Due to the limited data available, information on any AS users helps inform the very limited literature. The low number of participants and the clandestine nature of AS users also causes problems with interpretation due to the possibility of participant self-selection bias. Due to limitations of time and scanning options, no measures of left atrial volume were taken. Future studies should look to incorporate a left atrial measure to further help the understanding of changes to diastolic function. The limited number of blood sampling points and the lack of measurement of androgen levels including serum testosterone, also restricts the overall interpretation of the blood data. An increase in the number of testing points post exercise would help further understanding of the possible appearance of cardiac biomarkers post-resistance exercise. However, whilst the inclusion of serum androgen

levels would have aided the understanding of the findings, these findings are still a positive step forward in understanding the impact of AS use on cardiac function.

In conclusion, the present data has reported a number of novel measures of cardiac function as well as biomarkers of cardiac damage and stress in AS users following an acute bout of exercise. Despite alterations in diastolic function post-exercise, the changes were similar in both groups with global systolic function also maintained. The lack of meaningful changes in cardiac biomarkers adds to the conclusion that both AS and NAS groups coped with the cardiovascular stress induced by the current exercise protocol with some ease.

Disclosure Statement

The authors report no conflict of interest.

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