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ANABOLIC STEROID ABUSE IS ASSOCIATED WITH DYSFUNCTION OF THE AUTONOMIC SYSTEM

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ABSTRACT

The purpose of this study was to evaluate whether AAS abuse can induce cardiac autonomic dysfunction in trained individuals after a session. Employing a quasi-experimental design, 17 healthy men were divided into two groups: users of AAS (n=7), who reported self-administration for at least two years and non-users of AAS (n=10). All subjects performed an acute strength-training session consisting of three sets of 10 repetitions at 70% of 1RM for four exercises (bench press, leg press, seated row and leg extension), with an inter set rest interval of 60 seconds. HRV measurements were taken pre, post and during a 60-minute post-exercise recovery period. Results showed that AAS users had lower values for standard deviation of the NN intervals and root mean squared successive differences when compared to the non-AAS users Pre the resistance exercise. However, immediately after the resistance training, all indexes in the time domain, non-linear and symbolic analysis were similar between AAS and NAAS. We conclude that the use of AAS is consistent with a dysfunction of the autonomic system.

Key words: Cardiovascular. Exercise. Endocrinology. Metabolism.

RESUMO

O uso abusivo de esteroides anabolizantes está associado à disfunção do sistema nervoso autônomo

O objetivo deste estudo foi avaliar se o uso de esteroides androgênicos anabolizantes (AAS) pode induzir disfunção autonômica cardíaca em indivíduos treinados após uma sessão de exercício. Utilizando um delineamento quase-experimental, 17 homens saudáveis foram divididos em dois grupos: usuários de AAS (n=7), que relataram autoadministração por pelo menos dois anos, e não usuários de AAS (n=10). Todos os participantes realizaram uma sessão aguda de treinamento de força composta por três séries de 10 repetições a 70% de 1RM, em quatro exercícios (supino reto, leg press, remada sentada e extensão de pernas), com intervalo de 60 segundos entre as séries. As medições de variabilidade da frequência cardíaca (HRV) foram feitas antes, imediatamente após e durante um período de recuperação de 60 minutos após o exercício. Os resultados mostraram que os usuários de AAS apresentaram valores mais baixos para o desvio padrão dos intervalos NN e diferenças quadráticas médias sucessivas em comparação com os não usuários de AAS antes do exercício resistido. No entanto, imediatamente após o treino, todos os índices no domínio do tempo, análise não linear e análise simbólica foram semelhantes entre usuários e não usuários. Concluímos que o uso de AAS está associado a uma disfunção do sistema autonômico.

Palavras-chave: Cardiovascular. Exercício. Endocrinologia. Metabolismo.

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INTRODUCTION

The health benefits of resistance training (RT) are well-established (Corso et al., 2022).

Higher levels of muscular strength are associated with significantly lower cardiometabolic risk factors (Artero et al., 2012), lower risk of all-cause mortality, fewer cardiovascular disease events, and lower risk of developing functional limitations and nonfatal disease (Heffernan, et al., 2006).

However, these benefits potentially can be impaired by the abuse of anabolic-androgenic steroids (AAS), a family of hormones that includes the natural male hormone testosterone, together with numerous closely related chemical relatives (Pope e Brower, 2009). All AAS possess both anabolic (muscle-building) and androgenic (masculinizing) properties, and they affect a wide range of physiological systems.

AAS compounds are synthetic androgens commonly used by athletes to increase physical strength, endurance, and power, as well as to modify vascular function (Barbosa Neto et al., 2018).

A meta-regression of 187 studies that assessed the overall prevalence of AAS concluded that non-medical AAS use is a serious, public health problem with a high prevalence in the general population. This rate is significantly higher among men (6.4%) than women (1.6%) and has a higher regional prevalence among people in the Middle East (21.7%).

The highest prevalence is among recreational sportsmen (18.4%) and in individuals aged 19 years or less (2.5%) (Sagoe et al., 2014).

To minimize the possible side effects of AAS use, and consequently improve muscular gains, AAS users often administer these substances in cycles (Hartgens e Kuipers, 2004).

AAS cycling commonly consists of periods of chronic administration (often 5-10 weeks), alternated with similar periods of discontinued use (Parkinson e Evans, 2006; Mullen et al., 2020).

Positive effects of AAS use include improvements in muscle protein metabolism, bone metabolism, and cognitive function (Graham et al., 2008).

However, adverse effects, mainly related to continuous use without medical supervision, have also been described including conditions of the cardiovascular, liver, endocrinological, behavioral, and dermatological systems (Goldman e Basaria, 2018) as well as reproductive issues such as testicular atrophy and infertility (El Osta et al., 2016).

The prolonged misuse and abuse of AASs can lead to several adverse effects, even fatal, especially the ones regarding the cardiovascular system because chronic administration of high doses of AASs is responsible for the dysfunction in tonic cardiac autonomic regulation (Albano et al., 2021).

The prevalence and underlying mechanisms of AAS-induced cardiovascular toxicity remain poorly understood, but it appears that AAS may be directly toxic to cardiac tissue, resulting in a cardiomyopathy characterized by impaired systolic and diastolic function (Kanayama, Hudson e Pope, 2008; Baggish et al., 2010).

Rodent research indicates that chronic administration of supraphysiological doses of AAS impairs tonic cardiac autonomic regulation (Pereira-Junior et al., 2006).

Beutel et al., (2005) sugerem que ratos experimentam alterações variadas no controle reflexo da frequência cardíaca com diferentes doses de estanozolol. Studies in humans provide evidence that AAS self-administration increases muscle sympathetic nerve activity (MSNA) (Alves et al., 2010), which seems to have hemodynamic implications. Systolic and diastolic blood pressure levels are higher in AAS users than non-users (Junior et al., 2018).

Heart rate reduction after an exercise bout has been associated with autonomic function, especially cardiac vagal recovery (Cole et al., 1999).

Moreover, heart rate recovery (HRR) is a useful tool for risk factor stratification and is considered an independent predictor of mortality (Cole et al., 1999).

Alves et al., (2010) encontraram que a frequência cardíaca de repouso e a MSNA eram mais altas em usuários de AAS, o que favorece a possibilidade de desequilíbrio autonômico cardíaco, que pode ser avaliado por meio da variabilidade da frequência cardíaca (HRV) (Corso et al., 2022; Heffernan et al., 2006; Barbosa Neto et al., 2018).

HRV is defined as fluctuations in the intervals between R waves. When HRV is increased, it reflects a more efficient autonomic system. This efficiency is driven by positive

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changes in vagal tone, which are observed during the post-exercise hemodynamic recovery period.

Acutely, RT promotes a decrease in HRV, characterized by an increase in sympathetic tone and a reduction in vagal tone, as previously reported in studies evaluating different strength training protocols (Ie Iellamo et al., 2019; Paz et al., 2019).

These acute autonomic responses are distinct from those typically observed in aerobic training, which is associated with increased vagal tone (Junior et al., 2018).

However, evidence suggests that RT may contribute to cardiovascular health over time through chronic adaptations, even though the mechanisms underlying these effects remain unclear (Corso et al., 2022).

Research has established a strong link between autonomic dysfunction and chronic degenerative diseases, as well as increased mortality risk (Papaioannou, Pneumatikos e Maglaveras, 2013).

While evidence from aerobic training demonstrates the potential to mitigate cardiovascular risk through improved autonomic function (Furlan et al., 1993), further studies are required to determine if RT induces similar benefits, even in AAS users.

The mechanisms underlying the cardiac autonomic dysfunction observed post-resistance exercise in AAS-abusing individuals remain unknown.

Despite the adverse cardiovascular effects of high doses of AAS, few studies have used HRV analysis to assess cardiac autonomic dysfunction risk associated with AAS abuse (Kouidi et al., 2021; Júnior et al., 2021).

Kouidi et al., (2021) avaliaram o controle autonômico em resposta a mudanças posturais usando o teste de inclinação ortostática (head-up tilt test), enquanto Júnior et al., (2021) investigaram respostas autonômicas após exercício aeróbio.

However, to the best of our knowledge, we found no studies that evaluated autonomic responses after RT, which is the main type of training used by AAS users. In this context, the proposed study advances by exploring acute autonomic responses in these individuals after a RT session, contributing to fill this gap in literature.

Accordingly, this study aimed to evaluate whether AAS abuse induces cardiac autonomic dysfunction after a strength training session in a cohort of aspiring bodybuilders.

MATERIALS AND METHODS

Ethical approval

The experimental protocol received approval from the ethics board of the Federal University of Piauí (approval number: 2.402.659).

All volunteers were informed of the risks and benefits of study before any data collection and then signed an institutionally approved informed consent document. No clinical problems occurred during the study.

Participants

Seventeen young, resistance-trained men who self-reported training at least three times a week for a minimum of six months volunteered to participate in this study. Seven participants were AAS users (21 ± 1 years) and ten were non-AAS users (23 ± 3 years). Participants in the AAS user group, athletes in the Men's Physique novice category, reported self-administering for at least two years; all were between 2 and 7 weeks into their present cycle.

Table 2 displays the baseline characteristics of the participants. No significant differences were observed between the groups in any anthropometric variable, although the AAS users were 8 kg heavier than control. Significant differences were found in the 1RM test for the bench press, leg press, seated row and leg extension favoring the AAS users.

With respect to AAS users, surveys and testing were completed during their cycle (2-7 weeks), with reported weekly doses ranging between 150-700 mg/week. In addition, all volunteers reported having previously completed 3-14 cycles.

The AAS most used by volunteers were: boldenone 200.00±100.00 mg/week (3 users), durateston 216.66±104.08 mg/week (3 users), testosterone 275.00±35.35 mg/week (2 users), oxandrolone 200 mg/week (1 user), testosterone cypionate 200 mg/week (1 user), testosterone enanthate 300 mg/week (1 user) and turinabol 210 mg/week (1 user).

Participants were excluded if they had any chronic degenerative disease, used any supplements or substances that could modify hemodynamic responses, or had any condition that could compromise their physical integrity or performance.

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All volunteers were informed of the risks and benefits of the study prior to data collection and then signed an institutionally approved informed consent document. No clinical problems occurred during the course of the study.

Study design

The study investigated HRV responses at baseline, pre, and after an RT session in aspiring bodybuilders using and not using AAS, employing a quasi-experimental design (figure 1).

Volunteers were selected from a convenience sample and submitted to a three-stage protocol, with a 72-hour interval between each visit:

Baseline assessment: During the first visit, volunteers underwent anamnesis and baseline assessment, which included the measurement of HRV variables, as well as weight and height for body mass index (BMI) calculation.

One-repetition maximum assessment: On the second visit, maximum dynamic strength was assessed through one-repetition maximum (1RM) tests for the exercises included in the RT protocol: bench press, leg press, seated row, and leg extension.

Intervention and reassessment: On the third visit, volunteers first underwent a pre-exercise HRV assessment. They then performed an acute RT session at 70% of their previously determined 1RM, which consisted of the same exercises used in the strength assessment.

Post-exercise HRV was measured immediately after the session and at 10, 20, 30, 40, 50, and 60 minutes during the recovery period. All procedures were performed in the afternoon between 12:00 and 04:00 pm at a fitness facility.

Figure 1 provides a flow chart of the experimental design.

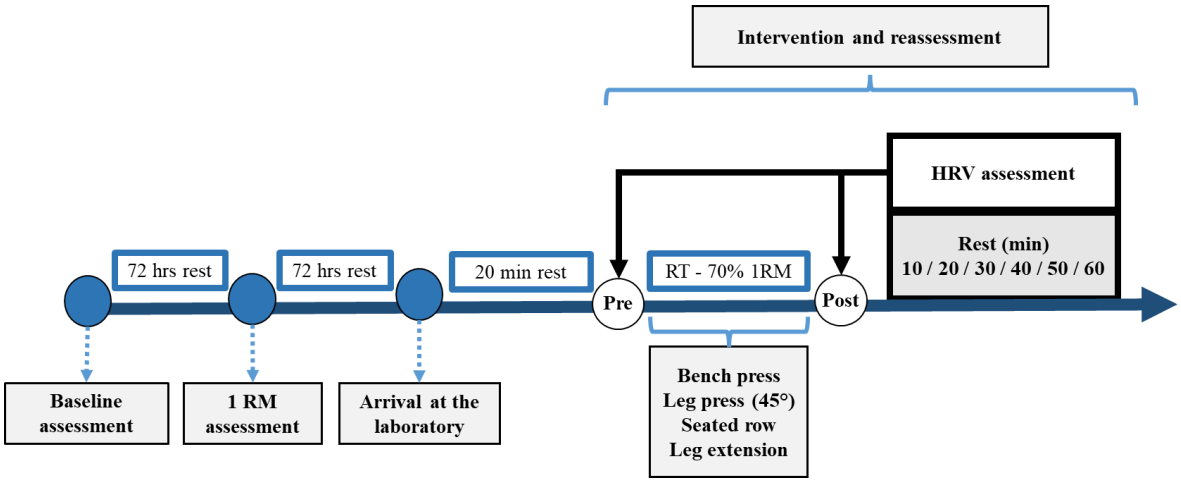

Figure 1 - Experimental design for the evaluation of heart rate variability (HRV) responses pre, during, and after resistance training in users and non-users of anabolic-androgenic steroids (AAS).

Participants answered the Physical Activity Readiness Questionnaire to assess contraindications for participation (American College of Sports Medicine, 2012).

After determining 1RM, participants were instructed not to perform any structured physical activity during the 24 hours preceding the assessment of HRV and participation in the RT protocol.

During this 24-hour period, the volunteers did not follow a standardized diet but were instructed to avoid any ergogenic foods or autonomic modulating foods such as coffee, tea, soda, energy drinks, alcoholic drinks, chocolates, and energy bars.

Maximal Dynamic Strength (One Repetition Maximum)

The RT protocol encompassed four exercises targeting large muscle groups in the following order: bench press, leg press, seated

row and leg extension (Technogym ®, Biomedical Line, Gambettola, FC, Italy).

To determine maximum dynamic strength, we used a 1RM test for each of these exercises following previously established and validated recommendations (Brown e Weir, 2001; Grgic et al., 2020).

The order of the exercises in the 1RM tests was the same as the RT protocol for all volunteers.

This choice was made to maximize participants' familiarity with the protocol and ensure consistency in results between individuals, a procedure like previous studies (Prestes et al., 2009; Silva et al., 2024).

Therefore, the 1RM tests were performed on the same day with a minimum of 10 minutes rest between exercises. After a general warm-up (10 minutes of low-intensity treadmill running), subjects performed 2 sets of a specific warm-up, the first for 8 repetitions at an estimated 50% 1RM for the given exercise using each subject's previous training experience as a guide, and after 1 minute rest, a set of 3 repetitions with an estimated 70% 1RM.

After a 3-minute rest period, subjects performed single repetitions with progressively heavier weights until the 1RM was determined within 3-5 attempts (with standardized range of motion and exercise techniques), with 3- to 5-minute rest periods between trials. This protocol was adapted from Brown e Weir (2001) e Abad et al., (2011) para aproximar a rotina de treino dos voluntários.

Research assistants verbally encouraged the participants to exert maximal force during each trial. The test was terminated when participants failed to complete the movement or when a voluntary concentric failure occurred (inability to perform the concentric phase of movement).

Resistance Training

Both groups performed the same RT session consisting of four exercises (bench press, leg press, seated row and leg extension). Three sets of 10 repetitions at 70% of 1RM were performed for each exercise.

The volume performed during the experimental session was standardized and the same for both groups, 120 reps (3 sets × 10 reps × 4 exercises).

A 1-minute rest interval was allowed between sets. This protocol is adapted from a previous study suggesting that a similar configuration can effectively promote neuromuscular adaptation in trained individuals (Lopes et al., 2014).

Measurements of heart rate were taken at baseline, pre and during exercise, and at 10-minute intervals during passive recovery up to 60 minutes post-exercise (Figura 1).

Data acquisition and pre-processing

RR intervals for HRV assessment were obtained and recorded using the Polar V800 heart rate monitor (Polar Electro In., Finland), previously validated for beat-to-beat capture (Giles, Draper e Neil, 2016).

Data were obtained with participants resting quietly in the supine position, and the test lasted approximately 5 minutes (Ziegler et al., 2015).

To ensure standardization and data quality (Catai et al., 2020), participants were instructed to avoid caffeine, nicotine, alcohol, and intense physical exercise in the 24 hours prior to the test, as well as to have a good night's sleep the night before.

The test was conducted in a quiet environment with a controlled temperature between 20-24°C, and participants remained in a supine position for 15 minutes prior to data acquisition to allow stabilization of physiological variables.

During data collection, no distractions, conversations, or movements were permitted, and any events such as coughing or sneezing were recorded.

Breathing was spontaneous, and participants' health status was verified on the day of the test to ensure data accuracy.

The data were extracted and converted into text with the Polar ProTrainer software (Polar Electro In., Finland). The analysis methods, HRV metrics and their respective physiological meanings (Shaffer e Ginsberg, 2017) are presented in Table 1.

In summary, the initial and final records were disregarded so that only 300 heartbeats were analyzed by the HRV software HRVAnalysis v1.2 (50% overlap, 1000 Hz sampling rate, 4 Hz interpolation, ANS Lab Tools) (Pichot et al., 2016). HRV was analyzed according to linear and non-linear methods.

Time domain (expressed in milliseconds) measurements included mean RR interval; standard deviation of the NN intervals (SDNN); root mean squared successive

differences (RMSSD) between adjacent normal RR intervals; percentage of adjacent RR intervals differing by >50ms (pNN50); and the triangular index.

A symbolic analysis was performed according to Guzzetti et al., (2005) that used selected 5 mins of RR intervals. A graining approach was used based on a uniform quantization procedure to transform the RR intervals into a sequence of symbols. The length (L) was fixed in all analyses. The full range of sequences was spread over six different levels (from 0 to 5), and patterns of length L = 3 were built. Each subject and each experimental condition had its specific range of RR intervals.

The Shannon entropy was calculated to provide the complexity of the distribution. The sequences were divided over six levels, and all patterns divided into three groups, consisting of patterns with: 1) no variation (0V, three equal symbols); 2) one variation (1V, two equal symbols and one different); 3) two variations (2V).

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For the beat-by-beat quantitative analysis of HRV, the Poincaré Plot diagram (a scatter plot in which each R-R interval is plotted as a function of the previous one) is useful for both qualitative and quantitative assessments (Woo et al., 1994; Tulppo et al., 1996).

Qualitatively, it provides a visual representation of the complexity of R-R interval variability (Woo et al., 1994). Quantitatively, as described by Tulppo et al., (1996), it allows the calculation of the standard deviation of instantaneous beat-to-beat variability (SD1) and the standard deviation of continuous long-term R-R intervals (SD2).

Both SD1 and SD2 are reported in absolute values and normalized units (SD1n and SD2n), which are obtained by dividing the absolute value by the mean R-R interval and multiplying by 1000.

Table 1 - Physiological meaning of HRV metrics across different analysis methods.

Analysis method	Analyzed variables	Physiological meaning
Time domain	- Mean RR interval	Represents the average time between successive heartbeats. It is directly related to heart rate, with higher values indicating lower heart rate and potentially greater vagal influence.
	- SDNN	Measures overall heart rate variability over time. It reflects the activity of all autonomic influences on the heart and is related to the body's ability to respond to internal and external stimuli.
	- RMSSD	Assesses short-term variability of RR intervals, serving as a reliable marker of parasympathetic activity. Higher values are associated with greater vagal modulation and efficient autonomic recovery.
	- pNN50	Measures the proportion of RR interval pairs that differ by more than 50ms. It is strongly related to vagal modulation and rapid parasympathetic response.

	- Triangular index	An index based on the distribution of RR intervals over time, reflecting the complexity and amplitude of heart rate variability. Higher values indicate greater variability and better autonomic adaptability.
Symbolic analysis	- 0V%	Represents RR patterns without variation between consecutive beats, indicating sympathetic predominance. Increased values are associated with enhanced sympathetic activity and reduced vagal modulation.
	- 1V%	Indicates the presence of a single variation within the sequence of beats, reflecting the interaction between sympathetic and parasympathetic activities. Intermediate values suggest autonomic balance.
	- 2V%	Represents patterns with greater variation within the RR sequence, acting as a strong marker of parasympathetic modulation. Higher values are associated with increased vagal influence and better autonomic regulation.
	- Shannon entropy	Measures the complexity of RR pattern distribution, reflecting the variability and adaptability of the autonomic system. Higher entropy suggests a more dynamic and responsive autonomic system.
Quantitative analysis (Poincaré plot)	- SD1	Measures the perpendicular dispersion to the line of identity in the Poincaré plot, serving as a specific marker of parasympathetic modulation and the rapid response of the autonomic nervous system. Lower values indicate reduced autonomic variability.
	- SD2	Measures dispersion along the line of identity in the Poincaré plot, reflecting long-term variability. It is associated with overall autonomic balance and the cardiovascular system's ability to adapt to different physiological conditions.

Table 1 - Mean RR interval: average time between successive R-R intervals; SDNN: standard deviation of NN intervals recorded over a period of time (ms); RMSSD: root mean squared successive differences between adjacent normal R-R intervals (ms); pNN50: percentage of adjacent R-R intervals differing by more than 50 ms; Triangular Index: measure based on the density distribution of R-R intervals; 0V%: no variation (three equal symbols, sympathetic modulation); 1V%: one variation (two equal symbols and one different, sympathetic and parasympathetic modulation); 2V%: two variations (parasympathetic modulation); Shannon entropy: complexity of R-R interval distribution; SD1: standard deviation of instantaneous beat-to-beat variability; SD2: standard deviation of continuous long-term R-R intervals.

Statistical Analyses

Data are presented as frequencies, means, standard deviations, confidence intervals and effect sizes (ES). The Shapiro-Wilk test and Levene were used to verify the data normality and homogeneity, respectively. Baseline characteristics of AAS and NAAS were compared with the t-test for independent samples. A split-plot analysis of variance with interactions within- and between-factors followed was used to compare time points

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between groups. When the variables did not show sphericity through the Mauchly test, the Geisser-Greenhouse correction was employed.

The Bonferroni post hoc was used to verify the multiple differences between the times pre, post, 10, 20, 30, 40, 50, and 60 minutes after resistance exercise in both AAS and NAAS groups.

The magnitude of the changes was assessed using ES according to the recommendations from Rhea (2004). Threshold values were as follows: trivial (<0.50), small (0.5 to 1.25), moderate (1.26 to 1.9), and large (>1.9). Results were considered significant at $P < 0.05$. All statistical analyses were performed using SPSS version 22 (IBM Corp, Armonk, NY), and GraphPad Prism version 8.0.0 for Windows, (GraphPad Software, San Diego, CA).

RESULTS

Table 2 presents the baseline characteristics of the participants. Individuals in the AAS group demonstrated significantly higher 1RM performance in the bench press, leg press, and leg extension compared to the NAAS group. However, no significant differences were observed between the groups in heart rate variability parameters, including time-domain and non-linear indices, at baseline assessments.

Table 2 also includes anthropometric variables such as age, weight, height, and BMI, which did not differ significantly between the groups.

Table 2 - Baseline characteristics.

Variables	NAAS (n=10)	AAS (n = 7)	p	ES
Age (years)	23.0 ± 3.0	21.0 ± 1.0	0.37	0.89
Weight (kg)	76.9 ± 9.3	84.8 ± 7.9	0.08	0.91
Height (cm)	1.7 ± 0.1	1.7 ± 0.1	0.47	2.48
BMI ($kg.m^{-2}$)	26.8 ± 3.4	28.6 ± 3.0	0.28	0.55
Bench press / 1RM (kg)	74.0 ± 15.0	92.0 ± 15.0	0.04*	1.20
Leg press / 1RM (kg)	232.0 ± 62.0	319.0 ± 75.0	0.04*	1.26
Seated Row / 1RM (kg)	111.0 ± 39.0	131.0 ± 23.0	0.24	0.62
Leg extension / 1RM (kg)	72.0 ± 9.0	95.0 ± 17.0	0.02*	1.69
Heart rate variability				
Heart rate (bpm)	77.8 ± 12.6	81.86 ± 13.5	0.52	
Mean RR (ms)	797.6 ± 124.8	758.66 ± 116.5	0.54	
SDNN (ms)	78.6 ± 38.9	77.91 ± 38.9	0.97	
RMSSD (ms)	45.1 ± 16.8	41.54 ± 19.2	0.69	
pNN50 (ms)	22.0 ± 14.5	20.9 ± 15.1	0.87	
VLF (ms2)	2505.6 ± 2530.3	4524.1 ± 5531.9	0.32	
LF (ms2)	1858.1 ± 889.0	1898.0 ± 957.6	0.93	
HF (ms2)	699.4 ± 421.9	717.9 ± 542.8	0.94	
LF/HF (ms2)	3.7 ± 3.0	4.4 ± 3.9	0.67	
SD1	31.9 ± 11.9	29.4 ± 13.1	0.69	
SD2	102.5 ± 52.7	105.9 ± 54.1	0.90	
shaEn	3.2 ± 0.3	3.4 ± 0.3	0.11	
apEn	1.1 ± 0.1	1.1 ± 0.21	0.66	

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Data are presented as mean ± standard deviation. NAAS: non-users of anabolic-androgenic steroids; AAS: users of anabolic-androgenic steroids; n: sample size; p: significance level; ES: effect size; BMI: body mass index; 1RM: one-repetition maximum; SDNN: standard deviation of NN intervals; RMSSD: root mean squared successive differences; pNN50: percentage of adjacent RR intervals differing by >50 ms; VLF: very low frequency; LF: low frequency; HF: high frequency; SD1: short-term HRV variability; SD2: long-term HRV variability; shaEn: Shannon entropy; apEn: approximate entropy. p<0.05.

In the symbolic analysis, users exhibited higher values of sympathetic modulation (0V% index) compared to non-users at pre RT session.

Post RT, 0V% remained higher in users at 50 and 60 minutes compared to non-users. Regarding parasympathetic modulation (2V% index), users showed lower values than non-users at pre. However, post-exercise, 2V%, was similar between groups across all analyzed periods.

These findings highlight the influence of anabolic-androgenic steroids (AAS) on autonomic modulation at pre and during recovery after RT session (table 3).

Table 3 - Symbolic analysis (0V%, 1V%, and 2V%) over time in users and non-users of AAS pre and post resistance training session.

Variables	Pre	Post	10 min	20 min	30 min	40 min	50 min	60 min
Non-Users								
0V%	31±7	71±7$^{\#}$	58±1$^{\#}$	65±8$^{\#}$	62±12$^{\#}$	54±10$^{\#\dagger}$	55±8$^{\#\dagger}$	51±7$^{\#\dagger}$
	(25;37)	(65;77)	(48;68)	(58;71)	(52;72)	(46;62)	(48;61)	(46;57)
1V%	45±4	24±7	35±3	28±4$^{\#}$	32±4$^{\#}$	37±5$^{\#}$	37±6$^{\#}$	38±3$^{\#}$
	(42;48)	(18;29)	(33;37)	(25;31)	(29;35)	(32;41)	(32;41)	(36;41)
2V%	25±6	5±2$^{\#}$	6±1$^{\#}$	7±3$^{\#}$	7±2$^{\#}$	8±3$^{\#}$	7±2$^{\#}$	9±2$^{\#\dagger}$
	(20;30)	(3;7)	(5;7)	(4;9)	(5;9)	(5;10)	(5;8)	(8;11)
Users								
0V%	40±14*	65±7$^{\#}$	59±9$^{\#}$	60±9$^{\#}$	64±14$^{\#}$	60±9$^{\#}$	59±12$^{\#*}$	60±14$^{\#*}$
	(25;55)	(57;72)	(50;68)	(51;70)	(49;78)	(51;69)	(47;71)	(45;75)
1V%	42±8	27±10	29±9	32±5	28±11	35±7	32±8	31±11
	(34;50)	(16;37)	(19;39)	(27;38)	(16;38)	(28;42)	(24;40)	(20;43)
2V%	15±5*	7±1$^{\#}$	6±2$^{\#}$	7±2$^{\#}$	7±5$^{\#}$	6±2$^{\#}$	8±5$^{\#}$	6±4$^{\#}$
	(10;20)	(6;8)	(4;8)	(6;9)	(2;13)	(3;8)	(2;12)	(2;10)

Data are presented as mean ± standard deviation (confidence interval). Statistical differences: * indicates vs. non-users in the same period; # indicates vs. pre-exercise; † indicates vs. post-exercise.

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In the symbolic analysis, users exhibited higher values of sympathetic modulation (0V% index) compared to non-users at pre RT session. Post RT session, 0V% remained higher in users at 50 and 60 minutes compared to non-users. Regarding parasympathetic modulation (2V% index), users showed lower values than non-users at pre RT session.

However, post RT session, 2V%, was similar between groups across all analyzed periods. These findings highlight the influence of anabolic-androgenic steroids (AAS) on autonomic modulation at pre and during recovery after RT session (table 4).

Table 4 - Effect sizes (IC95%) of time-course comparisons for heart rate variability indices between users and non-users of AAS pre and post resistance training session.

Variables	Pre Versus Pre	Post Versus Post	10 min versus 10 min	20 min versus 20 min	30 min versus 30 min	40 min versus 40 min	50 min versus 50 min	60 min versus 60 min
TIME DOMAIN								
SDNN (ms)	0.93 (0.78-1.08) (small)	0.86 (0.71-1.01) (small)	zero (-0.40-0.40)	0.56 (0.31-0.71) (small)	0.91 (0.76-1.06) (small)	1.04 (0.89-1.19) (small)	0.95 (0.80-1.10) (small)	1.22 (1.08-1.37) (small)
RMSSD (ms)	1.00 (0.69-1.31) (small)	0.33 (0.02-0.64) (trivial)	0.20 (-0.11-0.51) (trivial)	0.33 (0.02-0.64) (trivial)	0.82 (0.51-1.32) (small)	1.22 (0.91-1.53) (small)	1.20 (0.94-1.49) (small)	1.11 (0.80-1.42) (small)
NON-LINEAR								
SD1 (ms)	0.96 (0.69-1.23) (small)	zero (-0.45-0.45)	0.33 (0.07-0.60) (trivial)	0.50 (0.23-0.77) (small)	0.88 (0.61-1.49) (small)	1.17 (0.90-1.44) (small)	1.29 (1.02-1.56) (moderate)	1.17 (0.90-1.44) (small)
SD2 (ms)	3.17 (2.50-3.84) (large)	0.90 (0.22-1.58) (small)	zero (-0.51-0.51)	0.52 (-0.15-1.19) (small)	0.94 (0.26-1.61) (small)	0.74 (0.01-1.42) (small)	0.65 (0.03-1.32) (small)	1.28 (0.60-1.96) (moderate)
SYMBOLIC								
0V%	1.29 (0.98-1.60) (moderate)	0.86 (0.55-1.17) (small)	0.08 (-0.23-0.39) (trivial)	0.63 (0.31-0.94) (small)	0.17 (-0.14-0.48) (trivial)	0.60 (0.28-0.91) (small)	0.50 (0.18-0.81) (small)	1.29 (0.97-1.60) (moderate)
1V%	0.75 (0.32-1.17) (small)	0.43 (0.01-0.85) (trivial)	0.71 (0.29-1.13) (small)	1.00 (0.58-1.42) (small)	1.00 (0.49-1.50) (small)	0.40 (-0.02-0.82) (small)	0.83 (0.41-1.25) (small)	2.33 (1.91-2.75) (large)
2V%	1.67 (1.20-2.14) (moderate)	1.00 (0.53-1.47) (small)	zero (-0.48-0.48)	zero (-0.39-0.39)	zero (-0.53-0.53)	0.67 (0.20-1.14) (small)	0.50 (0.09-0.97) (small)	1.50 (1.03-1.97) (moderate)

SDNN: standard deviation of the NN intervals; RMSSD: root mean squared successive differences; SD1: standard deviation of the instantaneous beat-to-beat variability; SD2: standard deviation of the continuous long-term R-R intervals. Effect sizes are categorized as trivial, small, moderate, or large based on standard thresholds. Comparisons are made across time points and between groups (users and non-users of anabolic steroids).

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Figure 2 illustrates the differences in temporal recovery among the groups across each analyzed variable. Immediately post RT session, both NAAS and AAS groups exhibited significant decreases in mean RR (Figure 2A), RMSSD (Figure 2C), and pNN50 (Figure 2D) compared to pre RT session values ($p<0.05$).
In the NAAS group, the mean RR (Figure 2A) remained significantly lower at 10, 20, 30, and 40 minutes post RT session but returned to baseline levels at 50 and 60 minutes. Additionally, mean RR values at 50 and 60 minutes were significantly higher compared to 10, 20, and 30 minutes post RT session ($p<0.05$).

Similarly, in the AAS group, mean RR (Figure 2A), RMSSD (Figure 2C), and pNN50 (Figure 2D) decreased significantly immediately post RT session, with values returning to baseline at 50 and 60 minutes. No significant differences between groups were observed for the time-domain indices (mean RR, SDNN [Figure 2B], RMSSD [Figure 2C], and pNN50 [Figure 2D]).

However, in the non-linear analysis, NAAS demonstrated significantly higher SD1 (Figure 2E) at 60 minutes compared to AAS ($p<0.05$).

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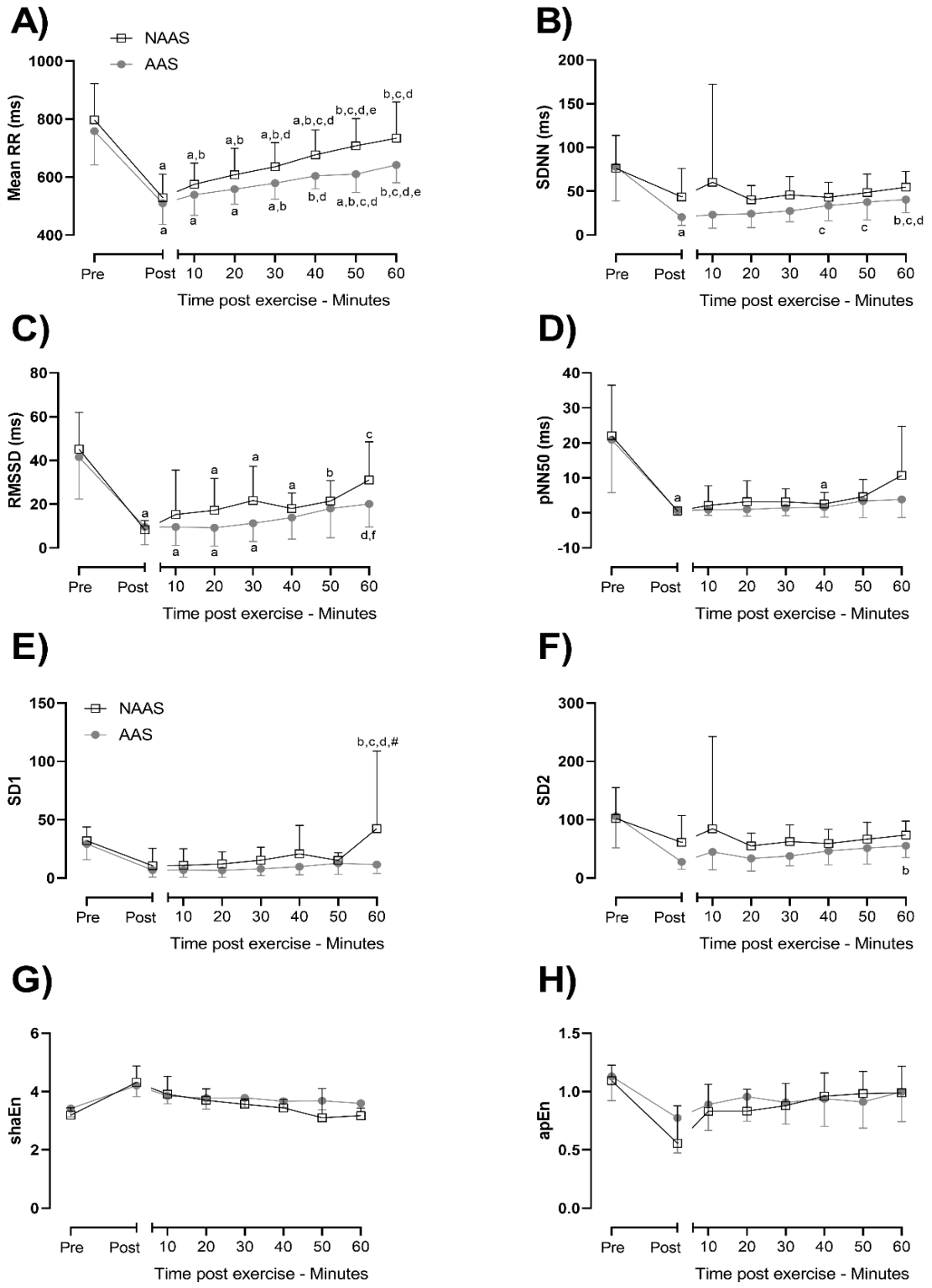

Figure 2 - Data are presented as mean ± standard deviation. NAAS: non-users of anabolic-androgenic steroids; AAS: users of anabolic-androgenic steroids; SDNN: standard deviation of NN intervals; RMSSD: root mean squared successive differences; pNN50: percentage of adjacent RR intervals differing by >50 ms; SD1: standard deviation of instantaneous beat-to-beat variability; SD2: standard

deviation of continuous long-term R-R intervals; shaEn: Shannon entropy; apEn: approximate entropy. Letters indicate statistically significant differences concerning the specified time points: a: vs. pre; b: vs. post; c: vs. 10 min post; d: vs. 20 min post; e: vs. 30 min post; f: vs. 40 min post; g: vs. 50 min post. #: indicates differences between groups at the same time point.

DISCUSSION

This study sought to evaluate if self-administered AAS use may induce cardiac autonomic dysfunction and altered autonomic recovery of HRV in recreationally trained men following a bout of resistance exercise. It was demonstrated that users of AAS exhibited autonomic dysfunction pre-exercise, with reduced HRV, characterized by greater sympathetic modulation and lower parasympathetic modulation compared to non-users.

However, after RT session, the HRV indices between the groups were similar, indicating that the acute impact of exercise was equivalent. These results highlight the effect of chronic AAS use on autonomic regulation at rest, without differences in immediate responses to exercise.

To our knowledge, few studies have investigated the post-exercise behavior of the autonomic variables by non-linear and symbolic evaluations in AAS users. Some authors have demonstrated that users of anabolic steroids have lower HRV and resting heart remodeling compared to non-users (Barbosa Neto et al., 2018; Kasikcioglu et al., 2009).

Our results demonstrated that AAS users exhibit significant autonomic dysfunction, as evidenced by reduced SDNN and RMSSD values post RT session, with delayed recovery compared to non-users (Figure 2B e 2C).

Additionally, symbolic analysis showed higher sympathetic modulation (increased 0V%) and impaired parasympathetic response (reduced 2V%) in AAS users during recovery (Tabela 3).

These findings align with previous studies that have consistently reported autonomic imbalances in AAS users. Santos, Oliveira e Silva (2014) observaram elevados valores de LF e LF/HF em usuários de AAS, indicativos de maior atividade simpática e aumento do risco cardiovascular.

Furthermore, parasympathetic control, measured by HF (nu), was found to be lower in AAS users, suggesting impaired vagal reactivation, as noted in other studies (Barbosa Neto et al., 2018; Santos, Oliveira e Silva, 2014).

These data corroborate the notion that AAS use is associated with long-term alterations in sympathovagal balance, reinforcing the cardiovascular risks linked to their use.

The autonomic dysfunction observed exclusively in AAS users, despite the similar behavior of SDNN and RMSSD indices between groups, may be explained by deeper alterations in autonomic modulation that are not fully reflected by these traditional metrics.

Although both groups exhibited significant reductions in SDNN and RMSSD after the RT session, AAS users showed a slower recovery of these indices, indicating a possible dysfunction in post-exercise autonomic control (Figura 2B e 2C). This reduced vagal reactivation capacity may be related to decreased baroreflex sensitivity, increased arterial stiffness, baseline sympathetic activity, and left ventricular hypertrophy, factors frequently associated with chronic AAS use that impair autonomic recovery following physical exertion (Albano et al., 2021; Kouidi et al., 2021).

Furthermore, symbolic analysis revealed important differences between groups, highlighting a significant increase in sympathetic modulation (higher 0V%) and a reduction in parasympathetic modulation (lower 2V%) in AAS users during recovery (Tabela 3).

This nonlinear approach has been identified as a more sensitive tool for detecting autonomic control patterns that may go unnoticed in traditional HRV analysis (Porta et al., 2007; Cysarz et al., 2015).

It has been previously reported that AAS users exhibit sustained sympathetic hyperactivity and reduced autonomic flexibility, which may contribute to an increased long-term cardiovascular risk (Fyksen et al., 2022).

Thus, the similarity in SDNN and RMSSD indices between groups does not necessarily indicate a preserved autonomic state in AAS users, as symbolic analysis demonstrated a post-exercise response pattern characterized by prolonged sympathetic predominance and reduced parasympathetic recovery.

Although the topic remains controversial, the deleterious effects of

indiscriminate use of AAS in supraphysiological doses include unfavorable changes in the lipid profile, reduced HRV (Kanayama, Hudson e Pope, 2008), negative modulation of the renin-angiotensin system and impaired sympathetic response, which may help to explain the reduction of variability and increase the risk of mortality (Kasikcioglu et al., 2009).

Supraphysiological AAS doses stimulate the renin-angiotensin system, thereby regulating the expression of angiotensinogen and renin mRNA, in addition to increasing the activity of angiotensin II and plasma renin and increasing the action of ANG II receptors (Chrostowski et al., 2011).

Moreover, high doses of plasma androgens increase the renal cortical expression of angiotensin-converting enzyme in rats (Roşca et al., 2016).

Autonomic dysfunction observed in AAS users was also reflected in post-exercise recovery. Although RMSSD (Figura 2C) returned to baseline more quickly in the AAS group (30 minutos) compared to the NAAS group (40 minutos), this does not indicate more efficient autonomic recovery. In fact, symbolic analysis (Tabela 3) revealed that AAS users maintained greater sympathetic modulation (increased 0V%) and lower parasympathetic recovery (reduced 2V%) throughout the recovery period.

Additionally, SDNN (Figura 2B), a global indicator of variability, also exhibited a slower recovery in AAS users. These findings suggest that, despite RMSSD behavior, autonomic recovery in AAS users was characterized by a less favorable sympathetic-parasympathetic balance, indicating a reduced capacity for efficient autonomic modulation.

Supporting these observations, prior studies have highlighted similar patterns in autonomic response following RT (Heffernan et al., 2006; Chen et al., 2011).

Heffernan et al., (2006) relataram maiores reduções na modulação vagal (HF power) 25 minutos após RT em comparação ao exercício aeróbio, utilizando um protocolo de oito exercícios a 10 repetições máximas com 90 segundos de descanso entre as séries.

Similarmente, Chen et al., (2011) observaram reduções significativas no HF power e aumentos no LFnu power após RT em homens jovens treinados, sugerindo uma predominância da atividade simpática. Esses estudos alinham-se com os nossos achados, enfatizando o impacto amplificado do RT sobre a recuperação autonômica em usuários de AAS.

Cole et al., (2000) observaram que a redução da frequência cardíaca logo após o término do exercício ocorre devido à diminuição da atividade simpática seguida por um aumento da atividade parassimpática.

Cole et al., (2000) acompanharam mais de 5000 adultos por 12 anos e monitoraram a recuperação da frequência cardíaca após um protocolo de esforço submáximo.

Os resultados mostraram que, entre os 312 voluntários que morreram durante o período do estudo, a recuperação anormal da frequência cardíaca foi um preditor significativo de mortalidade (risco relativo = 2,58) e manteve-se preditiva após ajuste para fatores de risco padrão, aptidão física, frequência cardíaca de repouso e durante o exercício (risco relativo ajustado = 1,55). Esses achados sugerem que o atraso na restauração da atividade do sistema nervoso autonômico pós-exercício pode estar associado a maiores chances de desenvolvimento de doenças cardíacas.

Despite the growing interest in the effects of AAS and RT on the autonomic nervous system, to the best of our knowledge, no studies have investigated autonomic responses using nonlinear and symbolic assessments, particularly after resistance exercise in AAS users. The existing literature predominantly focuses on traditional linear analyses of HRV (Kouidi et al., 2021; Porta et al., 2007; Maior et al., 2013).

However, symbolic analysis has shown significant potential in detecting subtle alterations in cardiac autonomic modulation. Symbolic analysis has been shown to outperform spectral analysis in assessing autonomic responses to the orthostatic tilt test, demonstrating greater sensitivity in detecting sympathetic-parasympathetic imbalances (Cysarz et al., 2015).

This approach is particularly suitable for evaluating subtle changes in cardiac autonomic modulation induced by a graded head-up tilt test (Porta et al., 2007). Thus, further studies are needed to explore autonomic responses using these more sensitive and informative methodologies in AAS users undergoing resistance exercise.

Some previous research indicates that AAS users have lower HRV and resting heart remodeling than non-users (Maior et al., 2013).

Our study expands on these findings, providing evidence about HRV responses in those who abuse AAS. These findings have potentially important implications as to the risk of cardiovascular disease in this population.

Consistent with our findings, research comparing the autonomic modulation of users and non-users of AAS found that users presented greater left ventricular hypertrophy, associated with greater sympathetic modulation, when compared to a group of non-using bodybuilders (Kouidi et al., 2021; Urhausen, Albers e Kindermann, 2004).

Our study has several limitations that must be considered when drawing practical inferences.

First, for ethical reasons, we were unable to perform a randomized study, and our quasi-experimental design introduces inherent bias in the sample. Second, our study is limited by the absence of a blood test to assess the level of blood testosterone; thus, we cannot draw dose-response conclusions from the data as to AAS use and HRV.

Third, the sample was relatively small and consisted of only men; more studies are needed with a larger number of volunteers of both sexes. Fourth, users self-reported their AAS types and dosages; it is therefore possible that some of the information may have been reported erroneously.

Fifth, to better clarify the role of AAS use in autonomic function, HRV response during the users off cycle should also be evaluated to more clearly elucidate the differences between the two periods.

Finally, other important limitations of the present study should be acknowledged. First, the use of a fixed order for performing the 1RM tests may have influenced the results due to the effects of accumulated fatigue, particularly in protocols with a larger number of exercises (more than five) (Figueiredo et al., 2016).

The decision to maintain a fixed order aimed to ensure participants' familiarity with the protocol and to provide greater consistency in data collection. However, to minimize the effects of fatigue and potential biases, we included only four exercises in our protocol.

Second, the absence of a test-retest procedure to assess the reliability of the 1RM measurements represents a limitation. Although validated methodological recommendations were followed for determining maximal strength (Brown e Weir, 2001; Grgic et al., 2020), incorporating a retest would have provided additional information on the reproducibility of the obtained values. Individual variability in 1RM testing can be influenced by factors such as motivation, technique consistency, and neuromuscular fatigue, underscoring the importance of including a reassessment protocol in future studies to improve measurement precision.

Third, the analysis of vagal response, measured by HRV, may have been influenced by factors that were not fully controlled in this study.

The AAS user group exhibited a potentially greater muscle mass (Tabela 2), which could have impacted metabolic demand and motor unit recruitment during exercise, thereby affecting post-exercise autonomic modulation (Porta et al., 2007).

Additionally, a potentially more pronounced chronotropic response during the resistance training session at 70% of 1RM in the AAS user group may have interfered with the HRV analysis, as indicated by studies suggesting that AAS users exhibit reduced baroreflex sensitivity and higher baseline sympathetic activity (Kouidi et al., 2021; Albano et a., 2021).

Thus, the lack of specific data on participants' chronotropic response and the control of these variables represents a limitation of the present study, as both may influence the interpretation of autonomic responses.

Future studies should consider assessing these variables to achieve a better understanding of autonomic control under different conditions and training contexts.

CONCLUSIONS

The results of this study indicate that users of AAS exhibit alterations in autonomic modulation after a resistance training session, characterized by greater sympathetic predominance and lower parasympathetic modulation during recovery.

Time-domain variables showed that both AAS users and non-users experienced significant post-exercise reductions. However, symbolic analysis revealed a distinct pattern in AAS users, suggesting a less efficient autonomic rebalancing compared to the NAAS group.

Although these findings reinforce the relationship between AAS use and autonomic alterations, the results should be interpreted with caution, considering the study's limitations.

Thus, future investigations should include assessments of muscle mass, chronotropic response, and improved control of training variables to gain a deeper understanding of autonomic modulation in AAS users.

Another important consideration is the differences between the classes of AAS, as well as the dosages and protocols used between the participants of this study. In this context, the dose-response may be important for understanding the magnitude of side effects on the cardiovascular system; a topic that warrants further investigation.

Strength and conditioning professionals should consider these adaptations in AAS users when designing training programs, especially with regard to post-session recovery. In addition, athletes should be advised on the risks involved with the abuse and indiscriminate use of AAS.

Furthermore, these findings highlight the importance of a detailed evaluation of autonomic modulation in individuals using AAS, especially given the cardiovascular risks associated with prolonged sympathetic activation.

DECLARATIONS CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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