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Research article

The alpha-melanocyte stimulating hormone is related to heart rate during exercise recovery

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ABSTRACT

Alpha-melanocyte-stimulating hormone (alpha-MSH) is a part of the hormonal stress system with proven cardiovascular effects. Heart rate recovery (HRR) following exercise is strongly correlated to overall fitness and future adverse cardiovascular events. The current study examined the predictive value of alpha-MSH for HRR following exercise testing.

Cardiopulmonary exercise testing (CPET) on a treadmill was used to measure HR and oxygen consumption (VO₂) in 16 elite male wrestlers (W), 21 water polo player (WP) and 20 sedentary subjects (C) matched for age. Plasma levels of alpha-MSH were measured by radioimmunoassay technique in four phases of CPET: 1) 10 min pre-CPET at rest; 2) at the initiation of CPET; 3) at peak CPET; and 4) at the third minute of recovery. The WP group had significantly higher HRR compared to than W and C groups, who did not have significantly different values. Significant difference in alpha-MSH measurements and patterns during CPET between groups was not observed ($p > 0.05$). When combining all three groups, we observed a significant correlation between VO₂ recovery and alpha-MSH recovery/peak ($r = -0.3$, $p = 0.022$). HRR and Δ HRR/peak significantly correlated with alpha-MSH at all four measurement points ($r = -0.4$; $p < 0.01$ for all). On multiple regression analysis, which included anthropometric and hormonal measures, the best independent predictor of HRR and Δ HRR/peak was alpha-MSH during recovery ($B = -1.0, -0.5$; $SE = 0.3, 0.1$; $CI = -1.5$ to $-0.4, -0.7$ to -0.2 ; $p = 0.001$ respectively). In conclusion, alpha-MSH measured during exercise recovery holds predictive value for HRR and Δ HRR/peak, suggesting a contributing role to integrative regulation of overall cardiopulmonary performance.

Condensed abstract: Present study examined the predictive value of alpha-melanocyte stimulating hormone (alpha-MSH) for heart rate recovery (HRR) in elite male wrestlers, water polo players and sedentary subjects matched for age. Alpha-MSH measured during exercise recovery holds predictive value for HRR and Δ HRR/peak, suggesting a contributing role to integrative regulation of overall cardiopulmonary performance.

1. Introduction

The recovery period after exercise, rather than a simple return to preexercise physiologic status, is a dynamic period in which many physiological changes develop [1]. Exercise is a critical stress that drives beneficial cardiovascular adaptations when performed routinely physical activity, yet it is during the exercise recovery period in which a number of these changes manifest. As such, the exercise recovery period is equally

important to assess as the exercise period itself. Due to vagal reactivation during exercise recovery, cardiopulmonary parameters such as arterial blood pressure, heart rate (HR), oxygen consumption (VO₂) and carbon dioxide production (VCO₂) decline [2]. Dynamics of these variables during the recovery phase is also related to the recovery of energy stores in active muscles [1, 3]. A direct link between blood lactate concentration built up during vigorous exercise and the amount of extra oxygen required to oxidize it, known as O₂ debt, was found. The exercise

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recovery period is a time when this debt is repaid [4]. This, gas exchange pattern after exercise represents cellular respiration coupled by cardiovascular and ventilatory mechanisms [4]. Moreover, HR shortly after exercise cessation has been shown to have robust prognostic value [5, 6, 7, 8].

Alpha-melanocyte stimulating hormone (alpha-MSH) is a peptide posttranslationally processed from proopiomelanocortin (POMC) released during stress and as such is a part of hormonal stress system [9, 10, 11]. Previously, it was considered as a primary regulator of energy balance that inhibits food intake, stimulates energy expenditure and regulates hair and skin pigmentation as well as reproductive and immune function [9, 10]. However, there are studies demonstrating a number of cardiovascular effects of alpha-MSH, including effects on heart rate (HR), systolic cardiac function, antiarrhythmic properties and an intensive dilatative stimulus on the coronary vasculature [9, 10, 11]. Alpha-MSH is also associated with mild sympathetic activation in the cardiovascular system that may influence systolic activity [11, 12].

To our knowledge, there are currently no studies assessing the role of alpha-MSH during exercise recovery period in athletes. As such, the aim of the current study was to examine the responses of alpha-MSH during exercise recovery in athletes and evaluate its' relation to HR. We hypothesize that alpha-MSH responses during exercise stress test recovery, which is considered as an acute stress model, may have predictive value for HR responses during that period.

2. Materials and methods

2.1. Patients

Present study examined fifty-seven male subjects matched for age, that were already analysed and described in details in our previous work: 1) 21 elite water-polo players (WP); 2) 16 elite wrestlers (W); and 3) 20 sedentary controls (C) [13]. The athletes groups have trained professionally for more than 10 years and all have been successfully competitive at the international level. Most subjects in the WP group were the members of the national team and all of members in the W group have won medals at the international level. Both WP and W groups performed combined strength and endurance training protocols and were in a period of preparation for international competition. The W group had 9 h of wrestling a week, 4 h of power training in the gym in order to improve the explosive strength, and 4 h of high intensity running a week (4 km per training, at HR 85–100% of maximal). The WP group trained 12 h a week in the pool, with at least 2 km of swimming per each training session, and three additional hours a week in the gym where they performed both power and endurance exercises. The C group was not engaged in sporting activities other than at the recreational level (less than 2 h a week for the last 10 years). Detailed personal and family medical history was obtained from all participants. No subjects included in the current study reported any diseases or associated risk factor for disease (e.g., hypertrophic cardiomyopathy, hypertension, arrhythmias, diabetes, renal diseases, cardiac and other infections, smoking, anabolic steroids usage, etc.), which served as an exclusion criteria due to their influence on cardiopulmonary function. Physical examinations and blood tests showed that all subjects were healthy, normotensive and had a normal resting ECG. The participants underwent the study after giving an informed consent. The local Ethical Committee approved the study.

2.2. Anthropometry

Body weight, fat mass (FM) and fat free mass (FFM) were obtained by bioelectrical impedance analysis using Tanita weight (phase sensitive multi-frequency analyzer Data Input GmbH 2000, using software Nutri 3, Kowloon, Hong Kong). Body surface area (BSA) was calculated according to the Du Bois and Du Bois formula [14].

2.3. Cardiopulmonary exercise testing

All the athletes underwent maximal cardiopulmonary exercise testing (CPET) on treadmill based with breath by breath ventilatory expired gas analysis according to current guidelines [15]. The protocol consisted of: 1) 3 min rest; 2) 2 min at speed 6 km/h and 2% inclination; 3) 2 min at speed 9 km/h and 2% inclination; 4) an increase of inclination for 2% every 2 min thereafter until criteria for maximal exertion was reached; and 5) 3 min recovery. The protocol was assessed prior to the study by testing 9 randomly chosen subjects in order to optimize the duration of the test (8–12 min), as recommended [14]. All subjects underwent CPET during the same time of the day. Ventilatory expired gas analysis was collected using a Cardiovit CS 200 (Schiller, Baar, Switzerland) throughout the assessment with four phases of primary interest: 1) 10 min before CPET at rest (phase 1); 2) at the beginning of CPET (phase 2); 3) at the peak effort (phase 3); and 4) at the 3rd min of recovery (phase 4). Recovery meant a complete cessation of movement. The following variables were determined from CPET: 1) HR; 2) oxygen uptake (VO_2); 3) carbon dioxide production (VCO_2); and 4) minute ventilation (VE). Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least 3 min during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. Knowing that recovery of energy stores and repayment of the O_2 deficit is most intensive during the first 30 s after exercise and that complete recovery of energy stores and acid-base status, as well as O_2 uptake, may last several minutes and continues even after 24h after high intensity exercise, to achieve pre-exercise levels [1, 3, 4], we arbitrarily chose the 3 min recovery timepoint for our analysis (180 s after peak exercise). HRR was considered HR after 3 min of recovery, and $\Delta\text{HRR}/\text{peak}$ the difference between HRR and HR peak. VE, VO_2 , and VCO_2 were acquired breath-by-breath, averaged over 30 s, and printed using rolling averages every 10 s. Peak respiratory exchange ratio (RER) was calculated as the highest 10-second averaged sample obtained during the last 20 s of testing, and was 1.1 in all subjects. VE and VCO_2 values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/ VCO_2 slope via least squares linear regression ($y = mx + b$, $m = \text{slope}$).

2.4. Blood analysis

Subjects were free of food and drink (except water) at least 3 h before collecting blood samples in order to avoid hormonal stimulation by needle punctation. All blood samples were taken from intravenous cannula which was placed into the patient's brachial vein before the test. Blood was taken in five phases of the test, as follows: 1) 20 ml at rest, 10 min before CPET (phase 1); 2) 20 ml at the beginning of CPET (phase 2); 3) 20 ml at the maximal effort (phase 3); and 4) 20 ml at the 3rd min of recovery (phase 4). Samples were centrifuged on 4000 rpm and kept at -80°C . Alpha-MSH was measured by radioimmunoassay technique (EURIA- α -MSH, Euro-Diagnostica, Malme, Sweden) with a lower sensitivity limit of 3 pmol/l; intra- and interassay coefficient of variation was less than 10%.

2.5. Statistics

The results are expressed by classic descriptive parameters such as mean and standard deviation for parametric variables, and median for non-normally distributed variables. To justify application of parametric analytical methods, the analysis of distribution of the observed variables was performed by Kolmogorov - Smirnov test. The differences between the groups were tested by analysis of variance (One-Way ANOVA). Kruskal Wallis nonparametric ANOVA followed by the Man Whitney test was used for the variables that deviated from normal distribution. If equal variances were assumed, for post hoc multiple group comparisons was used Bonferroni's method; if equal variances were not assumed it was

used Games-Howell method. Correlations between variables were performed by Pearson's correlation test and Spearman's rank correlation test. Multiple regression analysis was used to extricate predictive variables. The difference was considered significant when a p-value was less than 0.05, and highly significant when a p-value was less than 0.01. SPSS software (SPSS version 25, SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

3. Results

Clinical characteristics of the study groups are listed in Table 1. The participants did not have significantly different age and arterial blood pressure ($p > 0.05$). There were significant differences between subjects with respect to body weight, BSA, FM and FFM.

Cardiopulmonary parameters are shown in Table 2 and Figures 1a and 1b. ECG abnormalities during CPET and recovery of CPET were not observed. HR at rest was higher in the C group compared to both WP and W groups, who did not have significantly different values. There was no difference in peak HR between groups ($p > 0.05$). The WP group had a significantly higher HRR values than the W and C, who did not have significantly different values. WP and C did not have significantly different Δ HRR/peak; both groups had bigger Δ HRR/peak than W. Peak VO_2 was the highest in the WP group, and higher in the W group compared to the C group; resting and recovery values were not significantly different in all groups. The VE/VCO_2 slope was not significantly different amongst groups ($p > 0.05$).

We did not observe significant differences in alpha-MSH measurements and pattern during CPET between studied groups ($p > 0.05$) (Figure 2). There were also no significant correlations of alpha-MSH measurements and body composition variables ($p > 0.05$). In all three groups together, we observed significant correlation between VO_2 recovery and Δ alpha-MSH recovery/peak ($r = -0.3$, $p = 0.022$). HRR and Δ HRR/peak significantly correlated with alpha-MSH values observed in every of the four phases of the test ($r = -0.4$; $p < 0.01$ for all).

On multiple regression analysis, which included anthropometric and hormonal variables (BW, BSA, FM, FFM, alpha-MSH at all four phases of the test) and combined all three groups, the best independent predictor of HRR and Δ HRR/peak was alpha-MSH recovery ($F = 12.0, 13.3$; $r^2 = 0.2, 0.2$; $B = -1.0, -0.5$; $SE = 0.3, 0.1$; $CI = -1.5 - -0.4, -0.7 - -0.2$; $p = 0.001, 0.001$ respectively). Regression curves demonstrating correlation of HRR and Δ HRR/peak with alpha-MSH recovery are shown at Figures 3a and 3b.

4. Discussion

Present study revealed that HRR post maximal CPET behaved differently in two groups of athletes and a control population. While the WP group had a higher HRR compared to W and C groups, that latter two demonstrated similar values. Moreover, the WP and C groups had similar Δ HRR/peak, both significantly greater than the W group. However, significant differences in alpha-MSH measurements and pattern during CPET amongst the groups was not observed. The change of alpha-MSH recovery/peak correlated with VO_2 recovery, yet alpha-MSH recovery was found to be a predictor of HRR and Δ HRR/peak.

The recovery phase acutely following exercise has gained increasing attention in recent years [16]. HR during the recovery phase has consistently demonstrates prognostic value in specific patient groups as well as the general population [5, 6, 7, 8, 16]. During recovery from exercise, O_2 deficit produced during effort should be repayed as O_2 debt, keeping HR and VE higher than baseline resting values for a period of time [17]. The recovery kinetics of HR, a substantial part of VO_2 , are affected by physical conditioning, body position, type of exercise, hypoxia, metabolic disorders, vascular volume or peripheral resistance, ventricular dysfunction, blood volume, sinus node function and medications [16]. The abundance of HRR covariates implies complexity of regulatory mechanisms involved in the physiology of exercise recovery, supporting the prognostic importance of this singular and easily obtainable measure.

Table 1. Baseline characteristics of the study groups.

Parameter	C (n = 20)		WP (n = 21)		W (n = 16)		WP vs W (p)	WP vs C (p)	W vs C (p)
Age (years)	21.4	2.1	21.4	3.5	23.2	3.5	ns	ns	ns
BW (kg)	78.1	7.2	88.2	8.1	87.0	1.3	ns	<0.001	0.024
BSA (m ²)	2.0	0.1	2.1	0.1	2.1	0.3	ns	0.006	0.005
FFM (kg)	67.9	5.8	73.9	5.4	77.8	8.7	ns	0.015	<0.001
FM (kg)	10.1	4.3	14.1	4.9	9.2	6.5	0.021	ns	ns
SBP (mm Hg)	121	18	130	10	130	12	ns	ns	ns
DBP (mm Hg)	79	12	82	6	84	8	ns	ns	ns

Results are presented as mean SD. C – controls, W – wrestlers, WP – water polo players, BW - body weight, BSA - body surface area, FFM - fat free mass, FM - fat mass, SBP - systolic arterial blood pressure, DBP - diastolic arterial blood pressure.

Table 2. Cardiopulmonary parameters.

Parameter	C (n = 20)		WP (n = 21)		W (n = 16)		WP vs W (p)	WP vs C (p)	W vs C (p)
HR rest (min-1)	77	11	63	10	67	13	ns	<0.001	0.017
Peak HR (min-1)	194	10	192	9	189	10	ns	ns	ns
HR recovery (min-1)	99	11	108	11	98	12	0.009	0.015	ns
Δ HR recovery (min-1)	37	10	39	5	29	5	0.001	ns	0.011
VO_2 rest (ml·min-1·kg-1)	6.3	2.4	5.7	2.1	5.9	2.1	ns	ns	ns
Peak VO_2 (ml·min-1·kg-1)	49.5	1.1	59.3	4.9	54.1	2.7	0.024	<0.001	0.011
VO_2 recovery (ml·min-1·kg-1)	10.7	3.0	11.4	3.3	11.1	2.4	ns	ns	ns
VE/VCO_2 slope	30.6	3.7	28.5	3.4	28.6	1.8	ns	ns	ns

Results are presented as mean SD. C – controls, W – wrestlers, WP – water polo players, HR - heart rate, VO_2 - oxygen consumption, VCO_2 - carbon-dioxide output, VE - minute ventilation.

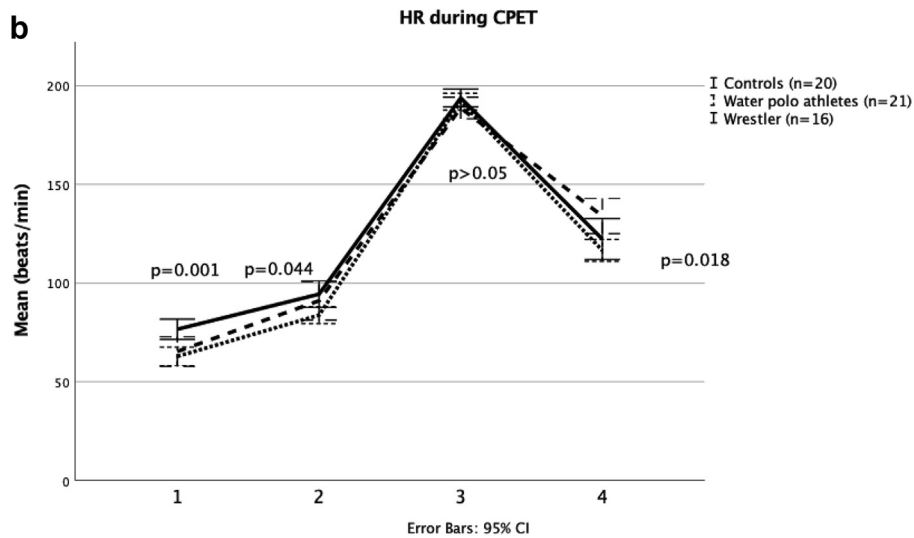
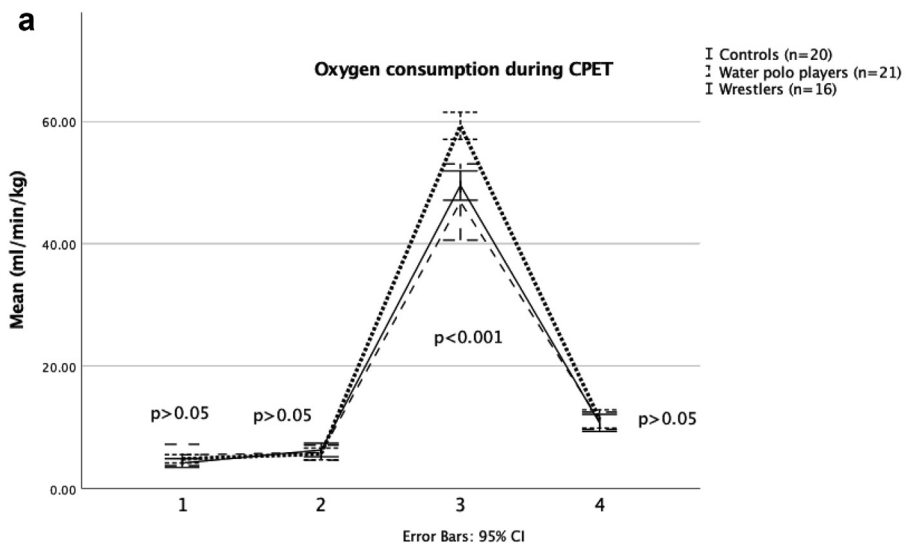


Figure 1. a and b. The heart rate and oxygen consumption during CPET.

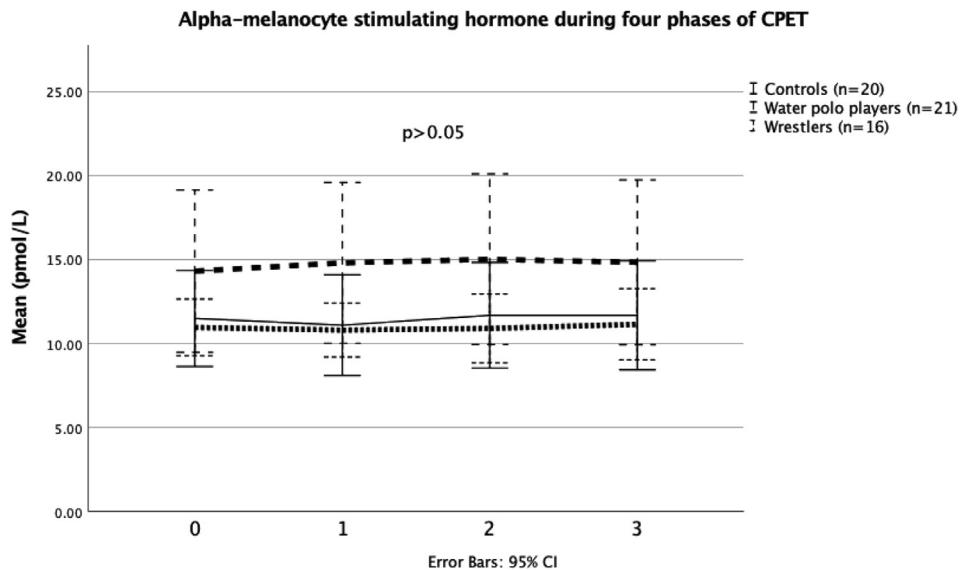


Figure 2. The alpha-MSH during CPET.

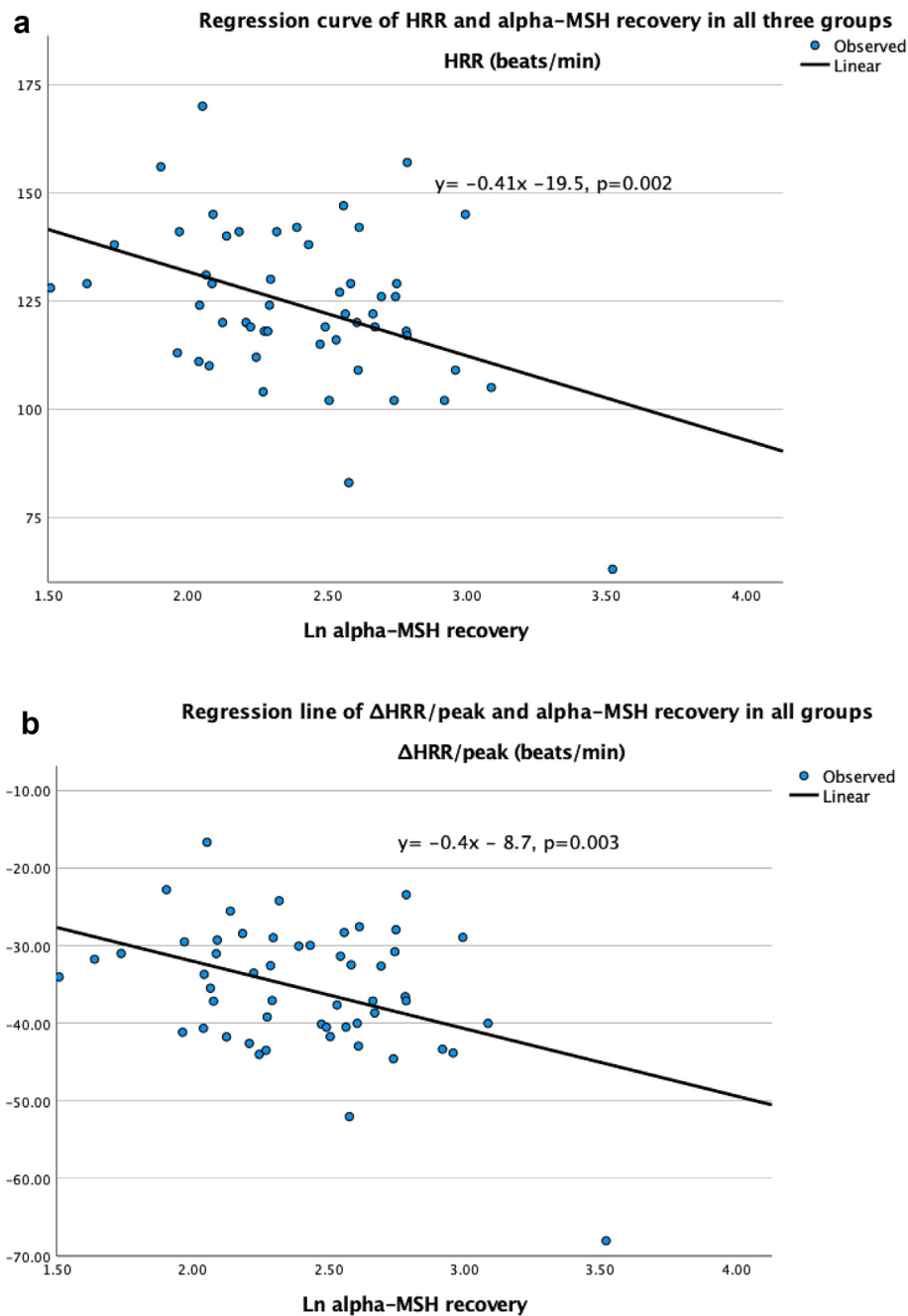


Figure 3. a and b. Regression curves demonstrating correlations of HRR and Δ HRR/peak with alpha-MSH recovery in all three groups together.

The endocrine system plays a dominant regulatory role during times of stress, which includes exercise stress testing used as a laboratory acute stress model [18]. During stress system activation, pituitary POMC is secreted, and consequently its' derivate alpha-MSH [11]. POMC secretion is altered during chronic stress, with certain variability depending on age, gender, race, genetic factors, nutrition, psychological factors, type of stress, and physical activity [13]. Biological effects of stress hormones are still not completely elucidated, although their role in complex interrelation of endocrine, immune, metabolic, neurological and cardiovascular system during times of stress is postulated [13]. Their actions lead to adaptation to stress, which can be analyzed in different groups of athletes who present with differing chronic physical stress adaptive models [13]. The adaptive changes in athletes move in the direction of whole body ability improvement, but these changes are different in different sport disciplines and levels of fitness, depending on the varying strength and endurance components of training for a specific sport [19]. In the present

study, as expected, the control group and two different athletic chronic stress models, WP and W, demonstrated different cardiopulmonary adaptive changes. Athletes had higher peak VO_2 ; WP demonstrated the highest level. Nonetheless, this study demonstrated that HRR behaved differently in two groups of athletes and control population, suggesting its' distinctive role in chronic stress exposure. The differences in cardiopulmonary parameters between study groups are adaptive response to metabolic demands with an important hormonal regulatory role. Stress axis activation is dependent on duration, type and intensity of training [13, 20]. This was explained as protective mechanism in conditions of repeated stress in order to keep the reserves of the body from exhaustion. Alpha-MSH has been shown to have effects on sympathetic activation in the cardiovascular system that may influence systolic activity, HR, blood pressure and physiologic responses of the coronary vasculature [10, 12], thus potentially playing a role during both acute and chronic physical stress. Animal studies demonstrate an increase in alpha-MSH after

exercise [21, 22]. Based on these observations, we hypothesized that stress axis activation and alpha-MSH secretion during acute physical stress may differ in three groups of subjects studied, with distinctive patterns of chronic stress and consequent adaptive changes. However, our hypothesis was not confirmed as all examined groups had similar patterns of alpha-MSH during CPET.

On the other hand, a significant correlation was found between VO_2 recovery and the change of alpha-MSH during recovery of exercise, suggesting its possible role in energy homeostasis during this period in all groups. The strong predictive value of alpha-MSH during the recovery phase for HRR and $\Delta HRR/\text{peak}$ are indicative of its important physiological role. Previous studies demonstrated tachycardic effects of alpha-MSH due to increased sympathetic and attenuated parasympathetic activity, and by this mechanism indirectly affecting energy expenditure [23]. Modulation of autonomic nervous system tone attributed to alpha-MSH may have an enormously important effect, since disorders of the autonomic nervous system is an underlying pathophysiological mechanism for major cardiovascular diseases, such as heart failure [24]. Indeed, circulating alpha-MSH was found to be increased in patients with chronic heart failure [24]. Moreover, some studies demonstrate that chronic melanocortin activation may provide cardioprotective regulation by enhancing vagal nerve activity and baroreflex control of HR [24, 25].

Summarizing the observations from this study, it is noticeable that these findings potentially pave the way to quantify stress and its role in cardiovascular regulation and overall health, which could lead to the development of the novel hormonal therapeutic approaches to prevent or mitigate disease development or progression, by stress reduction. The exact knowledge of hormonal regulation of stress effects, as well as objective measurement of these effects, should enable reduction of stress by hormonal manipulation.

5. Limitations

It should be noted that our data are preliminary and further investigations of this topic in different populations and in a higher number of participants are needed. Our hypothesis should be tested on more diverse stress adaptive models.

6. Conclusion

Alpha-MSH during recovery holds predictive value for HRR and $\Delta HRR/\text{peak}$, suggesting a contributing role to the integrative regulation of overall cardiopulmonary performance. This finding could lead to the development of the novel hormonal therapeutic approaches to reduce stress and prevent or mitigate disease.

Declarations

Author contribution statement

D. Popovic Conceived and designed the experiments; Wrote the paper.

B. Popovic, S. Seman and D. Labudovic: Performed the experiments.

R. Lasica: Performed the experiments; Analyzed and interpreted the data.

D. Jakovljevic, R. Arena and S. Damjanovic: Analyzed and interpreted the data.

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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