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BRIEF NOTE

24-hour dynamics for serum biomarkers of creatine metabolism after an acute session of exhaustive resistance exercise in active men



Cinétique sur 24 heures des biomarqueurs sériques du métabolisme de la créatine après une séance d'exercice exhaustif en résistance chez des sujets masculins pratiquant une activité physique

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Summary

Introduction. – Exhaustive exercise adversely affects biomarkers of creatine metabolism yet it remains unknown when the values back toward pre-disturbance conditions. Here, we evaluated a 24-hour post-exercise response in serum guanidinoacetic acid (GAA), creatine and creatinine in young active men subjected to a single session of exhaustive resistance exercise and matched it with exercise-induced changes in serum cortisol, interleukin 6 (IL-6), creatine kinase (CK), and lactate dehydrogenase (LDH).

Summary of facts and results. – Twelve healthy active men (age 22.7 ± 0.8 years; weight 79.8 ± 7.3 kg; height 182.4 ± 4.9 cm; weekly exercise 5.1 ± 1.6 hours) were subjected to a single session of bench press exercise until volitional exhaustion, with venous blood sampled before, immediately after exercise (~ 2 min), and after 15 min, 60 min and 24 h after the end of exercise. Baseline values for serum GAA, creatine and creatinine were 2.2 ± 0.5 $\mu\text{mol/L}$, 18.9 ± 3.6 $\mu\text{mol/L}$, and 72.4 ± 6.0 $\mu\text{mol/L}$, respectively. Serum GAA significantly dropped for $9.6 \pm 7.3\%$ immediately after bench press exercise (95% CI, 5.0 to 14.2; $P < 0.001$), while both creatine and creatinine increased immediately after the test for $5.0 \pm 2.5\%$ (95% CI, 3.4 to 6.6; $P < 0.001$) and $11.9 \pm 4.3\%$ (95% CI, 9.2 to 14.6; $P < 0.001$), respectively.

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MOTS CLÉS

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Exercice de
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GAA and creatine levels recovered to the baseline values after 24 hours post-exercise, yet creatinine remained significantly higher at 24-hour period as compared to the baseline values for $2.5 \pm 2.3\%$ (95% CI, 1.0 to 4.0; $P=0.002$). In addition, no significant correlations were found between serum cortisol, IL-6, CK and LDH and creatine metabolites ($P>0.05$).

Conclusion. – A single session of exhaustive resistance exercise induces transient alterations in biomarkers of creatine metabolism, with serum creatinine outlined as a most persistent marker of exhaustion. Exercise-induced changes in creatine metabolism poorly corresponded to perturbations in inflammation and muscle fatigue biomarkers following exercise.

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Résumé

Introduction. – Un exercice exagéré perturbe les biomarqueurs du métabolisme de la créatine, mais on ignore dans quel délai les valeurs retournent vers les conditions de pré-perturbation. Nous avons évalué la réponse post-exercice sur 24 heures de l'acide guanidinoacétique (GAA) sérique, de la créatine, de la créatinine, du cortisol sérique, de l'interleukine 6 (IL-6), de la créatine kinase (CK) et de la lactate déshydrogénase (LDH) chez de jeunes hommes actifs soumis à une seule séance d'exercice exhaustif en résistance.

Résumé des faits et des résultats. – Douze hommes actifs et en bonne santé (âge $22,7 \pm 0,8$ ans, poids $79,8 \pm 7,3$ kg, taille $182,4 \pm 4,9$ cm, volume d'exercice hebdomadaire $5,1 \pm 1,6$ heures) ont été soumis à une seule séance d'exercice de presse jusqu'à épuisement volontaire, avec prélèvement de sang veineux. Immédiatement après l'exercice (~ 2 min), et après 15 min, 60 min et 24 h après la fin de l'exercice. Les valeurs initiales pour le GAA sérique, la créatine et la créatinine étaient respectivement de $2,2 \pm 0,5 \mu\text{mol/L}$, $18,9 \pm 3,6 \mu\text{mol/L}$ et $72,4 \pm 6,0 \mu\text{mol/L}$. Le GAA sérique a significativement diminué de $9,6 \pm 7,3\%$ immédiatement après un exercice de bench press (IC 95 %, 5,0 à 14,2; $p<0,001$), tandis que la créatine et la créatinine ont augmenté immédiatement après de respectivement $5,0 \pm 2,5\%$ (IC 95 %, 3,4 à 6,6, $p<0,001$) et $11,9 \pm 4,3\%$ (IC à 95 %, 9,2 à 14,6, $p<0,001$). Les taux de GAA et de créatine se sont revenus aux valeurs initiales 24 heures après l'exercice, mais la créatinine est demeurée significativement plus élevée à 24 heures que les valeurs initiales de $2,5 \pm 2,3\%$ (IC à 95 %, 1,0 à 4,0; $p=0,002$). De plus, aucune corrélation significative n'a été trouvée entre le cortisol sérique, l'IL-6, la CK et la LDH et les métabolites de la créatine ($p>0,05$).

Conclusion. – Une seule séance d'exercice exhaustive en résistance induit des altérations transitoires des biomarqueurs du métabolisme de la créatine. La créatinine sérique apparaît comme le marqueur le plus persistant de l'épuisement. Les changements induits par l'exercice dans le métabolisme de la créatine ne sont pas parallèles aux perturbations de l'inflammation et des biomarqueurs de fatigue musculaire après l'exercice.

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1. Introduction

Exhaustive exercise negatively affects many biological pathways, including inflammation or oxidative stress, with the homeostatic control of energy balance might be specifically compromised by heavy exercise [1]. It appears that exercise to exhaustion acutely alters several biomarkers of creatine metabolism [2–4], suggesting possible exercise-induced disruption of creatine synthesis/re-synthesis, a fundamental metabolic process in cellular bioenergetics. Italian group [2] reported acute variations in serum creatine and guanidinoacetic acid (GAA) in young athletic

and non-athletic volunteers subjected to incremental cycle ergometer stress test. This has been confirmed in a recent study with healthy volunteers subjected to running to exhaustion and free-weight bench-press to volitional failure [3]. The authors reported that strenuous running induced a significant decrease in serum GAA, accompanied by a rise in serum creatine and creatinine, suggesting the possible use of serum GAA as a novel biomarker of exhaustion. However, no study so far evaluated an acute post-exercise dynamics for serum GAA and creatine, neither describe possible association with traditional biomarkers of post-exercise inflammation and muscle fatigue. In the present

study, we evaluated a 24-hour post-exercise response in serum GAA, creatine and creatinine in young active men subjected to a single session of exhaustive resistance exercise, and match it with exercise-induced changes in serum cortisol, interleukin 6 (IL-6), creatine kinase (CK), and lactate dehydrogenase (LDH).

2. Methods

2.1. Participants

Twelve healthy moderately physically active volunteers (age 22.7 ± 0.8 years; weight 79.8 ± 7.3 kg; height 182.4 ± 4.9 cm; weekly exercise 5.1 ± 1.6 hours) were recruited and signed an informed consent to participate in this study. Sample size ($n = 12$) was calculated using the power analysis (one-tail test, effect size $d = 0.80$, α error probability = 0.05, power = 0.80). Participants were free from acute and chronic cardiometabolic and musculoskeletal disorders and did not take any performance-enhancing agents at least 4 weeks before the study commenced. All experimental procedures were approved by the local IRB at the University of Novi Sad in accordance with the Declaration of Helsinki.

2.2. Experimental procedures

All participants were assessed on a single occasion where subjected to a bench press test until volitional exhaustion. The test started with a workload equal to 30% of participant's weight, with a participant completed as many bench press repetitions in a single set as one can until fatigue. Sets were repeated (with 60 s rest interval in-between) until the participant was unable to perform a minimum of 1 full repetition at a given workload. Each repetition was controlled by a strength and conditioning professional to be steady, starting with both arms extended, goes down until the bar hits the chest, and then returns back to the starting point. Participants were instructed to perform maximally and to maintain the exercise for as long as possible. Blood samples were drawn from an antecubital vein into a gel vacutainer before, immediately after test (~2 min post-exercise), and after 15 min, 60 min and 24 h post-exercise. Blood was immediately centrifuged at 3000g for 15 min (Premiere XC-2415, CA Scientific, Manassas, VA) with serum transported at -20°C and stored at -80°C within the next 30 min, and analyzed after the completion of the study for clinical chemistry panel. GAA, creatine and creatinine were analyzed using a modified LC-MS/MS (Agilent 1200 Series LC System, Agilent Technologies Inc., Santa Clara, Calif., USA). Serum cortisol, IL-6, CK and LDH were analyzed with COBAS C-6000 analyzer (Roche Diagnostics, Indianapolis, IN). All measurements were carried out between 07:00 and 11:30 after an overnight fast. Participants were requested not to participate in any heavy exercise before the bench press test and 24-h post test. All participants were accustomed to testing procedures as part of their exercise routine.

2.3. Statistical analyses

Baseline vs. follow-up measures were compared by one-way Anova to establish if any significant differences existed between participants' responses over time, with post-hoc Tukey test employed to identify differences among individual sampling pairs. The correlation between serum biomarkers of creatine metabolism and indicators of post-exercise fatigue were examined using Pearson's product-moment correlation coefficient. Significance level was set at $P \leq 0.05$. The data were analyzed with SPSS Statistics (IBM Corporation, Armonk, NY, USA).

3. Results

All research participants completed the study with the average number of bench press sets and total repetitions were 5 ± 2 sets (95% confidence interval [CI], 3 to 6), and 104 ± 33 repetitions (95% CI, 83 to 125). Baseline values for serum GAA, creatine and creatinine were 2.2 ± 0.5 $\mu\text{mol/L}$, 18.9 ± 3.6 $\mu\text{mol/L}$, and 72.4 ± 6.0 $\mu\text{mol/L}$, respectively. Serum GAA significantly dropped for $9.6 \pm 7.3\%$ immediately after bench press exercise (95% CI, 5.0 to 14.2; $P < 0.001$), while both creatine and creatinine increased immediately after the test for $5.0 \pm 2.5\%$ (95% CI, 3.4 to 6.6; $P < 0.001$) and $11.9 \pm 4.3\%$ (95% CI, 9.2 to 14.6; $P < 0.001$), respectively. Detailed changes in post-exercise dynamics for serum creatine metabolites are outlined in Fig. 1 (Shaded), with GAA and creatine levels sampled at 24-hour post-exercise period recovered to the baseline values ($P > 0.05$), while serum creatinine remained significantly higher as compared to the baseline concentrations for $2.5 \pm 2.3\%$ (95% CI, 1.0 to 4.0; $P = 0.002$). Post-exercise changes in serum cortisol, IL-6, CK and LDH were presented in Fig. 1, with no significant correlations found between traditional biomarkers of post-exercise fatigue and creatine metabolites ($P > 0.05$).

4. Discussion

In the present study, we confirmed exercise-related alterations of creatine metabolism, with serum GAA, creatine and creatinine notably (and immediately) responded to a session of exhaustive resistance exercise dispensed to a cohort of young active men. Our findings are in line with the previous studies that described this phenomenon in participants subjected to strenuous cycling, running or weightlifting exercise [2–4]. It has been recently suggested that exhaustive exercise might jeopardize creatine utilization through several possible mechanisms, including a down-regulation of GAA synthesis, an obstruction of creatine delivery to the target tissues, and/or an increased breakdown of creatine to creatinine [4]. Future mechanistic studies are highly warranted to trace down which pathway contributes the most to exercise-induced disturbances in circulating biomarkers of creatine metabolism, and specifically does above findings translates into tissue-relevant manner. However, we described for the first time an acute post-exhaustive exercise dynamics of individual creatine metabolites, disclosing a normalization of serum GAA and creatine levels as early as 24 hours after a single session of exhaustive resistance exercise. This perhaps means that one

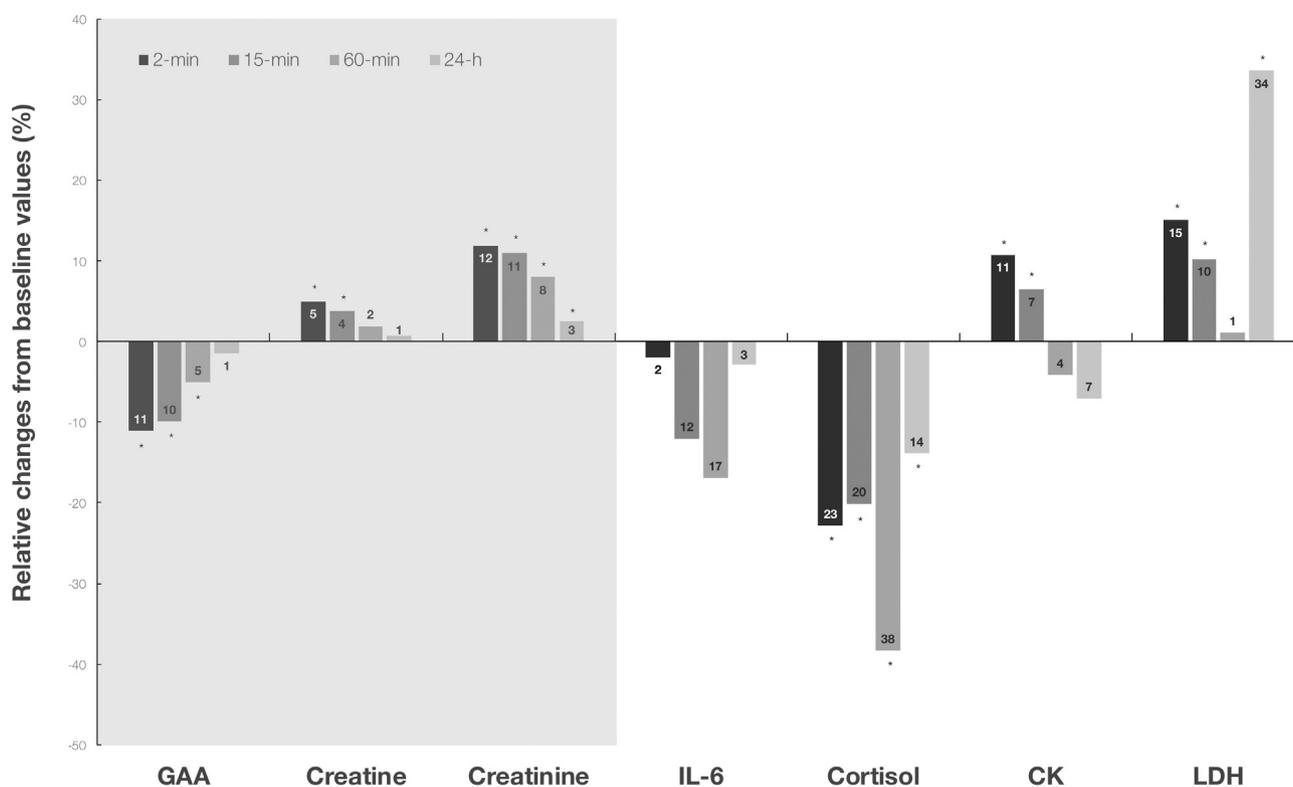


Figure 1 Post-exhaustive exercise changes in biomarkers of creatine metabolism (left panel) and traditional markers of muscular fatigue (right panel). Values are shown as percentage change from the baseline, with error bars removed for clarity. Asterisk (*) indicates difference for specific time points vs. baseline at $P \leq 0.05$. GAA: guanidinoacetic acid; IL-6: interleukin 6; CK: creatine kinase; LDH: lactate dehydrogenase.

might experience a recovered GAA-creatine balance for the next exhaustive exercise session set at subsequent day. Nevertheless, serum creatinine remained significantly elevated even at 24-hour post-exercise evaluation, suggesting more time is needed to offset this biomarker to pre-exercise concentrations. Since serum creatinine is a routine biomarker of renal function, elevated levels reported here might indicate a prolonged kidney stress induced by exhaustive exercise, an event that should be monitored closely for normalization in future long-term studies (values found were not above clinically reference ranges for men of $110 \mu\text{mol/L}$).

We also reported heavy exercise-induced alterations in traditional biomarkers of muscular fatigue, including a significant increase in clinical enzymes (CK and LDH) immediately after exercise, a notable drop in circulating cortisol throughout post-exercise period, and a tendency for an altered inflammatory response (as evaluated by down-swing of IL-6 for the time of evaluation). However, it appears that no significant correlation has been established between changes in traditional biomarkers of muscular fatigue of post-exercise fatigue and creatine metabolites. This perhaps suggest that no traditional biomarkers might be used as surrogate markers to describe alterations in cellular bioenergetics induced by exercise. Although traditional biomarkers used here were relatively sensible to exhaustive exercise, their 24-hour post-exercise dynamics appears to be rather irregular, while creatine metabolites have shown more predictable and stable biochemical behavior. This should foster further validation of biomarkers of

creatine metabolism in monitoring post-exhaustive exercise recovery in future studies, using different modes of exercise and advanced chemistry probes for creatine metabolism (including serum arginine, glycine, ornithine, and urinary metabolites) in well-powered studies that account for confounding variables such as age, gender or lifestyle.

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Disclosure of interest

The authors declare that they have no competing interest.

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