UNIVERSITY OF WISCONSIN-LA CROSSE

Graduate Studies

# PLASMA AMMONIUM, BLOOD LACTATE, AND RPE AS INDICATORS OF FATIGUE FOR THREE SQUAT TRAINING PROTOCOLS

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# ABSTRACT

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No accepted method for monitoring resistance exercise fatigue exists. Ammonium, lactate, and rating of perceived exertion (RPE) were measured for their utility in monitoring resistance exercise. Sixteen men (18-24 yrs.) participated in the study. Muscular endurance (ME), strength (STR), and hypertrophy (HYP) squat workouts were based on a one-repetition maximum squat. Protocols were performed at least 72 hours apart in random order. Work volume was equalized among protocols. Subjects reported RPE based on last set difficulty. Venous blood was obtained for ammonium and lactate analysis after five minutes of rest both before and after each workout. Differences among protocols were assessed by univariate ANOVA with Tukey post-hoc comparisons. Post exercise ammonium ($p<.01$) and lactate ($p<.01$) both increased from resting levels. However, no difference existed among protocols for post-exercise lactate ($p=.10$). A difference in post-exercise ammonium was found between the STR and ME protocols only ($p=.01$). Reported RPE differed between the HYP protocol and the STR ($p=.04$) and ME ($p=.02$) protocols, with no difference found between STR and ME ($p=.97$). Lactate levels appeared to correspond with total work volume whereas ammonium levels appeared to correspond with work density. Reported RPE appeared to be associated with both nervous system and metabolic stress.

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# INTRODUCTION

Monitoring exercise induced fatigue can be helpful to coaches and trainers in determining the abilities of athletes to perform under strenuous conditions, and to construct training programs for athletic improvement (10). Currently there is no universally accepted method for monitoring resistance exercise fatigue (25); however, ammonium, lactate, and rating of perceived exertion (RPE) have all been considered viable candidates for these assessments.

Blood ammonium and lactate levels both accumulate during exercise but their respective indications of exercise induced fatigue may be quite different. Lactate does not begin to accumulate until cycling is performed above lactate and ventilatory thresholds, whereas ammonium increases as exercise intensity increases (27, 34). Additionally, during cycle ergometer exercise at maximal lactate steady state (MLSS), lactate remains stable until exhaustion while ammonium continues to increase over time (3). Ammonium may reflect fatigue better than lactate while cycling, as ammonium is influenced by both exercise intensity and duration.

Measuring RPE is quick, easy, and non-invasive, making it an ideal technique for monitoring exercise intensity and fatigue. Despite its subjective nature, RPE has been shown to correlate well with lactate accumulation (21, 23, 32), and to be a good index of exercise intensity (8, 12, 23, 31). Increased RPE during exercise has not been adequately studied and may be a result of both metabolic and nervous system stress.

Plasma ammonium and blood lactate have previously been studied in relation to resistance exercise. Abernethy and Wehr studied plasma lactate and ammonium responses to leg press exercise during three sets of 15RM and 5RM loads (1). They found that the greatest ammonium and lactate was produced in the 15RM protocol, but they did not control for volume of work being completed (1). There is a need for an industry standard in assessing resistance exercise fatigue. Currently little is known about the utility of ammonium, lactate and RPE for assessing this form of fatigue. Therefore, the purpose of this study is to compare plasma ammonium, blood lactate, and RPE among resistance training protocols used to develop muscular endurance (ME), strength (STR), and hypertrophy (HYP) with an equated work volume across all trials.

## MATERIALS AND METHODS

Sixteen college age men (18-24 yrs.) with a 1RM parallel back squat of at least 1.5 times their body weight and currently using the back squat as part of their training program volunteered to participate in this study. No participant was using performance enhancement supplementation or drugs. The protocols and methods of this study were approved by the Institutional Review Board for the Protection of Human Subjects at the University of Wisconsin-La Crosse.

Prior to participation, each subject signed a written informed consent form approved by the Institutional Review Board of the University of Wisconsin-La Crosse. They then engaged in four testing sessions of various sets and repetitions of back squat exercise. The initial testing session assessed each subject's 1RM for the back squat, which was used to determine load in the subsequent testing sessions. The depth of each subject's squat was visually analyzed by the same investigator to ensure that each subject achieved a parallel depth (top of quadriceps parallel to the floor) for all testing sessions. Testing sessions were based on typical workout recommendations for ME, STR, and HYP (20, 28, 36). Order of the testing sessions was randomized for each subject to control for muscle adaptation or learning effects.

Workouts for ME consisted of two sets of 20 repetitions (2x20) at 53% of 1RM with a 45 second rest period between sets (20, 28, 36). For STR, workouts were 5x5 at 85% 1RM with a three minute rest period between sets (20, 28, 36). The HYP workouts consisted of 3x10 at 70% 1RM with a two minute rest period between sets (20, 28, 36).

All workouts for each subject were normalized to the same volume (p=0.98) using the equation: sets x reps x external load = volume. At least 72 hours separated exercise testing sessions, and subjects were asked to follow a consistent diet for the 12 hours prior to each session. Subjects recorded what they ate before the 1RM test and were reminded the day before each test to eat a meal similar in content and volume. After completion of the last set of each protocol, subjects were asked, "How hard was the last set?" based on a set of descriptors on the Borg Category 10 scale (6).

Blood was drawn (3ml) before and after exercise from the antecubital vein into a heparinized vacuum tube. Subjects sat for five minutes before each blood draw as blood lactate and plasma ammonium concentrations have been found to peak around five minutes post exercise (5). All blood samples were immediately placed into an ice bath until centrifugation, which was performed within 30 minutes of blood draw (18). Immediately before centrifugation, 1ml of whole blood was removed from the heparinized test tube, placed into 2ml of perchloric acid (PCA), and frozen for future enzymatic analysis of lactate concentration. The remaining sample then underwent centrifugation (5,000 RPM for 5 min) to separate the plasma which was immediately used for enzymatic determination of ammonium concentration. Standard precautions for handling blood ammonium specimens were taken as indicated by Huizenga et al (18).

Ammonium concentration was determined by adding 10µl of plasma to 1ml of ammonia reagent (Sigma No. A0853), and then adding 10µl of glutamate dehydrogenase (GLDH) (Sigma No. G2626). After adding the GLDH the decrease in absorbance was measured at 340 nanometers (nm) using the Spectronic 20D+ spectrophotometer (Thermo Electron Scientific Instruments LLC, Madison, WI USA). Ammonium values were then

determined by the following equation: (ΔA•TV•MW of ammonium•F)/(ε•d•SV), where ΔA=change in absorbance, TV=total assay volume, MW=molecular weight of ammonium (17 g/mole), F=dilution factor, ε=extinction coefficient for NADPH at 340 nm, d=light path, and SV=sample volume (Ammonia Assay Kit AA0100, Technical Bulletin, Sigma-Aldrich, St. Louis, MO USA).

Blood lactate concentration was measured from whole blood samples by first adding 1ml of whole blood to 2ml of PCA (Sigma No. 311421), inducing red blood cell lysis. Following red blood cell lysis the mixture underwent centrifugation (5,000 RPM for 5 minutes) and 25µl of the supernatant was added to a 0.8M hydrazine and 1.0M glycine buffer, pH 9.2 (Sigma No. 216046 and G7126 respectively). After the supernatant and hydrazine-glycine buffer were mixed, 2.5mg of NAD (Sigma No. N7004), and 50µl of lactate dehydrogenase (LDH) (Sigma No. L2625) were added. The increase in absorbance was then measured at 340 nm using the Spectronic 20D+ spectrophotometer (Thermo Electron Scientific Instruments LLC, Madison, WI USA). Lactate values were found by using the formula (ΔA•PCAB•TV)/(ε•d•VB•SV), where ΔA =change in absorbance,
PCAB = volume of blood and PCA mixture, TV = total volume, ε=extinction coefficient for NADH at 340 nm, d = light path, and VB = Volume of blood added to PCA (Enzymatic Assay of L-Lactic Dehydrogenase, Sigma-Aldrich, St. Louis, MO USA).

## Statistical Methods

Differences among dependant variables in the three protocols were assessed by means of univariate ANOVA (17) with Tukey post-hoc comparisons. A 95% confidence interval (CI) was used to assign bounds of expected discrepancy between the sample mean, and the population mean (7). Alpha was set at 0.05 and all statistics were generated using SPSS (Version 12, SPSS Inc., Chicago, IL USA).

## RESULTS

Volume of work (Figure 1) did not vary significantly among protocols for any subject (p=0.98) [STR 6961kg (SD 1093), 95% CI: 6401-7521], [HYP 6881kg (SD 1116), 95% CI: 6321-7441], [ME 6913kg (SD 1127), 95% CI: 6353-7472].

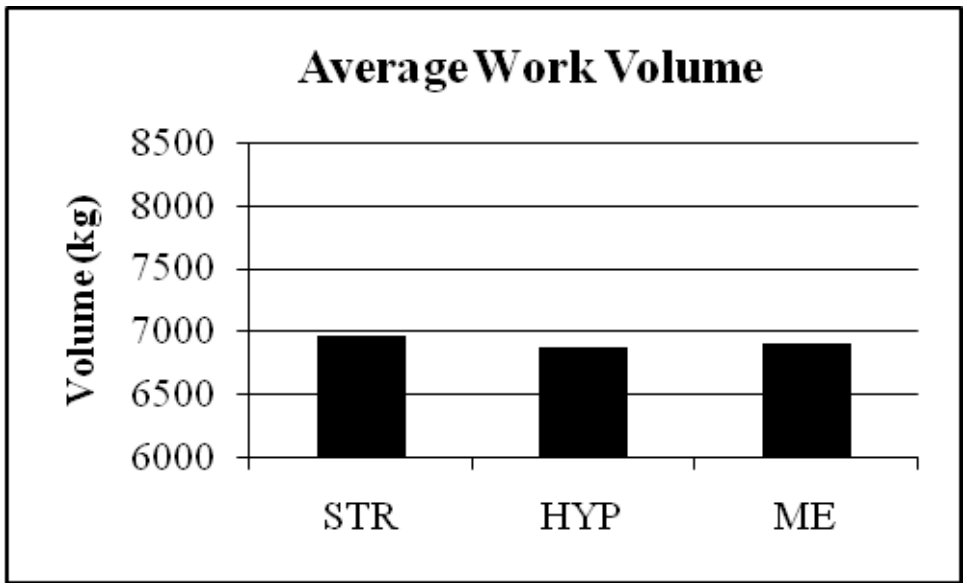


Figure 1. Average work volume among protocols. No significant difference was observed among protocols (p=0.98). Data presented as mean (SD).

Average plasma ammonium (p=0.06) [STR 47µM (SD 17.9), 95% CI: 30-64], [HYP 76µM (SD 40), 95% CI: 59-93], [ME 69µM (SD 39), 95% CI: 52-86] and blood lactate (p=0.55) [STR 1.4mM (SD 0.47), 95% CI: 1.2-1.6], [HYP 1.2mM (SD 0.27), 95% CI: 1.1-1.4], [ME 1.3mM (SD 0.33), 95% CI: 1.1-1.5] resting levels were similar among protocols. A significant difference existed between resting and post exercise levels of ammonium and lactate when the average of all protocols was combined into one total average.

Resting plasma ammonium [64µM (SD 35), 95% CI: 54-74] was lower compared to post exercise ammonium [116µM (SD 66), 95% CI: 98-134, p<0.01] and resting lactate [1.3mM (SD 0.4), 95% CI: 1.2-1.4] was also lower compared to post exercise lactate [6.3mM (SD 2.9), 95% CI: 5.5-7.1, p<0.01]. Post hoc analysis indicated that the ME protocol [149µM (SD 64), 95% CI: 118-179] produced higher plasma ammonium levels than the STR protocol [80µM (SD 57), 95% CI: 48-110, p=0.01], but that the HYP protocol [121µM (SD 61), 95% CI: 90-152] produced plasma ammonium levels similar to the ME (p=0.41) and STR (p=0.14) protocols (Figure 2).

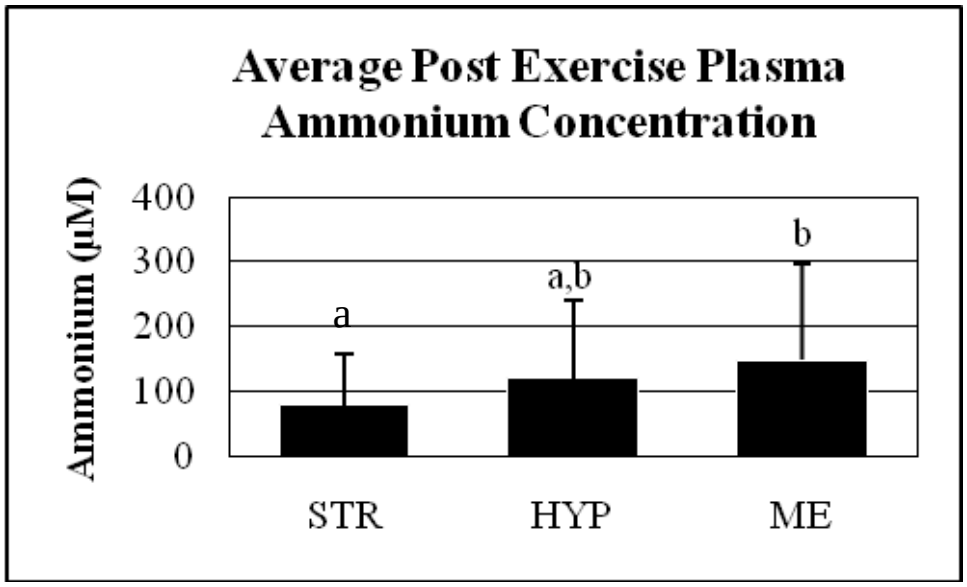


Figure 2. Accumulation of blood ammonium five minutes post exercise. Bars with different letters are significantly different from one another (p<0.05). Data presented as mean (SD).

Although the ME protocol produced the greatest blood lactate levels, no statistical differences were identified among the three protocols for post exercise blood lactate concentration (p=0.97) (Figure 3). Average post exercise lactate levels were [5.3mM (SD 2.7), 95% CI: 3.9-6.7], [6.2mM (SD 2.6), 95% CI: 4.8-7.6], and [7.5mM (SD 3.0), 95% CI: 6.1-8.9] for the STR, HYP, and, ME protocols respectively.

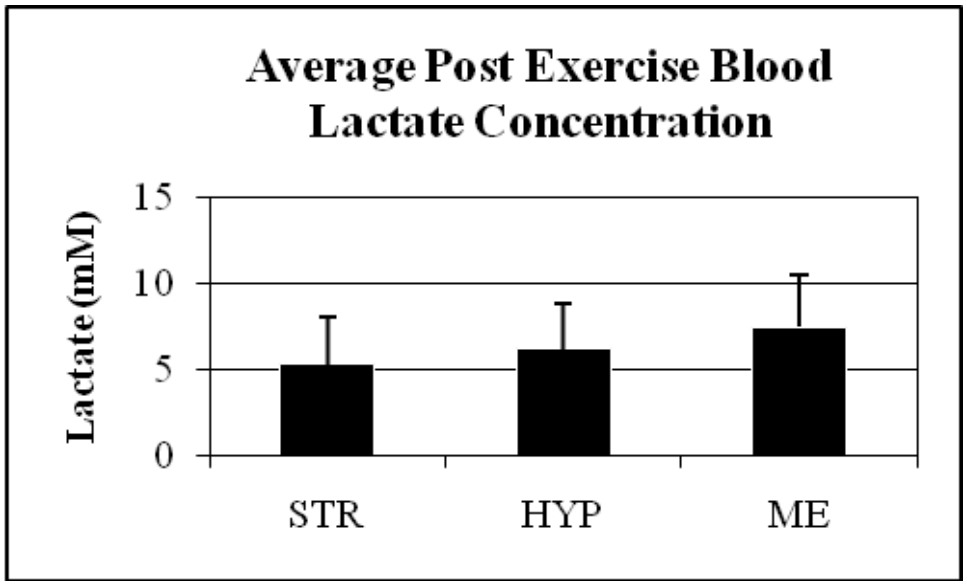


Figure 3. Accumulation of blood lactate five minutes post exercise. No significant difference was observed among protocols (p=0.97). Data presented as mean (SD).

Figure 4 shows that RPE was different among protocols (p=0.01). Post hoc analysis indicated no difference in RPE between the STR [7.3 (SD 1.6), 95% CI: 6.5-8.1] and the ME [7.4 (SD 1.5), 95% CI: 6.7-8.2] protocol (p=0.97); however RPE from the HYP protocol [6.0 (SD 1.4), 95% CI: 5.2-6.7] was found to be lower than the STR (p=0.04) and ME (p=0.02) protocols.

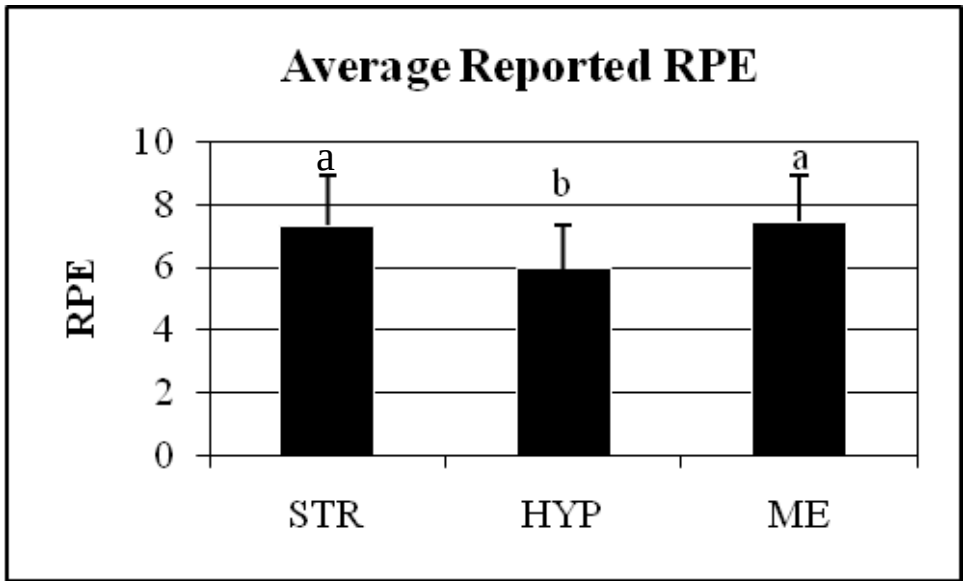


Figure 4. RPE following the last set of each protocol. Bars with different letters are significantly different from one another ($p<0.05$). Data presented as mean (SD).

## DISCUSSION

The purpose of this study was to determine the validity of using plasma ammonium, blood lactate, and RPE as measures of fatigue during resistance exercise. This study determined that each of these measures responded differently to equal volumes of work arranged in different prescribed sets, repetitions, and rest times. Findings of the present study are comparable to the lactate and ammonium response found by Abernethy and Wehr (1) in their leg press study. Our additional finding is that training density may be the stimulus for the ammonium response.

The present study normalized work volume for each training protocol while rest times between sets, number of sets, and number of repetitions were variable. This caused the time to complete the same amount of work to vary among training protocols. Protocols were established using commonly prescribed sets, repetitions, and rest times by strength and conditioning professionals (20, 28, 36). Work density was calculated by dividing total lifting volume (kg) by total time to complete the protocol, including rest periods (sec).

Plasma ammonium appeared to accumulate in a manner dependent on training density. The STR protocol resulted in the lowest training density at 2.6 kg/s with the least average post exercise blood ammonium concentration of [80µM (SD 57.4), 95% CI: 48-110). A moderate density of 6.4 kg/s was found for the HYP protocol along with a moderate average post exercise blood ammonium concentration [121µM (SD 61), 95% CI: 90-152]. The ME protocol contained the highest training density of 20 kg/s with the

greatest average post exercise blood ammonium concentration [149µM (SD 64), 95% CI: 118-180]. It is likely that ammonium is an indicator of resistance exercise density and fatigue since ammonium represents the depletion of ATP and phosphocreatine (PCr) (19, 24).

Rest between work sets of high intensity exercise allows levels of PCr, and therefore ATP, to be replenished by the aerobic energy system (4). Resynthesis of PCr is a biphasic response with a fast and slow component (14). Typically half of the PCr originally present in muscle is replenished within 20-22 seconds of rest for the fast component, and 170 seconds of rest for the slow component (14). Thus, the more rest allowed between exercise sets, the more PCr the muscles involved in exercise will have available for the next set. Rest sets for the STR protocol (three minutes) allowed an ample amount of time for resynthesis of PCr to near resting levels. However, the short rest times (45 seconds) associated with the ME protocol likely prevented PCr levels to resynthesize completely before starting the second set, which further depleted PCr stores. Ammonium indicates both the depletion of PCr (19) along with the depletion of the total adenine nucleotide (TAN) pool (24). Thus, it is likely that the accumulation of plasma ammonium is a good indicator of resistance exercise fatigue due to diminished levels of available ATP and PCr.

It is likely that the difference of ammonium accumulation between the ME and STR protocols ($p=0.01$) found in the current study would also be statistically different with a larger sample size. This is shown by a lack of overlap between the bounds of ME (118-179) and STR (48-110) protocols with a 95% CI. Statistical significance would likely not exist between the HYP protocol and the ME and STR protocols with a larger

sample size because the 95% CI showed an overlap of the HYP (90-152) protocol bounds with the ME (118-179) and STR (48-110) protocol bounds. This is in agreement with the lack of statistical difference between the HYP protocol and the STR ($p=0.14$) and ME ($p=0.41$) protocols.

In the present study similar blood lactate accumulation occurred for all three squat protocols ($p=0.10$). Lactate is produced from non-aerobic utilization of glycogen (30) and a higher rep number as in the ME protocol may allow more time for utilization of aerobic energy sources (11), resulting in lower lactate levels than expected (35). Moderate reps at a higher load, as in the HYP protocol, likely activate more Type II fibers than the ME protocol (16) causing a higher percentage of ATP to be obtained from glycolysis (33), but does not allow sufficient work time to produce much lactate (15). Low reps at even higher load, as in the STR protocol, likely allow the activation of even more Type II fibers than the HYP protocol (16); however, a greater percentage of ATP is likely provided by PCr (14), thus explaining the low accumulation of blood lactate. Patterns of blood lactate accumulation observed in our study may also be due to equalized work volume causing similar muscle glycogen consumption; and therefore lactate production, among protocols (29). Based on the overlap among protocol bounds (STR: 3.9-6.7; HYP: 4.8-7.6; ME: 6.1-8.9) for lactate with a 95% CI there would likely be a lack of statistical significance among protocols even with a larger sample size.

The results of this study add to the findings of Abernethy and Wehr (1) who measured plasma ammonium and plasma lactate responses in their subjects after completing three sets of 5RM and three sets of 15RM on a leg press machine with one

week between trials. Six minutes of rest was maintained between sets for both the 5RM and 15RM protocols without normalizing the total work load between protocols (1).

Abernethy and Wehr reported plasma ammonium accumulation from rest after the 15RM protocol but not after the 5RM protocol (1). Since a six minute rest period between sets allows substantial resynthesis of PCr (14) each work set of both protocols likely began with essentially the same amount of PCr. Greater depletion of ATP and PCr caused by a potential greater work volume and longer time under tension with the 15RM protocol likely caused the increase of plasma ammonium concentration from rest (19). This differs from the present study in that plasma ammonium, and most likely PCr levels, were variable in each protocol not only because of differences in the number of reps and sets but also because of differences in the recovery times between sets.

A difference in lactate accumulation was also found between the Abernethy and Wehr study (1) and the present study. We found no difference in blood lactate accumulation among the STR, HYP, and ME protocols, whereas Abernethy and Wehr found that the 15RM protocol produced significantly greater plasma lactate levels than the 5RM protocol (1). The different lactate response found in the Abernethy and Wehr (1) study was likely a result of differences in work volume between protocols (29). Our data, along with the research of Abernethy and Wehr (1), indicate that lactate accumulation levels reflect levels of muscle glycogen utilization due to total work volume, whereas ammonium appears to be an index of work density.

Previous investigators have reported a correlation between lactate accumulation and RPE during resistance training (21, 23, 32). This relationship was not observed in the present study and was most likely the result of differences in training protocols

among studies. Kraemer et al. normalized work volume and rest between sets (21). Lagally et al. (23) measured lactate and RPE after one set of biceps curls while normalizing work volume. Suminski et al. (32) used single bouts of resistance exercise with multiple intensities and did not normalize work volume. We normalized total work volume, varied rest sets, and required subjects to perform multiple sets of each training protocol.

There is consensus that RPE is a good predictor of workout intensity (2) during resistance exercise (8, 12, 23, 31). The present study however, showed that the ME protocol (lowest intensity at 54% 1RM) had a higher RPE than the HYP protocol (moderate intensity at 70% 1RM) and a similar RPE as the STR protocol (greatest intensity at 85% 1RM). This may be due to differences in the way that RPE was reported among studies. In a study by Day et al. (8) subjects were asked to "rate their effort," while in a study by Singh et al. (31) subjects were asked "how was your workout?" Gearhart et al. (12) collected RPE data after each repetition of each set. Both Gearhart et al. (12) and Lagally et al. (23) described RPE as: "the perception of physical exertion is defined as the subjective intensity of effort, strain, discomfort, and/or fatigue that you feel during exercise." In the present study, subjects were asked "how hard was the last set?"

The STR protocol may have caused a higher RPE because of the stress that high intensity resistance exercise places on the nervous system (16). Electrical activity of the muscle and RPE both increase with increasing intensity (9, 13, 22, 23). Thus, RPE may be an indicator of nervous system stress. The higher RPE reported for the ME protocol may have been the result of metabolic stress (26) due to high exercise density. A correlation exists between metabolite accumulation and RPE, suggesting that RPE may

be an indicator of metabolic stress (21, 23, 32). The results of the present study demonstrate that RPE is a product of both nervous system and metabolic stress, indicating that the traditional RPE scale may be too ambiguous for accurate assessment of each during resistance exercise. Differences of reported RPE ($p=0.01$) in the present study among protocols may not be statistically significant if a larger sample size was used. The potential loss of statistical significance among protocols with a larger sample size is indicated by an overlap among the bounds of all protocols (STR: 6.6-8.1; HYP: 5.2-6.7; ME: 6.7-8.2) based on a 95% CI.

Findings from the current study demonstrate the utility of blood lactate and plasma ammonium as metabolic markers during resistance exercise. When volume of work is equal across protocols, and the density of work manipulated, plasma ammonium appears to be a good indicator of fatigue. This is likely due to ammonium indicating the depletion of PCr and the TAN pool. Further, blood lactate may be a good indicator of the differences in total work volume and depletion of muscle glycogen as suggested by Abernethy and Wehr (1). The present study indicates that the traditional RPE scale may be too ambiguous for accurate assessment of both nervous system and metabolic stress. Additional research with a larger sample size analyzing intramuscular PCr, muscle glycogen, and the TAN pool along with blood lactate, plasma ammonium, RPE, and muscle activation during resistance exercise would be beneficial.

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# APPENDIX A

# INFORMED CONSENT

## INFORMED CONSENT

**Protocol Title:** Plasma Ammonium, Blood Lactate, and RPE as Indicators of Fatigue for Three Squat Training Protocols

**Principle Investigator:** Matthew Rogatzki
220 20th St. N.
La Crosse, WI 54601
(715) 216-2598

**•Purpose and Procedure**

- The purpose of this study is to compare levels of lactate and ammonium in the blood during resistance exercise.
- My participation in this study will involve a one repetition max. test on the parallel squat. I will also undergo three different testing procedures. The procedures will include 5 sets of 5 reps at 85% 1RM with a 3 minute rest period between sets, 3 sets of 10 reps at 70% of 1RM with a 2 minute rest period between sets, and 2 sets of 20 reps at 53% of 1RM with a 30 second rest period between sets. These tests will be performed with at least 72 hours of rest between tests.
- Blood will be drawn from my antecubital vein before exercise and 5 minutes post exercise to measure blood lactate and blood ammonia levels.
- The time requirement will be about one half hour per test for a total of 1.5 hours.
- Testing will take place in room 225, Mitchell Hall, UW-L.

**•Potential Risks**

- I may experience arm soreness from the needle pricks.
- I may experience excessive muscle soreness and substantial fatigue from the parallel squat testing procedures.
- Complications may occur in which the test will be terminated.
- The risk of serious or life-threatening complications for healthy individuals like me is very low.

•**Rights and Confidentiality**

- My participation is voluntary.
- I can withdraw from this study at any time for any reason without penalty.
- The results of this study may be published in scientific literature or presented at professional meetings using grouped data only.
- All information will be kept confidential through the use of number codes.
- Only the primary researcher and thesis advisor will have access to the coding key.
- My data will not be linked with personally identifiable information.

•**Possible Benefits**

- I and other athletes may benefit from the knowledge and understanding of ammonium and lactate accumulation in the blood during exercise. This knowledge may lead to a competitive advantage compared to others without this knowledge.

  In the unlikely event that any injury or illness occurs as a result of this research, the Board of Regents of the University of Wisconsin System, and the University of Wisconsin-La Crosse, their officers, agents, and employees, do not automatically provide reimbursement for medical care or other compensation. Payment for treatment of any injury or illness must be provided by you or your third-party payor, such as your health insurer or Medicare. If any injury or illness occurs in the course of research, or for more information, please notify the investigator in charge. I have been informed that I am not waiving any rights that I may have for injury resulting from negligence of any person or the institution.

  Questions regarding study procedures may be directed to student Matthew Rogatzki (715-216-2598), the principle investigator, or the study advisor, Dr. Glenn Wright (608-785-8689), Department of Exercise and Sport Science, 134 Mitchell Hall. Questions regarding the protection of human subjects may be addressed to the UW-La Crosse Institutional Review Board of Human Subjects, (608-785-8124 or irb@uwlax.edu)

**Participant_____ Date____**

**Researcher_____ Date____**

# APPENDIX B

# REVIEW OF LITERATURE

## REVIEW OF LITERATURE

Exercise cannot be performed for unlimited durations, and is most commonly terminated by lacking the desire to continue, or an inability to continue due to fatigue. Fatigue caused by exercise has been extensively researched, yet the mechanisms of exercise induced fatigue are still not completely understood. In this review, the literature suggesting a relationship between exercise induced fatigue, lactate and ammonium accumulation, and rating of perceived exertion (RPE) will be addressed.

### Ammonium in Muscle and Blood

Ammonium accumulation from endogenous sources in the human body is typically metabolized by the liver (5, 21, 68, 71). However, the metabolic processes of muscle contraction can produce ammonium levels that exceed the rate of liver metabolism. As muscles contract during exercise, ATP is hydrolyzed by ATPase forming ADP (56). The ADP byproduct is then resynthesized to ATP by cytoplasmic phosphocreatine (PCr) via creatine kinase (28). Resynthesis of ATP by PCr causes the levels of PCr within the cytoplasm of muscle to decline. As PCr in the cytoplasm of muscle loses its phosphate, the creatine is rephosphorylated via mitochondrial creatine kinase, depleting mitochondrial ATP (9). Depletion of mitochondrial ATP and the concomitant rise in ADP and inorganic phosphate (Pi) stimulate the electron transport system (ETS) to synthesize more ATP via aerobic metabolism (61). Rest between work sets of high intensity exercise allows levels of ATP and PCr to be replenished by the

aerobic energy system (10). Resynthesis of PCr is abiphasic response with a fast and slow component (36). Typically, half of the PCr originally present in muscle is replenished within 20-22 seconds of rest for the fast component and within 170 seconds of rest for the slow component after exhaustive exercise (36). Therefore, the more rest allowed between exercise sets, the more PCr the muscles involved in exercise will have available for the next set.

As PCr is depleted ADP accumulates stimulating the myokinase enzyme to catalyze a reaction utilizing two moles of ADP to form one mole of ATP and one mole of AMP (1). The AMP formed from myokinase is further deaminated by the enzyme adenylate deaminase, an enzyme involved in the purine nucleotide cycle (PNC), producing IMP and ammonium. The production of IMP and ammonium from AMP depletes the total adenine nucleotide pool (TAN) leaving less ATP available for use by the muscles (47). Adenylate deamina se activation in vivo occurs when a high ATP turnover rate is coupled with a low PCr level (41). Since ammonium indicates both the depletion of PCr along with the depletion of the TAN pool, it is very likely that the accumulation of ammonium in blood and muscle is a good indicator of muscular fatigue due to diminished levels of available ATP and PCr. This increase of ammonium due to diminished levels of PCr and ATP during exercise may exceed the rate of liver metabolism thus leading to hyperammonemia (51). Hyperammonemia is characterized as a blood ammonium level greater than rest caused by a metabolic disturbance.

During intense exercise fast twitch glycolytic fibers (FT IIx) and fast twitch oxidative fibers (FT IIa) produce the most ammonium, while slow twitch muscle fibers (ST) produce little to no ammonium (60). An inverse relationship between the

percentage of ST fibers and an increase in ammonium during $VO_2$ max tests confirms that FT fibers produce more ammonium than ST fibers during exercise (23). Higher adenylate deaminase activity is present in FT muscle fibers in comparison to ST muscle fibers, and is considered the primary reason that FT muscle produces more ammonium than ST muscle (24, 50, 78).

Increases in plasma and muscle ammonium have a high correlation with intensity of exercise during prolonged endurance exercise (35, 46, 49). It appears that the accumulation of ammonium is dependent upon exercise intensity. This is in agreement with adenylate deaminase being mainly present in the FT fibers, which are recruited during high intensity exercise (37). About 4.1 moles of ammonium are formed from each mole of ATP lost due to the deamination of AMP, suggesting that the increased need for ATP with high intensity exercise will cause a substantial accumulation of ammonium (70).

Direct interference with the electrophysiological response of skeletal muscle has been reported in the presence of ammonium accumulation. In frog skeletal muscle there is a substitution of ammonium for sodium in the extracellular fluid (ECF) (51) and in human subjects performing dynamic leg extensor exercises until exhaustion, ammonium competes with potassium for potassium channels (31). This combination of ammonium disrupting the sodium concentration in ECF and the concentration of potassium in intracellular fluid (ICF) of the muscle cell may significantly disrupt the action potentials associated with muscle contraction. Disruption of muscle action potentials by ammonium was demonstrated in frog muscle where twitch tension of muscle was

decreased with a prolonged action potential in proportion to the increase of ammonium (51).

Production of ATP is inhibited by ammonium concentrations greater than resting levels. Mitochondrial respiration in frog muscle decreases in the presence of ammonium (51) and ammonium interferes with the malate-aspartate shuttle (18), which carries the $H^+$ ions from NADH produced during glycolysis into the mitochondria to be used in the ETS. Enzymatic activity of PDH, a step that provides acetyl coenzyme A for use in the citric acid cycle (TCA), is also slowed in the presence of ammonium (79). The affects of ammonium on skeletal muscle metabolism, especially in FT fibers, inhibit ATP production via inhibition of the TCA cycle and the ETS which, at homeostatic blood ammonium levels (11.8-47.2 μM (51)), would provide a substantial amount of ATP during the rest periods of exercise between work sets.

Fast twitch fibers are most susceptible to producing ammonium due to the high activity of adenylate deaminase that they contain (24, 50, 78). Accumulation of ammonium in the muscle disrupts the normal electrical response of muscle contraction (51) along with ATP production (18, 31, 51, 79). Since FT muscle fibers are recruited during high intensity exercise (37) it is likely that the accumulation of ammonium monitors fatigue during high intensity exercise.

## Ammonium and the Blood Brain Barrier

Ammonium can pass the blood brain barrier (BBB) and it has been known for some time that ammonium in the brain causes coma and other functional abnormalities. Mice injected with ammonium salts displayed signs of coma shortly thereafter (76) and in portacaval shunted rats arterial ammonium correlates well with brain ammonium

concentrations (26). A direct correlation between altered consciousness and blood ammonium has also been reported in young primates (75).

Ammonium diffuses between blood, muscle, brain, and cerebral spinal fluid (CSF), while favoring diffusion toward a lower pH (64). Because ammonium congregates to a more acidic environment, blood with a low pH such as found during hypoventilation may put a person at higher risk for accumulation of ammonium in the brain due to a steeper pH gradient, whereas during intense exercise the accumulation of ammonium in the brain may be minimal because of decreases in blood pH. The indication that ammonium may not play a role in central fatigue during high intensity exercise was shown in a study where subjects cycled on a combined leg and arm cycle ergometer starting at 30% of their maximum capacity, with a 10% increase of resistance every two minutes until fatigue (19). This protocol took about 12 minutes to complete and resulted in decreased CSF ammonium levels after exercise compared to rest (19). Ammonium may, however, play a role in central fatigue during prolonged exercise since an increase of CSF ammonium has been found after three hours of cycle ergometer exercise at 60% $VO_2$ max (53). Although ammonium has the ability to cross the BBB, its diffusion ability is limited. Labeled ammonium in rhesus monkeys revealed that ammonia ($NH_3$), which is a gaseous form, crosses the BBB more easily than ammonium ($NH_4^+$) since ammonium is ionized and the BBB is relatively impermeable to ions (58). The permeability of the BBB to ammonium is about 0.5% that of the permeability of ammonia, but since ammonium is found more readily in the blood than ammonia it is responsible for most of the ammonium found in the brain (58).

## Lactate in Muscle and Blood

Before reviewing the literature pertaining to the relationship between fatigue and lactate, it is important to have a general understanding of how lactate is produced in the muscle. Glycolysis is accelerated during intense exercise, thus producing high levels of pyruvate. When pyruvate formation is increased to the Km value of lactate dehydrogenase (LDH) ,which is around 7mM (73), LDH will then reduce pyruvate into lactate. The reduction of pyruvate plays an important role since this redox reaction allows the coenzyme NADH to be oxidized forming $NAD^+$ so that $NAD^+$ can be recycled into glycolysis at the glyceraldehyde-3-phosphate dehydrogenase reaction, allowing glycolysis to continue and ATP to be produced.

Fast twitch muscle fibers cause greater lactate production than ST muscle fibers (16, 69). The production of lactate by FT fibers is partially due to the high rate of glycolysis during high intensity exercise, along with the relatively low number of mitochondria in FT fibers (7). Low numbers of mitochondria allow pyruvate to accumulate more rapidly thus reaching the Km level of LDH more quickly. An increased rate of glycolysis during high intensity exercise increases lactate accumulation (45), and high intensity exercise calls upon increasing numbers of FT fibers (37). This provides evidence that FT muscle does cause a greater accumulation of lactate than ST muscle.

Long duration exercise requires activation of ST muscle fibers without the use of many FT muscle fibers, and during long duration exercise the accumulation of lactate is minimal (16, 30, 62, 77). This gives supporting evidence that the recruitment of FT muscle associated with high intensity exercise is the primary cause for lactate accumulation. In continued support of lactate being more readily produced in FT muscle

fibers than ST muscle fibers, the enzymes phosphorylase, phosphofructokinase (PFK), and LDH, which are involved in glycolysis, have higher activity in FT than in ST muscle fibers (69). A higher activity of the enzymes involved with glycolysis will increase the rate of glycolysis thereby causing pyruvate to accumulate at a rate greater than it can be utilized by the mitochondria, thus reaching the Km of LDH sooner. On the other hand, ST muscle fibers have greater activity of the enzyme succinate dehydrogenase (involved in the Kreb's cycle) (69), and $LDH_{1,2}$ isozymes that favor the oxidation of lactate (73). Greater activity of oxidative enzymes allows pyruvate and lactate to undergo oxidative metabolism thus limiting the accumulation of lactate in ST muscle.

Lactate and fatigue have been found to correlate with one another. Twitch tension of the frog sartorius muscle decreases as muscle lactate increases, and there is recovery of twitch tension with a concomitant decrease in lactate during recovery (27). This suggests that as lactate accumulates in the muscle, the force that a muscle can produce decreases. In isokinetic exercise of knee extensors and flexors performed at 30, 120, and 300 degrees/sec with max effort for one minute, lactate accumulation in the blood highly correlated with the muscle fatigue index (22). This correlation shows that there is a relationship between the accumulation of lactate in the blood and perception of muscular fatigue. In swimmers performing 200 meter sprints with active or passive recovery, active recovery caused a quicker clearance of blood lactate along with increased performance on successive sprints than passive recovery (34). Better performance with quicker lactate clearance suggests that lactate may be a cause of fatigue and that its clearance improves performance.

A correlation between lactate and fatigue does not necessarily mean that lactate causes fatigue. In frog sartorius muscle after 30 seconds of recovery, contractile tension of the muscle increased without any change in muscle lactate concentration (69). In subjects cycling at 91% $VO_2$ max until fatigue, muscle lactate increased after the first five minutes of exercise, and then remained constant until fatigue (74). Similarly, a relationship of lactate and fatigue was not shown in repeated sprints on a treadmill (57). These sprints consisted of short and long work to rest intervals with the finding that although equated to the same volume, blood lactate was greater in the short work to rest periods with no difference in time to fatigue between protocols (57). In vitro addition of lactate directly to a muscle does not inhibit contraction (15) making the consideration of lactate as a cause of fatigue questionable.

Lactate has long been thought to cause fatigue by decreasing blood and muscle pH in a phenomenon termed "lactic acidosis" (40). However, no experimental evidence has ever shown a cause-and-effect relationship between lactate production and acidosis (59). After stimulation of frog sartorius and rat diaphragm muscle in solution it was shown that lactate does not represent total proton load, and therefore could not be the cause of lactic acidosis (8).

Biochemical analysis of glycolysis indicates that a net proton release occurs in glycolytic reactions that end in phosphoenolpyruvate (PEP), and that for every mole of pyruvate converted to lactate one proton is consumed (59). Proton release from glycolysis, not lactate, is likely the cause of acidosis and fatigue during exercise. Since lactate is an end product of fast glycolysis, and glycolysis releases protons, lactate accumulation may be a good indicator of glycolytic rate along with the acidosis and

fatigue that accompanies proton accumulation. According to Robergs (59), consumption of protons with the formation of lactate may have a slightly alkalizing effect on the cell. This may protect muscle from fatigue caused by the accumulation of protons and decreased pH (17). In these two ways lactate may indicate the onset of muscle fatigue while also protecting against it.

## Lactate and Ammonium Relationship

Despite differences in the mechanisms that produce ammonium and lactate, there appears to be an interrelationship of their appearance in blood. Ammonium is a potent stimulator of PFK (48, 66, 78), while the accumulation of protons and concurrent decrease in muscle pH caused by glycolysis stimulate adenylate deaminase (2, 60). Stimulation of PFK by ammonium would increase the rate of glycolysis resulting in acidosis and the appearance of lactate in the muscle and blood. At the same time, an increased activity of myokinase and adenylate deaminase stimulated by the protons produced during glycolysis would increase the production of ammonium in muscle and blood.

Evidence suggests a correlation between the accumulation of blood lactate and ammonium. During ramp exercise on a cycle ergometer there is a significant correlation between the rise in lactate and ammonium (4, 11, 14, 55, 80). Cycling at 50% and 75% $VO_2$ max causes a linear relationship of ammonium and lactate levels suggesting a direct relationship between the accumulation of ammonium and lactate (2, 39). Sprint exercise bouts of 15, 30, and 45 seconds on a cycle ergometer causes a significant linear relationship between the rise in blood ammonium and lactate for all sprint durations (38).

Correlation of lactate and ammonium accumulation during exercise indicates that ammonium and lactate may stimulate one another.

Despite the correlation between blood ammonium and lactate accumulation, it is likely that they represent different causes of fatigue. Endurance-trained athletes exercised on a cycle ergometer for 30 minutes at 85%, 95%, 100%, and 105% of individual anaerobic threshold with trials at least four weeks apart (72). Individual anaerobic threshold is defined as the point of time and workload at which the maximal rate of lactate elimination from the blood is in equilibrium with the rate of lactate diffusion from the muscle (65), also known as the maximal lactate steady state (MLSS). During the cycling tests blood ammonium levels increased with increasing intensity, while lactate increased only at the exercise intensity of 105% individual anaerobic threshold (72). Since ammonium rose with each increase of intensity, while lactate only increased at 105% individual anaerobic threshold, ammonium may be a better indicator of exercise intensity than lactate. Ammonium and lactate accumulated differently in healthy males exercising for 15 minutes at 80, 90, 100, 110, and 120% ventilatory threshold (VT) (using the V-slope method (55)) on separate days (54). Blood ammonium was significantly elevated starting at six minutes with a continued increase to the end of the 15 minute stage during all exercise intensities (54). In comparison, blood lactate only increased continuously at exercise intensities equivalent to 100, 110, and 120 % VT (54). This suggests that ammonium may be a more sensitive indicator of intensity than lactate, and may also be an indicator of exercise duration. Blood lactate remained stable throughout a test to exhaustion performed at MLSS on a cycle ergometer while ammonium levels continued to rise (6). These previous reports indicate that ammonium

may be the better metabolite to monitor for an indication of training load (exercise volume x intensity).

Using resistance exercise, Abernethy and Wehr compared plasma ammonium and lactate levels after completing 3 sets of either a 5 rep max (RM) or a 15RM protocol on a leg press machine (1). Ammonium did not increase from rest after the 5RM protocol but did increase following the 15RM protocol (1). This suggests that adenylate deaminase is increasingly activated as the volume-load on the muscle increases, and as ATP and PCr are depleted. Blood lactate concentrations progressively increased from rest after each set of the 5RM and 15RM protocol with higher lactates found with the 15RM protocol (1). The higher ammonium and lactate levels associated with the 15RM protocol compared to the 5RM protocol suggest that lactate and ammonium are both good indicators of combined exercise intensity and duration in reference to resistance exercise. Since the two protocols of this study were not equated to volume-load, it may be the combination of high intensity exercise (load) for some amount of total work (volume) that caused the differences.

## Rating of Perceived Exertion

Measuring RPE is quick, easy, and non-invasive thus making it an ideal technique to monitor exercise. Lactate has been found to correlate with rating of perceived exertion (RPE), yet there is no consensus as to whether or not this correlation is valid. Many of the studies finding correlation were done using graded exercise testing, with the subjects reporting their RPE at each level of intensity (12, 13, 52). This method of finding correlation is predictable (33), since subjects will arbitrarily report a higher RPE at each

increasing level of intensity, and lactate will also rise with each increasing level of intensity. During interval cycling above lactate threshold, only a moderate correlation between lactate accumulation and RPE was reported with the correlation being greater for RPE and heart rate (33). Differences in the reports of lactate and RPE correlation above the lactate threshold make the use of RPE as a predictor of lactate accumulation questionable during high intensity exercise.

Despite the subjective nature of RPE, it is considered a good predictor of workout intensity during resistance training (20, 29, 44, 63). Intensity with resistance training increases as the %1RM lifted increases (3). In a study by Day et al. (20), subjects were asked to "rate their effort." Singh et al. (63) asked "how was your workout?" Gearhart et al. (29) asked RPE after each repetition of each set. Gearhart et al. (29) along with Lagally et al. (44) described RPE such as: "the perception of physical exertion is defined as the subjective intensity of effort, strain, discomfort, and/or fatigue that you feel during exercise." Differences in how subjects are asked to rate RPE may cause different RPE values.

Both electrical activity of the muscle and RPE increase with increasing intensity (25, 32, 43, 44) indicating that RPE may be an indicator of nervous system stress (37). Correlation between metabolite accumulation and RPE may indicate metabolic stress (42, 44, 67). It is possible that RPE may be an ambiguous indicator of nervous system and metabolic stress, and the manner in which subjects are asked to report RPE may cause RPE to be a greater representation of one or the other.

## Conclusion

The study of fatigue associated with exercise is essential in developing training methods for fatigue resistance. Understanding exercise induced fatigue and metabolic markers that indicate an athlete's susceptibility to fatigue is important for coaches' evaluation of an athlete's potential to perform and to monitor training adaptations. Correlation between ammonium and lactate accumulation are in agreement with the enzymatic kinetics of PFK and adenylate deaminase. The rise in the metabolites of lactate and ammonium may monitor exercise fatigue. Lactate may be a monitor of work volume, and ammonium may indicate the intensity and duration of exercise. Further, RPE may be an ambiguous indicator of nervous system and metabolic stress during exercise. Additional research on resistance exercise should relate lactate, ammonium, and RPE with varying sets, reps, and intensity while normalizing total work volume to clarify the use of these variables in monitoring resistance exercise.

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