JEPonline
Journal of Exercise Physiologyonline

Official Journal of The American Society of Exercise Physiologists (ASEP)

ISSN 1097-9751
An International Electronic Journal
Volume 7 Number 2 April 2004

Altitude Physiology

ACUTE HYPOXIA ALTERS LACTATE THRESHOLD IN CHRONIC ALTITUDE RESIDENTS

TODD A. ASTORINO,[1] FARZANEH GHIASVAND,[2] ROBERT A. ROBERGS[2]

[1] Salisbury University, Salisbury, MD; [2] Exercise Physiology Laboratories, Exercise Science Program, University of New Mexico, Albuquerque, NM

ABSTRACT

ACUTE HYPOXIA ALTERS LACTATE THRESHOLD IN CHRONIC ALTITUDE RESIDENTS. **Todd A. Astorino, Farzaneh Ghiasvand, Robert A. Robergs**. **JEP**online 2004;7(2):6-15. At an identical workload, blood lactate concentration ([La]) is higher in acute hypoxia (H) versus normoxia (N). However, in altitude-acclimatized individuals, the lactate response to incremental exercise in H and with various VO_2max protocols is less clear. Subjects (N = 16) residing at moderate altitude completed VO_2max tests on a cycle ergometer in N and H (F_IO_2 = 0.15) using ramp (R) and step (S) protocols. Gas exchange data were obtained breath-by-breath during exercise. Blood samples were obtained for measurement of blood [La]. One-way ANOVA with repeated measures was used to examine differences between lactate threshold (LT) and blood [La] among the various protocols. LT was significantly higher ($p<0.05$) in S (68.1 ± 8.9 %VO_2max) and H (67.2 ± 9.6 %VO_2max) versus R (59.7 ± 8.9 %VO_2max). At VO_2max, blood [La] was higher ($p>0.05$) in R compared to S and H. At 50 %VO_2max, blood [La] was significantly higher ($p<0.05$) in S (2.0 ± 0.4 mmol/L) compared to R (1.7 ± 0.3 mmol/L and H (1.7 ± 0.6 mmol/L). In subjects acclimatized to altitude, the type of protocol used and gas fraction inspired alter the lactate response to incremental exercise. A standardized protocol for LT assessment is recommended to decrease discrepancies in LT between studies.

Key Words: Cycle Ergometry, VO_2max, Exercise Testing, Inspired Oxygen

INTRODUCTION

The blood lactate (La) response to incremental exercise to fatigue is well established, as typically blood [La] is maintained near 1 mmol/L at low to moderate workloads and increases non-linearly at higher workloads up to VO_2max. The oxygen uptake (VO_2) consequent with a rapid increase in blood [La], the lactate threshold (LT), represents a transition from primarily oxidative to non-oxidative pathways of ATP provision. Previously, researchers have described the LT using tracer methodology (1), activities of lactate (LDH) and pyruvate dehydrogenase (PDH) (2), and simple plots of blood [La] versus VO_2 (3,4). Nevertheless, no consensus

currently exists regarding a standardized technique of LT assessment, making comparisons of LT across different studies difficult.

Compared to normoxia (N), blood [La] in acute hypoxia (H) is higher at a given submaximal workload (2,5) but is similar (6) or higher (7) at VO_2max. For example, in a recent study (7), nine men completed incremental exercise to fatigue in 14 and 21 $\%O_2$. Results demonstrated that at workloads above 2.0 L/min, blood [La] was higher ($p<0.05$) in H versus N, similar to results in trained cyclists (8). At VO_2max, blood [La] was significantly higher in 14 $\%O_2$ (8.8 ± 0.3 mmol/L) versus 21 $\%O_2$ (7.0 ± 0.6 mmol/L), a result in discord with previous findings (9,10). These data suggest that blood [La] is significantly higher during submaximal exercise in acute H versus N, yet maximal blood [La] in H may or may not differ from N. Explanations for a higher blood [La] at VO_2max in acute H include anaerobiosis, enhanced glycolytic flux (11), and higher catecholamine levels (7). Due to the small sample size used in previous research, as well as the pivotal role of lactate metabolism in submaximal exercise performance, an additional study with more statistical power is warranted to identify differences in maximal blood [La] with manipulation of F_IO_2.

In regards to alterations in the LT in acute H, only a few studies (7,12,13) have investigated this topic. In the Cooper (1986) study (7), ten men completed VO_2max tests on separate days in H (15 $\%O_2$) and N. Results demonstrated that compared to N, LT from gas exchange data occurred at a lower work rate and VO_2 (19 % lower) in H. Similar findings were demonstrated in recent work (7) requiring trained men to complete incremental cycle ergometry in 14 $\%O_2$ and N. No difference ($p>0.05$) in relative LT was demonstrated in eight subjects undergoing incremental exercise in N, 12, and 15 $\%O_2$ (13). Nevertheless, this study did show that the absolute LT (expressed in L/min) is lower in H versus N. However, in this study (13), the LT was determined using the V-slope method, a gas exchange indicator of blood lactate accumulation. Nevertheless, no study to date has described the LT in H using a plot of log blood [La] to assess the LT, as recommended by Beaver (3).

Blood [La] may also be altered by the specific work rate increment administered during incremental exercise. It would be expected that compared to a ramp protocol with a modest continuous increase in work per stage, a step protocol characterized by large work rate increases per stage would induce a greater increase in lactate accumulation and thus earlier appearance of the LT. However, previous research (14,15) in sedentary men demonstrated no significant differences in anaerobic (ventilatory) threshold and other gas exchange parameters during ramp cycle ergometry with various work rate increments. However, blood [La] was not obtained in these investigations. Since the LT and ventilatory threshold appear to be caused by different mechanisms (16) and can differ by as much as 8 $\%VO_2$max (17), it is unknown if the LT is altered by variations in work rate increment during progressive exercise to fatigue.

Chronic altitude exposure also affects the lactate response to exercise. Past findings (18,19) demonstrate a lower blood [La] during exercise with chronic exposure to high altitude compared to acute H. During intense exercise, a reduction in maximal blood lactate accumulation was reported in subjects acclimatized to an altitude equal to 5,350 m (20). However, the majority of previous research investigating the lactate response in H has been performed at moderate to high altitudes (above 4,300 m), yet most sojourners to altitude reside at low to moderate elevations (580–2,500 m). Consequently, there is a need for additional research examining the lactate response to exercise at low to moderate altitudes.

The primary purpose of the study was to examine changes in LT and maximal blood [La] in response to manipulation of work rate increment and F_IO_2 during exercise to volitional fatigue. A secondary aim was to examine the blood lactate response to incremental exercise in altitude (~ 1,500–2,000 m) residents. It is hypothesized that in acute H, and in response to a step protocol, the LT will occur at a lower fraction of VO_2max compared to a normoxic ramp protocol.

METHODS

Subjects

Healthy, active subjects (12 men and 4 women) were recruited from the faculty, undergraduate, and graduate student populations of the university, as well as the surrounding community. The mean age, height, weight, and VO_2max of the subjects were 31.6 ± 8.9 yr, 172.0 ± 6.6 cm, 70.9 ± 12.7 kg, and 3,212.3 ± 651.8 mL/min, respectively. All subjects provided their informed consent before volunteering for the study, and all procedures were approved by the university's Human Subjects Institutional Review Board. All subjects resided at and were acclimatized to altitudes between 1,500 and 2,000 m above sea level. All data were collected at an altitude equal to 1,500 m (inspired PO_2 ~ 122 mm Hg).

Experimental Procedures

Each subject completed three different VO_2max protocols; a 75 Watt/3 min normoxic step protocol (S), a 25 Watt/min normoxic ramp protocol with workload set at 50 Watt for the first two minutes (R), and the identical ramp protocol under hypoxic (F_IO_2 = 0.15, P_B = 630 mmHg, P_IO_2 = 88.1 mmHg) conditions (H). In our study, "normoxia" represented a control condition with F_IO_2 = 0.2093 and P_IO_2 = 122 mm Hg, respectively. The order of these tests was assigned to subjects based on subject number according to a Latin Squares design (21). Subjects and all researchers with the exception of those operating the gas exchange system were blinded as to the specific VO_2max test to be administered that day. Prior to each trial, subjects were allowed approximately 10 min to accommodate to the selected gas mixture. Breath-by-breath gas exchange data were obtained using a metabolic cart (MedGraphics, Minneapolis, MN). These data were smoothed using an 11-breath moving average and were obtained continuously throughout exercise. Details of other gas exchange measurements are described in a recent paper (22). Humidified inspired air was directed from the high-pressure tank through a sample of distilled water, and then collected in a 100 L Tissot spirometric tank. Subjects inspired air from the tank and expired through a plastic mouthpiece and 3-way valve (Hans Rudolph Inc., Kansas City, MO). This metabolic cart measures expired airflow by means of a pneumotach connected to the mouthpiece. A sample line is connected to the pneumotach from which air is continuously pumped to O_2 and CO_2 gas analyzers. Prior to testing, the pneumotach was calibrated with ten samples from a 3 L calibration syringe. The gas analyzers were also calibrated before each test to room air and medically certified calibration gases (12.29 % O_2 and 5.12% CO_2, respectively).

Upon entering the laboratory, a catheter (Becton Dickinson, Sandy, UT) was inserted into the antecubital vein, connected to a three-way stopcock (B. Braun Medical Inc., Bethlehem, PA), and infused with sterile saline to prevent blood clotting. Seat and bar height of the cycle ergometer (Lode bv, Groningen, the Netherlands) were set according to the subject's specifications. A resting blood sample (1 mL) was obtained while the participant was sitting on the bike. Exercise was then started, with subjects completed the predetermined VO_2max protocol of between eight and twelve minutes duration. Subjects were instructed to maintain a pedal cadence between 80 and 100 rev/min during exercise and to exercise to volitional fatigue. Power output of the cycle ergometer was independent of pedal cadence. Termination of the test occurred when the subject was unable to maintain a pedaling cadence of 40 rev/min.

During the initial five minutes of exercise, 1 mL blood samples were obtained in standard 3 mL syringes every minute. From minute 5 to minute 10, blood samples were obtained at 30 s intervals, after which blood samples were taken every minute until cessation of exercise. Blood was immediately transferred to borosilicate tubes containing anticoagulant and antiglycolytic agents (heparin, potassium oxalate, and sodium fluoride), and these tubes were repeatedly shaken to prevent clotting. Maximal oxygen consumption was confirmed with appearance of two of the following criteria (22): (1) a plateau ($\Delta VO_2 \leq 50$ mL/min at VO_2max and the closest neighboring data point) in VO_2 with an increase in external work, (2) maximal respiratory exchange ratio (RER) ≥ 1.10, and (3) maximal HR within 10 beats/min of the age-predicted maximum (220-age). All subjects met the first two criteria.

Analytical procedures

Whole blood (0.5 mL) was pipetted into 1 mL of 6 % perchloric acid. Samples were mixed and centrifuged at 4 °C at 3500 rev/min for ten minutes. The supernatant was removed and refrigerated for subsequent analysis of blood [La]. Lactate concentration was obtained using a modification of an enzymatic spectrophotometric assay (23). Due to clotting of blood and occasional problems with sampling, blood samples from all trials were only obtained from 12 subjects.

The lactate threshold (LT) was detected by plotting log [La] (in mmol/L) versus time (min) for the different VO_2max protocols. Incidence of the LT was then transformed to a VO_2 equivalent based on the VO_2 versus time plot for each subject during each protocol. Bi-segmental linear regression was performed on the data resulting two regression lines that fit the data with the smallest residual error. The intersection of these lines denoted the LT (3). A traditional plot of log blood [La] versus log VO_2 was not used as this method induced dramatic variability in the blood lactate response to progressive exercise. Blood [La] was also obtained at relative (50 % protocol-specific VO_2max) and absolute (150 Watt) workloads to ascertain differences in blood [La] at submaximal work rates. The 150 Watt workload was selected as it was a sub-LT power output for the majority of subjects, and allowed comparison of our data to previous research (6).

Statistical Analyses

Data (mean ± SD) were analyzed using SPSS (Version 8.0). One-way analysis of variance (ANOVA) with repeated measures was used to examine differences between lactate thresholds, submaximal and maximal blood [La], VO_2max, and power output among the various VO_2max protocols. If a significant F ratio was obtained, Tukey's HSD was used to locate differences between means. Statistical significance was set at $p<0.05$.

RESULTS

Lactate threshold data

The relative lactate threshold in H (68.1 ± 8.9 %VO_2max) and S (67.2 ± 9.6 %VO_2max) was significantly higher (HSD=12.9, $p<0.05$, and HSD=1.3, $p<0.05$) than R (59.7 ± 8.9 %VO_2max) (Figure 1a). However, absolute lactate threshold (expressed in mL/min) was not significantly different ($p>0.05$) across protocols (Figure 1b).

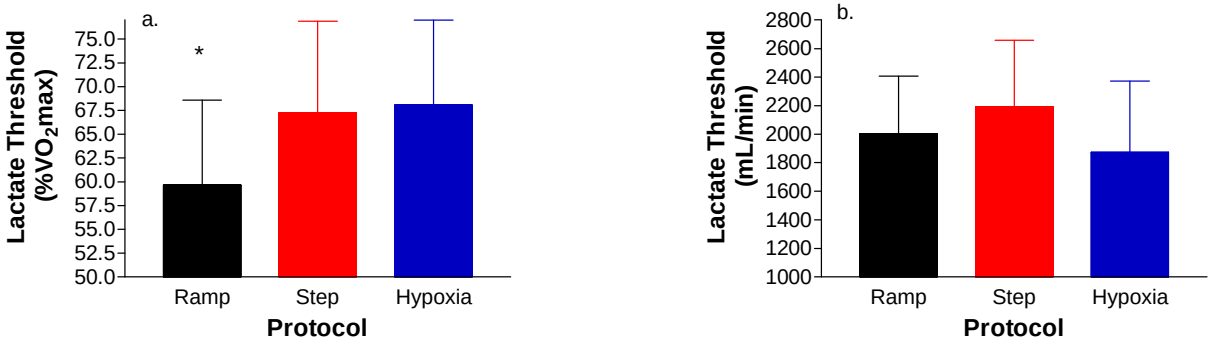

Figure 1: Mean ± SD data from the different protocols for a) relative lactate threshold and b) absolute lactate threshold. * = significantly different in R and S protocols compared to H

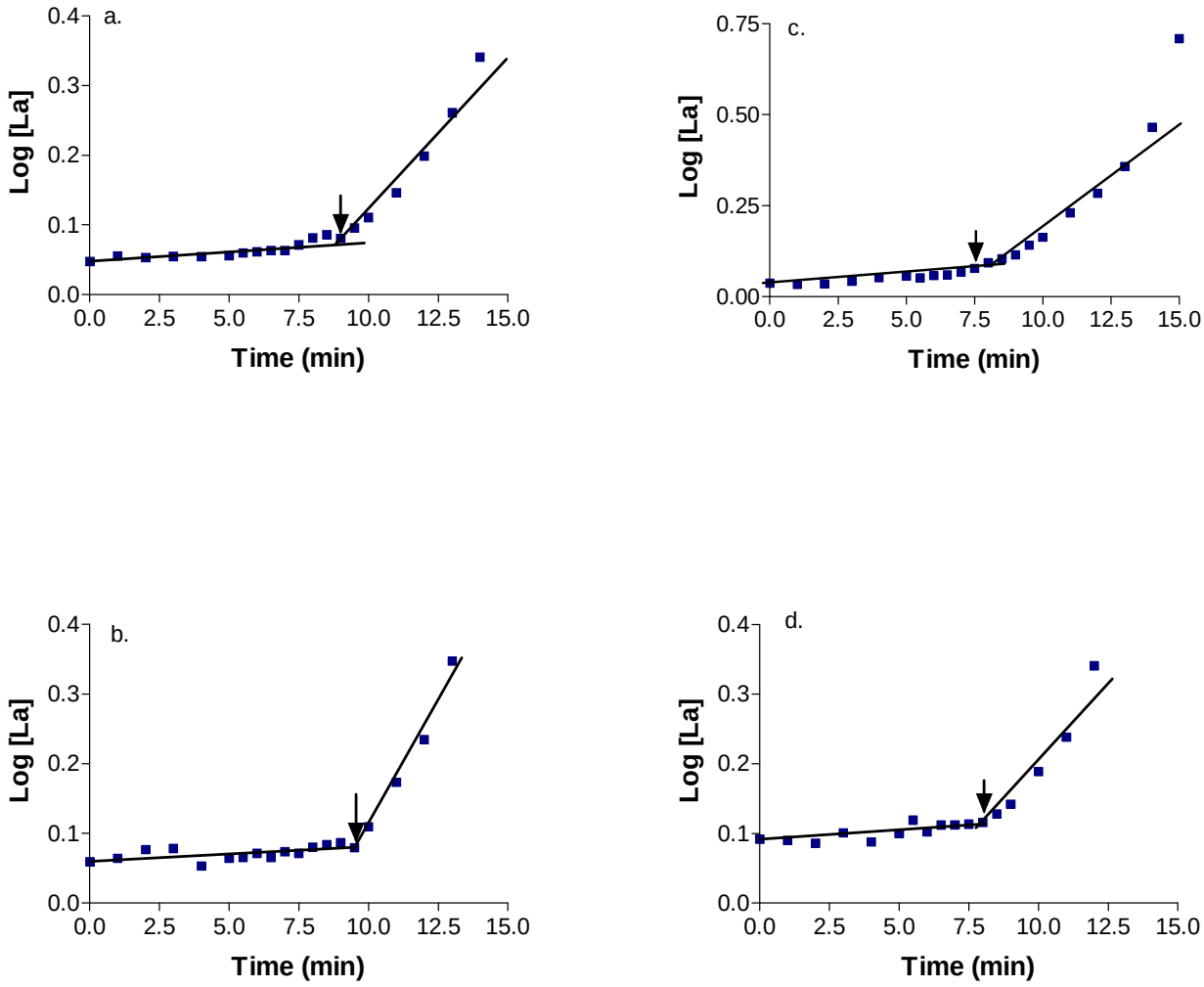

Figure 2. Determination of the LT for a) subject #2 in R and b) H, c) subject #5 in R and d) H.

Comparison of LT determination across protocols is shown in Figures 2a – 2d and 3a - 3d. These figures represent the blood lactate response to different incremental protocols and inspired gas fractions for four subjects. In each case, the LT occurred at a lower VO_2 in R versus the S and H protocols.

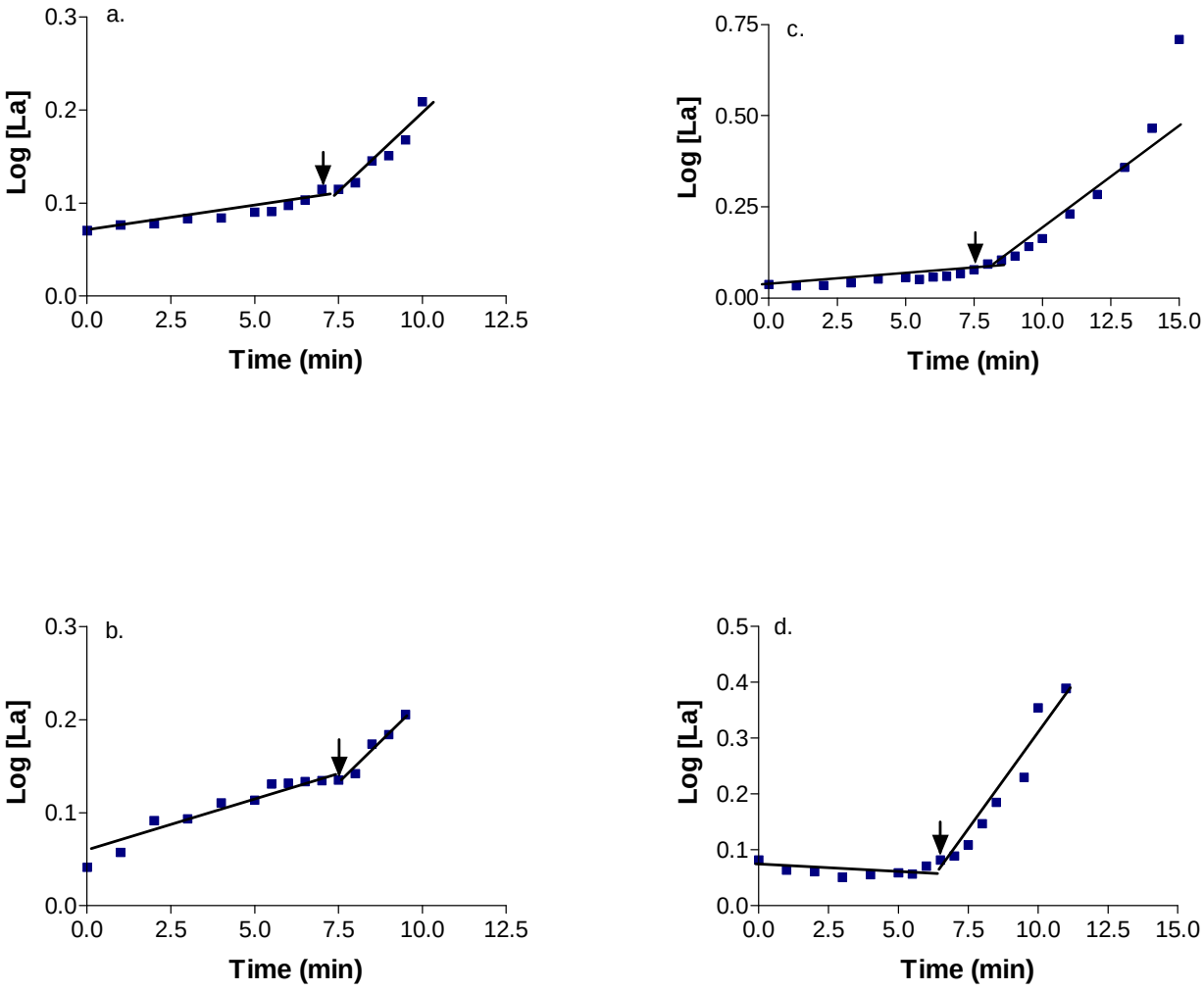

Figure 3. Determination of the LT for a) subject #1 in R and b) S, c) subject #9 in R and d) S.

Blood [La] at VO_2max

Mean blood [La] was not significantly different ($p>0.05$) among protocols. However, blood [La] was higher ($p=0.17$) in R (7.8 ± 3.1 mmol/L) compared to S (6.6 ± 2.8 mmol/L) and H (6.7 ± 2.4 mmol/L).

Blood [La] at Submaximal Workloads

At an identical relative work rate (50 %VO_2max), blood [La] was significantly higher ($p<0.001$) in S (2.0 ± 0.4 mmol/L) compared to R (1.7 ± 0.3 mmol/L) and H (1.7 ± 0.6 mmol/L). At 150 W, blood [La] was similar ($p>0.05$) among the protocols, although blood [La] was higher in H (2.4 ± 1.3 mmol/L) versus R (1.8 ± 0.6 mmol/L) or S (2.0 ± 0.6 mmol/L).

Gas Exchange Data

VO_2max was significantly different ($p<0.001$) across protocol. VO_2max in H (2,531.6 ± 562.4 mL/min) was significantly lower (HSD=14.5, $p<0.001$, and HSD=17.0, $p< 0.001$) compared to S (3,112.4 ± 660.1 mL/min) and R (3,212.3 ± 651.8 mL/min). Maximal power output was significantly higher ($p<0.001$) in R (307.7 ± 55.7 Watts) and S (309.4 ± 53.9 Watts) compared to H (262.5 ± 41.7 Watts).

DISCUSSION

The primary aim of the present investigation was to examine changes in LT and blood [La] in chronic altitude residents in response to various VO_2max protocols and inspired fractions of oxygen. Results demonstrated that relative LT occurred at a significantly higher fraction of VO_2max in H and S compared to R. Blood [La] at VO_2max was similar among protocols, although blood [La] in R was higher ($p>0.05$) than H. At a workload equal to 50 %VO_2max, blood [La] was significantly higher in response to the S protocol. At an identical absolute workload (150 W), blood [La] was not different among protocols. Overall, these data indicate that the specific incremental protocol used and gas fraction inspired alter the lactate response during exercise testing to volitional fatigue in altitude residents.

Our findings are in discord with previous work examining changes in LT in acute H. Previous research (12) required ten men to perform incremental cycle ergometry in H (15 %O_2) and N. Results demonstrated that the absolute LT occurred at a significantly lower workload in H compared to N. These findings are corroborated in female distance runners completing incremental treadmill exercise (24). However, relative LT in N and H was not reported by the authors, and they gave no explanation for earlier onset of the LT in H versus N. However, their results are in accord with recent data (25) revealing displacement of the arterial [La] - power output curve to the left in H (12 %O_2), indicating a trend toward earlier onset of blood lactate accumulation. Similarly, compared to N (1,939±89 mL/min and 46.5 %VO_2max, respectively), during acute H (14 %O_2) the absolute (1,547± 86 mL/min) and relative LT (42.5 %VO_2max) occurred at lower work rates in nine healthy men (7). Earlier research (6) demonstrated no differences in the lactate breakpoint between H (17 % O_2) and N (Figure 2, Table 3), although the LT occurred at a higher fraction of VO_2max in H (76 %) compared to N (73 %). However, this difference was not statistically significant, most likely due to a small sample size. These results are similar to our findings and data in highly-trained athletes (10). A higher relative LT in H may be explained by the marked decrease in VO_2max in response to acute H reported in the literature (7,22), yet alternative factors explaining these results are unknown. It is likely that during exercise, the more severe H equal to 15 %O_2 in combination with chronic altitude residence affected the blood lactate response of our subjects, although their individual effects are unknown. A recent study (26) demonstrated lower blood [La], and thus higher LT, at various stages of the Bruce protocol in six mountain climbers intermittently exposed to hypobaric hypoxia simulating altitudes of 4,000 to 5,500 m. However, is hypobaric hypoxic exposure via an altitude chamber similar to hypoxia from chronic altitude residence, and are their effects on lactate metabolism similar? Additional research is warranted to elucidate incidence of the LT in chronic H.

Potential factors explaining changes in the LT in response to acute H include the selected mode of exercise and work rate increment characterizing incremental exercise. The present study and others (6,7,25) required subjects to exercise to fatigue on a cycle ergometer, whereas subjects in the study of Yoshida et al. (24) completed treadmill exercise to exhaustion. Recent research (27) indicated that relative LT is significantly lower (53.5 ± 2.8 %VO_2max) in an exercise mode unfamiliar to the subject, and reported a markedly lower LT in competitive cyclists (65.3 ± 3.8 %VO_2max) running on a treadmill. VO_2max may be underestimated if incremental exercise lasts longer than 14 minutes, as stated in previous research (28) and based on our own unpublished observations. In the present study, VO_2max was attained by all subjects in 8–12 minutes; however, procedures in previous research (6,7,10) are characterized by incremental exercise lasting longer than twenty minutes. A prolonged protocol may induce greater subject fatigue and subsequent underestimation of VO_2max, which will increase the value of the relative LT.

An additional element leading to inconsistencies in the lactate response in acute H is the exact technique used to quantify the LT. In a similar procedure to our methods, Hogan et al. (6) assessed the LT by mathematically developing two linear combinations of blood [La] versus work rate, with the breakpoint representing the intersection of two lines with the lowest sum of squared residuals. In contrast, Koistinen et al. (10) graphically determined the LT as that VO_2 expressing a rapid increase in blood [La], whereas scientists in other research

(12,13,15) acquired the LT from gas exchange data. In the present study, log blood [La] was plotted versus time. The method of Beaver (3) using log-log transformation of blood [La] and VO_2 produces a fairly linear pattern of the lactate response to increasing workload, yet its application in the present study induced enhanced variability in determination of the LT. In addition, six of our twelve subjects expressed two lactate thresholds (Figure 4), a phenomenon also reported using electromyography in elite cyclists (29). When this occurred, the second threshold was selected as that subject's LT. Physiologically, this second threshold appears to be coincident with greater recruitment of primarily fast-twitch motor units that would promote lactate accumulation (29). This may account for the observed significantly higher LT in response to the S and H protocols. These discrepancies in relative LT in N and H warrant a standardized method of LT assessment, which would allow direct comparison of LT across studies, and perhaps enhance the understanding of the lactate threshold concept.

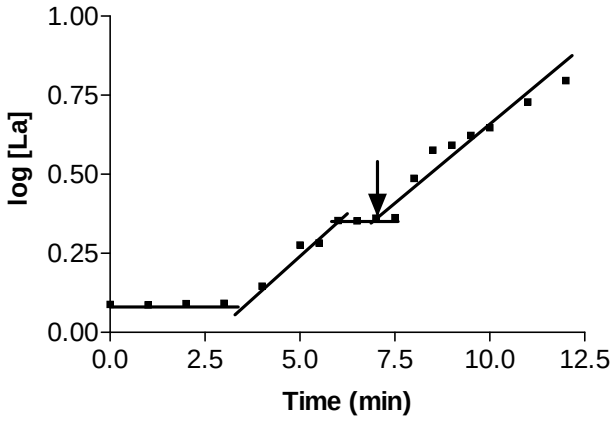

Figure 4. Determination of LT for subject #11 expressing multiple LT in response to R.

No difference in maximal blood [La] among the protocols was evident in the present study, although blood [La] was higher ($p>0.05$) in R versus H and S. Similar findings were reported in trained men ($VO_2max>57$ mL/kg/min) (25) and in healthy men (6). In contrast, other research in trained men (VO_2max ~ 4,200 mL/min) (5,7) noted that maximal blood [La] is significantly higher in H (8.8 ± 0.3 mmol/L and 9.1 mmol/L) compared to N (7.0 ± 0.6 mmol/L and 7.2 mmol/L, respectively). It is likely that the magnitude of H administered in these studies cannot explain the dissimilar findings, since F_IO_2 ranged from 0.12 to 0.17. Similarly, it is unlikely that the specific work rate increase of incremental exercise can account for the discrepant results, as suggested by these authors (6). Consequently, other factors including different training status of subjects may explain previously-reported differences in blood [La] at VO_2max in H versus N.

In the present study, blood [La] at the same absolute and relative submaximal workload was similar in H and R. This is in discord with previous research demonstrating a significantly higher blood [La] in H at the same absolute workload (2,8,30). Parolin et al. (2) noted that during the initial stages of exercise in acute H, glycogenolysis is accelerated and PDH activity is attenuated, leading to a transient imbalance between pyruvate production and oxidation, resulting in greater lactate production. This expedited glycolytic flux in H is mediated by greater degradation of phosphocreatine (PCr), yielding a larger pool of inorganic phosphate and AMP, which activates phosphorylase and thus increases glycogenolysis. Alternatively, it is plausible that our subjects' acclimatization and its accompanying blunting of the lactate response may explain the lack of differences in submaximal [La] between R and H, thus justifying the need in future research to elucidate the lactate response to exercise in more severe hypoxia in chronic low altitude residents.

Our results demonstrated that specific VO_2max protocol administered to subjects does not alter either the maximal or submaximal lactate response at the same absolute exercise intensity. However, at the same relative workload, blood [La] was significantly higher in S compared to R and H. In contrast, previous data (31) reveal higher blood [La] at both submaximal and maximal workloads in a slow (8 Watts/min) versus fast (50 Watts/min) ramp protocol. This was attributed to a longer duration for lactate efflux from skeletal muscle. Anecdotal reports from subjects in the present study revealed that the S protocol induces greater local muscle fatigue and soreness in comparison to other protocols, which may imply greater acidosis and coincident glycolytic flux in this protocol. Nevertheless, it is possible that compared to R and H, characterized by a 25 Watts/min work increment, the 75 Watts/3 min increment in work rate of S may generate a larger oxygen

deficit, and hence greater reliance on PCr degradation and glycolysis for ATP provision during the metabolic transient. These events should foster greater lactate accumulation, which may account for the higher ($p>0.05$) submaximal and maximal blood [La] in S. However, the 3-min stages in S may promote enhanced lactate clearance from muscle, but since lactate clearance has yet to be quantified in response to various VO_2max protocols or exposure to chronic hypoxia, it is speculative to suggest that a protocol with a larger work rate increment induces greater lactate accumulation compared to VO_2max tests with a more gradual increase in work rate. Overall, additional research is warranted to elucidate the lactate response to VO_2max protocols of varying work rate increment.

CONCLUSIONS

In summary, the LT occurred at a significantly higher fraction of VO_2max in H and S compared to R. No difference in blood [La] at VO_2max was demonstrated, although blood [La] was approximately 20 % higher in R compared to H and S. At 50 %VO_2max, exercise in S revealed a significantly higher [La] versus R and H. Consequently, it is plausible that protocol and fractional inspired oxygen content may alter the lactate response to incremental exercise. Ultimately, it is not practical to compare LT across studies due to widespread use of different methods of LT assessment. This should encourage investigators to adopt a standardized assessment technique for LT determination. Research investigating changes in the lactate response of low to moderate altitude residents is also warranted.

Address for correspondence: Todd A. Astorino, Ph. D, EPC, Program Director, Exercise Science Assistant Professor, Department of Physical Education, **Salisbury University,** 1101 Camden Avenue, Maggs PAC, Salisbury, MD 21801; Phone: (410) 677-5342; Fax: (410) 543-6434; Email: taastorino@salisbury.edu

ACKNOWLEDGEMENTS

The authors are indebted to the diligence, understanding, and dedication of our subjects who made this study possible.

REFERENCES

1. Brooks GA. Anaerobic threshold: review of the concept and directions for future research. ***Med Sci Sports Exerc*** 1985;17:22-31.
2. Parolin M, Spriet LL, Hultman E, Hollidge-Horvat M, Jones NL, and Heigenhauser G. Regulation of glycogen phosphorylase and PDH during exercise in human skeletal muscle during hypoxia. ***J Appl Physiol*** 2000;278:E522-34.
3. Beaver W, Wasserman K, and Whipp BJ. Improved detection of lactate threshold during exercise using a log-log transformation. ***J Appl Physiol*** 1985;59:1936-40.
4. Coyle EF, Coggan A, Hopper M, and Walters TJ. Determinants of endurance in well-trained cyclists. ***J Appl Physiol*** 1988;64:2622-30.
5. Adams R and Welch HG. Oxygen uptake, acid-base status, and performance with varied inspired oxygen fractions. ***J Appl Physiol*** 1980;49:863-8**.**
6. Hogan M, Cox R, and Welch HG. Lactate accumulation during incremental exercise with varied inspired oxygen fractions. ***J Appl Physiol*** 1983;55:1134-40.
7. Hughson R, Green HJ, and Sharratt M. Gas exchange, blood lactate, and plasma catecholamines during incremental exercise in hypoxia and normoxia. ***J Appl Physiol*** 1995; 79:1134-41.
8. Richardson RA, Noyszewski E, Leigh J, and Wagner PD. Lactate efflux from exercising human skeletal muscle: role of intracellular PO_2. ***J Appl Physiol*** 1998;85:627-34.
9. Knight D, Schaffartzik W, Poole DC, Hogan MC, Bebout D, and Wagner PD. Effects of hyperoxia on maximal leg O_2 supply and utilization in men. ***J Appl Physiol*** 1993;75:2586-94.

10. Koistinen P, Takala T, Martikkala V, and Leppaluoto J. Aerobic fitness influences the response of maximal oxygen uptake and lactate threshold in acute hypobaric hypoxia. ***Int JSports Med*** 1995;16:78-81.
11. Reeves JT, Groves BM, Sutton JR, Wagner PD, Green HJ, Cymerman A, et al. Adaptations to hypoxia: Lessons from Operation Everest II. In: Simmons, DH editor. **Current Pulmonology**. St. Louis, MO: Mosby Year Book, 1991:23-50.
12. Cooper D, Wasserman D, Vranic M, and Wasserman K. Glucose turnover in response to exercise during high- and low-F_IO_2 breathing in man. ***Am J Physiol*** 1986;251:E209-14.
13. Engelen M, Porszasz J, Riley M, Wasserman K, Maehara K, and Barstow TJ. Effects of hypoxic hypoxia on O_2 uptake and heart rate kinetics during heavy exercise. ***J Appl Physiol*** 1996;81(6):2500-8.
14. Zhang Y, Johnson M, Chow N, and Wasserman K. Effect of exercise testing protocol on parameters of aerobic function. ***Med Sci Sports Exerc*** 1991;23:625-30.
15. Davis JA, Whipp BJ, Lamarra N, Huntsman DJ, Frank MH, and Wasserman K. Effect of ramp slope on determination of aerobic parameters from the ramp exercise test. ***Med Sci Sports Exerc*** 1982;14:339-43.
16. Gaesser GA and Poole DC. Lactate and ventilatory thresholds: disparity in time course of adaptations to training. ***J Appl Physiol*** 1986;61(3):999-1004.
17. Gladden LB, Yates JW, Stremel RW, and Stamford BA. Gas exchange and lactate anaerobic thresholds: inter- and intraevaluator agreement. ***J Appl Physiol*** 1985;58:2082-9.
18. Bender P, Groves P, and McCullough R. Decreased exercise muscle lactate release after high altitude acclimatization. ***J Appl Physiol*** 1989;67(2):1456-62.
19. Brooks GA, Wolfel EE, Groves B, Bender PR, Butterfield GE, Cymerman A et al. Muscle accounts for glucose disposal but not blood lactate appearance during exercise after acclimatization to 4,300 m. **J Appl Physiol** 1992;72(6):2435-45.
20. Cerretelli P, Veicsteinas A, and Marconi C. Anaerobic metabolism at high altitude: the lactacid mechanism. In Brendel W, Zink RA, editors. **High altitude physiology and medicine**. New York: Springer-Verlag, 1982.
21. Keppel G. **Design and analysis: A researcher's handbook**. London: Prentice Hall, 1983.
22. Astorino TA, Robergs RA, Ghiasvand F, Marks D, and Burns S. Incidence of the oxygen plateau at VO_2max during exercise testing to volitional fatigue. ***J Exerc Physiol*** 2000;3:1-12.
23. Bergmeyer H. **Methods of enzymatic analysis**. New York: Academic, 1983.
24. Yoshida T, Udo M, Chida M, Makiguchi K, Ichioka M, and Muraoka I. Arterial blood gases, acid-base balance, and lactate and gas exchange variables during hypoxic exercise. ***Int J Sports Med*** 1989;10:279-85.
25. Knight D, Poole DC, Hogan MC, Bebout D, and Wagner PD. Effect of inspired oxygen concentration on leg lactate release during incremental exercise. ***J Appl Physiol*** 1996;81:246-51.
26. Casas, M., Casas, H., Pages, T., Rama, R., Ricart, A., Ventura, J.L., et al. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. ***Aviat Space Environ Med*** 2000;71(2):125-30.
27. Mazzeo R and Marshall P. Influence of plasma catecholamines on the lactate threshold during graded exercise. ***J Appl Physiol*** 1995;67:1319-22.
28. Howley ET, Bassett DR, and Welch HG. Criteria for maximal oxygen uptake: review and commentary. ***Med Sci Sports Exerc*** 1995;27:1292-01.
29. Lucia A, Sanchez O, Carvajal A, and Chicharro J. Analysis of the aerobic-anaerobic transition in elite cyclists during incremental exercise with the use of electromyography.
Br J Sports Med 1999;33:178-85.
30. Mazzeo RS, Bender PR, Brooks GA, Butterfield GE, Groves BM, Sutton JR et al. Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. ***J Appl Physiol*** 1991;261(24):E419-24.
31. Campbell M, Hughson R, and Green H. Continuous increase in blood lactate concentration during different ramp exercise protocols. ***J Appl Physiol*** 1989;66:1104-7.