Relationship Between Lactate and Ammonia Thresholds in Heart Transplant Patients

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The purpose of this investigation was to study the relationship between both blood ammonia thresholds (AmT) and lactate thresholds (LT) during dynamic exercise in cardiac transplant patients (CTPs). Eleven male patients who had undergone orthotopic cardiac transplantation (age: 54±11 years, mean±SD; height: 165.1±6.6 cm; body mass: 78.3±16.1 kg) participated in this study. Each of them performed a bicycle ergometer test (ramp protocol) until volitional fatigue. During each test, gas exchange parameters and ECG responses were determined continuously. In addition, blood lactate and ammonia concentrations were measured every 2 min for determination of both LT and AmT, respectively. Peak values of oxygen uptake (V<sub>O2</sub>), respiratory exchange ratio, ventilation, and heart rate averaged 15.9±3.03 mL·kg<sup>-1</sup>·min<sup>-1</sup>, 1.02±0.06, 46.69±5.69 L·min<sup>-1</sup>, and 124±16 beats per minute, respectively. However, blood concentrations of lactate and ammonia at peak exercise were 3.7±0.4 mmol·L<sup>-1</sup> and 85.6±31.7 μg·dl<sup>-1</sup>, respectively. LT and AmT were detected in 8 (72.7% of total) and 9 (81.8% of total) of 11 subjects, respectively. No significant differences were found between mean values of LT and AmT, when both were expressed either as V<sub>O2</sub> (10.01±1.19 vs 10.5±2.38 mL·kg<sup>-1</sup>·min<sup>-1</sup>, respectively) or as percent V<sub>O2</sub> peak (64.62±11.362 vs 66.48±9.19%, respectively). In addition, LT and AmT were significantly correlated (p<0.05) when both were expressed either as V<sub>O2</sub> (mL·kg<sup>-1</sup>·min<sup>-1</sup>) or as percent V<sub>O2</sub> peak (r=0.70 and r=0.68, respectively). Our findings suggest that in CTPs, both LT and AmT occur at similar workloads, probably as a result of skeletal muscle alterations associated with chronic deconditioning and immunosuppressive therapy.

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Key words: ammonia; anaerobic threshold; cardiac transplantation; lactate threshold

Abbreviations: ADP = adenosine diphosphate; AmT = ammonia threshold; ATP = adenosine triphosphate; CTP = cardiac transplant patients; HR = heart rate; IMP = inosine 5’-monophosphate; LT = lactate threshold; NH<sub>3</sub> = ammonia; PCr = phosphocreatine; V<sub>O2</sub> = oxygen consumption

Due to the surgical heart denervation in cardiac transplant patients (CTPs), the prescription of exercise intensity based on conventional heart rate (HR) monitoring is difficult in this special population group.¹,² Most clinicians, indeed, must rely on other parameters, such as the rate of perceived exertion or the anaerobic threshold, to monitor exercise intensity in these patients.³

During highly intense exercise, an increased amount of adenosine diphosphate (ADP) is produced when the rate of adenosine triphosphate (ATP) resynthesis does not match the rate of ATP hydrolysis. ADP molecules in excess, in turn, are degraded to form both inosine 5’-monophosphate (IMP) and ammonia (NH<sub>3</sub>).⁴⁻⁷ It has been suggested previously that ammonia concentration in blood significantly increases over resting values at an exercise intensity—the “ammonia threshold” (AmT)—higher than that intensity at which lactate levels begin to accumulate.⁸ Some studies, however, have shown a high correlation between blood levels of ammonia and lactate during exercise.⁹⁻¹² Moreover, such a relationship between both parameters might reflect the fact that accelerated rates of glycolysis and adenosine monophosphate deamination are linked mechanisms.⁹ To our knowledge, no study has been published to date concerning the relationship between ammonia and lactate responses during exercise in CTPs. However, in these patients, the muscle metabolic responses to exercise might be altered due to peripheral skeletal muscle or vascular abnormalities associated with previous chronic deconditioning before transplantation and to immunosuppression therapy.¹³,¹⁴

The purpose of this investigation was to study the
relationship between both blood AmT and lactate thresholds (LT) during dynamic exercise in CTPs.

MATERIALS AND METHODS

Patient Population

Eleven male patients who had undergone orthotopic cardiac transplantation (age: 54±11 years, mean±SD; height: 165.1±6.6 cm; body mass: 78.3±16.1 kg) participated in this study. In accordance with the institutional human subjects guidelines (Escuela de Medicina del Deporte de la Universidad Complutense de Madrid), written informed consent was given prior to participation in the experiments. At the time of evaluation, all patients were less than 1 year posttransplant (mean: 20.2 weeks; range: 8 to 29 weeks). All the patients were receiving immunosuppressive therapy consisting of cyclosporine, azathioprine, and prednisone, and had no signs of acute rejection.

Study Protocol

Prior to each exercise testing session, patients were familiarized with the equipment and procedures used in this study. All the subjects performed a bicycle ergometer test (Ergoline 900; Ergometrics; Barcelona, Spain) in a thermally moderate environment (21 to 24°C, 45 to 55% relative humidity). Each of the tests consisted of a ramp protocol, starting at 0 W; the workload was increased in 10 W·min⁻¹, and pedaling frequency was kept constant at 60 to 80 rpm. HRs were monitored continuously during the tests from modified 12-lead ECG tracings (Hellige, EK56). Exercise tests were terminated voluntarily by the subjects or when established test termination criteria were met.¹⁵

Expired Gas Analysis

During the exercise tests, gas exchange data were collected continuously using an automated breath-by-breath system (CPX; Medical Graphics; St. Paul, Minn),¹⁶ which was calibrated prior to each test using a standard 3-L syringe and precision reference gases; corrections were made for barometric pressure, ambient temperature, and humidity. Breath-by-breath data were transformed by interpolation into plots constructed using an eight-breath-moving average. The following parameters were recorded in each test: (1) exercise time (seconds); (2) work (watt [W]); (3) heart rate (beats per minute [bpm]) obtained from CM₅ precordial lead; (4) oxygen uptake (V̇O₂ in mL·kg⁻¹·min⁻¹); (5) respiratory exchange ratio (equal to VCO₂·VO₂); and (6) pulmonary ventilation (in L·min⁻¹).

Blood Lactate and Ammonia Concentrations

Capillary blood samples (50 μL) for the measurement of both blood lactate [YSI 231D; Yellow Springs Instruments; Yellow Springs, Ohio] and ammonia (Ammonia Checker II; Menarini Diagnostics; Kyoto, Japan) were taken from fingertips at rest, every 2 min during the tests, and immediately after termination of exercise.

LT and AmT Determinations

LT and AmT were determined by visual inspection of the blood lactate-V̇O₂ relationship and of the blood ammonia-V̇O₂ relationship observed on the exercise tests,¹⁷ respectively. Two independent, experienced observers manually detected LT and AmT by plotting lactate and ammonia concentrations against V̇O₂. If they did not agree, the opinion of a third investigator was included.

The V̇O₂ at both the LT and the AmT was expressed in absolute (mL·kg⁻¹·min⁻¹) and relative (percent of the peak V̇O₂) terms. Results were expressed as mean±SD. Student’s t test for paired data was used to determine if there was a significant difference (p<0.05) in V̇O₂ (mL·kg⁻¹·min⁻¹) and in percent V̇O₂ peak at the threshold as derived by each method. In addition, the relationship between LT and AmT was assessed by using the Pearson correlation coefficient (r) at the 0.05 level of significance.

RESULTS

Exercise Termination

All patients terminated voluntarily the exercise tests due to either leg/general fatigue or dyspnea, and not because of abnormal hemodynamic responses, arrhythmias, or ECG abnormalities. The average duration of tests was of 532±20 s.

Peak Values

Peak values of V̇O₂, respiratory exchange ratio, pulmonary ventilation, and HR averaged 15.9±3.03 mL·kg⁻¹·min⁻¹, 1.02±0.06, 46.69±5.69 L·min⁻¹, and 124±16 beats per minute, respectively. However, blood concentrations of lactate and ammonia at peak exercise were 3.7±0.4 mmol·L⁻¹ and 85.6±31.7 μg·dL⁻¹, respectively. The subjects reached an average

FIGURE 1. Example of determination of both LT and AmT in one patient.

FIGURE 2. Average values of LT and AmT. LT and AmT are expressed both as V̇O₂ (mL·kg⁻¹·min⁻¹) and as percent V̇O₂ peak. No significant difference (p>0.05) existed between means.
value of peak work of 83.6 W (range: 60 to 90 W) at the end of exercise.

Lactate and Ammonia Thresholds

Using both methods mentioned above, LT and AmT were detected in 8 (72.7% of total) and 9 (81.8% of total) of 11 subjects, respectively (72.7% of total) (Fig 1). No significant differences were found between mean values of LT and AmT, when both were expressed either as VO₂ (10.01±1.19 vs 10.5±2.38 mL·kg⁻¹·min⁻¹, respectively) or as percent VO₂ peak (64.62±11.362 vs 66.48±9.19%, respectively) (Fig 2). In addition, LT and AmT were significantly correlated (p<0.05) when both were expressed either as VO₂ (mL·kg⁻¹·min⁻¹) (Fig 3) or as percent VO₂ peak (r=0.70 and r=0.68, respectively) (Fig 4).

FIGURE 3. Relationship between LT and AmT when both expressed as VO₂ (mL·kg⁻¹·min⁻¹).

Discussion

The low values of VO₂ peak obtained in our investigation are in agreement with those reported for CTPs in previous studies.¹⁸,¹⁹ Such low values, in turn, are the result of peripheral muscle abnormalities attributed to both immunosuppressive medication and chronic deconditioning.¹⁸

Lactate levels at peak exercise, however, were lower than those obtained by other authors.¹⁶,²⁰,²¹ Such difference might be attributed to the protocol (ramp test) used in our study. During such types of exercise protocols, indeed, the blood lactate response to exercise might be delayed.²² In addition, the lower lactate concentrations found by us may also reflect age-related changes at a cellular level, since our subjects (mean of 54 years of age) were generally older than those selected in previous research. In this perspective, it has been documented that the motor recruitment pattern of fibers with a high glycolytic activity (type II fibers) might be altered with aging, resulting in lower lactate levels during exercise.²³

In the present investigation, the percent VO₂ peak corresponding to the LT (approximately 64%) was higher than the values (between 50% and 60%) reported in other studies.¹⁸,²⁰ As mentioned above, such difference might be due to the ramp protocol chosen in our study or to the older age of our subjects.

In healthy humans, during highly intense exercise, circulating ammonia levels begin to increase over resting values after the occurrence of the LT.³ This lack of coincidence between AmT and LT, in turn, has been attributed to the activation of type IIb fibers which occurs at high intensities (above LT) since human muscle mainly confines adenosine monophosphate deamination to fast-twitch fibers.²⁴ In the present investigation, however, both lactate and ammonia turnpoints seemed to occur at similar exercise intensities in CTPs. Several mechanisms might be involved. First, the results of muscle biopsies performed in patients with heart failure have evidenced that muscle atrophy is frequent in these individuals.²⁵ Moreover, a decrease in the percentage of type I fibers and in the activity of oxidative enzymes such as succinate dehydrogenase and citrate synthase, and an increase in the percentage of type IIa fibers have been reported in these patients.²⁵,²¹ Furthermore, such alterations might persist after cardiac transplantation, partly due to the sedentary life-style of CTPs.²⁶ The coincidence of AmT and LT in CTPs might therefore reflect metabolic abnormalities in muscle tissue induced by long-term inactivity,²⁷ although immunosuppressive therapy might also play an important role.²⁵,²⁰

In addition, the rate of muscle phosphocreatine (PCr) depletion with exercise might be increased in patients with heart failure,³⁰ contributing to the appearance of both AmT and LT at the same time. To maintain adequate muscle function during exercise, hydrolysis of ATP to ADP must be paralleled by an equal rate of ATP formation. Phosphorylation of ADP to ATP is mainly achieved through oxidative phospho-

FIGURE 4. Relationship between LT and AmT when both expressed as percent VO₂ peak.
rulation, but during intense exercise also through anaerobic processes such as formation of lactate and breakdown of PCr.5 However, when the rate of ATP resynthesis does not match the rate of ATP hydrolysis, adenine nucleotides in excess are degraded to form both IMP and NH3.4,7 Thus, the coincidence of both increases in both blood lactate and NH3 in CTPs might reflect a decreased potential for ATP rephosphorylation through the breakdown of PCr in these individuals.37 In any case, it might be kept in mind that blood ammonia concentration is the result of the balance between NH3 production in skeletal muscles and NH3 removal from liver.38 In addition, the ramp protocol used in our study might have also contributed to the observed delay in the occurrence of the LT,22 as mentioned above.

The AmT and the LT could not be detected in two and three patients, respectively. A major limitation of our study, indeed, comes from the fact that in some cases, the ramp protocol being used might not be sensitive enough to detect both thresholds in CTPs. In untrained individuals, AmT and LT appear at low intensities, such that it might sometimes be difficult to obtain a sufficient number of exercise levels before the occurrence of ammonia or lactate turnpoints. Some other types of incremental exercise protocols, including several intensity levels, ie, 6- or more 3-min stages at increasing intensities until exhaustion—can be used for LT or AmT detection in trained individuals. Such protocols, however, might not be easily tolerated by CTPs. In any case, further research is necessary using new, sensitive exercise tests for detecting AmT and LT in these patients. In this perspective, it would also be of great use to compare the response of both turnpoints in CTPs with that obtained in age-matched control groups.

Two main clinical implications might be derived from our findings. First, the measurement of the response of blood NH3 to exertion in CTPs could be of great utility when prescribing exercise programs in such patients, mainly in order to avoid excessively high work intensities. At exercise intensities above AmT, indeed, the rate of ATP breakdown considerably increases, which in turn results in an increased rate of IMP formation; in such conditions, muscle local fatigue might appear rapidly.8 However, blood NH3 determination could be of great prognostic value for assessing the effectiveness of an exercise rehabilitation program in improving the functional capacity of CTPs. In this perspective, a shift of AmT to a higher percentage of V02max—higher than that corresponding to the LT—should be expected with training. This response would indeed reflect an improvement in muscle utilization of aerobic metabolism, leading to a balance between ATP synthesis and degradation through a broader range of exercise intensities.

In conclusion, our results indicate that in CTPs, both LT and AMT occur at the same exercise intensity, probably as a result of alterations in skeletal muscle metabolism associated with chronic deconditioning and immunosuppressive medications. Further research is necessary to evaluate the practical applications of our findings.

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