Ammonia response to exercise in patients with congestive heart failure


Abstract

Objective—To assess energy depletion in skeletal muscle in patients with congestive heart failure by measuring blood purine metabolites during exercise and, at the same time, determine the implications of the ammonia response to exercise in these patients.

Setting—Tottori University Hospital, Yonago, Japan.

Patients—49 heart failure patients (New York Heart Association [NYHA] grades I-III) and 16 normal subjects.

Main outcome measures—Blood lactate, ammonia, and hypoxanthine levels were measured during exercise with expired gas analysis.

Results—In normal exercising subjects as well as in each heart failure subgroup, the ammonia threshold was significantly higher than both the lactate threshold [control: 21.8 (SD 5.5) v 17.4 (3.3) ml/kg/min; NYHA class I: 18.9 (3.8) v 15.5 (2.6); class II: 14.8 (2.5) v 12.7 (2.4); class III: 13.5 (2.6) v 11.8 (2.5)] and the ventilatory threshold (P < 0.01). The difference between the ammonia and lactate thresholds was noted in all normal subjects and in all heart failure patients. The ammonia threshold, however, was significantly lower in heart failure patients than in normal subjects and it decreased with increasing NYHA class (P < 0.01). Maximum ammonia levels were lower in the heart failure group and decreased further with higher NYHA classifications [control: 198 (52) mg/dl; NYHA class I: 170 (74); class II: 134 (58); class III: 72 (15); P < 0.01]. There were significant correlations between maximum ammonia values and maximum lactate, oxygen consumption, and hypoxanthine levels (r = 0.74, 0.48, and 0.87, respectively; P < 0.001).

Conclusions—The ammonia threshold may reflect the onset of ATP depletion in exercising skeletal muscles, as opposed to the onset of anaerobic respiration. It seems therefore that energy depletion in skeletal muscles during exercise occurs after attaining the anaerobic threshold. Both aerobic and anaerobic capacities of skeletal muscle are reduced in patients with congestive heart failure.

Keywords: congestive heart failure; exercise; ammonia threshold; lactate threshold

To determine the anaerobic threshold, blood lactate concentrations or expired gas analyses during exercise are commonly used.1–3 During exercise, blood lactate levels increase as skeletal muscle metabolism changes from aerobic to anaerobic by acceleration of the glycolytic pathway to compensate for adenosine triphosphate (ATP) depletion.1 In other words, the “anaerobic threshold” is the point at which energy begins to be supplied from the glycolytic pathway—as well as the oxidative pathway—so that the laboratory determined “lactate threshold” is equivalent to the physiological anaerobic threshold.

Rapid ATP consumption in skeletal muscle during exercise leads to the degradation of ATP and the accumulation of adenosine monophosphate (AMP). The accumulated AMP accelerates the purine nucleotide cycle and is degraded to several purine metabolites, namely, inosine, hypoxanthine, xanthine, and uric acid (fig 1).14 It is reported that blood and urine uric acid and its precursors (inosine and hypoxanthine) increase during exercise in patients with glycogen storage disease, and that ATP consumption and AMP accumulation are responsible for the overproduction of these purine metabolites.1 This phenomenon is referred to as “cell energy crisis”.9 Thus blood purine metabolite concentrations during exercise are thought to reflect energy depletion in skeletal muscles. On the other hand, ammonia is produced during conversion of AMP to inosine monophosphate in the purine nucleotide cycle (fig 1)15 and blood ammonia levels, like those of hypoxanthine, may also be related to energy metabolism in skeletal muscles.12–10 There are reports that blood ammonia concentrations during exercise vary independently of lactate.11–13 It has been determined, for instance, that a significant increase in blood ammonia occurred at 82.5% of maximum exercise intensity, while lactic anaerobic conditions were already provoked at lower levels.14 However, the exact cause of this difference between blood lactate and ammonia responses is unclear.

Recently, several investigators have shown abnormalities in skeletal muscle metabolism which are responsible for determining exercise tolerance in patients with heart failure;15–17 and Sullivan et al have shown that aerobic enzyme activity in skeletal muscle is reduced in patients with congestive heart failure.18 These reports indicate a problem with energy utilisa-
tion by skeletal muscle in patients with congestive heart failure.

Most studies on the ammonia response to exercise have been done in animals or sprinters. The implications of changes in the ammonia level during exercise in patients with congestive heart failure have not been evaluated or determined directly. The purpose of this study was therefore to assess energy depletion in skeletal muscle in patients with congestive heart failure by measuring blood purine metabolites during exercise, and at the same time to determine the implications of the ammonia response to exercise in such patients.

Methods

Patients

Forty nine patients with congestive heart failure and 16 normal subjects were studied. Among the congestive heart failure patients, 18 were in New York Heart Association (NYHA) class I, 17 in class II, and 14 in class III (table). The congestive heart failure group consisted of 15 patients with idiopathic dilated cardiomyopathy, 16 with an old myocardial infarction, 16 with valvar heart disease, and two with congenital heart disease. Patients with any pulmonary, hepatic, or renal disease were excluded because liver and kidney function play a significant role in purine metabolism. Patients receiving allopurinol and patients with signs or symptoms of ischaemia during exercise (chest pain or significant ST depression) were also excluded from this study. Forty two of the 49 patients were taking diuretics and 39 were taking digoxin. Twenty two were on long acting isosorbide dinitrate, and 17 were on an angiotensin converting enzyme inhibitor. Nineteen of the patients with old myocardial infarction or hypertension were taking long acting calcium channel antagonists. The following studies were performed in patients while on their respective medications.

Exercise Testing

Ramp exercise testing was performed using an upright bicycle ergometer (50 rpm) and expired gas analysis. All subjects rested at least 30 min before starting exercise. After 4 min of unloaded cycling, the exercise load was increased by increments of 20 W/min for the normal subjects, or by 10 W/min for NYHA class III patients. The increments of exercise load for NYHA class I and II patients were 10 or 20 W/min, so that exercise durations were equivalent between the groups. Exercise was discontinued when the subject was unable to continue pedalling or with the development of severe dyspnoea, that is, 7 on the new Borg scale. Heart rate and ECG were monitored continuously using CASE12 (Marquette Electronics). Blood pressures were measured every minute by cuff technique using STBP 680 (Nippon Kolin).

Cardiopulmonary Gas Analysis

Expired gas analyses was performed continuously during rest, exercise, and the recovery period using an automated breath-by-breath system (Medical Graphic). The ventilatory threshold was determined using the V-slope method.

Blood Sampling and Measurements

Blood was collected from the brachial artery through a short indwelling polyethylene catheter. Blood samples for lactate and ammonia determinations were obtained at rest, at the end of warming up, at 1 min intervals during exercise, immediately after exercise, and at 1, 2, and 3 min thereafter. Samples for hypoxanthine were obtained at rest, immediately after exercise, and 10, 20, and 30 min into the recovery period. Blood lactate and ammonia concentrations were defined by enzymatic methods (model 23L, YSI, and COBAS-FARA, Roche, respectively). Blood hypoxanthine concentrations were measured by high performance liquid chromatography (HPLC; model 510, Waters).

Lactate and ammonia concentration points were fitted according to the regression analysis of a two segment logarithmic plot of the respective serum concentrations versus log (oxygen consumption: \( V_{O_2} \)) and the lactate threshold and the ammonia threshold were defined as the \( V_{O_2} \) at which the blood lactate.
and ammonia concentrations began to increase above a resting level.\textsuperscript{27}

**Statistics**

Comparisons of mean values were performed using one way analysis of variance. Analyses of correlations were performed using Spearman rank correlation. Statistical values are expressed as mean (SD) and statistical significance is defined as $P < 0.05$.

**Results**

In expired gas analysis, both maximum oxygen consumption (peak $V_O_2$) and ventilatory threshold in all congestive heart failure patients were lower than in normal patients, at 19.9 (SD 5.4) v 29.8 (6.2) ml/kg/min and 14.2 (3.3) v 18.1 (3.7) ml/kg/min respectively; $P < 0.01$. In congestive heart failure patients, both peak $V_O_2$ and ventilatory threshold were lower in proportion to NYHA functional class: peak $V_O_2$: NYHA class I, 25.2 (4.1) ml/kg/min; class II, 19.0 (2.3); class III, 14.5 (2.4); ventilatory threshold: NYHA class I, 16.7 (2.9) ml/kg/min; class II, 13.2 (2.4); class III, 12.1 (2.9) (table). The peak work rate in congestive heart failure patients was significantly lower than in normal subjects, and also lower in proportion to NYHA class, as were the peak $V_O_2$ and ventilatory thresholds (table).

**Figure 2**

A representative example of blood ammonia, lactate, and hypoxanthine (HX) responses to exercise in a normal subject (60 year old male) and a NYHA class II patient (58 year old male). The blood ammonia and lactate levels increased during exercise and both peaked within 2 min after exercise. HX levels increased a little during exercise and the peak was observed 10 or 20 min after exercise. Ammonia threshold (AmT) of the congestive heart failure patient occurred at lower exercise intensity than in a normal subject as did the lactate threshold (LT), and the maximum ammonia levels of the patient were lower than those of the normal subject. Note that the ammonia threshold occurred after the lactate threshold in both the normal subject and the patient.

**Figure 3**

Ventilatory threshold (VT), lactate threshold (LT), and ammonia threshold (AmT) in normal subjects and in each congestive heart failure subgroup. AmT decreased significantly in parallel with the NYHA class, as did LT and VT.
and congestive heart failure patient (NYHA I-III).

The lactate and ventilatory thresholds were similar in normal subjects and in each congestive heart failure subgroup. However, the ammonia thresholds ([mmol/litre] control, 3.5 (1.5); NYHA class I, 3.5 (2.0); class II, 2.2 (1.3); class III, 1.2 (0.5)] and hypoxanthine concentrations ([mmol/litre] control, 198 (52); NYHA class I, 170 (74); class II, 134 (58); class III, 72 (15)] were significantly lower in the patients with congestive heart failure, as were peak VO₂ and maximum lactate concentrations ([mmol/litre] control, 6.7 (1.4); NYHA class I, 5.8 (1.4); class II, 5.6 (1.2); class III, 3.6 (0.7)]. Note that in the congestive heart failure patients, these variables also decreased according to the NYHA classification (fig 4).

Significant correlations were observed between the maximum ammonia and the maximum lactate and peak VO₂ levels (r = 0.74, 0.48, respectively, P < 0.001) (fig 5). In addition, and importantly, we noted a strong correlation between the maximum ammonia and hypoxanthine levels (r = 0.87, P < 0.001).

Discussion

ATP consumption and consequent AMP accumulation are responsible for the overproduction of the purine metabolites (inosine, hypoxanthine, xanthine, and uric acid) during exercise.29-30 Thus purine metabolites are considered to be markers for a so called “cell energy crisis”9 and are thought to reflect energy depletion in skeletal muscles. The increase in plasma ammonia concentrations during exercise is derived from the purine nucleotide cycle by the action of myoadenylate deaminase.8 Moreover, in patients with myoadenylate deaminase deficiency, blood ammonia does not increase during exercise,29-30 supporting the concept that excess degradation of metabolites in the purine nucleotide cycle induces the observed increase in blood ammonia during exercise. In this study, there was a strong correlation between the maximum ammonia and hypoxanthine levels, which is reasonable because both ammonia and hypoxanthine are derived from the purine nucleotide pathway. While AMP deaminase has been reported to be activated not only by the increase of AMP but also by hydrogen ions (H⁺)31 formed as a result of lactate accumulation, Dudley and Terjung were able to show an increase in inosine monophosphate despite the absence of a change in pH.32 Moreover, nucleotide loss has been demonstrated in the absence of lactate formation and acidosis, as has the lack of an H⁺/ammonia relation.33-35 These findings point to an accumulation of AMP as the main stimulus to ammonia production. The blood ammoo
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Ammonia level, therefore, may reflect energy depletion (AMP accumulation) in skeletal muscles during exercise.

To the best of our knowledge there have not been any previous reports on the relation between the ammonia threshold and the lactate threshold. In this study, the lactate threshold was slightly lower than ventilatory threshold in each group. However, these differences were not significant. On the other hand, the ammonia threshold was significantly higher than the lactate threshold and the ventilatory threshold in all the normal controls and all the congestive heart failure patients without exception. This shows that ammonia is produced at a higher exercise intensity, particularly beyond the anaerobic threshold. In other words, the purine nucleotide cycle was accelerated at a higher levels of exercise than were needed to achieve the anaerobic threshold. Several reports have shown that ammonia responses are different from lactate responses during exercise of varying intensities, and in particular that blood ammonia begins to increase at higher exercise levels than blood lactate. However, the reason for this difference is not known. If the onset of excess degradation of the purine nucleotide cycle indicates the depletion of ATP and accumulation of AMP, then the ammonia threshold may well imply the onset of the energy depletion in exercising skeletal muscle.

We speculate, therefore, that there may be three stages of exercise intensity. First, during exercise below the anaerobic threshold, skeletal muscles are supplied with ATP through the oxidative pathway and the ATP level is sufficient. Second, during exercise above the anaerobic threshold but below the ammonia threshold, ATP is supplied by both the oxidative and glycolytic pathways and ATP depletion does not yet occur; at this time blood lactate increases but blood ammonia does not. Lastly, when the exercise intensity rises above the ammonia threshold, rapid consumption of ATP occurs in excess of its synthesis by the oxidative and glycolytic pathways, and both the blood lactate and the blood ammonia concentrations will increase. These three stages of exercise intensity according to energy supply and consumption may be the cause of the differences in ammonia and lactate responses. This phenomenon is naturally observed in both normal subjects and congestive heart failure patients.

Because we used brachial arterial sampling instead of central venous sampling, there is another possibility—that the higher ammonia threshold is due the high rates of ventilation achieved during exercise which might enhance ammonia excretion but not lactate excretion. Indeed, expired air has been shown to contain ammonia, and some investigators have speculated that the lung is the major clearance organ for ammonia during exercise. However, no one has examined the differences between central venous and arterial ammonia concentrations during exercise to determine the impact of hyperventilation on measured ammonia levels. Nevertheless, previous studies using venous sampling for measuring ammonia and lactate levels have documented this difference in ammonia and lactate thresholds.

In this study, we note that blood ammonia levels increased during exercise while hypoxanthine levels increased primarily after exercise. This observation is consistent with previous reports. Although the underlying cause of this time lag between ammonia and hypoxanthine levels is not clear, several mechanisms have been proposed. First, ammonia is produced at the beginning of the purine nucleotide cycle while hypoxanthine is produced following the degradation of inosine (fig 1). Thus the time lag at this level may cause the observed delay between the ammonia and hypoxanthine responses during exercise. Second, ammonia readily enters the blood across cell membranes, while it may take longer for hypoxanthine to do so. This difference in responses are dependent on pH. If and in skeletal muscle with acidosis from the accumulation of lactate during exercise it becomes increasingly difficult for hypoxanthine to cross the cell membrane. After exercise, however, when the acidosis is compensated, the hypoxanthine accumulated in skeletal muscle may suddenly enter the blood. Finally, if the ATP consumed during exercise is reconstituted after exercise, then the purine nucleotide salvage pathway will be accelerated after exercise. Patterson and colleagues have referred to this as "purine debt". The existence and importance of each of these possible mechanisms are, respectively, unconfirmed and unknown, and warrant further study.

We did not measure ammonia concentrations in skeletal muscle in this study. In previous studies, a rise in plasma ammonia correlated with both muscle ammonia concentration and muscle ammonia efflux, and changes in plasma ammonia, hypoxanthine, and uric acid each correlated significantly with the change in ATP content measured in the skeletal muscle. These data imply that changes in plasma ammonia really reflect the changes in ammonia and the loss of ATP in skeletal muscle during exercise.

In this study, ammonia thresholds and maximum ammonia levels in congestive heart failure patients were lower than those in normal subjects. These results suggest that energy depletion in skeletal muscle occurred earlier in heart failure and that maximum energy depletion at peak exercise was lower in congestive heart failure patients than in normal subjects. In other words, patients with congestive heart failure are more intolerant of energy depletion. This may imply that there is reduced anaerobic and aerobic capacity in skeletal muscle in congestive heart failure patients. Maximum ammonia levels during exercise may be partly dependent on exercising skeletal muscle volume, as are maximum lactate levels. We did not measure muscle volume, and body mass index (BMI) in NYHA III patients was lower than the other groups (table); but when normalised to BMI, maximum blood ammonia
levels also decreased according to the NYHA class: (mg/kg/dl^2) control, 9-08 (1-3); NYHA class I, 6-94 (1-2); class II, 5-96 (1-1); class III, 3-64 (0-3); P < 0-05.

The results from this study indicate that the ammonia threshold was invariably higher than the anaerobic threshold, and that both the ammonia threshold and the maximum ammonia levels were lower in chronic heart failure patients than in normal subjects. Thus the accumulation of ammonia (excess degradation of AMP) in working skeletal muscles during exercise occurs after the anaerobic threshold. Further, both aerobic and anaerobic capacity of skeletal muscle is reduced in patients with heart failure.

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1 Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol 1964;14:844-52.
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