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 5.3) 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 level increases 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).4 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.5 This phenomenon is referred to as "cell energy crisis".6 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)7 and blood ammonia levels, like those of hypoxanthine, may also be related to energy metabolism in skeletal muscles.8-10 There are reports that blood ammonia concentrations during exercise vary independently of lactate.11,12 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.12 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,5-17 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-
monary, hepatic, or renal disease were excluded because liver and kidney function play significant roles 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.17 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 were 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.22-25

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 measured 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: \( V_{\text{O}_2} \)).25 26 and the lactate threshold and the ammonia threshold were defined as the \( V_{\text{O}_2} \) at which the blood lactate

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**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 pulmonarion by skeletal muscle in patients with congestive heart failure.

Most studies on the ammonia response to exercise have been done in animals or sprinters.19 20 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, ammonia metabolites during exercise, and at the same time to determine the implications of the ammonia response to exercise in such patients.

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**Figure 1** Purine nucleotide cycle in skeletal muscle. Ammonia is produced at the beginning of the purine nucleotide cycle, while hypoxanthine is produced following the degradation of inosine. Excess degradation of ATP leads to the accumulation of AMP and the purine nucleotide cycle is accelerated, which results in the increase in blood ammonia and hypoxanthine levels. ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; IMP, inosine monophosphate.
and ammonia concentrations began to increase above a resting level.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 \( \text{VO}_2 \)) 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 \( \text{VO}_2 \) and ventilatory threshold were lower in proportion to NYHA functional class: peak \( \text{VO}_2 \); 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 \( \text{VO}_2 \) and ventilatory thresholds (table).

![Graphs showing lactate, ammonia, and hypoxanthine levels](image)

Figure 2 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.

![Graphs showing lactate, ammonia, and hypoxanthine levels](image)

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 ([ml/kg/min] control, 21.8 (5-3); NYHA class I, 18.9 (3-8); class II, 14.8 (2-5); class III, 13.5 (2-6)) were significantly lower than both the lactate threshold ([ml/kg/min] control, 17.4 (3-3); NYHA class I, 15.5 (2-6); class II, 12.7 (2-4); class III, 11.8 (2-5)) and the ventilatory threshold (P < 0.01, control v each congestive heart failure group). This difference between ammonia and lactate thresholds—and ventilatory threshold—was noted in all normal and all congestive heart failure patients without exception. The ammonia threshold was significantly lower in the congestive heart failure groups than in the normal controls, and the ammonia threshold decreased significantly with increasing NYHA class, as did both lactate and ventilatory thresholds (fig 3).

Maximum hypoxanthine ([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 ammonia concentrations ([mg/dl] control, 198 (52); NYHA class I, 170 (74); class II, 134 (58); class III, 72 (15)) were all 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 (fig 1). ATP purine metabolites are considered to be markers for so-called "cell energy crisis," 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. In patients with myoadenylate deaminase deficiency, blood ammonia does not increase during exercise, 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+) 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. Moreover, nucleotide loss has been demonstrated in the absence of lactate formation and acidosis, as has the lack of an H+/ammonia relation. These findings point to an accumulation of AMP as the main stimulus to ammonia production. The blood ammoo-
Ammonia response to exercise in patients with congestive heart failure

Ammonia level, therefore, may reflect energy deple-
tion (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 lac-
tate threshold. In this study, the lactate thresh-
old was slightly lower than ventilatory
threshold in each group. However, these dif-
fferences were not significant. On the other
hand, the ammonia threshold was significantly
higher than the lactate threshold and the venti-
latory threshold in all the normal controls and
all the congestive heart failure patients without
exception. This shows that ammonia is pro-
duced at a higher exercise intensity, particu-
larly beyond the anaerobic threshold. In other
words, the purine nucleotide cycle was acceler-
ated 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 response
during exercise of varying intensities, and in
particular that blood ammonia begins to
increase at higher exercise levels than blood
lactate.11-13  However, the reason for this dif-
fERENCE is not known. If the onset of excess
degradation of the purine nucleotide cycle
indicates the depletion of ATP and accumula-
tion of AMP, then the ammonia threshold
may well imply the onset of the energy deple-
tion in exercising skeletal muscle.

We speculate, therefore, that there may be
three stages of exercise intensity. First, during
exercise below the anaerobic threshold, skele-
tal muscles are supplied with ATP through the
oxidative pathway and the ATP level is suffi-
cient. Second, during exercise above the
anaerobic threshold but below the ammonia
threshold, ATP is supplied by both the oxidat-
ive and glycolytic pathways and ATP deple-
tion 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 con-
centrations will increase. These three stages of
exercise intensity according to energy supply
and consumption may be the cause of the dif-
fferences in ammonia and lactate responses.
This phenomenon is naturally observed in
both normal subjects and congestive heart fail-
ure 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 specu-
lated 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 concen-
trations during exercise to determine the
impact of hyperventilation on measured
ammonia levels.36-38  Nevertheless, previous
studies using venous sampling for measuring
ammonia and lactate levels have documented
this difference in ammonia and lactate thresh-
olds.11-13 14

In this study, we note that blood ammonia
levels increased during exercise while hypox-
anthine levels increased primarily after exer-
cise. This observation is consistent with pre-
vious reports.39-40  Although the underlying
cause of this time lag between ammonia and
hypoxanthine levels is not clear, several mech-
isms can be proposed. First, ammonia is pro-
duced at the beginning of the purine nucleo-
tide cycle while hypoxanthine is pro-
duced 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 differ-
ence in permeability is increased by pH,41-42
and in skeletal muscle with acidosis from the
accumulation of lactate during exercise it
becomes increasingly difficult for hypoxan-
thine to cross the cell membrane. After exer-
cise, 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 col-
leagues have referred to this as “purine debt”.
39  The existence and importance of each
of these possible mechanisms are, respectively,
unconfirmed and unknown, and warrant fur-
ther study.

We did not measure ammonia concentra-
tions in skeletal muscle in this study. In pre-
vious studies, a rise in plasma ammonia
levels in congestive heart failure patients
was lower than those in normal sub-
jects. These results suggest that energy
depression in skeletal muscle occurred earlier in
heart failure and that maximum energy deple-
tion 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 anaero-
bic and aerobic capacity in skeletal muscle in
congestive heart failure patients.18  Maximum
ammonia levels during exercise may be partly
dependent on exercising skeletal muscle vol-
ume, 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 nor-
malised to BMI, maximum blood ammonia
levels also decreased according to the NYHA class: (mg/kg/dl²/m²) 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 congestive 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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33. Jacobs JA, Popell JW, Jeltsch R. Partial pressure of ammno-