# Altered Purine and Glycogen Metabolism in Skeletal Muscle During Exercise in Patients With Heart Failure

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**Plasma levels of ammonia and hypoxanthine (HX) can be indices of purine nucleotide degradation. The present study determined if patients with heart failure (HF) have altered exercise plasma ammonia and HX levels relative to the peak work rate performed. Blood lactate, plasma ammonia, and plasma HX levels were measured in 59 patients with HF (New York Heart Association [NYHA] classes I:20, II:21, and III:18) and 21 controls at rest and after a maximal cardiopulmonary exercise test. The peak work rate (normal and NYHA I, II, and III, 163 ± 11, 152 ± 9, 94 ± 5, and 69 ± 5 W) and peak oxygen uptake ([$VO_2$] 32.3 ± 1.7, 25.1 ± 0.9, 18.6 ± 0.5, and 14.1 ± 0.6 mL/min/kg) decreased as the NYHA functional class increased. The increment from rest to peak exercise (Δ) for lactate ([Δlactate] 6.1 ± 0.3, 4.8 ± 0.4, 4.6 ± 0.3, and 2.9 ± 0.3 mmol/L), Δammonia (132 ± 14, 119 ± 20, 94 ± 13, and 32 ± 6 μg/dL), and ΔHX (33.5 ± 3.4, 24.9 ± 4.7, 20.6 ± 3.0, and 9.9 ± 1.2 μmol/L) was progressively smaller as HF worsened. The ratio for Δlactate to peak work rate (0.037 ± 0.003, 0.032 ± 0.004, 0.049 ± 0.003, and 0.042 ± 0.005) was higher in classes II to III HF, while the ratio for Δammonia to peak work rate (0.81 ± 0.14, 0.78 ± 0.16, 0.99 ± 0.11, and 0.47 ± 0.11) was significantly lower in class III HF. In summary, patients with HF exhibited a smaller ammonia response with a higher lactate response to exercise when normalized with the peak work rate. These results suggest there may be an altered purine and glycogen metabolism during exercise in skeletal muscle in patients with HF.**


STRENUOUS MUSCLE EXERCISE causes rapid consumption of adenosine 5′-triphosphate (ATP) and associated increases in adenosine 5′-diphosphate (ADP) and adenosine 5′-monophosphate (AMP).[1,2] Accumulated adenosine phosphates accelerate purine nucleotide degradation, producing inosine 5′-monophosphate (IMP), inosine, hypoxanthine (HX), and in some tissues xanthine and uric acid[3-5] (Fig 1). In this degradation cascade, AMP is deaminated to form IMP by AMP deaminase, and ammonia is produced.[6,7] AMP deaminase is a rate-limiting allosteric enzyme and HX is a main metabolite in skeletal muscle, which subsequently appears in the plasma. Thus, plasma levels of ammonia and HX can be indices of purine nucleotide degradation during exercise. It has been well demonstrated that purine nucleotide metabolites in blood are reduced or absent postexercise in patients with inherited defects in glycolysis[8] and AMP deaminase deficiency.[9] These observations together with findings from muscle biopsy studies[1,2] confirm that postexercise increases in ammonia and HX are derived from the breakdown of adenine nucleotides in skeletal muscle.

A previous study from our laboratory[10] demonstrated that peak plasma ammonia and HX levels were lower in patients with heart failure (HF) after maximal exercise, suggesting that purine nucleotide degradation is decreased after maximal exercise. This speculation is of interest in relation to the recently reported findings of increased plasma adenosine levels in patients with HF.[11] The increase in adenosine is associated with an increase in 5′-nucleotidase, an enzyme responsible for adenosine production.[12] Taken together, the decreased purine nucleotide degradation during exercise with augmented adenosine production may be due to the alteration of adenine nucleotide catabolism in HF. Smaller peak levels of plasma ammonia and HX could be due to the smaller workload performed in patients with HF. However, in our previous study, the response of ammonia and HX were not assessed in relation to the exercise workload achieved. Therefore, we investigated the plasma ammonia and HX and blood lactate concentrations to determine if purine nucleotide and glycogen metabolism is altered in patients with varying degrees of HF when normalized with the peak workload.

## SUBJECTS AND METHODS

### *Subjects*

We studied fifty-nine patients (42 men and 17 women) with chronic stable HF and 21 normal subjects (16 men and five women). The results for the medical history, physical examination, electrocardiogram, chest x-ray, and echocardiogram were negative for cardiovascular disease in these 21 normal subjects. Of 59 HF patients, 20 were in New York Heart Association (NYHA) functional class I, 21 in class II, and 18 in class III. The mean age (normal and NYHA I, II, and III, 53 ± 2, 55 ± 3, 60 ± 3, and 63 ± 3 years) of the patients with HF was greater than for the controls, but the difference was not statistically significant. The gender distribution (male:female) was 16:5, 17:3, 15:6, and 10:8 for normal and NYHA I, II, and III HF subjects, respectively. The etiologic basis for heart disease included idiopathic dilated cardiomyopathy (18 patients), valvular heart disease (21 patients), old myocardial infarction (16 patients), hypertensive heart disease (two patients), and congenital heart disease (two patients). The presence of coronary artery disease was established by coronary angiography or a history of documented myocardial infarction. Patients with valvular heart disease had regurgitant valvular lesions with either mitral regurgitation, aortic regurgitation, or both. Patients with recent myocardial infarction, postinfarct angina, significant aortic stenosis, or significant renal and hepatic dysfunction and patients receiving allopurinol were excluded from the study.

The body mass index (normal and NYHA I, II, and III, 21.8 ± 2.2, 24.5 ± 3.2, 22.5 ± 2.7, and 19.8 ± 2.4 kg/$m^2$, $P < .05$) was significantly smaller in patients with NYHA class III HF. Patients with HF had

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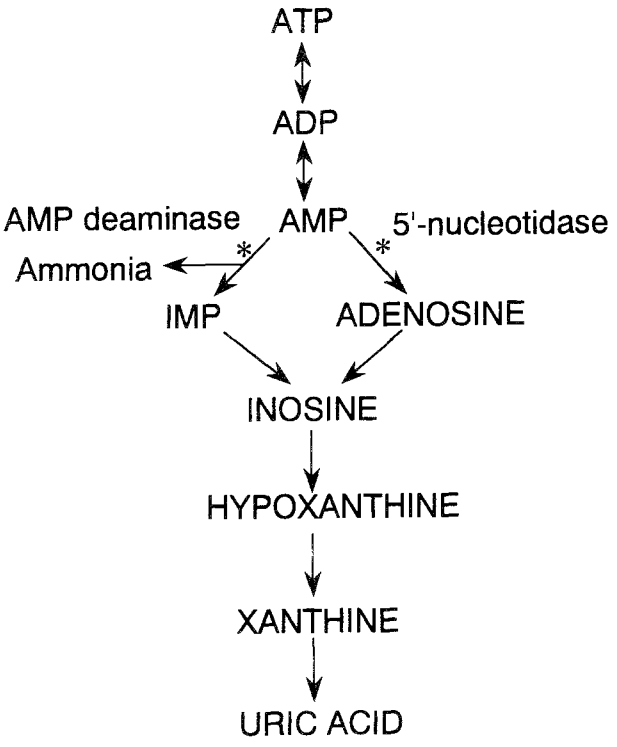


**Fig 1. Purine metabolism in skeletal muscle.**

a larger cardiothoracic ratio (normal and NYHA I, II, and III, 46 ± 1, 51 ± 1, 56 ± 2, and 63 ± 3%, $P < .05$) on chest x-ray and a reduced left ventricular ejection fraction (normal and NYHA I, II, and III, 68 ± 2, 54 ± 4, 51 ± 4, and 42 ± 4%, $P < .05$) as assessed by echocardiography. Drug treatment for HF included digitalis in 37 patients, furosemide in 31, spironolactone in nine, vasodilators such as nitrates and angiotensin-converting enzyme inhibitors in 17, $Ca^{2+}$ antagonists in 12, and denopamine in five, and the study was performed while using these medications. Renal function (blood urea nitrogen: normal and NYHA I, II, and III, 13 ± 1, 17 ± 1, 18 ± 1, and 18 ± 1 mg/dL, nonsignificant [NS]; creatinine: normal and NYHA I, II, and III, 0.8 ± 0.1, 1.0 ± 0.1, 0.9 ± 0.1, and 0.9 ± 0.1 mg/dL, NS) and liver function (aspartate aminotransferase, normal and NYHA I, II, and III, 21 ± 1, 27 ± 3, 25 ± 3, and 24 ± 2 IU/L, NS; alanine aminotransferase, normal and NYHA I, II, and III, 20 ± 2, 30 ± 4, 27 ± 3, and 18 ± 2 IU/L, NS) were not compromised in our subjects with HF.

The study protocol was approved by the Ethics Committee of Tottori University School of Medicine, and all subjects provided written informed consent for the study.

### *Exercise Test*

A symptom-limited ramp exercise test was performed using an upright bicycle ergometer (Ergomedic model 829 E; Monark Exercise Ab, Varberg, Sweden) in a temperature-controlled room. After a 4-minute unloading period of cycling at 50 rpm, the exercise load was increased by an incremental loading of 10 or 20 W/min for patients with HF and 20 W/min for normal subjects. The heart rate and electrocardiogram were monitored continuously (CASE 12; Marquette Electronics, Milwaukee, WI), and blood pressure was measured every minute during exercise by the cuff technique. All normal subjects and patients with HF stopped the exercise because of severe fatigue, dyspnea, or both symptoms when they were unable to maintain a pedaling rate of 50 rpm. Oxygen uptake ($VO_2$), carbon dioxide output, and minute ventilation were measured at rest and throughout the exercise period using a Cardiopulmonary Exercise System (Medical Graphics, St. Paul, MN). The anaerobic threshold (defined as the threshold at which an anaerobic component of metabolism begins during incremental exercise) was determined by the V-slope method.[13,14] Peak $VO_2$ was defined as the highest $VO_2$ value attained during exercise.

### *Plasma Samples*

A short polyethylene cannula was placed in a brachial artery for arterial blood sampling. Blood samples for lactate and ammonia were collected at rest and immediately after exercise. Blood lactate was determined by an enzymatic method using a lactate analyzer (model 23L; YSI, Yellow Springs, OH),[15] and plasma ammonia levels were determined by an enzymatic method (COBAS-FARA II; Roche, Tegimenta AG, Basel, Switzerland). Blood specimens for plasma HX were obtained at rest (30 minutes of bed rest), immediately after exercise, and 10, 20, and 30 minutes postexercise. Plasma HX concentrations were measured by high-performance liquid chromatography (model 510; Waters, Milford, MA) as described previously,[16] and peak HX levels were determined.

### *Statistical Analysis*

Statistical analysis for the comparisons of cardiac and ventilatory variables and lactate, ammonia, and HX was performed using ANOVA. When an overall difference was noted, Fisher's range test was applied. All analyses were performed with the StatView statistical program (Version 4.11; SAS Institute, Cary, NC) Differences were considered significant at a $P$ value less than .05. Results are presented as the mean ± SEM.

## RESULTS

The peak work rate was significantly decreased in patients with NYHA class II and III HF compared with normal subjects or NYHA class I patients. The anaerobic threshold and peak $VO_2$ decreased progressively as HF worsened. The resting heart rate was higher in NYHA class II and III HF, and the peak heart rate was insignificantly lower as the NYHA functional class increased. Resting systolic blood pressure were comparable among the groups, and peak systolic blood pressure was significantly lower in patients with NYHA class II and III HF (Table 1).

**Table 1. Peak Work Rate, Ventilatory Indices, Heart Rate, and Systolic Blood Pressure in Normal Subjects and Patients With HF (mean ± SEM)**

| Parameter | Normal Subjects | HF Patients | | |
|---|---|---|---|---|
| | | NYHA I | NYHA II | NYHA III |
| Peak work rate (W) | 163 ± 11 | 152 ± 9 | 94 ± 5*† | 69 ± 5*† |
| AT (mL/min/kg) | 18.7 ± 1.1 | 16.4 ± 0.7* | 13.0 ± 0.5*† | 11.1 ± 0.6*† |
| Peak $VO_2$ (mL/min/kg) | 32.3 ± 1.7 | 25.1 ± 0.9* | 18.6 ± 0.5*† | 14.1 ± 0 6*†‡ |
| HR (beats/min) | | | | |
| Rest | 67 ± 2 | 73 ± 3 | 81 ± 4* | 87 ± 4*† |
| Peak | 160 ± 4 | 155 ± 4 | 153 ± 7 | 143 ± 9 |
| SBP (mm Hg) | | | | |
| Rest | 137 ± 3 | 138 ± 6 | 134 ± 6 | 131 ± 6 |
| Peak | 206 ± 6 | 198 ± 9 | 164 ± 7*† | 157 ± 10*† |

Abbreviations: AT, anaerobic threshold, HR, heart rate; SBP, systolic blood pressure.

*$P < .05$ *v* normal.

†$P < .05$ *v* NYHA I.

‡$P < .05$ *v* NYHA II.

Resting levels of blood lactate, plasma ammonia, and plasma HX were similar among normal subjects and patients with HF, except for the lower resting plasma ammonia level in patients with NYHA class II HF. Blood lactate, plasma ammonia, and plasma HX increased significantly after maximal exercise both in normal subjects and in patients with HF. The peak level and the increment from rest to peak exercise for lactate (Δlactate), ammonia (Δammonia), and HX (ΔHX) became progressively smaller according to the NYHA functional class, and patients with NYHA class III HF exhibited significantly smaller peak values and increments compared with the other groups (Table 2). The increments in blood lactate, plasma ammonia, and plasma HX adjusted for the peak work rate are summarized in Table 3. The ratio for Δlactate to peak work rate was significantly higher in patients with NYHA class II and III HF, and the ratio for Δammonia to peak work rate was significantly smaller in patients with NYHA class III HF. There were no significant differences in the ratio for ΔHX to peak work rate among the groups.

Figure 2 shows the ratio for Δammonia to Δlactate and ΔHX to Δlactate in normal subjects and patients with HF. The ratio for Δammonia to Δlactate (normal and NYHA I, II, and III, 22.2 ± 2.2, 21.8 ± 2.7, 18.7 ± 1.9, and 11.2 ± 1.6, $P = .0022$) was significantly smaller in patients with NYHA class III HF compared with the other groups. The ratio for ΔHX to Δlactate (normal and NYHA I, II, and III, 5.4 ± 0.4, 4.8 ± 0.7, 4.2 ± 0.4, and 3.4 ± 0.3, $P = .038$) was significantly smaller in patients with NYHA class III HF compared with the normal subjects.

## DISCUSSION

The major findings of the present study are as follows: (1) the exercise-induced increase in blood lactate was augmented and the increase in plasma ammonia during exercise was smaller in patients with HF when normalized by the peak work rate; and (2) the ratio of the increase in plasma ammonia or HX to the increase in blood lactate during exercise was smaller in patients with HF.

**Table 2. Blood Lactate, Plasma Ammonia, and Plasma HX Concentrations at Rest and After Peak Exercise in Normal Subjects and Patients With HF (mean ± SEM)**

| Parameter | Normal Subjects | HF Patients | | |
|---|---|---|---|---|
| | | NYHA I | NYHA II | NYHA III |
| Lactate (mmol/L) | | | | |
| Rest | 0.62 ± 0.04 | 0.71 ± 0.06 | 0.65 ± 0.05 | 0.78 ± 0.06 |
| Peak | 6.68 ± 0.33 | 5.54 ± 0.36* | 5.29 ± 0.33* | 3.67 ± 0.27*†‡ |
| Δ | 6.06 ± 0.34 | 4.83 ± 0.36* | 4.64 ± 0.31* | 2.88 ± 0.25*†‡ |
| Ammonia (μg/dL) | | | | |
| Rest | 51 ± 4 | 52 ± 4 | 38 ± 2*† | 44 ± 3 |
| Peak | 182 ± 13 | 171 ± 20 | 133 ± 14* | 76 ± 5*†‡ |
| Δ | 132 ± 14 | 119 ± 20 | 94 ± 13 | 32 ± 6*†‡ |
| HX (μmol/L) | | | | |
| Rest | 3.1 ± 0.4 | 3.3 ± 0.3 | 3.5 ± 0.4 | 3.9 ± 0.6 |
| Peak | 36.6 ± 3.5 | 28.2 ± 4.9 | 24.1 ± 3.1* | 13.8 ± 1.2*†‡ |
| Δ | 33.5 ± 3.4 | 24.9 ± 4.7 | 20.6 ± 3.0* | 9.9 ± 1.2*†‡ |

Abbreviation: Δ, increment from rest to peak exercise.
*$P < .05$ v normal.
†$P < .05$ v NYHA I.
‡$P < .05$ v NYHA II.

In our previous study,[10] we determined serial blood lactate and plasma ammonia concentrations during ramp exercise, and found that both the lactate and ammonia threshold occurred at a lower exercise workload in patients with HF compared with normal subjects. In the current study, we determined workload-adjusted purine metabolite and lactate changes during exercise in patients with various severities of HF, since the degree of purine nucleotide degradation and anaerobic glycolysis during exercise is related to the amount and duration of the power output.[17,18] We found that the peak blood lactate ratio was increased in patients with HF, consistent with reduced $O_2$ delivery to skeletal muscle and reduced oxidative capacity of skeletal muscle in HF patients. On the other hand, the usual route of adenine nucleotide catabolism (ie, AMP-IMP pathway), with the production of ammonia and HX, was not accelerated in parallel with the increase in lactate production. In addition, the ratio for Δammonia to Δlactate was lower in patients with NYHA class III HF, suggesting that maximal purine nucleotide degradation during exercise may be lower in skeletal muscle in patients with HF. Weber and Janicki[19] have previously examined serial mixed venous lactate concentrations during incremental exercise in HF. Although they did not normalize the peak blood lactate level by the peak work rate, their data showed that the more severe the functional status, the higher the peak blood lactate to peak $VO_2$ ratio in patients with HF, consistent with our observations.

The mechanisms responsible for reduced purine nucleotide degradation in HF are not clear from our study, but several possibilities should be considered. First, reduced purine degradation in severe HF can be due to the smaller exercise capacity. However, patients with severe HF still exhibited a reduced ammonia response to exercise when normalized to the exercise workload. Thus, the reduced maximal purine degradation was not totally explained by the smaller exercise capacity. Second, the reduced peak ammonia and peak HX levels in HF could be due to the decreased activity of AMP deaminase, an enzyme responsible for purine degradation. In AMP deaminase–deficient patients, the exercise-induced increase in plasma ammonia has been reduced.[20] Most cases of AMP deaminase deficiency are primary,[21] but a secondary form of this disorder has been reported.[22-24] Thus, a reduced AMP deaminase activity, if present in patients with HF, would explain the decreased purine degradation during exercise. Third, a previous study by Sabina et al[25] demonstrated that there is a decrease in purine degradation (accumulation of AMP and ADP) and shunting of AMP in another catabolic pathway (adenosine formation) in skeletal muscle of AMP deaminase–deficient patients. Recent reports by Funaya et al[11,12] showed that patients with HF have elevated plasma adenosine levels according to the severity of HF, with an increase in 5′-nucleotidase activity. Based on these observations, we speculate that the decreased purine

**Table 3. Changes in Blood Lactate, Plasma Ammonia, and Plasma HX Relative to the Peak Work Rate in Normal Subjects and Patients With HF (mean ± SEM)**

| Parameter | Normal Subjects | HF Patients | | |
|---|---|---|---|---|
| | | NYHA I | NYHA II | NYHA III |
| ΔLA/peak WR | 0.037 ± 0.003 | 0.032 ± 0.004 | 0.049 ± 0.003*† | 0.042 ± 0.005† |
| ΔAmmonia/peak WR | 0.81 ± 0.14 | 0.78 ± 0.16 | 0.99 ± 0.11 | 0.47 ± 0.11*‡ |
| ΔHX/peak WR | 0.21 ± 0.02 | 0.16 ± 0.03 | 0.22 ± 0.02 | 0.14 ± 0.03 |

Abbreviations: Δ, increment from rest to peak exercise; LA, lactate; WR, work rate.
*$P < .05$ *v* normal.
†$P < .05$ *v* NYHA I.
‡$P < .05$ *v* NYHA II.

degradation during exercise in HF could be attributed to the shunting of the catabolic pathway from AMP-IMP toward AMP-adenosine, although the current study does not address these issues.

We acknowledge that there are several limitations to our study. First, we obtained metabolic data only after maximal exercise in HF patients with limited exercise capacity, and compared these variables with those obtained from well-conditioned normal subjects. Since the exercise capacity is different among the groups, one would suspect that the observed metabolic difference can really be attributed to the abnormal muscle metabolism in HF per se. A more appropriate control group would be subjects who are deconditioned by other chronic diseases. However, we accounted for the work capacity difference by the normalized ratio. We believe that the reduced workload-adjusted metabolic ratio strongly suggests an altered purine degradation during exercise. Second, a lack of metabolic data at submaximal workloads is another limitation. Although we did not obtain such data in this study, we have previously examined purine degradation after submaximal exercise in patients with NYHA class II HF.[26] We found that some patients with HF exhibited excess purine degradation during submaximal exercise. The inconsistent results may be explained by the difference in the plasma HX response in normal subjects, in that normal subjects had only a modest increase in plasma HX after submaximal exercise. Third, plasma levels of these metabolites are determined by the balance between their synthesis and renal clearance. The kinetics of HX after exercise has been evaluated in normal subjects,[5] and the urinary HX level reaches a peak 1 hour after strenuous exercise[27]; however, information about HX clearance in patients with HF is limited. There is one study by Zhang et al[28] that measured plasma HX levels in patients with NYHA class II and III HF and normal controls. They showed higher resting plasma HX levels in HF, but did not report any clearance information on the metabolite. We acknowledge that the absence of clearance data for these metabolites is a limitation of our study, but our subjects did not have significant renal or hepatic dysfunction, which could significantly influence the plasma concentrations of purine metabolites.

In summary, the peak levels of blood lactate, plasma ammonia, and plasma HX after maximal exercise became smaller as HF worsened. When values were normalized by the peak work rate, patients with HF exhibited a lower ammonia response with a higher lactate response. These results suggest that there may be an altered purine and glycogen metabolism during exercise in skeletal muscle in patients with HF. Further study should be directed to determine if the activities of AMP deaminase, 5′-nucleotidase, and adenine nucleotide metabolites are altered in muscle specimens obtained from patients with HF.

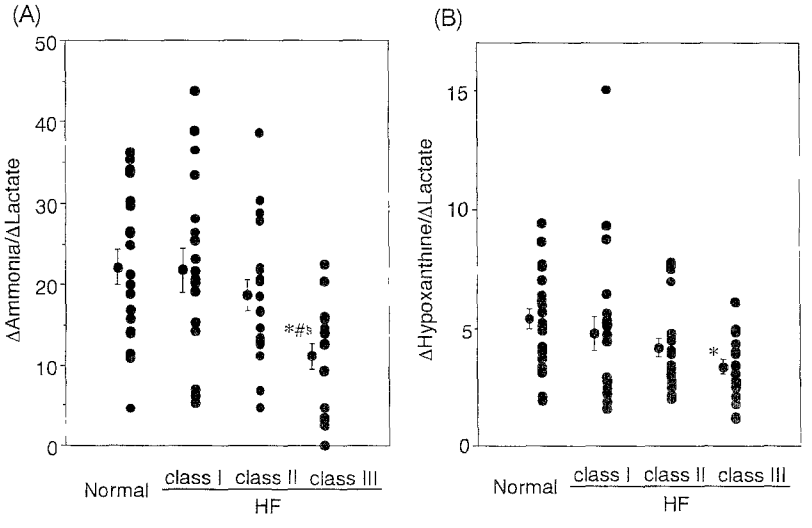


**Fig 2. (A) Ratio for Δammonia to Δlactate in normal subjects and patients with HF. Mean ± SEM is also depicted. ΔAmmonia/Δlactate was significantly smaller in patients with NYHA class III HF *v* other groups. (B) Ratio for Δhypoxanthine to Δlactate in normal subjects and patients with HF. ΔHypoxanthine/Δlactate was significantly smaller in patients with NYHA class III HF *v* normal subjects. *$P < .05$ *v* normal subjects, #$P < .05$ *v* NYHA class I, §$P < .05$ *v* NYHA class II.**

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