Uric Acid in Chronic Heart Failure: A Measure of the Anaerobic Threshold

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The anaerobic threshold (AT) is a measure of the balance between aerobic and anaerobic cellular metabolism. Hyperuricemia occurs in conditions that involve an imbalance between cellular oxygen consumption and carbon dioxide production, such as chronic heart failure (CHF). We therefore hypothesized that in CHF, serum uric acid might be related to the AT. Patients with CHF (n = 40, aged 58.7 ± 1.9 years; New York Heart Association Class I-IV; maximal oxygen consumption [$\dot{M}Vo_2$], 18.7 ± 01.1 mL/kg/min; left ventricular ejection fraction, 26% ± 2%) and 10 age-matched healthy controls underwent measurement of the serum uric acid level at rest and assessment of the AT. This was derived from $\dot{M}Vo_2$ and the regression slope relating minute ventilation to carbon dioxide output ($VE - \dot{V}co_2$) during a maximal treadmill exercise test. Compared with the healthy controls, patients with CHF had a lower AT (11.8 ± 0.7 *v* 16.9 ± 1.1 mL/kg/min, $P < .001$) and a higher serum uric acid concentration (493.8 ± 22.4 *v* 308.7 ± 21.5 μmol/L, $P < .001$). In univariate analyses of the CHF group, the AT correlated with serum uric acid ($r = -.56$, $P < .001$; AT = 19.93 − (0.016 · uric acid), $R^2 = .31$, $P < .001$) and plasma creatinine ($r = -.43$, $P < .01$), but not with the diuretic dose. In stepwise regression analyses of the CHF group, serum uric acid emerged as a predictor of the AT (standardized coefficient = −.56, $P < .001$), whereas the diuretic dose and plasma creatinine failed to enter into the final models (multiple $R^2 = .31$, $P < .001$). In conclusion, in CHF there is an inverse relationship between the AT and the resting serum uric acid concentration. This is consistent with the known links between uric acid production and the imbalance in aerobic/anaerobic metabolism that occur in CHF. These findings provide the basis for using the simple measurement of the serum uric acid level as a surrogate measure of the AT.

AT THE CELLULAR LEVEL, the anaerobic threshold (AT) is the point at which glycolytic flux accelerates to compensate for depletion of high-energy phosphates. Thus, a lower AT implies an earlier accumulation of glycolytic intermediates in relation to the availability of high-energy phosphates. The production of uric acid, the final product of purine degradation, is intimately linked to both oxidative and nonoxidative cellular metabolism. An accelerated consumption of adenosine triphosphate (ATP) in excess of synthetic capacity promotes degradation of adenine nucleotides to inosine, hypoxanthine, xanthine, and uric acid.[1] Accordingly, hyperuricemia occurs in conditions of global hypoxia such as obstructive pulmonary disease,[2-4] neonatal hypoxia,[5,6] and cyanotic heart disease.[7,8]

Chronic heart failure (CHF) involves multiple disturbances of energy metabolism. In addition to defects in oxidative and lipolytic enzymes, histological abnormalities such as a shift in skeletal muscle fiber distribution and derangements in mitochondrial structure[9] have also been shown to occur in CHF. Thus, during exercise, patients with CHF exhibit a relatively low AT, reflecting an early depletion of ATP and an excessive dependence on anaerobic metabolism. Whole-body measures of the AT have been widely used to assess disease severity in patients with CHF. The ventilatory AT, derived from measures of whole-body oxygen consumption and carbon dioxide production during a treadmill exercise test, closely parallels the less widely used "metabolic" thresholds such as the lactate[10,11] and ammonia[12] thresholds.

Given that CHF is a hyperuricemic condition[13] involving an increased production of uric acid[14] and an imbalance between oxidative and nonoxidative metabolism,[15] we hypothesized that in CHF, the serum uric acid level could provide a measure of the AT.

SUBJECTS AND METHODS

The study group consisted of 40 patients with CHF due to coronary heart disease (n = 21) or dilated cardiomyopathy (n = 19) (Table 1). Concurrent medications in the CHF group included angiotensin-converting enzyme inhibitors, loop diuretics, digoxin, warfarin, nitrates, amiodarone, and thiazide diuretics either alone or in combination. No patients were taking hypouricemic medication. All patients had CHF for longer than 3 months. All subjects provided written informed consent, and the study was approved by the local Ethics Committee.

Functional Capacity

During cardiopulmonary exercise testing, all patients exercised to exhaustion (respiratory exchange ratio > 1.1). A one-way valve connected to a respiratory spectrometer (model 2000; Amis, Odense, Denmark) was used. Maximal oxygen consumption ($\dot{M}Vo_2$) was calculated on-line using a standard inert gas dilution technique.[16,17] The slope of the regression line relating minute ventilation to carbon dioxide output ($VE - \dot{V}co_2$) was used as an index of the ventilatory response to exercise.[18] These measures were obtained during a maximal exercise test, using a modified Bruce protocol for patients with CHF.

The ventilatory AT was calculated according to the technique of Beaver et al.[19] Briefly, the AT is selected as the $\dot{V}o_2$ at which the slope of the $\dot{V}co_2$ versus $\dot{V}o_2$ changes from 1 or slightly less than 1 to a slope steeper than 1. The intersection of these slopes is taken as the $\dot{V}o_2$ above which the increased $\dot{V}co_2$ can only be explained by the increase in metabolic acidosis.

Laboratory Determinations

Serum uric acid was determined using the uricase-peroxidase method on venous blood samples taken after a 12-hour fast, at rest, and before the exercise test.[20]

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Table 1. Characteristics of the Study and Control Groups

Characteristic	CHF Patients (n = 40)	Healthy Controls (n = 10)	P†
Age (yr)	58.7 ± 1.9	59.5 ± 2.1	NS
Left ventricular ejection fraction (%)	26.0 ± 2.2	ND	
Systolic blood pressure (mm Hg)	113.0 ± 2.8	132.0 ± 4.2	.003
Diastolic blood pressure (mm Hg)	70.5 ± 1.6	84.3 ± 2.9	<.001
NYHA class			
I	6	—	
II	11	—	
III	20	—	
IV	3	—	
$M\dot{V}O_2$ (mL/kg/min)	18.7 ± 1.1	33.1 ± 2.2	<.001
VE − $\dot{V}CO_2$ slope	33.7 ± 1.8	24.3 ± 0.9	.014
AT (mL/kg/min)	11.8 ± 0.7	16.9 ± 1.1	.001
Exercise time (s)*	519.6 ± 33.1	641.0 ± 50.8	NS
Creatinine (pmol/L)	126.4 ± 7.4	92.2 ± 2.5	.027
Uric acid (μmol/L)	493.8 ± 22.4	308.7 ± 21.5	<.001

NOTE. Results are expressed as the mean ± SEM.

Abbreviations: NYHA, New York Heart Association; VE − $\dot{V}CO_2$, regression slope relating minute ventilation to carbon dioxide output; ND, not determined.

*Maximum time to exhaustion during a treadmill exercise test.

†Differences between the groups by ANOVA.

Statistical Analyses

Statistical analyses were made using the SYSTAT (SYSTAT, Evanston, IL) statistical package. Univariate Pearson correlation coefficients were derived. Group differences were assessed by ANOVA. A general linear model was used in multivariate analyses of pooled subjects, and a minimum tolerance of .01 was used for entry into the models. In all analyses, a P value less than .05 was considered statistically significant.

RESULTS

Compared with age-matched controls, patients with CHF had a significantly lower mean AT (mean ± SEM, 11.8 ± 0.7 *v* 16.9 ± 1.1 mL/kg/min, $P < .001$), a lower mean $M\dot{V}O_2$ (18.7 ± 1.1 *v* 33.1 ± 2.2 mL/kg/min, $P < .001$), and a higher mean VE − $\dot{V}CO_2$ slope (33.7 ± 1.8 *v* 24.3 ± 0.9, $P = .014$). In addition, patients with CHF had higher serum uric acid (493.8 ± 22.4 *v* 308.7 ± 21.5 μmol/L, $P < .001$), higher plasma creatinine (126 ± 7.4 *v* 92.2 ± 2.5 pmol/L), and lower systolic (113.0 ± 2.8 *v* 132.0 ± 4.2 mm Hg, $P = .003$) and diastolic (70.5 ± 1.6 *v* 84.3 ± 2.9 mm Hg, $P < .001$) blood pressure.

In univariate analyses of the CHF group, the AT correlated negatively with serum uric acid ($r = -.56$, $P < .001$; AT = 19.93 − (0.016 · uric acid), $R^2 = .31$, $P < .001$), plasma creatinine ($r = -.43$, $P < 0.01$), and age ($r = -.49$, $P < .01$). There was a significant correlation between the AT and diastolic blood pressure ($r = .38$, $P < .05$), whereas no significant correlations emerged between the AT and the diuretic dose. Univariate analyses of the AT in pooled subjects showed a similar picture, except for the emergence of a significant correlation between the AT and both the diuretic dose and systolic blood pressure (Table 2 and Fig 1).

In stepwise multiple linear regression analyses of the CHF group, serum uric acid emerged as the strongest predictor of the AT (standardized coefficient = −.56, $P < .001$), whereas the diuretic dose and plasma creatinine failed to enter into final models (multiple $R^2 = .31$, $P < .001$) (Table 3). Since CHF involves a reduction of the AT and hyperuricemia,[13] we considered that the diagnosis of heart failure could potentially become a significant predictor of the AT in multivariate analyses with the AT as an independent variable. In analyses of pooled subjects, the serum uric acid concentration emerged as a significant predictor of the AT regardless of the diagnosis of heart failure. The independence from the diuretic dose, age, plasma creatinine, and blood pressure was evident in all analyses.

Table 2. Univariate Pearson Correlation Analysis of the AT Against Other Variables in Patients With CHF and in Pooled Subjects

Variable	CHF (n = 40)	All Subjects (n = 50)
Age (yr)	−.49†	−.35†
Left ventricular ejection fraction (%)	.09	—
Systolic blood pressure (mm Hg)	.20	.29*
Diastolic blood pressure (mm Hg)	.38*	.43*
Diuretic dose (mg)§	−.29	−.42†
Creatinine (pmol/L)	−.43†	−.50‡
Uric acid (μmol/L)	−.56‡	−.63‡

*$P < .05$.

†$P < .01$.

‡$P < .001$.

§Quantified in terms of furosemide-equivalent dose (1 mg bumetanide = 40 mg furosemide).

DISCUSSION

We have shown that in patients with CHF, the serum uric acid concentration is inversely related to the ventilatory AT independently of the hyperuricemic effects of renal impairment and diuretic therapy. This relationship might be expected in view of the fact that the AT reflects the balance between whole-body oxygen consumption and carbon dioxide output, which at the cellular level translates to the balance between oxidative and nonoxidative metabolism.

An early switch to anaerobic metabolism leads to an inappropriate increase in the availability of glycolytic metabolites. Accordingly, direct products of glycolytic metabolism, such as lactate, increase rapidly in the blood of patients with CHF.[21,22]

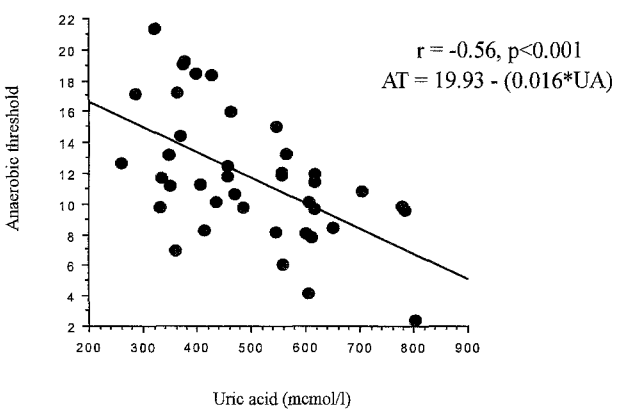

Fig 1. Regression scatterplot of serum uric acid against the AT in patients with CHF. *r*, Pearson correlation coefficient; UA, serum uric acid.

Table 3. Multivariate Analysis Using AT as the Dependent Variable

Group	F Ratio	P		F Ratio	P
All subjects*					
Independent variables					
Uric acid	17.9	<.001	Uric acid	13.2	.001
Disease group	2.2	.144	Age	5.5	.023
			Disease group	3.7	.062
Variables that failed to enter into final model					
Diuretic dose			Systolic blood pressure		
Creatinine			Creatinine		
			Diuretic dose		
	$R^2 = .43, P < .001$			$R^2 = .49, P < .001$	
	SC	P		SC	P
CHF group					
Independent variables					
Uric acid	−.56	<.001	Uric acid	−.45	.001
			Age	−.35	.011
Variables that failed to enter into final model					
Diuretic dose			Creatinine		
Creatinine			Systolic blood pressure		
			Diuretic dose		
	$R^2 = .31, P < .001$			$R^2 = .42, P < .001$	

*The general linear model was used for regression analyses of pooled subjects. R^2, multiple squared regression coefficient for analysis.

Although recent evidence suggests that intrinsic muscle abnormalities contribute to such disturbances,[23] reduced oxygen availability has also been implicated in the early lactate accumulation in CHF.[24] Reduced cellular availability of oxygen, by causing depletion of ATP and accumulation of hypoxanthine and uric acid, could also account for the observed association between the AT and serum uric acid. Our recent finding in CHF patients of a negative relationship between maximum leg blood flow and serum uric acid is consistent with this concept.[25]

It has been shown that in CHF patients undergoing bicycle ergometry, the peaks in plasma lactate and ammonia occur within 2 minutes of exercise and the peak in plasma hypoxanthine occurs at 20 minutes into the recovery period.[12] As suggested by this group, the time interval between the ammonia and hypoxanthine peaks may relate to the fact that ammonia is produced at the beginning of the purine nucleotide cycle, whereas hypoxanthine is produced following degradation of inosine. This finding, which is in agreement with other reports,[26,27] suggests that these two metabolites mark different metabolic phases of exercise. Speculatively, increased uric acid production in CHF[14] may reflect the chronicity of ATP depletion and accompanying purine degradation.

We conclude that in patients with CHF, there is a positive relationship between the resting serum uric acid level and the ventilatory AT embodied in the formula, AT = 19.93 − (0.016 · uric acid). Pathophysiologically, this relationship is consistent with the known mechanistic links between ATP depletion, purine degradation, and glycolysis. Regardless of the pathophysiological mechanism, our findings provide the basis for using the simple measurement of this metabolite at rest as a complementary measure of the AT.

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