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Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure

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Background Elevated serum uric acid concentrations have been observed in clinical conditions associated with hypoxia. Since chronic heart failure is a state of impaired oxidative metabolism, we sought to determine whether serum uric acid concentrations correlate with measures of functional capacity and disease severity.

Methods Fifty nine patients with a diagnosis of chronic heart failure due to coronary heart disease (n=34) or idiopathic dilated cardiomyopathy (n=25) and 20 healthy controls underwent assessment of functional capacity. Maximal oxygen uptake (MVO_2) and regression slope relating to minute ventilation to carbon dioxide output ($VE–VCO_2$) were measured during a maximal treadmill exercise test. Metabolic assessment consisted of measuring serum uric acid and fasting lipids, and insulin sensitivity, obtained by minimal modelling analysis of glucose and insulin responses during an intravenous glucose tolerance test. Clustering of indices of functional disease capacity and metabolic factors was explored using factor analysis and multivariate regression analysis.

Results Compared to 20 healthy controls, patients with chronic heart failure had a 52% lower MVO_2 ($P<0·001$), 56·8% higher serum uric acid concentrations ($P<0·001$) as well as a 60·5% lower insulin sensitivity ($P<0·001$). Salient univariate correlations in the chronic heart failure group included serum uric acid concentrations with exercise time during the exercise test ($r=-0·53$), MVO_2 ($r=-0·50$) (both $P<0·001$), $VE–VCO_2$ slope ($r=0·45$), and NYHA functional class ($r=0·36$) (both $P<0·01$). In factor analysis of the chronic heart failure group, serum uric acid formed part of a principal cluster of metabolic variables which included MVO_2 and $VE–VCO_2$ slope. In multivariate regression analysis, serum uric acid concentrations emerged as a significant predictor of MVO_2, exercise time (both $P<0·001$,) $VE–VCO_2$ slope and NYHA functional class (both $P<0·02$), independent of diuretic dose, age, body mass index, serum creatinine, alcohol intake, plasma insulin levels, and insulin sensitivity index.

Conclusions There is an inverse relationship between serum uric acid concentrations and measures of functional capacity in patients with cardiac failure. The strong correlation between serum uric acid and MVO_2 suggests that in chronic heart failure, serum uric acid concentrations reflect an impairment of oxidative metabolism.
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Key Words: Uric acid, congestive cardiac failure, hypoxia, insulin resistance.

Introduction

It has long been recognised that gout and hyperuricaemia are associated with coronary heart disease and with its risk factors, such as obesity, hypertension, hypertriglyceridaemia, dyslipidaemias and diabetes mellitus[1–7]. Considerable interest has focused on the fact that certain aspects of metabolism are common to coronary heart disease, hypertension and non-insulin-dependent diabetes mellitus. In 1988, Reaven proposed the existence of a metabolic syndrome of cardiovascular risk in which insulin resistance played a pivotal role[8]. The finding of correlations between serum uric acid levels and measures of insulin resistance has led to the inclusion of hyperuricaemia in the insulin resistance syndrome[8–10].

Elevation of serum uric acid levels has also been observed in hypoxic states, such as in obstructive pulmonary disease[11–13], neonatal hypoxia[14–16], cyanotic heart disease[17–18], and acute heart failure[19]. Uric acid levels have been shown to increase within minutes in

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coronary sinus blood following consecutive balloon inflations during coronary angioplasty[20–22] and during coronary artery bypass operations[23].

Hitherto, there appear to have been no studies of serum uric acid levels in patients with chronic heart failure. Elevations in serum uric acid might be expected since patients with chronic heart failure have an impaired uptake of oxygen at rest and during exercise. We have previously shown that chronic heart failure is an insulin resistant, hyperinsulinaemic state[24]. Both hyperinsulinaemia and insulin resistance are associated with elevations in serum uric acid[25,26] and for this reason we have included measures of carbohydrate metabolism in the present study. Factor analysis was used to explore the pathophysiological interrelationships of serum uric acid. With this statistical technique[27,28] it is possible to address whether a metabolic relationship is multidimensional, or if it can be reduced to a single *factor* (an unobservable variable) which reflects an underlying pathogenetic link.

Patients and Methods

Fifty-nine male patients with chronic heart failure due to coronary heart disease (n=34) or dilated cardiomyopathy (n=25) [mean age (± SD) 60·1 (11·1) years; body mass index of 25·5 (4·1) kg . m^{-2}] and 16 healthy control subjects were included in this study. In the chronic heart failure group, 46 patients were taking angiotensin-converting enzyme inhibitors, 52 were taking loop diuretics, 10 were taking thiazide diuretics, and 20 were taking pottasium sparing diuretics, either alone or in combination. No patients were taking hypouricaemic medication. All patients had been in chronic heart failure for >3 months. All patients gave written, informed consent and the study was approved by the local Ethics Committee.

Procedures

Studies were carried out in our metabolic day ward. Participants were asked to consume more than 200 g . day^{-1} carbohydrate in their diet for 3 days prior to their visit, to have fasted for 12 h, and to have refrained from smoking on the morning of the test. After resting for 15 min in a semi-recumbent position, systolic and diastolic blood pressures were measured by a cuff method with a mercury sphygmomanometer. First- and fifth-phase Korotkoff sounds were recorded. A cannula was inserted into an antecubital vein in one arm for sampling, the arm having been previously rested on a heating pad in order to assist blood flow. Blood samples were taken for fasting plasma glucose and insulin concentrations, and serum lipid and uric acid concentrations. A further sample was taken for repeat measurement of fasting plasma glucose and insulin concentrations. The participant then underwent an intravenous glucose tolerance test (0·5 g . kg^{-1} body weight dextrose administered as a 50% solution) with sampling for plasma glucose and insulin at 3, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 150, and 180 min after injection of the glucose solution.

Laboratory determinations

Serum uric acid was determined by the uricase-peroxidase method[29] using a Cobas Mira discrete analyser (Roche, Switzerland). Plasma glucose was determined on the same day using glucose oxidase procedures with aminophenazone[30]. Plasma insulin concentrations were measured on samples stored at −20 °C using the radioimmunoassay procedure of Albano *et al.*[31]. Triglycerides were measured by fully enzymatic assays[32,33]. Concentrations of HDL-cholesterol were measured after separation by sequential precipitation with heparin/manganese ions[34]. Within and between-batch precision was monitored throughout the study using frozen plasma and serum pools and commercially available lyophylised sera, and by participation in national quality assurance schemes.

Functional capacity

During cardiopulmonary exercise testing, all patients were exercised to exhaustion (respiratory exchange ratio >1·1). MVO_2 and $VE–VCO_2$ were estimated from a metabolic gas exchange analysis performed during a maximal exercise test, using a modified Bruce protocol for patients with chronic heart failure. A one-way valve connected to a respiratory spectrometer (Amis 2000, Odense, Denmark) was employed. Oxygen consumption was calculated on-line using a standard inert gas dilution technique[35,36]. The slope of the regression line relating minute ventilation to carbon dioxide output ($VE–VCO_2$) was employed as an index of the ventilatory response to exercise[37]. Left ventricular ejection fraction was estimated at rest by radionuclide ventriculography using a stannous fluoride red cell labelling agent, a bolus injection of radio-labelled ^{99}Tc and gamma camera imaging.

Data analyses

Clinical and metabolic variables were selected from the full range of measurements made, on the basis of previous evidence of their involvement in chronic heart failure and uric acid metabolism. Statistical analyses were carried out using the SYSTAT (SYSTAT inc, Evanston, Illinois, U.S.A.) statistical package. Fasting plasma concentrations of glucose and insulin were taken as the mean of the two pre-test samples. Incremental areas under the intravenous glucose tolerance test concentration profiles were calculated using the trapezium rule. In the derivation of mean values, insulin measures and triglyceride concentrations were logarithmically or

Table 1 Clinical and metabolic characteristics of the study and control groups*

	CHF group (n=59)	Controls (n=20)	*P* value
Age (years)	60·1 (11·1)	52·8 (11·4)	0·014
Body mass index ($kg . m^{-2}$)	25·5 (4·1)	26·4 (3·9)	ns
Systolic blood pressure (mmHg)	115·3 (19·0)	128·0 (11·8)	0·006
Diastolic blood pressure (mmHg)	71·7 (11·0)	80·65 (8·5)	<0·001
Creatinine ($\mu mol . l^{-1}$)	122·0 (41·6)	90·7 (8·3)	<0·001
Uric acid ($\mu mol . l^{-1}$)	488·9 (153·6)	311·8 (65·0)	<0·001
Total cholesterol ($mmol . l^{-1}$)	5·6 (1·1)	5·0 (0·8)	0·033
Triglycerides ($mmol . l^{-1}$)	1·65 (−0·95, +2·86)	1·00 (−0·62, +1·63)	0·003
HDL-cholesterol (mmol . l)	1·15 (0·378)	1·263 (0·265)	ns
Fasting glucose ($mmol . l^{-1}$)	5·7 (1·7)	5·1 (0·4)	ns
Incremental glucose area ($10^3 . mmol . l^{-1} . min$)	9·80 (3·68)	10·33 (10·22)	ns
Fasting insulin ($pmol . l^{-1}$)	58·1 (− 26·3, +128·3)	29·3 (−12·4, +69·3)	0·007
Incremental insulin area ($10^4 . pmol . l^{-1}$)	2·38 (−1·30, +4·34)	2·10 (−1·40, +3·16)	ns
Insulin sensitivity ($10^5 . min^{-1}/[pmol . l^{-1}]$)	1·91 (−0·60, +3·96)	4·84 (−2·41, +8·10)	<0·001
LVEF (%)	25·8 (14·1)	nd	
MVO_2 ($ml . kg^{-1} . min^{-1}$)	17·6 (6·3)	36·7 (7·5)	<0·001
VE–VO_2 slope	36·7 (13·1)	25·2 (3·5)	<0·001
Exercise time (s)	458·1 (29·6)	692·1 (148·0)	<0·001
NYHA class			
I	6	—	
II	16	—	
III	29	—	
IV	8	—	

*Results are expressed as mean value ± SD, except for plasma triglycerides, insulin concentrations and insulin sensitivity index, which are expressed as mean and asymmetrical SD. LVEF=left ventricular ejection fraction; MVO_2=maximal oxygen consumption; VE–VCO_2 slope=regression slope relating to minute ventilation to carbon dioxide output; NYHA=New York Heart Association; nd=not done.

square-root transformed. Insulin sensitivity, inversely related to insulin resistance, was assessed using the minimal model approach of Bergman *et al.*[38], as previously described[24]. For multivariate regression and factor analysis, data were adjusted to the mean age of the chronic heart failure group using the univariate regression coefficient with age for each variable. Univariate Pearson correlation coefficients were derived. Group differences were assessed by the Mann–Whitney U test.

Significant clustering of correlated metabolic disturbances was identified by factor analysis. Factor analysis assumes that intercorrelations between observed variables are influenced by a smaller number of hypothetical underlying variables, termed *factors*[27]. Factors are characterized by the variables which, according to their so-called factor loadings, most strongly correlate with the factor concerned. Principal components analysis was used to extract the initial components. The varimax method of rotation was used to obtain the final factors and their loadings for each variable. Variables with factor loadings equal to or greater than 0·40 were primarily used for interpretation of the factors thus obtained, although, as recommended by Stevens[27], loadings above 0·30 were also noted. In place of separate measures of diastolic and systolic blood pressure in the factor analysis, a single measure of mean blood pressure (diastolic+systolic/3) was employed. This avoided the emergence of a separate factor consisting solely of the two blood pressure measures (diastolic and systolic blood pressure and mean arterial pressure behaved very similarly in univariate analysis, and when entered as alternatives in the factor analysis).

Results

There were no significant differences in any of the clinical and metabolic characteristics between chronic heart failure patients when classified according to aetiology of chronic heart failure (data not shown). Compared to controls, patients with chronic heart failure were older, had lower systolic and diastolic blood pressures, and higher levels of serum creatinine, total plasma cholesterol and triglycerides, fasting insulin and serum uric acid (Table 1). Patients with chronic heart failure also had a lower insulin sensitivity (S_I) and MVO_2, and higher VE–VCO_2 slopes and exercise times.

Univariate correlation coefficients between variables of patients with chronic heart failure are shown in Table 2. The strongest correlations for uric acid were with exercise time (r=−0·53), MVO_2 (r=−0·50) (both $P<0·001$), VE–VCO_2 slope (r=0·45), and NYHA class (r=0·36) (both $P<0·01$) (Fig. 1). Loop diuretic dose, entered as the frusemide-equivalent dose (1 mg of bumetanide was taken as equivalent to 40 mg of frusemide), correlated positively with NYHA

Table 2 Univariate Pearson correlation coefficients between variables of patients with chronic heart failure

	BMI	SBP	DBP	CREAT	UA	FG	FI	IGAREA	IIAREA	S(I)	MVO_2	$VE–VCO_2$	ET	LVEF	NYHA	ALC	DIU
Age	−0·35**	−0·10	−0·35**	0·41**	0·27*	−0·08	0·07	0·07	−0·10	−0·21	−0·44**	0·26	−0·32*	0·10	0·13	−0·18	−0·07
BMI	—	0·24	0·43**	−0·14	−0·14	−0·11	0·48**	−0·13	0·52***	−0·06	0·17	−0·20	−0·11	−0·14	−0·03	−0·10	0·20
SBP	—	—	0·77***	−0·24	−0·25	−0·00	0·24	0·08	0·13	−0·01	0·10	−0·20	−0·04	0·15	−0·02	−0·15	0·05
DBP	—	—	—	−0·33*	−0·40**	0·10	0·27	0·15	0·09	0·01	0·24	−0·19	−0·06	−0·01	0·01	−0·07	0·01
CREAT	—	—	—	—	0·58***	−0·02	0·16	0·11	−0·02	0·01	−0·30*	0·28	−0·23	−0·01	0·13	−0·09	0·20
UA	—	—	—	—	—	0·33*	0·26	0·37*	−0·11	−0·03	−0·50***	0·45**	−0·53***	−0·18	0·36**	−0·08	0·32*
FG	—	—	—	—	—	—	0·62***	−0·29*	−0·20	−0·16	0·44**	−0·32*	−0·27*	0·33*	−0·04	−0·00	
FI	—	—	—	—	—	—	—	0·16	0·69***	−0·16	−0·23	0·19	−0·48**	−0·18	0·25	−0·21	0·32*
IGAREA	—	—	—	—	—	—	—	—	−0·20	−0·20	−0·22	0·29	−0·46**	−0·36**	0·31*	−0·16	0·08
IIAREA	—	—	—	—	—	—	—	—	—	−0·34*	−0·02	−0·10	−0·16	0·01	0·01	−0·14	0·20
S(I)	—	—	—	—	—	—	—	—	—	—	0·28*	−0·10	0·27	0·24	−0·22	0·33*	−0·03
MVO_2	—	—	—	—	—	—	—	—	—	—	—	−0·48**	0·78***	0·24	−0·63***	0·44**	−0·22
VCO_2	—	—	—	—	—	—	—	—	—	—	—	—	−0·50***	−0·34*	0·53***	−0·10	0·13
ET	—	—	—	—	—	—	—	—	—	—	—	—	—	0·47**	−0·79***	0·49**	−0·44**
LVEF	—	—	—	—	—	—	—	—	—	—	—	—	—	—	−0·48***	0·06	−0·15
NYHA	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	−0·28*	0·39**
ALC	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	−0·19

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; CREAT=plasma creatinine; UA=serum uric acid; FG=fasting glucose; FI=fasting insulin; IGAREA=incremental glucose area; IIAREA=incremental insulin area; S(I)=insulin sensitivity; MVO_2=maximal oxygen uptake; $VE–VCO_2$=regression slope relating to minute ventilation to carbon dioxide output; ET=exercise time to exhaustion during exercise test; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association class; ALC=alcohol intake; DIU=diuretic dose. *P<0·05; **P<0·01; ***P<0·001.

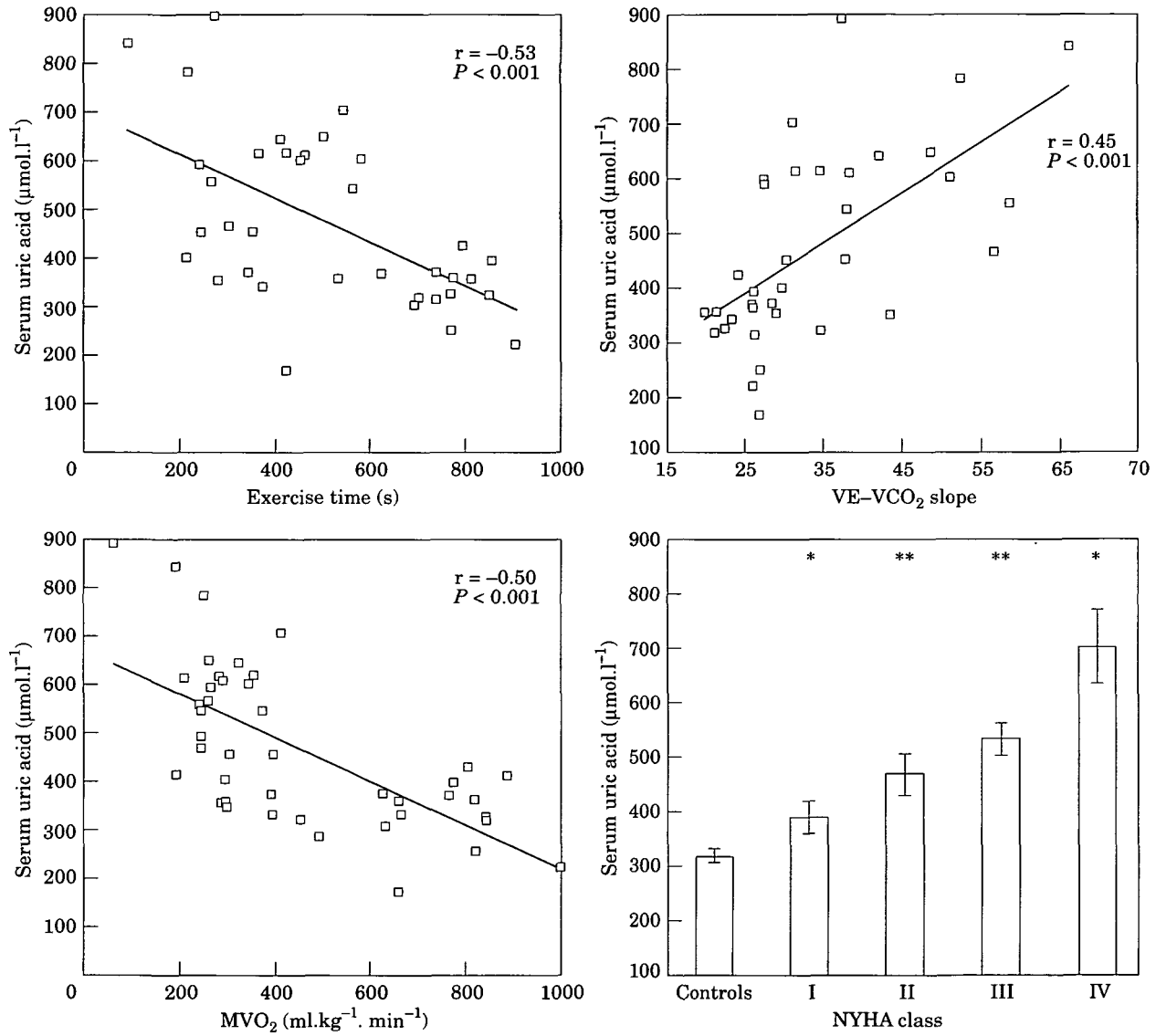

Figure 1 **Plots of serum uric acid concentrations against indices of functional capacity in patients with chronic heart failure. For New York Heart Association (NYHA) class, uric acid values are plotted as mean ± SEM. Asterisks relate to the significance of differences between the groups according to NYHA class and healthy controls. *$P<0.05$, **$P<0.01$. MVO_2=maximal oxygen uptake; VE–VCO_2=regression slope relating to minute ventilation to carbon dioxide output.**

class (0·39, $P<0.01$) and to a lesser degree with serum uric acid (r=0·32, $P<0.05$). When the chronic heart failure group was divided into those who were taking thiazide diuretics (n=11) and those who were not (n=52), the only significant difference was a low body mass index ($P<0.01$) in the thiazide group (data not shown), whilst insulin sensitivity, triglycerides, fasting and intravenous glucose tolerance test insulin were similar.

Because of the significant age dependence of body mass index, diastolic blood pressure and MVO_2, age-adjusted values were used in further analyses. In stepwise multivariate linear regression analysis using age-adjusted values, serum uric acid emerged as the most significant predictor of MVO_2, VE–VCO_2 slope, exercise time and NYHA class, independent of alcohol intake, body mass index, insulin sensitivity, serum creatinine, plasma insulin or diuretic dose (Table 3). In further analyses, aetiology of chronic heart failure did not enter into the final regression models (data not shown) and no metabolic predictors emerged for left ventricular ejection fraction.

In factor analysis of the chronic heart failure group, 12 intercorrelated variables were reduced to four uncorrelated factors (Table 4). The factor which accounted for most of the variance in the dataset (factor 1, 22·7% of the variance) comprised (in order of factor loading) uric acid, MVO_2, VE–VCO_2 slope, mean

Table 3 Results of the final models obtained by stepwise multivariate linear regression analysis on the chronic heart failure group, with indices of functional capacity as the dependent variables

Dependent variables							
	MVO_2		NYHA class		$VE-VCO_2$ slope		Exercise time
Independent variables							
Uric acid	−0·46***	Uric acid	0·31**	Uric acid	0·38*	Uric acid	−0·44***
Alcohol intake	0·41**	Diuretic dose	0·25**	BMI	−0·34*	Alcohol intake	0·32**
BMI	0·25*	Alcohol intake	−0·23	Fasting insulin	0·24	Fasting insulin	−0·24
						$S_{(I)}$	0·16
Variables that failed to enter into final models							
Creatinine		BMI		Alcohol intake		BMI	
Fasting insulin		$S_{(I)}$		$S_{(I)}$		Creatinine	
IIAREA		Creatinine		Creatinine		IIAREA	
Diuretic dose‡		Fasting insulin		IIAREA		Diuretic dose	
$S_{(I)}$		IIAREA		Diuretic dose			
R^2	0·60***		0·29***		0·38***		0·63***

Data are expressed as standardized regression coefficients. ‡Diuretic dose entered as frusemide-equivalent dose; MVO_2=maximal oxygen consumption; NYHA=New York Heart Association; $VE-VCO_2$=regression slope relating to minute ventilation to carbon dioxide output; BMI=body mass index; $S_{(I)}$=insulin sensitivity index; IIAREA=incremental insulin area; R^2=squared multiple regression coefficient for analysis. *P<0·05; **P<0·01; ***P<0·001.

Table 4 Results of factor analysis*

Factors	1	2	3	4
Uric acid	**−0·82**	0·01	0·22	−0·03
MVO_2	**0·81**	0·04	−0·08	0·37
$VE \pm VCO_2$ slope	**−0·77**	−0·04	0·31	0·02
Mean arterial pressure	**0·66**	**0·46**	0·29	0·09
Body mass index	**0·51**	**0·72**	0·09	0·05
Fasting insulin	−0·34	**0·86**	0·16	−0·03
Incremental insulin area	0·08	**0·86**	−0·27	−0·17
Triglycerides	0·33	**0·71**	0·03	**−0·43**
Fasting glucose	−0·02	−0·07	**0·92**	0·04
Incremental glucose area	−0·21	−0·06	**0·79**	−0·25
Left ventricular ejection fraction	0·12	−0·13	**−0·54**	0·21
HDL-cholesterol	0·03	−0·14	−0·18	**0·79**
Insulin sensitivity	0·21	−0·08	−0·11	**0·73**
% total variance explained	22·7	21·2	16·5	12·5

*Expressed in terms of loadings following rotation of principal components. Rotated loadings greater than 0·40 are shown in bold. MVO_2=maximal oxygen· uptake; $VE-VCO_2$ slope=regression slope relating to minute ventilation to carbon dioxide output.

arterial blood pressure and body mass index. Taking the highest two loadings in each factor, factor 1 is interpreted as the high uric acid/low MVO_2; factor 2, as the high plasma insulin factor; factor 3, as the impaired glucose tolerance factor; and, factor 4, as the low HDL/insulin resistance factor. Together, these factors accounted for 72·9% of the total variance in the dataset.

Discussion

To our knowledge, this is the first study to analyse serum uric acid concentrations in patients with chronic heart failure. We have found an inverse relationship between serum uric acid concentrations and MVO_2, independent of diuretic dose, serum creatinine, fasting insulin and incremental insulin area, alcohol intake, body mass index and insulin sensitivity. The observation that the aetiology of chronic heart failure did not influence this relationship suggests that elevated serum uric acid is a result of chronic heart failure per se. That hypoxia and impaired oxidative metabolism play a significant role in the elevations of serum uric acid in chronic heart failure is supported by the finding of a positive correlation between serum uric acid levels $VE-VCO_2$. Factor analysis served to illustrate the findings of univariate correlation analyses. Whether or not the *factors* identified by factor analysis merely represent statistical associations depends on the extent to which pathophysiological meaning can be ascribed to the different factors. In this study, factor analysis served to emphasize that the particularly strong relationship between uric acid and cardiopulmonary measures of functional capacity can be discerned in the background of a large panel of metabolic variables.

Although elevations in serum uric acid levels that accompany hypoxic states have been attributed to diminished renal excretion[39], uric acid overproduction is likely to be an important contributor[17]. This is suggested by the finding that hypoxia leads to accumulation of the precursors of uric acid (hypoxanthine and xanthine)[40] and activation of xanthine oxidase/dehydrogenase. Although the liver is the principal source of uric acid, the endothelium also contributes to its production. Xanthine oxidase is absent in endothelial cells from large vessels, where purine degradation ceases with the formation of hypoxanthine[41]. In the heart, xanthine oxidase is localized solely in the capillary endothelium[42] and therefore, the uric acid generated in hypoxic states originates from capillary endothelial cells rather than from the myocardium[43,44]. Accordingly, elevated serum uric acid would be expected to reflect the metabolic effects of hypoxia on the microvasculature, as found in the present study.

Cardiac failure is an insulin resistant state[24] in which there is an accelerated rate of glycolytic metabolism. The only oxidative step in glycolysis is that catalysed by the enzyme glyceraldehyde 3-phosphate dehydrogenase, the activity of which is known to be regulated by insulin[45,46]. This step is particularly susceptible to hypoxia[47] and could be affected by insulin resistance. Decreased activity of this enzyme can lead to back-up of early glycolytic intermediates and increased availability of ribose-5-phosphate and phosphoribosyl pyrophosphate, which would favour uric acid production. Accordingly, increased uric acid production in chronic heart failure may result from the combined effects of hypoxia and insulin resistance on this oxidative step of glycolysis.

An inverse relationship between uric acid excretion and insulin concentrations has been demonstrated in several studies[3,48], and impaired renal elimination of uric acid has been proposed as the principal reason for the involvement of elevated uric acid levels in the insulin resistance syndrome. In a study of healthy individuals, serum uric acid excretion has been shown to decrease in response to prolonged hyperinsulinaemia, suggesting that an inhibitory effect of insulin on renal uric acid elimination underlies the positive association between insulin and serum uric acid levels[49]. In the present study, the association of serum uric acid with MVO_2 or $VE–VCO_2$ remained significant when serum creatinine and plasma insulin levels were taken into account. The additional finding from factor analysis, that insulin levels load predominantly on a separate factor to that comprising serum uric acid suggests that hypoxia rather than hyperinsulinaemia per se is the main pathogenetic link between chronic heart failure and elevated serum uric acid levels.

Diuretic therapy is a possible confounder in the observed inverse relationship between serum uric acid and measures of functional capacity. Thiazide and loop diuretics cause a dose-dependent elevation of serum uric acid by increasing its tubular reabsorption in the context of volume depletion. In this study, however, the only univariate correlation detected for diuretic dose was with NYHA class. Diuretic dose failed to emerge as a predictor of MVO_2 in multiple regression analyses, and when it was entered as the 14th variable in factor analysis, it only loaded significantly on a fourth factor together with NYHA class (loadings, 0·54 and 0·88, respectively) (data not shown). Since, by definition, factors isolated in factor analyses are uncorrelated, it would appear that increasing doses of diuretics improve functional class without having a significant effect on serum uric acid concentrations.

A relationship between left ventricular ejection fraction and serum uric acid might be expected in view of the cardioprotective effects of xanthine oxidase inhibition by allopurinol[50–52]. This relationship, however, is not suggested by the findings of this study, in which no significant univariate correlation emerged between serum uric acid and left ventricular ejection fraction. These findings are supported by those of factor analysis, in which left ventricular ejection fraction failed to load significantly on the same factor as uric acid. Interestingly, left ventricular ejection fraction loaded significantly on the impaired glucose tolerance factor (factor 3), in agreement with previous reports of associations between insulin resistance and both impaired left ventricular function[53] and physical activity[54].

In conclusion, the observation of a strong inverse relationship between serum uric acid levels and MVO_2 in patients with chronic heart failure suggests that impaired oxidative metabolism may be a pathogenetic link between chronic heart failure and its attendant hyperuricaemia. Further studies are needed to determine whether elevations in serum uric acid in chronic heart failure are a result of increased uric acid synthesis and whether such elevations reflect the metabolic effects of hypoxia on the capillary endothelium.

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