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Uric acid in chronic heart failure:

A marker of chronic inflammation

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Background Chronic heart failure is associated with hyperuricaemia and elevations in circulating markers of inflammation. Activation of xanthine oxidase, through free radical release, causes leukocyte and endothelial cell activation. Associations could therefore be expected between serum uric acid level, as a marker of increased xanthine oxidase activity, and markers of inflammation. We have explored these associations in patients with chronic heart failure, taking into account the hyperuricaemic effects of diuretic therapy and insulin resistance.

Methods and Results Circulating uric acid and markers of inflammation were measured in 39 male patients with chronic heart failure and 16 healthy controls. All patients underwent a metabolic assessment, which provided a measure of insulin sensitivity (intravenous glucose tolerance tests and minimal modelling analysis). Compared to controls, patients with chronic heart failure had significantly higher levels of circulating uric acid, interleukin-6, soluble tumour necrosis factor receptor (sTNFR)-1, soluble intercellular adhesion molecule-1 (ICAM-1, all $P<0{\cdot}001$), E-selectin and sTNFR2 (both $P<0{\cdot}05$). In patients with chronic heart failure, serum uric acid concentrations correlated with circulating levels of sTNFR1 ($r=0{\cdot}74$), interleukin-6 ($r=0{\cdot}66$), sTNFR2 ($r=0{\cdot}63$), TNFα ($r=0{\cdot}60$) (all $P<0{\cdot}001$), and ICAM-1 ($r=0{\cdot}41$, $P<0{\cdot}01$). In stepwise regression analyses, serum uric acid emerged as the strongest predictor of ICAM-1, interleukin-6, TNF, sTNFR1 and sTNFR2, independent of diuretic dose, age, body mass index, alcohol intake, serum creatinine, plasma insulin and glucose, and insulin sensitivity.

Conclusions Serum uric acid is strongly related to circulating markers of inflammation in patients with chronic heart failure. This is consistent with a role for increased xanthine oxidase activity in the inflammatory response in patients with chronic heart failure.
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Key Words: Uric acid, chronic heart failure, cytokines, xanthine oxidase activity.

See page 1746 for the Editorial comment on this article.

Introduction

The association between hyperuricaemia and cardiovascular disease has long been recognised, but no mechanism has been proposed for this association. We have recently shown that compared to age-matched controls, patients with chronic heart failure are hyperuricaemic, independent of the effects of diuretics, renal impairment and other metabolic factors which are known to cluster with hyperuricaemia[1].

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The finding of hyperuricaemia in chronic heart failure has emerged in the context of an increasing recognition that chronic heart failure is associated with chronic inflammation, as suggested by the findings of elevations in circulating cytokines[2–4], their soluble receptors[5,6] and increased levels of soluble adhesion molecules[7]. Adhesion molecules, integrins and cytokines are mechanistically interrelated. The integrin E-selectin, which is present on endothelial cells, contributes to the induction of rolling and adherence of leukocytes to endothelial cells. Intercellular adhesion molecule (ICAM)-1 interacts with integrins on leukocytes and is instrumental in forming attachments to endothelial cells. Accordingly, ICAM-1 is an indicator of the cellular activation that accompanies inflammation. Both ICAM-1[8,9] and E-selectin[10] are up-regulated in vitro and in vivo by tumour necrosis factor (TNF)-α, whose

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Table 1 Clinical characteristics of study and control groups*

	CHF group			Controls (n=16)	*P* value
	CHD (n=23)	DCM (n=16)	All (n=39)		
Age (years)	63·6 (9·7)	57·3 (13·1)	61·0 (11·5)	54·3 (9·8)	<0·05
Body mass index (kg . m^{-2})	24·7 (3·9)	24·7 (4·8)	24·7 (4·3)	26·9 (4·2)	ns
Systolic blood pressure (mmHg)	109·7 (17·8)	115·8 (20·7)	112·2 (19·0)	130·0 (12·0)	0·001
Diastolic blood pressure (mmHg)	69·1 (9·4)	69·9 (12·3)	69·4 (10·5)	82·1 (8·6)	<0·001
Left ventricular ejection fraction (%)	22·3 (11·7)	26·3 (16·4)	23·9 (13·7)	nd	
Maximal oxygen consumption (ml . kg . min^{-1})	15·7 (3·8)	17·4 (7·5)	16·4 (5·6)	36·4 (7·7)	<0·001
Exercise time (s)	405·3 (154·5)	462·1 (190·1)	428·6 (169·9)	707·7 (139·2)	<0·001
NYHA class					
II	4	8	12	—	
III	16	6	22	—	
IV	3	2	5	—	
Diuretic dose (mg)†	123·9 (114·6)	120·6 (69·7)	122·6 (97·6)	—	

*Data are presented as means (± SD). †Entered as frusemide-equivalent dose (1 mg of bumetanide equivalent to 40 mg frusemide). NYHA=New York Heart Association; CHF=chronic heart failure; CHD=coronary heart disease; DCM=dilated cardiomyopathy, nd=not done. *P* values refer to Mann–Whitney U tests for differences between the pooled sample of patients with chronic heart failure and controls. No differences in any of the variables emerged between the group of patients with CHF due to CHD and that with CHF due to DCM.

biological effects are modulated by tumour necrosis factor receptors (TNFR) 1 and 2[11]. Exposure of rat myocytes to interleukin 1β stimulates the release from monocytes of chemoattractant protein-1, which is known to promote ICAM-1. It has been suggested that circulating soluble intercellular adhesion molecule (ICAM)-1[12], is of prognostic value in patients with chronic heart failure.

A number of studies have linked uric acid metabolism to inflammatory responses. Xanthine oxidase, which converts xanthine or hypoxanthine to uric acid, is an important mediator of inflammatory responses and cellular damage in ischaemia–reperfusion, rheumatic and renal disease, and exercise-induced muscular inflammation[13]. The ability of xanthine oxidase to generate superoxide free radicals[14–17] is important in stimulating the expression of adhesion molecules by leukocytes[18] and in the activation[19–21] and adherence of leukocytes to damaged endothelium[22,23] — a pre-requisite for endothelial injury. Accordingly, xanthine oxidase inhibition by allopurinol has been shown to reduce leukocyte adherence and extravasation into the vascular intima[24,25]. Recent evidence suggest that, via release of reactive oxygen species, activation of xanthine oxidase activates matrix metalloproteinases[26] — species which are implicated in early rupture of atherosclerotic plaques. We have recently demonstrated that in male patients with coronary heart disease, there is a positive correlation between MMP-2 and serum uric acid[27].

Since increased activity of xanthine oxidase leads to elevations in serum uric acid, we hypothesized that in patients with chronic heart failure, serum uric acid levels might relate to circulating markers of chronic inflammation. In testing this hypothesis, it is necessary to consider that concurrent diuretic therapy and renal impairment also cause elevations in serum uric acid. In addition, chronic heart failure is an insulin resistant, hyperinsulinaemic state[28,29], and both insulin resistance and hyperinsulinaemia are also associated with hyperuricaemia[30,31]. We have focused on circulating sICAM-1, E-selectin, sTNFR1 and sTNFR2, TNFα and interleukin-6 on the basis of previous studies demonstrating that circulating levels of these markers may be raised in patients with chronic heart failure.

Subjects and methods

Thirty nine patients with chronic heart failure due to coronary heart disease (n=23) or dilated cardiomyopathy (n=16), aged 61·0 ± 11·5 years (mean ± SD), with a body mass index of 24·7 ± 4·3 kg . m^{-2} and in NYHA class II (n=12), III (n=22) and IV (n=5), were included in this study together with 16 healthy controls (Table 1). Concurrent medication in the chronic heart failure group, either alone or in combination, included: angiotensin-converting enzyme inhibitors (n=32); loop diuretics (n=38); thiazide diuretics (n=10); and potassium sparing diuretics (n=17). No patients were taking hypouricaemic medication. All patients had been in chronic heart failure for >3 months, none had pulmonary or peripheral oedema at the time of assessment, and none had clinical signs of acute infection, rheumatoid arthritis, or cancer.

Metabolic studies

These were carried out in our metabolic day ward. Participants were asked to have fasted for 12 h, and to have refrained from smoking on the morning of the test. After resting for 20 min in a semi-recumbent position, participants underwent an intravenous glucose tolerance test (0·5 g . kg^{-1} body weight dextrose administered as

a 50% solution) with multiple sampling for plasma glucose and insulin, as previously described[32]. Insulin sensitivity (S_I), inversely related to insulin resistance, was obtained using the minimal model approach[33]. All subjects gave informed consent, and the study was approved by the local ethics committee.

Functional capacity

During cardiopulmonary exercise testing, all subjects were exercised to exhaustion (respiratory exchange ratio >1·1). Maximal oxygen consumption was estimated from a metabolic gas exchange analysis performed during a maximal exercise test, using a modified Bruce protocol for patients with chronic heart failure and an on-line inert gas dilution technique[34,35]. Left ventricular ejection fraction was estimated at rest by radionuclide ventriculography using a stannous fluoride red cell labelling agent, a bolus injection of radiolabelled ^{99}Tc and gamma camera imaging.

Laboratory determinations

Plasma glucose was determined on the same day using glucose oxidase procedures with aminophenazone[36]. Plasma insulin was measured on samples stored at − 20 °C using a radioimmunoassay procedure[37]. Serum uric acid was determined by the uricase–peroxidase method. Within- and between-batch precision was monitored throughout the study using frozen plasma and serum pools and commercially available lyophilized sera, and by participation in national quality assurance schemes. Commercially available ELISA kits were used for assay of immune function markers in venous samples taken after 20 min supine rest. After centrifugation, aliquots were stored at − 70 °C until analysis. Measurement of total TNF-α (Medgenix, Fleurus, Belgium, lower limit of detectability, 3·0 pg . ml^{-1}) was not influenced by soluble TNF receptors. Test kits from R&D systems (Minneapolis, MN, U.S.A.) were employed for duplicate measurement of sTNFR-1 and -2 (sensitivities, 25 pg . ml^{-1} and 2 pg . ml^{-1}, respectively), ICAM-1 (sensitivity 7 ng . ml^{-1}), E-selectin (sensitivity 2 ng . ml^{-1}), IL-1β (sensitivity 0·01 pg . ml^{-1}) and IL-6 (sensitivity, 0·094 pg . ml^{-1}). The interassay and intra-assay coefficients of variation did not exceed 7% in any of these measurements.

Data analyses

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. Because of skewed distributions, erythrocyte sedimentation rate, and concentrations of insulin, ICAM-1, TNFα, sTNFR1, sTNFR2, IL-1β and IL-6 were logarithmically transformed. The distribution of insulin sensitivity in healthy individuals and in disease groups is almost invariably skewed[1,38] and for reasons outlined in detail elsewhere[39], the square-root tranformation has been used in the present analyses. Univariate Pearson correlation coefficients with Bonferroni correction were derived. Group differences were assessed by the Mann–Whitney U test. Statistical analyses were carried out using the SYSTAT (SYSTAT Inc., Evanston, Illinois, U.S.A.) statistical package.

Results

Compared to controls, patients with chronic heart failure were older (P<0·05), had lower systolic and diastolic blood pressures (both P<0·001), and higher levels of serum creatinine (P<0·001), fasting insulin (P<0·04) and serum uric acid (P<0·001) (Tables 1 and 2). Patients with chronic heart failure also had a lower S_I (P<0·001) and intravenous glucose tolerance test glucose response (P<0·05). Patients with chronic heart failure had higher levels of ICAM-1, sTNFR1 and IL-6 (all P<0·001), sTNFR2 and E-selectin (both P<0·05), but not TNFα or IL-1β. No significant differences emerged in any of the variables of patients with chronic heart failure due to coronary heart disease and those with chronic heart failure due to idiopathic dilated cardiomyopathy (data not shown).

Univariate correlation analyses revealed significant correlations between serum uric acid and measures of chronic inflammation in the chronic heart failure group (Fig. 1), but not in controls (Table 3). In stepwise multiple linear regression analyses (Table 4), serum uric acid emerged as the strongest predictor of ICAM-1, TNFα, sTNFR1, sTNFR2 and IL-6, independent of diuretic dose, age, body mass index, alcohol intake, serum creatinine, fasting and intravenous glucose tolerance test glucose, and fasting and intravenous glucose tolerance test insulin. Serum uric acid was not a predictor of aetiology of chronic heart failure, E-selectin, IL-1β, white cell count or erythrocyte sedimentation rate (data not shown). As shown in Table 5, serum uric acid levels and markers of chronic inflammation correlated negatively with exercise time and maximal oxygen consumption during a treadmill exercise test.

Discussion

In agreement with previous studies, we have shown that, compared to healthy controls, patients with chronic heart failure exhibit elevations in serum uric acid and in circulating markers of chronic inflammation. No differences were observed between the chronic heart failure groups with coronary heart disease or dilated cardiomyopathy, in agreement with previous demonstrations

Table 2 Metabolic variables and markers of chronic inflammation in patients with chronic heart failure and controls

	All CHF patients (n=39)	Controls (n=16)	*P* value
Uric acid ($\mu mol \cdot l^{-1}$)	537·0 (156·9)	316·4 (55·5)	<0·001
Creatinine ($\mu mol \cdot l^{-1}$)	132·5 (47·0)	91·1 (8·7)	<0·001
Fasting glucose ($mmol \cdot l^{-1}$)	5·9 (2·1)	5·2 (0·3)	ns
IVGTT glucose area ($mmol \cdot l^{-1} \cdot min^{-1}$)	569·9 (217·2)	476·1 (126·1)	ns
Fasting insulin ($pmol \cdot l^{-1}$)	58·9 (− 32·7,+73·5)	33·2 (− 14·1,+78·2)	0·04
IVGTT insulin area ($10^4 \cdot pmol \cdot l^{-1}$)	2·24 (− 1·09,+2·12)	2·37 (− 1·7,+3·36)	ns
Insulin sensitivity ($10^5 \cdot min^{-1}$ [$pmol \cdot l^{-1}$])	1·87 (− 1·26,+1·96)	4·00 (− 1·83,+2·40)	0·001
ESR (mm)	17·2 (− 8·6,+17·3)	2·6 (− 1·65,+4·5)	<0·001
WBC ($10^9 \cdot l^{-1}$)	7·15 (1·98)	5·06 (1·15)	<0·001
ICAM-1 ($ng \cdot ml^{-1}$)	388·2 (− 77·0,+96·0)	269·2 (− 48·4,+59·0)	<0·001
E-selectin ($ng \cdot ml^{-1}$)	50·2 (19·0)	37·0 (13·1)	0·021
TNF-α ($pg \cdot ml^{-1}$)	8·49 (− 4·68,+10·43)	6·75 (− 2·07,+2·98)	ns
sTNFR1 ($pg \cdot ml^{-1}$)	1148 (− 494,+866)	552 (− 225,+379)	<0·001
sTNFR2 ($pg \cdot ml^{-1}$)	2449 (− 868,+1344)	1633 (− 780,+1493)	0·020
Interleukin-1β ($pg \cdot ml^{-1}$)	0·23 (− 0·17,+0·62)	0·12 (− 0·09,+0·43)	ns
Interleukin-6 ($pg \cdot ml^{-1}$)	2·72 (− 1·52,+3·43)	0·80 (− 0·37,+0·68)	<0·001

*Results are expressed as mean (± SD), except for insulin concentrations and markers of immune activation which, because of skewed distributions, are expressed as mean and asymmetrical SD. IVGTT=intravenous glucose tolerance test; ESR=erythrocyte sedimentation rate; WBC=white cell count; ICAM-1=intercellular adhesion molecule-1; sTNFR=soluble tumour necrosis factor receptor. **P* values refer to Mann–Whitney U tests.

Table 3 Univariate Pearson correlation coefficients (Bonferroni-adjusted) between uric acid and markers of chronic inflammation in the study and control groups

	CHF (n=39)	Controls (n=16)
sTNFR1	0·74***	0·30
Interleukin-6	0·66***	−0·10
sTNFR2	0·63***	−0·29
TNF-α	0·60***	0·01
ICAM-1	0·41**	0·15
ESR	0·25*	0·03
WBC	0·15	−0·06
E-selectin	0·07	0·47
Interleukin-1β	0·12	+0·10

sTNFR=soluble tumour necrosis factor receptor, TNF-α=tumour necrosis factor-α, ICAM-1=soluble intercellular adhesion molecule-1, ESR=erythrocyte sedimentation rate; WBC=white cell count. *P<0·05, **P<0·01, ***P<0·001.

that cellular activation occurs in atherosclerosis[40] as well as in dilated cardiomyopathy[41].

The novel finding from this study is that in chronic heart failure, serum uric acid is strongly related to measures of chronic inflammation. The dose-dependent hyperuricaemic effects of concurrent diuretic therapy might reasonably account for this observation. However, prolonged treatment with thiazide diuretics typically elevates serum uric acid by about 10%[42], which is in contrast to the 70% increase observed in patients with chronic heart failure in this study. Obesity[43,44], alcohol intake, hyperinsulinaemia and insulin resistance[30,45,46] are also relevant in this respect, given that these affect renal urate excretion. However, our study reveals that metabolic factors do not prevent serum uric acid from emerging as the strongest predictor of various measures of chronic inflammation. Similarly, the degree of renal impairment, assessed by the level of plasma creatinine, was not a strong predictor of serum urate levels, suggesting that decreased excretion of urate is not the main determinant of increased elevations in circulating urate in these patients. On the other hand, coronary artery-to-coronary sinus gradients of uric acid concentrations have been shown to occur in patients with chronic myocardial ischaemia[47], a finding which is consistent with the demonstration of a net release of urate in the coronary sinus following coronary artery angioplasty in patients with coronary heart disease[48]. These findings, together with the fact that xanthine oxidase is present in the human heart[49,50], suggest that in chronic heart failure, increased urate production in the heart contributes to elevations in serum urate.

A possible explanation for our findings relates to the known interplay between leukocyte activation and xanthine oxidase activity[22–25]. Xanthine oxidase-derived free radical release has been implicated in the increased expression of adhesion molecules by leukocytes[18] — a prerequisite for leukocyte adhesion to the vascular intima. That xanthine oxidase-derived free radicals play an important part in the cellular processes that culminate in endothelial injury is supported by the observation that inhibition of xanthine oxidase by allopurinol reduces leukocyte adherence, rolling and extravasation[24,25] and prevents phagocytosis of particles by leukocytes adhered to the endothelium of rat aorta[51]. Thus, it is possible that the association between circulating uric acid and markers of chronic inflammation reflects the relationship between xanthine oxidase activity and leukocyte activation in the vicinity of the vascular endothelium.

To our knowledge, serum uric acid has not hitherto been studied in relation to endothelial injury in cardiovascular disease. It is noteworthy, however, that in pre-eclampsia — a disorder characterized by endothelial injury — serum uric acid correlates with markers of endothelial damage, such as plasma levels of thrombomodulin[52] and endothelin-1[53]. Increased production of uric acid by endothelial cells might then represent a more sensitive marker of endothelial injury, since activation of uric acid production must occur before cellular damage.

As to the origin of the putative increase in xanthine oxidase activity in chronic heart failure, it is noteworthy that in the peripheral vasculature and the heart, endothelial cells are the predominant site of uric acid production[54]. Xanthine oxidase/dehydrogenase is abundant in the capillary endothelium[55–58] but absent from large vessels, and it is on this basis that xanthine oxidase/dehydrogenase has been regarded as a marker enzyme of the capillary endothelium[55,59]. Thus, our demonstration of a strong relationship between serum uric acid and ICAM-1 points to the microvascular endothelium as a possible site of increased xanthine oxidase activity in chronic heart failure.

Elevations of serum uric acid levels have been shown to occur in various hypoxic states, including obstructive pulmonary disease[60,61], neonatal hypoxia[62,63], cyanotic heart disease[64,65] and acute heart failure[66]. Regional ischaemia, such as that produced during coronary angioplasty[67] or tourniquet exsanguination of the forearm[68] also produces elevations in serum uric acid. We have previously shown that in chronic heart failure, serum uric acid is inversely related to maximal oxygen consumption during a maximal treadmill exercise test[1] and to maximal leg blood flow[69]. Our observation in the present study that serum uric acid is also related to circulating markers of chronic inflammation is consistent with the concept that in chronic heart failure, reduced tissue availability of oxygen may be linked to activation of xanthine oxidase, with release of free radicals and consequent cellular activation.

Importantly, serum uric acid levels and markers of immune activation were negatively correlated with exercise time and maximal oxygen consumption during a treadmill exercise test, both of which provide continuous measures of functional capacity and disease severity. These findings suggest that serum uric acid levels parallel the chronic inflammatory response which appears to

Table 4 Stepwise linear regression analyses of the chronic heart failure group

Dependent variables									
ICAM-1		TNF-α		sTNFR1		sTNFR2		IL-6	
Independent variables									
Uric acid	0·52***	Uric acid	0·58***	Uric acid	0·64***	Uric acid	0·54***	Uric acid	0·81***
Alcohol intake	0·28	BMI	− 0·28*	Age	0·29**	Age	0·31**	Diuretic dose	− 0·38**
Diuretic dose†	− 0·26			BMI	− 0·20*				
Variables that failed to enter into stepwise regression models									
Creatinine		Creatinine		Creatinine		Creatinine		Creatinine	
		Diuretic dose		Diuretic dose		Diuretic dose			
Age		Age						Age	
BMI						BMI		BMI	
		Alcohol intake		Alcohol intake		Alcohol intake		Alcohol intake	
Fasting glucose		Fasting glucose		Fasting glucose		Fasting glucose		Fasting glucose	
IVGTT glucose		IVGTT glucose		IVGTT glucose		IVGTT glucose		IVGTT glucose	
Fasting insulin		Fasting insulin		Fasting insulin		Fasting insulin		Fasting insulin	
IVGTT insulin		IVGTT insulin		IVGTT insulin		IVGTT insulin		IVGTT insulin	
S_I		S_I		S_I		S_I		S_I	
r^2	0·33***		0·44***		0·71***		0·48***		0·57***

†Diuretic dose is entered as frusemide-equivalent dose. SC=standardized coefficient; ICAM-1=intercellular adhesion molecule-1; sTNFR=soluble tumour necrosis factor receptor; IL-6=interleukin-6; TNF-α=tumour necrosis factor-α; IVGTT=intravenous glucose tolerance test; BMI=body mass index; S_I=insulin sensitivity. *P<0·05, **P<0·01,***P<0·001.

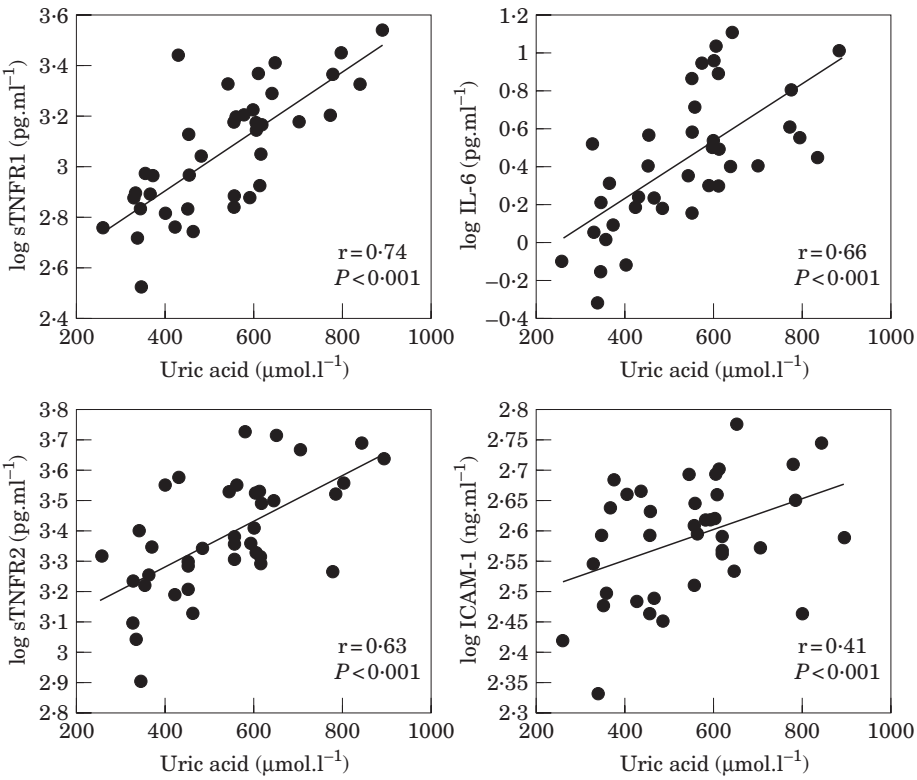

Figure 1 **Scatterplots of serum uric acid against markers of chronic inflammation in patients with chronic heart failure. sTNFR=soluble tumour necrosis factor receptor, ICAM-1=soluble intercellular adhesion molecule-1; IL-6=interleukin-6, r=Pearson correlation coefficient.**

Table 5 Univariate correlations between measures of functional capacity, serum uric acid and markers of chronic inflammation

	Exercise time	MVO_2
Uric acid	−0·52**	−0·59***
sTNFR1	−0·36*	−0·53**
Interleukin-6	−0·25	−0·42**
sTNFR2	−0·33	−0·41*
TNF-*α*	−0·41**	−0·38*
ICAM-1	−0·12	−0·15
ESR	−0·12	−0·21
WBC	−0·28	−0·03
E-selectin	0·12	0·24
Interleukin-1*β*	−0·15	−0·08

MVO_2=maximal oxygen consumption during a treadmill exercise test. sTNFR=soluble tumour necrosis factor receptor, TNF-*α*=tumour necrosis factor-*α*, ICAM-1=intercellular adhesion molecule-1, ESR=erythrocyte sedimentation rate; WBC=white cell count. *P<0·05, **P<0·01, ***P<0·001.

occur with increasing severity of chronic heart failure. Whilst the findings of our study do not clarify the possible causal links between elevations in these measures and disease severity, they are consistent with our recent demonstration[70] that serum uric acid levels predict mortality in patients with chronic heart failure.

This study has limitations. The finding of a relationship between serum uric acid and markers of chronic inflammation is a statistical finding which does not clarify causality. The effect of diuretics on serum uric acid was assessed in a statistical rather than in an experimental manner and therefore, we cannot discount the possibility that diuretics contribute to the relationship between serum uric acid and markers of chronic inflammation in chronic heart failure. Although these limitations are relevant with respect to the putative pathophysiological link between serum uric acid and markers of chronic inflammation, they do not detract from the conclusion that serum uric acid levels mark the inflammatory response in chronic heart failure.

In conclusion, we have demonstrated that serum uric acid levels in patients with chronic heart failure are strongly related to circulating markers of chronic inflammation. Although further studies are needed to determine whether such a relationship is causal, the findings from the present study suggests that xanthine oxidase activity may be important in the chronic inflammation that characterizes chronic heart failure. The effects of xanthine oxidase inhibition on inflammatory responses and endothelial injury in patients with chronic heart failure warrants further investigation.

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