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*SHORT REPORT*

# Hyperuricaemia in patients with right or left heart failure

M.M. Hoeper, J.M. Hohlfeld, H. Fabel

*Hyperuricaemia in patients with right or left heart failure. M.M. Hoeper, J.M. Hohlfeld, H. Fabel. ©ERS Journals Ltd 1999.*

**ABSTRACT: Based on the clinical observation that patients with right or left heart failure often present with hyperuricaemia, the relation between serum urate values and haemodynamic variables was studied in patients with primary pulmonary hypertension (PPH) as well as in patients with advanced ischaemic heart disease or dilated cardiomyopathy.**

**The study was a retrospective analysis of 39 patients with PPH and 36 patients with left heart disease, examining serum urate levels in association with haemodynamic variables.**

**Elevated urate concentrations were found in 79% of the PPH patients. There was no association between serum urate levels and mean pulmonary artery pressures, but a significant correlation was found between urate levels and the cardiac index ($r=0.48$; $p=0.0021$) and an even stronger correlation between serum urate levels and mean right atrial pressures ($r=0.83$; $p<0.0001$). A similar association was found in a subgroup of 21 PPH patients not receiving diuretics. In 36 patients with ischaemic heart disease or dilated cardiomyopathy, hyperuricaemia was present in 78% and was significantly associated with elevated right atrial pressures ($r=0.40$; $p=0.031$) and even more so with elevated left atrial pressures ($r=0.55$; $p=0.0005$) but not with the cardiac index ($r=0.034$; $p=0.86$).**

**The data show that hyperuricaemia in patients with cardiac dysfunction is closely related to elevated right or left atrial filling pressures.**

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Dept of Pulmonary Medicine, Hanover Medical School, Hanover, Germany.

Correspondence: M.M. Hoeper
Dept of Pulmonary Medicine
Hanover Medical School
30623 Hanover
Germany
Fax: 49 5115323353

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Hyperuricaemia is a metabolic disorder frequently encountered in clinical practice. Elevated serum uric acid levels are present in 2–18% of the population, depending on age, sex, and several other factors. In most patients, hyperuricaemia is caused by altered renal excretion of uric acid but in many instances the exact mechanisms causing hyperuricaemia are not fully understood [1].

Two young female patients with primary pulmonary hypertension (PPH) were recently observed, who presented with acute gouty arthritis and markedly elevated serum uric acid levels. In one of these patients, the gout attack and the detection of unexplained hyperuricaemia led to a diagnostic work-up that revealed pulmonary hypertension (unpublished data). Both hyperuricaemia and gout attacks are uncommon in young females. Therefore, it was hypothesized that the elevated uric acid levels might have been related to pulmonary hypertension. Comparing haemodynamic variables and serum uric acid levels in patients with PPH, it was found that hyperuricaemia was a common finding in this group of patients and that there was a striking relation between right heart dysfunction and serum uric acid levels.

To find out whether this finding was unique for patients with pulmonary hypertension, the relation between haemodynamics and uric acid levels was studied in patients with predominantly left heart dysfunction due to congestive cardiomyopathy or ischaemic heart disease. In these patients, there was also a high prevalence of hyperuricaemia and a significant correlation between serum uric acid levels and atrial filling pressures.

The following paper reports in detail findings on hyperuricaemia in patients with cardiac dysfunction.

## Patients and methods

Data was reviewed from all 61 patients with PPH referred for lung transplantation between 1993 and 1997. PPH was defined according to published criteria [2]. Furthermore, the charts were analysed from 100 consecutive patients with ischaemic heart disease (IHD) or dilated cardiomyopathy (DCM) referred for heart transplantation.

Serum uric acid levels were compared with the haemodynamic variables obtained during heart catherization. Patients were excluded from the analysis when haemodynamic variables and serum values of uric acid and creatinine were not available from the same time point (defined as a maximum interval of 7 days), when the patients received treatment with the xanthine oxidase inhibitor allopurinol or an uricosuric agent, and when a coexisting renal disease was present, or when the kidney function was severely impaired (*e.g.* serum creatinine levels >200 $mmol \cdot L^{-1}$).

### *Statistical analysis*

The statistical analysis was carried out on a Macintosh computer using Statview 512 software (Brainpower, Agoura Hills, CA, USA). Results are presented as mean±SD.

Table 1. – Baseline characteristics of the patients

| | Pulmonary hypertension | Left heart disease |
|---|---|---|
| No. of patients | 39 | 36 |
| Age yrs | 41±13 (19–75) | 54±8 (29–68) |
| Male/Female | 14/25 | 33/3 |
| Functional class n | | |
| NYHA II | 3 | 5 |
| NYHA III | 25 | 21 |
| NYHA IV | 11 | 10 |
| Diuretic therapy n | | |
| Yes | 18 | 36 |
| No | 21 | 0 |
| Haemodynamic variables | | |
| CI $L \cdot min^{-1} \cdot m^{-2}$ | 2.0±0.7 (1.1–3.8) | 2.1±0.6 (1.0–3.7) |
| PAP mmHg | 58±14 (34–95) | 26±12 (15–52)* |
| PVR $dynes \cdot s \cdot cm^{-5}$ | 1287±579 (322–2543) | 319±146 (118–640)* |
| $P_{RA}$ mmHg | 8±5 (1–21) | 7±5 (1–19)* |
| $P_{pcw}/P_{LA}$ mmHg | 7±3 (4–11) | 20±9 (5–38) |
| Kidney function | | |
| Serum creatinine $\mu ol \cdot L^{-1}$ | 88±29 (46–180) | 102±26 (65–173) |
| Serum uric acid $\mu mol \cdot L^{-1}$ | 504±150 (265–912) | 524±169 (238–1071) |

Data given as absolute number or mean±SD (range) where appropriate. Left heart disease includes ischaemic heart disease and dilated cardiomyopathy. NYHA: New York Heart Association; PAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; PRA: right atrial pressure; $P_{pcw}/P_{LA}$: pulmonary capillary wedge pressure/left atrial pressure; *: data from right heart catherization were available from 29 patients in the left heart disease group.

A univariate linear regression analysis was performed to compare serum urate concentrations with haemodynamic variables. A multivariate regression analysis was performed to test the possibility that the urate concentrations were related to serum creatinine concentrations. The significance level was set at $p<0.05$.

## Results

A total of 39 patients with PPH and 36 patients with left heart disease (IHD: n=15; DCM: n=21) were eligible for analysis. The demographic data as well as the renal function parameters and the haemodynamic variables of these patients are shown in table 1.

### *Patients with primary pulmonary hypertension*

The upper normal values for urate in the general population are 360 $mmol \cdot L^{-1}$ in females and 415 $mmol \cdot L^{-1}$ in males [1]. Based on this definition, in the present PPH group, hyperuricaemia was found in 10 of 14 (71%) male patients as well as in 21 of 25 (84%) female patients. Hyperuricaemia was found in all patients who had evidence of an impaired cardiac function (as indicated by a mean right atrial pressure >8 mmHg and a cardiac index <2.0 $L \cdot min^{-1} \cdot m^{-2}$).

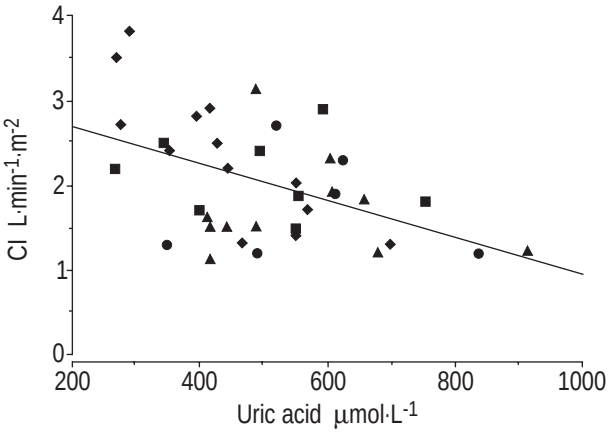


Fig. 1. – Correlation between serum urate levels and cardiac index (CI) in primary pulmonary hypertension. ●: males with diuretics; ■: males without diuretics; ▲: females with diuretics; ♦: females without diuretics. r=0.48, p=0.0021, n=39.

No association was found between the mean pulmonary artery pressures and uric acid levels (r=0.018; p=0.91) or between the pulmonary vascular resistances and uric acid levels (r=0.29; p=0.07; data not shown). In contrast, there was a significant correlation between the cardiac index and uric acid levels (r=0.48; p=0.0021; fig. 1). An even stronger and highly significant correlation was found between uric acid levels and mean right atrial pressures (r=0.83, p<0.0001; fig. 2).

A multivariate regression analysis was performed to exclude the possibility that the elevated uric acid concentration was simply due to impaired kidney function. This analysis showed that the association between the urate concentrations and right atrial pressures was independent from serum creatinine levels (p=0.0001) whereas the correlation between cardiac index and serum urate levels was no longer of statistical significance when corrected for creatinine levels (p=0.27).

The correlation between right atrial pressures and serum uric acid levels remained highly significant when males (r=0.773, p=0.0012) and females (r=0.862; p<0.0001) were

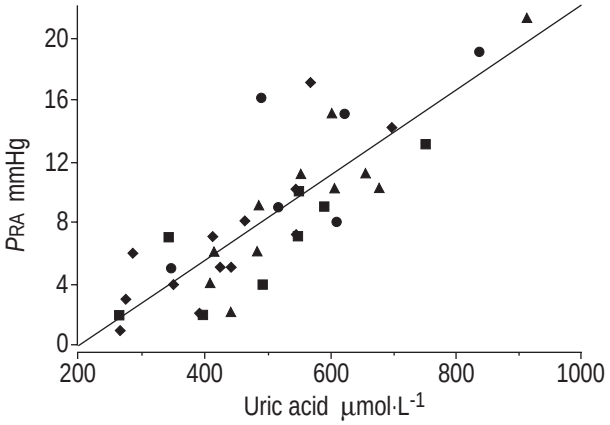


Fig. 2. – Correlation between serum urate levels and mean right atrial pressure ($P_{RA}$) in primary pulmonary hypertension. ●: males with diuretics; ■: males without diuretics; ▲: females with diuretics; ♦: females without diuretics. r=0.83, p<0.0001, n=39.

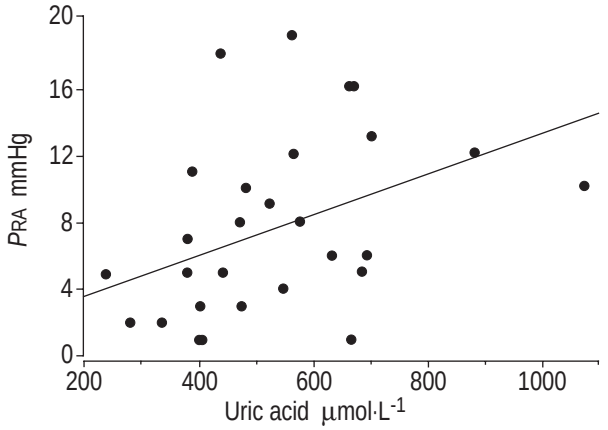


Fig. 3. – Correlation between serum urate levels and right atrial pressures ($P_{RA}$) in patients with ischaemic heart disease or dilated cardiomyopathy (right heart catheterization data were available from 29 patients). r=0.4, p=0.031, n=29.

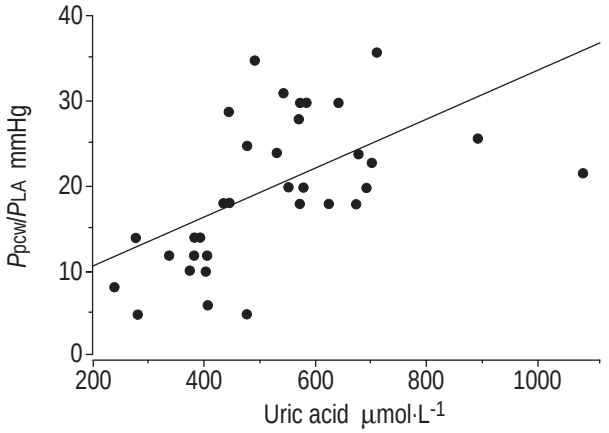


Fig. 4. – Correlation between serum urate levels and pulmonary capillary wedge pressures ($P_{pcw}$)/left atrial pressures ($P_{LA}$) in patients with ischaemic heart disease or dilated cardiomyopathy. r=0.55, p=0.0005, n=36.

analysed separately. In contrast, the correlation between cardiac index and uric acid levels was only significant in females (r=0.611, p=0.0012) but not in males (r=0.178; p=0.54; data not shown).

Since loop diuretics and thiazids are known to impair renal uric acid excretion and may cause hyperuricaemia, a subgroup analysis of the 21 PPH patients who were not treated with diuretics was performed. In this subgroup, uric acid levels were elevated in 5 of 8 male and 9 of 13 female patients (mean±SD: 473±133 µmol·L$^{-1}$; range 266–732 µmol·L$^{-1}$). Both, the correlation between cardiac index and urate levels (r=0.63; p=0.0024) and the correlation between right atrial pressures and serum uric acid levels remained highly significant (r=0.80; p<0.0001) in this subset of patients.

*Patients with ischaemic heart disease/dilated cardiomyopathy*

To further address the question whether hyperuricaemia might be related to low cardiac output or to an elevated filling pressure, the data were evaluated from 36 unselected patients with left heart failure who had been referred for heart transplantation. Hyperuricaemia was a common finding in this group, occurring in 28 out of 36 (78%) patients. As in patients with PPH, there was a significant correlation between serum uric acid levels and right atrial pressures (r=0.40; p=0.031, fig. 3). However, in the patients with IHD/DCM, there was no association between serum uric acid levels and the cardiac index (r=0.034; p=0.86) but a highly significant correlation between the serum uric acid levels and pulmonary capillary wedge pressures/left atrial pressures (r=0.55, p=0.0005; fig. 4). A multivariate regression analysis showed that the association between left atrial pressures and uric acid levels was independent from serum creatinine (p=0.0045), whereas the association between right atrial pressures and uric acid levels was no longer statistically significant (p=0.29). A more detailed comparison between the PPH group and the IHD/DCM group was not performed since the two groups differed too much with regard to age and sex, variables which are known to influence serum uric acid levels [1]. Since there were only three females in the IHD/DCM group, a sex-based subgroup analysis was not performed. Moreover, all eligible patients with IHD/DCM were receiving diuretic therapy so that a subgroup analysis of patients without diuretics was not feasible.

## Discussion

Elevated serum urate concentrations proved to be a common finding in patients with PPH as well as in patients with severe left heart disease. In both groups, hyperuricaemia was strongly related to elevated cardiac filling pressures. Notably, there was a striking correlation between serum urate levels and right atrial pressures in patients with PPH and between serum urate levels and left atrial pressures in patients with IHD/DCM. In the PPH group, there was also a significant correlation between uric acid levels and cardiac index. This association, however, was no longer significant when the results were corrected for the serum creatinine concentrations. In patients with IHD/DCM, hyperuricaemia did not correlate with cardiac index. These findings indicate that hyperuricaemia in patients with cardiac disease is primarily related to increased filling pressures rather than to low cardiac output.

The mechanisms responsible for the elevated serum urate concentrations in patients with heart failure are unclear. Uric acid is formed by catabolism of the purine bases adenine and guanine. Approximately two-thirds of the uric acid is excreted through the kidneys and one-third through the gastrointestinal tract [1]. Hyperuricaemia can result from overproduction or reduced excretion of uric acid, or both. Overproduction of uric acid in advanced heart failure could be related to tissue hypoxia which is known to increase adenosine triphosphate degradation [3] and to stimulate the expression of xanthine oxidase [4]. On the other hand, it is reasonable to assume that low cardiac output and venous congestion result in impaired glomerular filtration and tubular excretion of uric acid. Hormonal factors or circulating substances such as catecholamines, angiotensin II, endothelin, thromboxane, atrial natriuretic peptide, or brain natriuretic peptide may also be involved in the impaired renal removal of uric acid.

A high prevalence of hyperuricaemia has previously been described in children and adults with cyanotic congenital heart disease and has been linked to abnormal uric acid excretion rather than urate overproduction [5–7] but the exact mechanisms have not been elucidated. To the authors′ knowledge, a potential correlation between right atrial filling pressures and serum uric acid levels has not been investigated in this group of patients.

Hyperuricaemia, a part of the so-called metabolic syndrome, has been identified as a risk factor for coronary heart disease and there have been reports linking increased levels of uric acid to mortality in IHD, thereby raising speculation about a possible pathogenetic role of hyperuricaemia in IHD [8]. The present findings suggest that in these patients, hyperuricaemia may be merely an indicator of cardiac dysfunction and therefore, of an increased risk of death.

The present study has several limitations. The most important is the fact that most of the patients received diuretics. These drugs have a well known potential for increasing serum urate concentrations [1]. However, the fact that a subgroup analysis of 21 PPH patients without diuretics gave results similar to the whole group suggests that, at least in PPH, hyperuricaemia cannot simply be explained by diuretic therapy. Unfortunately, it was not possible to find patients with advanced left heart failure who were not receiving diuretics. There was also no data on creatinine clearance and urinary urate excretion so that it was not possible to differentiate between overproduction, decreased glomerular filtration, and impaired tubular secretion of uric acid. Future studies will have to address these issues and will have to identify whether the findings presented here also apply to different categories of diseases such thromboembolic pulmonary hypertension, congenital heart disease, or pulmonary hypertension due to chronic obstructive pulmonary disease or interstitial lung disease.

Despite these limitations, the present findings appear clinically important for several reasons. Hyperuricaemia can result in acute and chronic arthritis, and may itself contribute to renal dysfunction in patients with cardiac disease. Thus, physicians should be aware of the high incidence of hyperuricaemia in patients with cardiac dysfunction. In addition, cardiac disease and pulmonary hypertension should be ruled out in patients with otherwise unexplained hyperuricaemia, especially in young females in whom hyperuricaemia is uncommon. Furthermore, the detection of progressive hyperuricaemia in patients with cardiac disease may be an indicator of deteriorating cardiac function and thus may have prognostic implications. Finally, a clarification of the mechanisms leading to hyperuricaemia in patients with cardiac disease will improve our understanding of renal dysfunction in cardiovascular disease.

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