Hyperuricemia as a prognostic factor in pulmonary arterial hypertension

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Abstract Pulmonary arterial hypertension is a malignant disease with a median survival of 3 years. Uric acid levels are elevated in severe heart failure and in states of hypoxemia. Early data suggest a correlation between hyperuricemia and severe pulmonary arterial hypertension. We studied 29 patients with pulmonary arterial hypertension diagnosed and treated between 1998 and 2001. Clinical characteristics (6 min walk test and New York Heart Association class) and hemodynamic parameters (pulmonary artery pressure, pulmonary vascular resistance and cardiac output) were evaluated and correlated to uric acid level in a retrospective study. Uric acid levels correlated positively with New York Heart Association class ($r=0.66$, $P<0.001$) and negatively with 6 min walk test ($r=-0.35$, $P=0.03$). Uric acid levels were higher in patients who died than in patients who survived at the end of the follow-up period (8.8 *vs.* 5.7 mg/dl, $P=0.001$). This study shows that uric acid levels are elevated in severe pulmonary arterial hypertension and can be used as a prognostic marker of disease severity.

Available online at http://www.sciencedirect.com

Keywords uric acid, pulmonary arterial hypertension, prognostic marker.

INTRODUCTION

Serum uric acid, the final product of purine degradation, is elevated in states of urate overproduction (myelo- and lymphoproliferative diseases), decreased uric acid excretion (renal insufficiency) or as a part of a metabolic syndrome (insulin resistance) (1). Hyperuricemia is reported to have a strong independant correlation with the severity of symptoms and mortality of patients with heart failure (2). It has also been shown to be released from ischemic heart tissue during anginal syndrome (3). Two previously published studies have suggested that uric acid level is elevated in primary pulmonary arterial hypertension (PPH) and may predict mortality (4,5). The aim of this study is to evaluate the correlation between serum uric acid level and the severity of PPH, and to investigate the use of uric acid level as a prognostic marker in these patients.

METHODS

Patient selection

We studied consecutive patients treated for pulmonary arterial hypertension (mean pulmonary arterial pressure >25 mmHg with normal pulmonary capillary wedge pressure) at the Rabin Medical Center and the Ramban Hospital between 1998 and 2001. Other causes of pulmonary hypertension were excluded by lung perfusion scanning, spiral CT and pulmonary function test. Patient evaluation included a clinical profile comprised of New York Heart Association (NYHA) class, 6 min walk test and oxygen saturation; and a hemodynamic profile comprised of pulmonary arterial pressure, pulmonary vascular resistance and cardiac output (measured by Fick's method) at right heart catheterization. Patients who did not undergo catheterization were diagnosed and followed up by means of transthoracic echocardiography. Blood was tested for glucose, uric acid and kidney function at the start of follow-up. Uric acid was considered elevated if the baseline level was greater than 6 mg/dl for women or 7 mg/dl for men.

All the patients were treated with anticoagulants and diuretics. Seventeen patients were treated with prostacycline (10 subcutaneous, six intravenous, one inhalation), and 12 patients were treated with calcium blockers.

Stastitical analysis

Associations between dependent and independent variables were computed using Kendall's tau-b correlation coefficient. Kendall's tau-b, which measures the

Received 17 June 2002, accepted in revised form 27 August 2002
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association between rank orders of variables, is not limited by the constraints of normality required for Pearson's correlation coefficient, and thus may be used for non-parametric quantitative and ordered category data. It is the preferred correlation coefficient for small data sets with tied ranks, and may provide a better estimate of correlation in the population than other coefficients. Student's t-test for independent means was used to compare uric acid levels across categories of the dichotomous variables sex and survival. Analyses were performed using SPSS© for Windows (SPSS Inc. Chicago, IL). All reported p-values are two-tailed, and values of less than 0.05 were considered statistically significant.

RESULTS

Twenty-nine patients (25 females, four males) were enrolled in the study. Table I shows the clinical and hemodynamic characteristics of the patients. Mean age was 54.9 (range from 16 to 80). After 3 years of follow-up there were eight deaths (27.5%). The mean 6 min walk distance was 341 $\pm$126 m. Two patients were NYHA class IV, 17 were NYHA class III, and the remainder NYHA class II. Six patients had resting oxygen saturation less than 90%. The mean systolic pulmonary arterial pressure was 74 $\pm$ 23 mmHg, and the mean cardiac output was 3.6 $\pm$ 1.5 l/min. Sixteen patients (55%: 13 females, three males) were hyperuricemic, while kidney function and glucose levels were normal in all patients.

Uric acid correlation (Table 2)

Uric acid was significantly higher in non-survivors than in survivors (8.8 *vs.* 5.7 mg/dl, P=0.001) (Fig. 1). Serum uric acid level showed a strong positive correlation with the NYHA functional class (r=0.66, $P<0.001$), indicating that a higher uric acid value was associated with a worse NYHA class (Fig. 2). Serum uric acid level showed a negative correlation with the 6 min walk test ($r=-0.35$, P=0.03), indicating that a higher uric acid value was associated with poorer exercice capacity. Serum uric acid was not significantly correlated with mean pulmonary

Table I. Patient characteristics

No.	Age, sex	PAP Syst (mmHg)	CO (L/mn)	NYHA class	6 min (m)	O_2 Sat (%)	Uric acid (mg/dl)	Follow-up (months—alive/dead)
1.	26, F	72	2.8	II	370	98	2.9	36
2.	61, F	70	2.3	II	572	95	2.7	24
3.	34, F	38	7.6	II	473	98	2.8	36
4.	47, F	52	5.4	II	292	90	4.2	36
5.	43, F	42	4.0	II	426	98	4.0	24
6.	53, F	92	3.0	II	450	94	6.1	36
7.	65, M	90	2.5	II	360	90	5.7	36
8.	16, F	50	2.7	II	—	96	5.3	18
9.	67, F	85	—	II	459	94	3.0	30
10.	67, M	85	—	II	423	90	6.0	18
11.	65, M	55	4.2	III	400	98	7.0	24
12.	25, M	63	3.0	III	439	97	7.0	24
13.	72F	56	3.9	III	262	94	9.4	36
14.	52, F	52	6.3	III	219	91	8.5	12
15.	68, F	59	2.5	III	330	88	4.0	36
16.	55F	120	2.2	III	120	95	4.3	6
17.	56, F	100	4.5	III	100	85	7.0	12
18.	56, F	110	3.8	III	324	92	8.6	36
19.	53, F	85	3.0	III	333	95	8.9	6
20.	80, F	85	—	III	430	96	7.9	24
21.	69, F	58	—	III	430	96	7.9	36
22.	65, F	90	—	III	250	97	7.7	36
23.	68, F	45	—	III	420	92	6.3	36
24.	45, F	75	—	III	—	92	9.4	6
25.	52, F	100	2.0	III	—	91	7.1	36
26.	54, F	45	2.7	III	—	89	8.7	24
27.	56, F	90	—	III	—	98	7	6
28.	49, F	110	2.1	IV	100	90	14.2	6
29.	75, F	75	—	IV	—	94	10.5	24

Table 2. Correlation coefficients for serum uric acid and study variables

Variable	Correlation coefficient	*P* value
Age	0.11	0.41
NYHA	0.66	0.001*
Oxygen saturation	−0.18	0.20
Six-min. walk test	−0.35	0.03*
PAP	0.19	0.17
CO	0.06	0.72
Survival	0.66	0.001*

*Correlation significant at 0.05 level.

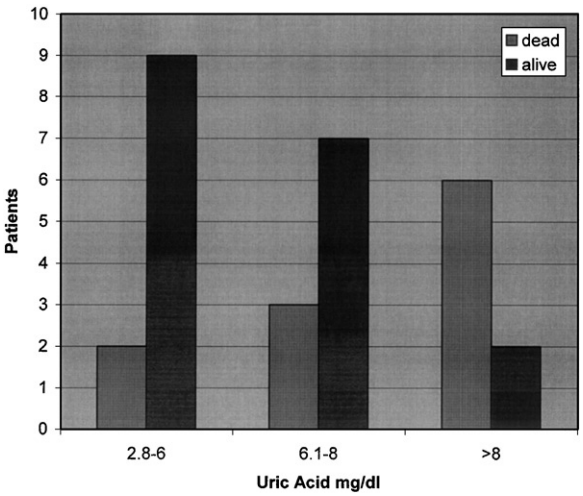

Fig 1. Correlation between uric acid level and the mortality rate: the uric acid levels were higher in patients who died than in patients who survived (*P*=0.001).

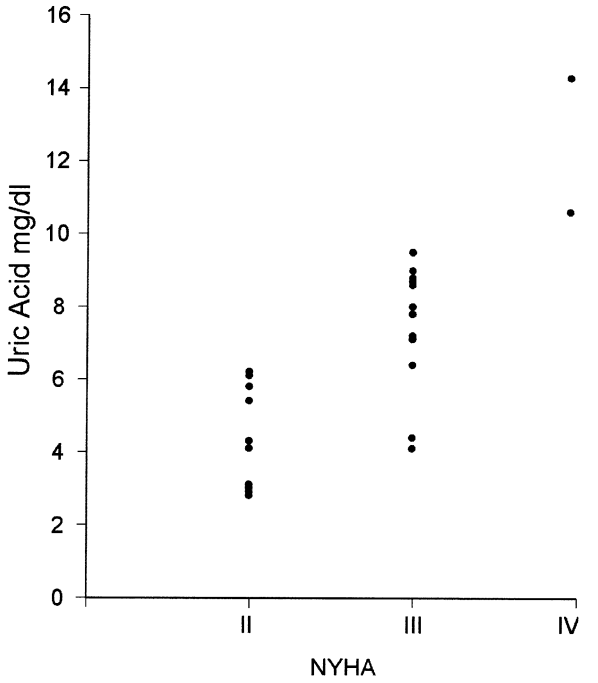

Fig 2. Correlation between the NYHA class and the uric acid level.

arterial pressure, cardiac output, oxygen saturation or age.

There was no correlation with the systemic arterial hypertension, nor with the pulmonary vascular resistance.

DISCUSSION

Pulmonary arterial hypertension is a severe progressive disease characterized by vasoconstriction, vessel wall remodelling and platelet aggregation. Elevated pulmonary vascular resistance and low cardiac output are strongly correlated to mortality, so that monitoring of pulmonary arterial pressure requires repeated invasive procedures such as right heart catheterization for assessing the benefit of the treatment or the need for transplantation (6,7). The findings of non-invasive procedures are of clinical importance for patient follow-up, and have been studied intensively during the last years. Miyamoto *et al.* found that patients who walked less than 332 m during 6 min had a significantly lower survival than those who walked farther (8). Plasma brain natriuretic peptide levels and urinary cGMP concentration have been also found to be elevated in severe pulmonary arterial pressure and to correlate closely with hemodynamic and clinical parameters (9,10).

Nagaya demonstrated that hyperuricemia is common in severe pulmonary hypertension, positively correlates with pulmonary resistance, decreases during vasodilator therapy in association with a reduction of pulmonary resistance and positively correlated with mortality. Our study also demonstrates a strong correlation between elevated uric acid level, the NYHA class and mortality of patients with pulmonary arterial pressure. Of the eight patients with hyperuricemia, six died; all patients in NYHA class IV were hyperuricemic.

The possible explanation of hyperuricemia in severe pulmonary hypertension is that tissue hypoxia provokes urate overproduction. Tissue ischemia depletes ATP and stimulates the expression of the xanthine oxydase enzyme that elevates the xanthine, hypoxanthine and uric acid levels (11). In fact, uric acid has been found to be elevated in patients with severe COPD or in severe OSA and corrected after oxygen delivery or non-invasive ventilation treatment (12,13). However, in our study, we did not find a significant correlation between the oxygen saturation and uric acid level and we suggest that this correlation is perhaps at the tissue level.

Despite the fact that low CO correlates positively with the mortality (14), our study did not show a

statistical correlation between mortality and CO or between uric acid and CO.

All the patients received diuretics. It is well known that thiazide and loop diuretics cause elevation of serum uric acid by increasing its tubular reabsorption. However, the kidney function was normal in all the patients and the elevated uric acid level cannot be explained by diuretic therapy.

We conclude that although the number of patients studied was small, we have a strong correlation between hyperuricemia and mortality and between hyperuricemia and the NYHA class. We suggest that uric acid level could be a prognostic factor in pulmonary hypertension and peharps a guide to therapy. Further studies are needed to evaluate the effect of prostacycline or endothelin receptor blockade therapy on uric acid level.

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