

Relationship between serum uric acid levels and ventricular function in patients with idiopathic pulmonary hypertension

Chun-Yan Zhang RN¹, Long-Le Ma MD^{2,3}, Le-Xin Wang MD, PhD^{2,3}

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OBJECTIVE: To investigate the relationship between serum uric acid levels and pulmonary hypertension in patients with idiopathic pulmonary artery hypertension (IPAH).

METHODS: Serum uric acid levels were measured in 86 patients (mean [± SD] age 35.2±12.3 years; 36 men) with IPAH. Pulmonary arterial pressure and ventricular function were assessed using echocardiography. Serum uric acid levels were also measured in 40 healthy subjects (35.9±11.6 years of age; 15 men).

RESULTS: Serum uric acid levels in IPAH patients were higher compared with control subjects (405±130 μmol/L versus 344±96 μmol/L; P<0.05). Fifty-two (60.4%) of the 86 patients with IPAH had elevated serum uric

acid levels. The pulmonary systolic pressure and mean pulmonary pressure in the high uric acid group were higher than in the normal uric acid group (P<0.05). The left and right ventricular ejection fractions were lower in the high uric acid group compared with the normal uric acid group (P<0.05). Serum uric acid levels were correlated with the mean pulmonary arterial pressure (r=0.387; P<0.01) and New York Heart Association class (r=0.41; P<0.01). There was also an inverse correlation between uric acid levels and the left (r=-0.550; P<0.01) and right ventricular ejection fractions (r=-0.481; P<0.05).

CONCLUSION: Serum uric acid levels are associated with IPAH severity and the severity of ventricular dysfunction.

Key Words: Idiopathic pulmonary artery hypertension; Uric acid; Ventricular function

Previous studies have demonstrated that serum uric acid is elevated in several hypoxic states such as chronic heart failure (1), cyanotic congenital heart disease (2) and obstructive pulmonary disease (3). It has also been suggested that serum uric acid is an independent predictor of death in patients with chronic heart failure (4). Idiopathic pulmonary artery hypertension (IPAH) is a serious pulmonary arterial disease characterized by progressive pulmonary hypertension, ultimately producing severe right ventricular failure associated with markedly reduced cardiac output and mild hypoxia (5). Up to 79% of patients with primary pulmonary hypertension have hyperuricemia (6). However, the association between uric acid levels and the pathogenesis or prognosis of IPAH has not yet been established.

The primary purpose of the present study was to investigate serum uric acid levels and evaluate their relationship with the severity of pulmonary hypertension and right ventricular dysfunction.

METHODS

Patient selection

The present study was approved by the Institutional Review Board of Liaocheng People's Hospital of Taishan Medical University (Liaocheng, China) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants. Between 2007 and 2010, 86 patients with IPAH were selected from patients admitted to the hospital. Patients with a history of primary hypertension, diabetes mellitus, renal dysfunction, hepatic disease, chronic lung disease and ventricular dysfunction caused by factors other than pulmonary hypertension were excluded from the study. A total of 36 men and 50 women (mean [± SD] age 35.2±12.3 years [range 24 to 63 years]) were included in the present study.

Forty healthy subjects (mean age 35.9±11.6 years [range 28 to 66 years]; 15 men, 25 women) were also recruited from the hospital clinic for the measurement of serum uric acid levels.

Diagnosis of IPAH

The diagnosis of IPAH was based on the results of echocardiographic studies: pulmonary arterial systolic pressure ≥50 mmHg or a mean pulmonary arterial pressure (MPAP) ≥25 mmHg at rest, in the absence of other causes of precapillary pulmonary hypertension such as pulmonary hypertension due to lung diseases or chronic thromboembolic pulmonary hypertension (7).

Transthoracic echocardiography

Pulmonary arterial systolic pressure and ventricular function were evaluated using colour Doppler echocardiography (HP-SONOS 5500, Hewlett-Packard, USA). Pulmonary arterial systolic pressure was calculated using the tricuspid regurgitation velocity and pressure gradient and the estimated right atrial pressure, according to the following formula (7):

$$\text{Pulmonary arterial systolic pressure} = \text{tricuspid regurgitation pressure gradient} + \text{estimated right atrial pressure}$$

The MPAP was calculated according to the following formula (7):

$$\text{MPAP} = 0.61 \times \text{pulmonary arterial systolic pressure} + 2 \text{ mmHg}$$

Standard parasternal long-axis, short-axis, and apical four- and two-chamber views were obtained, and the right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) were calculated using a modified Simpson's formula. The cardiologists who performed echocardiographic studies and New York Heart Association (NYHA) class assessments were unaware of the patient's serum uric acid levels.

Measurement of serum uric acid

Venous blood was obtained for the measurement of serum uric acid and creatinine levels after an overnight fast, 24 h before echocardiography was performed. No changes in clinical status or medication regimens occurred between blood sampling and echocardiographic studies.

¹Department of Cardiac Surgery; ²Cardiology, Liaocheng People's Hospital of Taishan Medical University, Liaocheng, Shandong, People's Republic of China;

³School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, New South Wales, Australia

Correspondence: Dr Le-Xin Wang, School of Biomedical Sciences, Charles Sturt University, Wagga Wagga, New South Wales 2678, Australia.

Telephone 61-2-69-332905, fax 61-2-69-332587, e-mail lwang@csu.edu.au

TABLE 1
Comparison of laboratory and hemodynamic data between normal and high uric acid groups in patients with idiopathic pulmonary arterial hypertension

	Uric acid levels		P
	Normal (n=34)	High (n=52)	
Age, years	35.7±10.1	36.4±11.9	NS
Sex, male/female, n/n	11/23	19/33	NS
Serum creatinine, µmol/L	65.7±10.1	100.2±18.4	<0.001
Serum uric nitrogen, µmol/L	4.2±1.1	8.3±2.6	0.002
Blood pH	7.40±0.33	7.42±0.34	NS
Blood oxygen pressure, mmHg	72±14	68±16	NS
Blood CO ₂ , mmHg	28±7	27±6	NS
Blood oxygen saturation, %	87±10	85±9	NS
Heart rate, beats/min	74±15	88±16	0.017
Systolic blood pressure, mmHg	118±16	116±17	NS
Diastolic blood pressure, mmHg	71±10	74±11	NS
Systolic pulmonary pressure, mmHg	68±12	79±11	0.012
MPAP, mmHg	48±9	58±12	0.013
Left ventricular ejection fraction, %	45.9±4.1	42.3±3.9	0.04
Right ventricular ejection fraction, %	49.5±5.0	41.2±4.3	0.02
New York Heart Association class	2.0±0.3	2.7±0.5	0.04

Data presented as mean ± SD unless otherwise indicated. CO₂ Carbon dioxide; MPAP Mean pulmonary arterial pressure; NS Not significant

Serum uric acid levels were determined using the uricase-peroxidase method. Because of the differences in mean uric acid values between men and women, the reference values used for men and women were 420 µmol/L and 360 µmol/L, respectively (8).

Statistics

Data were expressed as mean ± SD. Statistical analysis was performed using SPSS version 13.0 (IBM Corporation, USA). The comparison of uric acid levels between groups and among different NYHA classes was performed using a one-way ANOVA. Categorical data were examined using Fisher's exact test. The correlations between uric acid levels and the pulmonary arterial pressure or NYHA class were analyzed using Pearson's correlation coefficients; P<0.05 was considered to be statistically significant.

RESULTS

General findings

NYHA class II, III and IV were recorded in 30 (34.8%), 48 (55.8%) and eight (9.3%) patients, respectively. All patients received standard pharmacological therapy such as calcium channel blockers, angiotensin-converting enzyme inhibitors or diuretics. Digoxin was also administered to patients who were NYHA class III and IV.

The mean serum uric acid levels in IPAH patients and healthy controls were 405±130 µmol/L and 344±96 µmol/L, respectively (P<0.05).

Comparison of IPAH patients with normal and high uric acid levels

As presented in Table 1, 52 (60.4%) of the 86 patients with IPAH exhibited elevated serum uric acid levels. There were no significant differences with regard to age and sex between the normal and high uric acid groups (P>0.05). Compared with the normal uric acid group, the high uric acid group demonstrated higher levels of serum creatinine and uric nitrogen, in addition to a faster heart rate. The pulmonary systolic pressure and MPAP in the high uric acid group were also higher than in the normal uric acid group. The LVEF and RVEF in the high uric acid group were lower than in the normal uric acid group (P<0.05).

Correlation between serum uric acid and hemodynamics

Pearson correlation analysis showed that serum uric acid levels were correlated with MPAP and left ventricular function (Table 2). There

TABLE 2
Correlation between serum uric acid levels and mean pulmonary arterial pressure (MPAP), left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF)

	Correlation coefficient	P
MPAP	0.387	<0.01
LVEF	-0.550	<0.01
RVEF	-0.481	<0.05
NYHA class	0.41	<0.01

NYHA New York Heart Association

were no statistically significant correlations between uric acid levels and heart rate or systemic blood pressure (P>0.05).

Relationship between serum uric acid and ventricular function

The mean serum uric acid levels in NYHA class II, III and IV were 348±70 µmol/L, 416±126 µmol/L and 610±147 µmol/L, respectively (II versus III, P<0.05; III versus IV, P<0.001). There was a moderate but statistically significant correlation between uric acid levels and NYHA class (r=0.41; P<0.01). There was also an inverse correlation between uric acid levels and LVEF (r=-0.550; P<0.01) and RVEF (r=-0.481; P<0.05).

DISCUSSION

The main findings of our study are: the serum levels of uric acid in patients with IPAH were higher than in the healthy subjects; there was a positive correlation between uric acid levels and the MPAP; and there was an inverse correlation between uric acid levels and right ventricular function. These results are in agreement with other reports (9,10). However, only 52% of the patients with pulmonary hypertension exhibited elevated uric acid levels. In individuals with increased uric acid levels, the MPAP was higher than in patients with normal uric acid levels. The serum creatinine and uric nitrogen levels were also higher, but there were no statistically significant differences in age, sex and NYHA class between the normal and high uric acid groups.

The exact metabolic mechanism leading to increased uric acid levels in patients with IPAH is not clear. Lung tissue ischemia may be a key contributor to the elevation of uric acid levels. Previous studies have demonstrated that the production of uric acid is increased in proportion to the severity of hypoxia in patients with chronic obstructive pulmonary disease and obstructive sleep apnea (10). Tissue ischemia is believed to deplete ATP levels and activate the purine nucleotide degradation pathway to uric acid, resulting in urate overproduction in the heart, lungs, liver and skeletal muscle (10).

The other factor that may lead to the elevation of uric acid levels in patients with IPAH is reduced renal perfusion and urinary excretion of uric acid. Several previous studies have linked serum uric acid levels with cardiac output and renal blood perfusion (10,11). The present study revealed an inverse correlation between uric acid levels and the cardiac index, suggesting lower perfusion to the kidneys may have compromised the renal excretion of uric acid. In addition, lower perfusion to the lungs in patients with low cardiac index may also lead to hypoxia and, therefore, increased production of uric acid.

The elevated uric acid levels in patients with IPAH may contribute to the worsening of pulmonary hypertension and the prognosis of patients. Recent evidence suggests that uric acid inhibits acetylcholine-mediated vasodilation by acting on the vascular endothelium (12). In isolated porcine pulmonary artery segments, uric acid reduced nitric oxide levels in pulmonary arterial endothelial cells and inhibited acetylcholine-induced vasodilation (13). Treatment with ibuprofen for three months has been found to improve endothelial function in patients with hyperuricemia (14). In a study involving 29 patients with pulmonary arterial hypertension, uric acid levels correlated positively with NYHA class and negatively with 6 min

walk test scores (15). Uric acid levels were higher in patients who died than in patients who survived at the end of the follow-up period. A study by Nagaya et al (10) involving 90 patients with primary pulmonary hypertension found that patients with high serum uric acid levels exhibited a significantly higher mortality rate compared with patients with low serum uric acid levels.

SUMMARY

Serum uric acid levels were elevated in more than one-half of the patients with IPAH. The levels of serum uric acid were related to the severity of pulmonary hypertension and the ventricular dysfunction.

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