Association of changes in NT-proBNP, hsTnT and uric acid levels with haemodynamic changes after targeted medical therapies in patients with idiopathic pulmonary arterial hypertension

Wen-ting Li, Chang-wei Wu, Jin-ming Liu

Abstract

Background: During pulmonary arterial hypertension (PAH)-targeted therapies for patients with idiopathic pulmonary arterial hypertension (IPAH), regular follow up to evaluate treatment efficacy is essential. Serum biomarkers can reflect various pathobiological processes in IPAH and have the advantages of being non-invasive, simple to carry out and low cost. The aim of our study was to evaluate whether serum biomarkers could serve as non-invasive markers to reflect haemodynamic changes after PAH-targeted therapies in patients with IPAH.

Methods: A total of 31 eligible patients aged 38.1 ± 12.1 years (25 were female) were included in this study. Changes in haemodynamic parameters and several serum biomarkers (cardiac markers, serum uric acid, high-sensitivity C-reactive protein, hepatic and kidney function markers) were compared before and after at least six months of PAH-targeted therapies. The time interval between the blood assays and right heart catheterisation was within five days.

Results: After at least six months of PAH-targeted therapies, the N-terminal pro-brain natriuretic peptide (NT-proBNP) level decreased from 579 (191–905) to 135 pg/ml (60–395) (p < 0.01), high-sensitivity cardiac troponin T (hsTnT) level decreased from 0.009 (0.006–0.012) to 0.007 ng/ml (0.005–0.01) (p < 0.01), and serum uric acid level decreased from 381.5 ± 131.4 to 327.2 ± 110.0 μmol/l (p = 0.011). The change in NT-proBNP level was positively correlated with changes in pulmonary vascular resistance (r = 0.538, p < 0.01) and mean pulmonary arterial pressure (r = 0.440, p = 0.013). The change in hsTnT level was positively correlated with the change in mean right atrium pressure (r = 0.504, p < 0.01). The change in serum uric acid level was negatively correlated with that of cardiac index (r = -0.471, p < 0.01).

Conclusion: NT-proBNP, hsTnT and serum uric acid levels can be used as non-invasive tools for evaluating the efficacy of PAH-targeted medications for IPAH patients. The role of these biomarkers in the follow up should be emphasised.

Keywords: biomarker, high-sensitivity cardiac troponin T (hsTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP), uric acid, idiopathic pulmonary arterial hypertension, haemodynamics

Submitted 21/12/20, accepted 14/4/21
Cardiovasc J Afr 2021; 32: online publication www.cvja.co.za
DOI: 10.5830/CVJA-2021-018

Idiopathic pulmonary arterial hypertension (IPAH) is a disease characterised by increased pulmonary vascular resistance and associated with the development of right heart failure.1,2 Pulmonary arterial hypertension (PAH)-targeted drugs, including endothelin receptor antagonist, phosphodiesterase inhibitor and prostacyclin analogue may improve the symptoms and quality of life, and slow the time to clinical worsening in IPAH patients.3,4 During PAH-targeted therapies, regular follow up to evaluate treatment efficacy is essential.

Right heart catheterisation (RHC) is the gold-standard test for clinical assessment in pulmonary hypertension, including IPAH.4 Due to its invasiveness and expense, IPAH patients in China have a low acceptance level of RHC as a follow-up tool. Therefore non-invasive parameters are needed to assess the efficacy of treatment in patients with IPAH. Serum biomarker levels are a simple tool commonly used in clinical practice, which can reflect various pathobiological processes in IPAH.

This study compared the changes in several biomarker levels, including cardiac markers, serum uric acid, high-sensitivity C-reactive protein, hepatic and kidney function markers before and after at least six months of PAH-targeted therapies in 31 patients with IPAH. We further investigated whether haemodynamic changes observed during the PAH-targeted therapies could be reflected by changes in these serum biomarker levels.

Department of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University, People’s Republic of China
Wen-ting Li, MD

Emergency Department, Shanghai Pulmonary Hospital, Tongji University, People’s Republic of China
Chang-wei Wu, MD

Department of Pulmonary Circulation, Shanghai Pulmonary Hospital, Tongji University, People’s Republic of China
Jin-ming Liu, MD, jinmingliu2020@163.com
Methods

We retrospectively studied 31 patients with IPAH, diagnosed and treated in our centre between March 2017 and April 2020. IPAH was defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, and a capillary pulmonary wedge pressure (PCWP) ≤ 15 mmHg with pulmonary vascular resistance (PVR) > 3 Wood units, without known triggering factors. The haemodynamic parameters were measured by RHC.

Patients were included in this study if they met the following criteria: (1) underwent RHC at least twice, the first before starting PAH-targeted therapy and the second at least six months later; (2) had complete data of cardiac markers [N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hsTnT), isoenzyme MB of creatine kinase (CKMB)], serum uric acid, hepatic and kidney function markers (serum creatinine, urea nitrogen, alanine aminotransferase, aspartate aminotransferase, total bilirubin) and inflammatory markers (high-sensitivity C-reactive protein) within five days before or after the day of RHC. Patients with left heart disease, malignant tumour, or severe liver and kidney dysfunction were excluded.

All patients were treated with standardised PAH-targeted medications. Baseline clinical data, including demographic information, assessment of the World Health Organisation functional class (WHO-FC), six-minute walk distance (6MWD), body mass index (BMI), heart rate and oxygen saturation in the radial artery were recorded.

Haemodynamic parameters were measured by RHC, including mean right atrial pressure (mRAP), mPAP, mPCWP and cardiac output (CO). CO was measured by the direct Fick method. PVR was calculated using the conventional formula:

\[ \text{PVR} = \frac{(\text{mPAP} - \text{mPCWP})}{\text{CO}} \]

Cardiac index (CI) was calculated by dividing CO by the body surface area.

Blood samples were extracted from the elbow on an empty stomach in the morning, within five days before or after the day of RHC, and the serum was separated for analysis. Concentrations of uric acid, creatinine, urea nitrogen and total bilirubin were determined using a spectrophotometric method (Siemens Healthcare Diagnostics) on an automatic biochemical analyser (Siemens Advia2400). Concentrations of alanine transaminase and aspartate aminotransferase were determined using a kinetic method (Siemens Healthcare Diagnostics) on an automatic biochemical analyser (Siemens Advia2400). Concentrations of NT-proBNP, hsTnT and CKMB were measured by electrochemiluminescence immunoassay (Roche Diagnostics) on an automatic immunoanalyzer (Roche Cobase 411). High-sensitivity C-reactive protein (hsCRP) was determined using the immune transmission turbidimetry method with a specific protein analyser (Golisite Aristo and original reagent).

Statistical analysis

Statistical analysis was performed with the SPSS 17.0 package. All continuous variables were tested for normality using the Shapiro–Wilk test before analysis. The variables with normal distributions are expressed as means ± standard deviation (SD). Data with non-normal distributions are expressed as median (first quartile–third quartile). Categorical variables are described as counts and percentages. Categorical variables were compared with the chi-squared test for a 3 × 2 contingency table.

Comparison of WHO-FC among patients with different treatment strategies was performed using a Kruskal–Wallis rank test. Changes in normally distributed data before and after treatment were compared with the paired Student’s t-test. Changes in non-normally distributed data before and after treatment were compared by the Wilcoxon test. Changes in categorical variables before and after treatment were compared by McNemar’s test.

Comparison of normally distributed variables among the three groups was performed using one-way ANOVA. Comparison of non-normally distributed variables among the three groups was performed using a non-parametric test (median test). Correlations between normally distributed variables were analysed using Pearson’s correlation coefficients. Correlations between non-normally distributed variables were analysed using Spearman’s correlation coefficients. In all analyses, a p-value < 0.05 was considered statistically significant.

Results

The analysis included 31 eligible patients aged 38.1 ± 12.1 years (80.6% were female). The characteristics of the study patients are summarised in Table 1. Eleven of the patients were in WHO-FC II, 12 in III and eight in IV. All were started on a single targeted drug: phosphodiesterase-5 inhibitor (PDE-5i) in 14 patients, endothelin receptor antagonist (ERA) in 12, and oral prostacyclin analogue in five.

There was no significant difference in demographic characteristics, 6MWD, WHO-FC and main haemodynamic variables among patients with different initial treatment strategies. Before the follow-up RHC, 10 patients had been converted to combination targeted therapies on re-evaluation of WHO-FC (PDE-5i and ERA, six patients; ERA and oral prostacyclin analogue, two; PDE-5i and oral prostacyclin analogue, two).

We had recommended the patients perform follow-up RHC six months after starting the targeted therapies. In reality, the follow-up RHC was performed 8.0 ± 1.8 months after starting the targeted therapies. All study patients tolerated the PAH-targeted medications well, and there were no severe adverse

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PDE-5i: phosphodiesterase-5 inhibitor; ERA: endothelin receptor antagonist; BMI: body mass index; WHO-FC: World Health Organisation functional class; 6MWD: six-minute walk distance; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; PVR: pulmonary vascular resistance.
events or deaths. No drug-induced hepatic or renal impairment occurred.

After the PAH-targeted therapies, the number of patients in WHO-FC III and IV decreased from 20 (64.5%) to eight (25.8%) (p < 0.01). The 6MWD increased from 338.2 ± 73.2 to 363.2 ± 64.4 m (p < 0.01). Oxygen saturation in the radial artery increased from 93.6 ± 5.3 to 95.2 ± 2.9% (p = 0.03).

We found the following changes in haemodynamic parameters at baseline and after the PAH-targeted therapies (Table 2): PVR decreased from 12.1 ± 5.0 to 8.4 ± 4.4 Wood units (p < 0.01), mPAP decreased from 56.6 ± 12.4 to 46.2 ± 14.9 mmHg (p < 0.01), mRAP decreased from 6.8 ± 2.8 to 5.1 ± 1.5 mmHg (p < 0.001), and CI increased from 2.7 ± 0.6 to 3.1 ± 0.8 l/min/m² (p = 0.015).

Levels of NT-proBNP, hsTnT and serum uric acid significantly decreased after the PAH-targeted therapies (Table 2). NT-proBNP level decreased from 579 (191–905) to 135 (60–395) (p < 0.01), hsTnT level decreased from 0.009 (0.006–0.012) to 0.007 ng/ml (0.005–0.01) (p < 0.01), and serum uric acid decreased from 381.5 ± 131.4 to 327.2 ± 110.0 μmol/l (p = 0.011). The changes in other serum biomarker levels before and after treatment were not statistically significant (Table 2).

Before the PAH-targeted therapies, NT-proBNP levels significantly correlated with the severity of WHO-FC. The median NT-proBNP level in WHO-FC II, III and IV were 138 (22–260), 622 (433–778) and 1 296 (908–1645) pg/ml, respectively (II vs III, p = 0.007; III vs IV, p = 0.011) (Fig. 1). There were no statistical differences in serum uric acid and hsTnT levels among different WHO-FC.

Discussion

In this study of 31 patients with IPAH, haemodynamic and functional parameters generally improved after a period of PAH-targeted therapies, which shows the efficacy of the medications. At the same time, the NT-proBNP, hsTnT and serum uric acid levels decreased significantly. NT-proBNP secretion is associated with increased ventricular wall tension and reflects impairment in cardiac function.12 Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin, which is highly specific to myocardial injury.13 Uric acid is an end-product of purine metabolism, and has been reported to be elevated in several hypoxic states such as chronic heart failure,14 congenital heart disease15 and pulmonary hypertension.12 We further explored the relationship between changes in these biomarkers and haemodynamic changes, which
are discussed below.

pro-BNP is a pro-hormone, secreted mainly by the ventricles, which is cleaved into an N-terminal fragment (NT)-proBNP and active BNP.\textsuperscript{13} Compared with active BNP, NT-proBNP has a longer half-life and better stability.\textsuperscript{14} Therefore, the clinical application of NT-proBNP is more extensive. An elevated NT-proBNP level is associated with the degree of myocardial stretch and stress.\textsuperscript{7} PAH guidelines recommend NT-proBNP as a biomarker in risk stratification.\textsuperscript{15}

In our study, NT-proBNP level increased significantly with the severity of WHO-FC and had a close correlation with haemodynamic parameters at baseline. The results of our study were similar to those of previous studies. A study of 42 IPAH patients reported that NT-proBNP level not only had a strong correlation with haemodynamic parameters but also differed among New York Heart Association functional class.\textsuperscript{16} Our study further demonstrated that NT-proBNP level markedly decreased after PAH-targeted therapy, and the changes in NT-proBNP level were positively correlated with those in parameters of right ventricular afterload (mPAP and PVR). The results of our study are consistent with an earlier study by Andreassen et al. Levels of NT-proBNP were significantly reduced between baseline and three months in 17 medically treated patients with pre-capillary pulmonary hypertension, and the decrease in NT-proBNP level was correlated with a reduction in pulmonary vascular resistance.\textsuperscript{17} These findings indicate that NT-proBNP may serve as a non-invasive marker to reflect the efficacy of PAH-targeted drugs on reducing right ventricular overload, especially afterload.

Cardiac troponin T is the preferred biomarker for the detection of myocardial injury.\textsuperscript{7} The more recent high-sensitivity troponin assays possess greater sensitivity than previous assays and have improved precision at lower limits of detection.\textsuperscript{18} In IPAH, pathological changes in pulmonary haemodynamics may trigger myocardial injury. Previous studies have reported that elevated hsTnT level was associated with right ventricular dysfunction and it has value in predicting the prognosis in patients with PAH.\textsuperscript{19} In our study, hsTnT levels were positively correlated with mRAP at baseline. RAP is considered a surrogate for right ventricular volume load. We infer from this that the increased tension of the right ventricular myocardium during the filling period may disturb the physiological pattern of right ventricular myocardial perfusion, which contributes to the production of troponin T. Reduction in hsTnT concentration was observed in our study after PAH-targeted therapy and it was correlated with a decrease in mRAP. This indicates that myocardial injury is reversible after PAH-targeted therapy and the reduction in hsTnT level could reflect the decrease in right ventricular volume load.

Uric acid is an end-product of purine metabolism that is generated from xanthine by xanthine oxidoreductase, and mainly excreted by the kidney.\textsuperscript{20} Elevated serum uric acid levels have been observed in clinical conditions such as ischaemia and hypoxia.\textsuperscript{20-22} It is possible that tissue ischaemia and hypoxia deplete ATP and

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activate the purine nucleotide degradation pathway. This process increases uric acid production. Reduced renal perfusion and excretion of uric acid may be another factor.20

IPAH is a disease characterised by progressive pulmonary hypertension, ultimately producing reduced CO and hypoperfusion, with increasing production of uric acid.21 In our study, at baseline the level of serum uric acid was positively correlated with PVR, mPAP and mRAP, and negatively correlated with CI. Among these haemodynamic parameters, CI had the strongest correlation with serum uric acid. This result is in agreement with earlier studies,2026 which revealed an inverse correlation between uric acid and CO. In our study, the serum uric acid level decreased markedly after PAH-targeted therapies and it decreased in association with an increase in CI. This finding indicates that a decrease in serum uric acid level could reflect an improvement in cardiac pump function and blood perfusion due to PAH-targeted therapy.

The main limitation of this study lies in the small number of research cases. Inclusion criteria for this study required performing RHC at least twice. But due to the invasiveness and expense of RHC, IPAH patients in China have a low acceptance level of RHC as a follow-up tool. It is therefore difficult to recruit large numbers of study cases in a single centre. Extending the time frame of case inclusion or organising multi-centre studies may be the direction of future work.

Conclusion

Measurements of NT-proBNP, hsTnT and serum uric acid levels are simple, non-invasive and relatively inexpensive. These serum biomarkers may serve as non-invasive markers in evaluating the efficacy of PAH-targeted medications for IPAH patients. The role of these biomarkers in the follow-up of IPAH patients should be emphasised.

We thank Prof Yuan Ping, Zhao Qinhu, He Jing and all the other study investigators, fellows and nurses who participated in this study. This work was supported by the 13th Five-year National Science and Technology Major Project for Infectious Disease (Grant No. 2018ZX10722302).

References