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Original Article

Correlating Uric Acid levels with Echocardiographic findings in Pulmonary Hypertension

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Abstract
Introduction: *Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure and secondary right ventricular failure and can be a diagnostic challenge. This study aimed at assessing how uric acid levels correlate with echocardiographic findings of PH.*
Methodology: *We performed a case-control study in the Department of Medicine, DY Patil School of Medicine and Hospital, Navi Mumbai from July 2017 till July 2018. All consecutive patients who were diagnosed with PH at our centre during the study period and age/gender matched controls were enrolled in the study. Transthoracic echocardiography and relevant haematological investigations were ordered.*
Results: *Demographic variables of both the study groups were similar at the baseline. Serum uric acid levels were significantly higher among cases (9.17 ± 1.37 mg/dl) as compared to controls (6.62 ± 1.83 mg/dl, p value <0.05). Echocardiography revealed that the systolic and diastolic ejection fractions were not significantly different among cases or controls. Systolic pulmonary artery pressure was significantly higher among cases as compared to controls (27.2 ± 2.2 vs 18.5 ± 2.7 mm Hg, p value <0.05). Similarly, diastolic and mean pulmonary artery pressures were also higher among cases as compared to controls. Furthermore, we found the uric acid levels to be significantly positively correlated with systolic pulmonary artery pressure (r = 0.75, p value <0.001), and inversely correlated with left ventricular ejection fraction (r = -0.44, p value <0.01) and right ventricular ejection fraction (r= -0.62, p value < 0.01).*
Conclusions: *There is a strong and significant positive correlation between systolic pulmonary artery pressure and uric acid levels and inverse correlation with ejection fractions.*
Keywords: *uric acid; pulmonary hypertension; pulmonary arterial pressure; hyperuricemia.*

Introduction

Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure and secondary right ventricular failure. It is a progressive, fatal disease if untreated, although the rate of progression is highly variable. Symptoms and signs of PH may be difficult to recognize because they are nonspecific. This is particularly true if the PH is caused by an underlying condition, since the clinical manifestations of PH

are often obscured by the underlying disease (eg, chronic obstructive pulmonary disease). Diagnostic testing is indicated whenever PH is suspected. The purpose of the diagnostic testing is to confirm that PH exists, determine its severity, and identify its cause. When the echocardiogram does not suggest PH, clinicians need to be guided by clinical suspicion. The diagnostic evaluation should be directed toward alternative diagnoses if the clinical suspicion for PH is low, whereas right heart catheterization should be considered if the clinical suspicion for PH is high. Therefore, the presentation of a patient with PH may become a diagnostic challenge for a clinician. Elevated serum uric acid has been analysed in patients with chronic heart disease,[1] cyanotic congenital heart disease,[2] and chronic obstructive lung disease[3] and a strong correlation has been suggested by few authors. This study aimed at assessing how uric acid levels correlate with echocardiographic findings of PH.

Methodology

Study Design and Setting

We performed a case-control study in the Department of Medicine, DY Patil School of Medicine and Hospital, Navi Mumbai from July 2017 till July 2018. Diagnosis of PH was defined as systolic pulmonary artery pressure (SPAP) derived by echocardiography more than 50 mmHg in the absence of right ventricular outflow tract obstruction[4] or mean pulmonary artery (PA) pressure more than 25 mmHg during cardiac catheterization.[5] Although, Mukerjee et al demonstrated that almost all patients with tricuspid gradient of higher than 45 mmHg on an echocardiography were found to have PH at catheterization, a higher threshold (50 mm Hg) was used in this study to improve the diagnostic accuracy.[6] DY Patil School of Medicine and Hospital, Navi Mumbai is a tertiary level care hospital which caters to a large population of Navi Mumbai, Mumbai and nearby villages. During the study period we enrolled 40 patients who were diagnosed with PH and an equal number of age and gender matched controls were enrolled in the study as well. The study was approved by the institutional ethics committee. The purpose of the study was explained to the study participants and an informed written consent was obtained from them.

Sample population and study procedures

All consecutive patients who were diagnosed with PH at our centre during the study period and age/gender matched controls were enrolled in the study. We excluded patients who had chronic renal insufficiency, bronchial asthma, left sided failure, immunocompromised state like HIV, autoimmune conditions, those who did not undergo echocardiography or those taking uric acid lowering agents. All the study participants underwent transthoracic echocardiography (TTE) by a certified technician at our centre. We obtained standard parasternal long-axis, short-axis, and apical four- and two-chamber views, and Simpson's rule[7] was used to measure the right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF). Pulmonary artery pressure was estimated using modified Bernoulli equation in the absence of right ventricular outflow obstruction.[8] Following the standard aseptic protocol, 5 ml blood samples for all study participants were collected in a plain tube. Hematological investigations like complete blood count, blood urea, serum creatinine, serum uric acid and bilirubin were obtained.

Data Collection and Data Analysis

We designed and pre-tested a semi-structured questionnaire for noting the demographic variables of all study participants. All data were analysed in SPSS version 21 (IBM, New York). Quantitative variables were expressed as mean and standard deviation and qualitative variables as frequency and percentages. Normality of the data were checked using the Kolmogorov–Smirnov test. Means were compared between cases and controls using the Students' t test or Mann-Whitney rank sum test. For correlating uric acid levels with echocardiography variables Pearson's

correlation was used. All statistical analysis were significant at 5% error.

Results

Table 1 describes the baseline demographic profile of the patients and controls included in the study. Mean age, gender distribution, height and weight of the study participants in both the groups were comparable. We found the total cell count, platelet count, serum creatinine and total bilirubin levels to be higher among cases of pulmonary hypertension, however the difference was not statistically significant. Blood urea was found to be significantly higher among cases as compared to controls (12.52 ± 4.64 mg/dl vs 8.76 ± 1.39 mg/dl, p value < 0.05). Additionally, serum uric acid levels were found to be significantly higher among cases (9.17 ± 1.37 mg/dl) as compared to controls (6.62 ± 1.83 mg/dl, p value <0.05). Echocardiography revealed that the systolic and diastolic ejection fractions were not significantly different among cases or controls. Systolic pulmonary artery pressure was significantly higher among cases as compared to controls (27.2 ± 2.2 vs 18.5 ± 2.7 mm Hg, p value <0.05). Similarly, diastolic and mean pulmonary artery pressures were also higher among cases as compared to controls. Furthermore, we found the uric acid levels to be significantly positively correlated with systolic pulmonary artery pressure (r = 0.75, p value <0.001), and inversely correlated with left ventricular ejection fraction (r = -0.44, p value <0.01) and right ventricular ejection fraction (r= -0.62, p value <0.01).

Table 1 Distribution of patients according to their demographic and clinical variables

	Cases (n=40)	Controls (n=40)	p value
Demography			
Age (in years)	42.4 ± 10.29	40.22 ± 11.02	NS
Gender (male/female)	18/22	21/19	NS
Height (in cm)	173.4 ± 9.23	175.9 ± 10.44	NS
Weight (in kg)	67.4 ± 12.9	65.2 ± 10.7	NS
Hematological investigations			
Hemoglobin (gm%)	9.87 ± 2.43	10.54 ± 1.73	NS
Total leucocyte count (per cumm)	11.47 ± 4.72	9.72 ± 6.18	NS
Platelet count (thousand/ml)	482.5 ± 188.7	423.4 ± 190.5	NS
Blood urea (mg/dl)	12.52 ± 4.64	8.76 ± 1.39	<0.05
Serum creatinine (mg/dl)	0.91 ± 0.24	0.82 ± 0.47	NS
Total bilirubin (mg/dl)	3.16 ± 1.95	2.97 ± 1.81	NS
Serum uric acid (mg/dl)	9.17 ± 1.37	6.62 ± 1.83	<0.05
Echocardiography findings			
Systolic pulmonary artery pressure (mm Hg)	27.2 ± 2.2	18.5 ± 2.7	<0.05
Diastolic pulmonary artery pressure (mm Hg)	15.5 ± 1.6	9.8 ± 1.9	<0.05
Mean pulmonary artery pressure (mm Hg)	18.7 ± 1.9	12.3 ± 0.8	<0.05
Left ventricular ejection fraction (%)	43.5 ± 5.4	45.6 ± 2.8	NS
Right ventricular ejection fraction (%)	39.7 ± 3.6	47.6 ± 3.7	NS

Table 2 Correlating uric acid levels with pulmonary artery pressure and ejection fraction

Variable	Correlation coefficient	p value
Systolic pulmonary artery pressure	0.75	<0.001
Left ventricular ejection fraction	-0.44	<0.01
Right ventricular ejection fraction	-0.62	<0.01

Discussion

Echocardiography is performed to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function. In addition, echocardiography can evaluate right atrial size, left ventricular systolic and diastolic function, and valve function, while detecting pericardial effusions and intracardiac shunts.[9] Echocardiography uses Doppler ultrasound to estimate the pulmonary artery systolic pressure. This technique takes advantage of the tricuspid regurgitation that usually exists. The maximum

tricuspid regurgitant jet velocity is recorded and the pulmonary artery systolic pressure (PASP) is then calculated as PASP = (4 x [TRV] 2) + RAP, where TRV is the maximum tricuspid regurgitant jet velocity and RAP is the right atrial pressure estimated from the size and respiratory variation of flow in the inferior vena cava. Doppler echocardiography is limited when an adequate tricuspid regurgitant jet cannot be identified.

Serum uric acid levels depict how purines are catabolized by xantine oxidase and how uric acid is disposed off by the kidneys. Impaired oxidative metabolism such as chronic heart failure or PH can result in increase of uric acid.[10] PAH due to unknownaetiology has been associated with increased levels of serum uric acid levels in adult as well aspediatric patients. Furthermore, the concentrations of uric acid may also correlate with hemodynamic variables and functional pulmonary parameters.[11] Voelkel et al observed high serum uric acid levels in patients with PH and was most frequently in those with elevated mean right arterial pressure, which suggest the possibility that the elevation of serum uric acid is related to right heart failure.[12] This further suggests that a low cardiac output, hypo-perfusion, and liver congestion account for the elevated serum uric acid. Leyva et al found elevated serum uric acid levels in patients with chronic heart failure due to coronary artery disease or idiopathic dilated cardiomyopathy.[1] The authors also found a significant correlation between serum uric acid levels and maximal oxygen uptake, and serum creatinine. However, the authors did not find a correlation between serum uric levels and left ventricular ejection fraction, which is different from what we observed in our study group.

In the present study, uric acid levels were inversely correlated with ejection fractions. Although, uric acid was earlier thought of as a marker for poor renal function, accumulating evidence support the prognostic use of serum uric acid in heart failure patients. Treatment with allopurinol in a large cohort of Israeli patients with chronic heart failure was independently associated with improved survival at median follow-up of 1.4 years.[13] Furthermore, the La Plata study demonstrated that inhibition of xanthine oxidase by oxypurinol in patients with chronic heart failure improved left ventricular ejection fraction in patients with left ventricular ejection fraction less than 40% after 1 month of treatment.[14]

There a few limitations of this study. Firstly, cardiac catherization, which would be the gold standard for measuring systolic pulmonary artery pressure, was not part of the study protocol. Secondly, we did not note the final clinical outcome of the patients while collecting data, so we cannot comment on how uric acid levels affect survival in PH. Lastly, echocardiography was performed by multiple technicians.

Conclusion

The results of this study establish that hyperuricemia is common in patients with PH. Addition, there is a strong and significant positive correlation between systolic pulmonary artery pressure and uric acid levels and inverse correlation with ejection fractions. Prospective studies measuring serum uric acid levels, degree of cardiac ischemia, and right ventricular wall strain and effect of uric acid lowering agents on clinical outcome of PH patients are needed in future.

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Conflict of interest: None

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