Liver Function Tests and Uric Acid Serum levels in Relation to Hemodynamic Profile: A Comparison between Heart Failure and Pulmonary Arterial Hypertension Patients

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Abstract

Background-Systemic venous congestion has been considered the main cause of liver dysfunction in heart failure patients. In this study, we assessed the relation of liver function tests to hemodynamic profile in patients with systolic heart failure (SHF) and primary pulmonary arterial hypertension (PAH).

Methods- Fifty patients with left ventricular ejection fraction < 35% and 27 patients with mean PAH> 25 mmHg were enrolled. Hemodynamic indices, including PAP, right atrial and ventricular pressures (RAP &RVP), pulmonary capillary wedge pressure (PCWP), and cardiac index (CI), were obtained and liver function tests and serum uric acid levels were measured simultaneously. Fifty age- and sex-matched normal controls were also studied.

Results- CO was significantly lower in the HF group (P= 0.006). Multivariate analysis showed a significant correlation between total bilirubin level and mean PAP (R=0.04, P=0.004), RAP (R=0.33, P<0.03), RVP (R=0.43,P <0.004), PCWP(R=0.36,P<0.01), and direct bilirubin with mean PAP(R=0.01, P=0.02), RVP(R=0.33, P<0.03), PCWP(R=0.32, P<0.03), and CI(R=0.33, P<0.01). In the PAH group, such correlations were mostly absent.

Conclusion- Systemic venous congestion, more prominent in PAH, might not play the main role in deteriorating liver function. Further studies are needed to determine whether hepatic blood flow, which is significantly decreased in SHF, is a more important factor ***(Iranian Heart Journal 2012; 12 (4):6 -15*).**

Keywords: Heart failure■ Pulmonary Arterial hypertension■ Catheterization■ Liver function tests

Heart Failure is a major and growing public health problem because of the aging of the population and improved survival of patients. Systolic heart failure is known as impaired organ perfusion due to inefficient cardiovascular pump function and affects other organs like liver and kidneys[1].

Complex vascular system of the liver and its high metabolic activity makes it vulnerable to circulation disturbances [2] .Liver function test abnormalities are frequently found in heart failure patients and are related to poor outcome[3].

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Uric acid is a marker of oxidative stress and myocardial damage, and increasing serum levels can be a manifestation of toxic myocardium.[4] It has a pathophysiological significance in the progression of heart failure and is predictive of a higher New York Heart Association (NYHA) class and is independently associated with poor prognosis and increased mortality[5].

Primary pulmonary arterial hypertension, defined as idiopathic increase in mean pulmonary arterial pressure over 25 mmHg with characteristic histopathology findings in pulmonary vasculature tree, seems to share common pathologic mechanisms with systolic heart failure in increasing the afterload on the right ventricle and disturbing the liver function with systemic venous congestion and low cardiac output due to right ventricular dysfunction[6].

In this study, we sought to assess the relation between liver function test abnormalities and uric acid serum levels and clinical and hemodynamic profiles in patients with chronic systolic heart failure (LVEF <35% by echocardiography) and compared them in PAH patients.

Methods and Materials

A single-center case series study was done. Fifty HF patients referring to the heart failure clinic of Rajaei cardiovascular, Medical and Research Center between DEC 2009 and JUNE 2010 who had left ventricular ejection fraction (LVEF) less than 35% were included unless they had uncontrolled diabetes, known previous liver disease (chronic viral/autoimmune/drug related hepatitis, liver malignancy, and known biliary tract disease), known hematological disease other than anemia of chronic disease (hemoglobinopathies and hemolytic states), significant rheumatismal heart disease, and significant congenital heart disease. Also, we excluded those on continuous consumption of xanthine oxidize inhibitor, and a history of gout, kidney stone, and renal dysfunction (creatinine > 2 or glomerular filtration rate (GFR) < 30 ml/min/m2).

Twenty-seven Primary pulmonary hypertension patients with mean PAP>25 mmHg and normal LVEF on echocardiography were consecutively enrolled.

A complete history and physical examination was done for each patient and clinical signs and symptoms and standard NYHA functional class were determined. Fifty age- and sex-matched controls, who had non-anginal chest pain and normal echocardiography (LVEF>55%), were enrolled from the referrals for a routine check-up.

Right Heart Catheterization: The patients were all evaluated by standard right heart catheterization using Edwards Life Science Swan Ganz catheters placed in their right pulmonary arteries. Pressures were read through a fluid filled system, including right atrial pressure (RAP), pulmonary arterial pressure (PAP), and pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) and cardiac index (CI) were determined via the standard thermo dilution method. Pulmonary arterial pressure and pulmonary capillary wedge pressure were measured in three cycles at end expiration and averaged. The patients did not receive any intravenous medication during catheterization.

***LAB DATA*:** Blood samples were drawn at the time of catheterization and the following

indices were measured using the PAP method (KIMIA PAZHOUHAN kit): AST, ALT, bilirubin (total and direct), alkaline phosphates, and uric acid[7].

According to the references and laboratory data, the normal cut points for the liver function tests were as follows:

AST and ALT: 1-25mg/dl, ALP: 0-140mg/dl, total bilirubin: 0-1.5 mg/dl, and direct bilirubin: 0-0.5mg/dl.

As for serum uric acid level, different values have been proposed as a normal cut point, e.g. 6, 7, and 8 mg/dl due to the dependence of uric acid on the body surface area, physical activity, diet, and renal function[8]. In order to have a more reliable comparison, a control group of 50 persons with a normal cardiac function, matched in sex, age, diet, habits, and race, was studied for serum uric acid levels. The mean uric acid level in the control group was 4.26±0.9mg/dl.

The normal values for right heart catheterization were 25/9mmHg for PAP, 24/0-4mmHg for RVP, 5 mmHg for RAP, and 8-15 mmHg for PCWP.[9]

Statistical analysis: The data are presented as mean ± standard deviation when normally distributed and as frequencies and percentages for the categorical variables. Differences between the baseline variables were evaluated with the Student *t*-test, comparison of functional class by liver function tests with the Kruskal Wallis Test, relation between the clinical variables and mean with the Writney U Test, and hemodynamic profile with liver function tests and uric acid with Initial Linear Regression analysis using Partial correlation Coefficient. P values less than 0.05 were considered significant. The statistical analyses were performed using SPSS 15, Chicago.

Results

The baseline characteristics of the patient population are shown in Table I.

Table I: Baseline Characteristics in HF group

	MEAN	MINIMUM	MAXIMUM
AGE(years)	38.24+-14.22	11	72
PAP(SYS,mmHg)	40.18+-16.5	15	84
PAP(DIA,mmHg)	20.7+-16.5	6	40
PCWP(mmHg)	18.41+-9.5	4	40
RAP(mmHg)	9.33+-4.6	3	24
RVP(mmHg)	40.6+-15.9	15	84
PVR(wood)	5.7+-5.7	0.4	26
CO(ml/min)	3.88+-0.92	2	6.3
CI(ml/min/m2)	2.39+-0.6	1.3	3.9
AST(mg/dl)	42.39+-72.06	9	435
ALT(mg/dl)	44.8+-66.6	5	440
ALP(mg/dl)	99.3+-47.9	38	286
TBILI(mg/dl)	2.17+-1.27	0.8	6.5
DIRBILI(mg/dl)	0.67+-0.4	0.1	2
URICACID(mg/dl)	7.06+-2.2	3	12

PAP: pulmonary arterial pressure, PCWP: wedge pressure, RAP: right atrial pressure, RVP: right ventricular pressure, PVR: pulmonary vascular resistance, CO: cardiac output, CI: cardiac index, AST, ALT: liver aminotranspherases, DCM: dilated cardiomyopathy, ICM: ischemic cardiomyopathy

Men accounted for 74.5% (38 patients) of the study population, and 73.6% (81patients) had ischemic cardiomyopathy.

The respective mean systolic PAP and diastolic PAP was 40 ± 16.5mmHg and 20 ± 9.5 mmHg, the respective mean RAP and PCWP was 9 ± 4.6mmHg and 18 ± 9.5 mmHg, and the mean cardiac output was 3.8 ± 0.9L/m2/min.

Assuming the above-mentioned normal values, 72.2% of the patients had high systolic PAP, 92.5% high diastolic PAP, 66.6% high RAP, 83.3% high mean PAP, and 57.4% high PCWP.

The mean uric acid serum level was 7.2 ± 3.8 mg/dL, which was significantly higher than

that in the control group (mean uric acid serum levels was 4.26+-0.96mg/dl), ($P < 0.001$).

Considering the standard NYHA classification, 34% of the patients were in class IV, 50% in class III, and 15.5% in class II. All the patients received oral furosemide mostly at daily doses of 40-80 mg; 21.3% of the patients received more than 80 mg daily. The mean LVEF in the HF patients was 19 ± 6.5% on echocardiography. In the evaluation of the right ventricular function with respect to the echocardiographic data, a tissue Doppler-derived systolic motion of the right ventricle at the lateral tricuspid ring in the four-chamber view (Sm) of less than 7 cm/sec and an M-mode-derived tricuspid annular plane systolic excursion (Tapse) of less than 10 mm were considered as severe right ventricular systolic function and Sm greater than 10 cm/sec and Tapse greater than 17 mm were regarded as a normal right ventricular systolic function. [10] Furthermore, 15% of the patients in the HF group and 23% in the PAH group had severe right ventricular systolic function and 70% in the HF group and 65% in the PAH patients had mild to moderate systolic dysfunction, there being no significant difference in terms of PAP, PCWP, and uric acid levels between these groups.

Mean AST was 42±77mg/dl, mean ALT: 44±66, mean ALP: 99±47, mean total bilirubin: 2.1±1.2, and mean direct bilirubin:0.6±0.4mg/dl. According to the reference cut points mentioned in the texts, 13.7% had high AST levels (>25mg/dl), 29.4% high ALT levels (>25mg/dl), 7.8% high ALP levels (>150mg/dl), 41.2% total bilirubin>1.5mg/dl, and 58.8% direct bilirubin >0.5mg/dl levels.

In the PAH patients, the mean age was 40.35±15.9 years, 73% (19 patients) were female, the respective mean systolic PAP and diastolic PAP was 77±27 and42.9±15.9mmHg, the respective mean RAP and PCWP was 15±3.8 and 18.5±10.8mmHg, and the mean cardiac output was 4.5±1.4L/min/m2.

Mean AST level was 24.3±16.8mg/dl, mean ALT: 23.8±25, mean ALP: 76±37.3mg/dl, mean total bilirubin:1.6±0.7mg/dl, mean direct bilirubin: 0.5±0.28mg/dl, and mean uric acid: 6.38+-1.8 mg/dl. Also, 73% had uric acid>6mg/dl, 26% AST levels >25 mg/dl, 23% ALT>25 mg/dl, 34.6% total bilirubin>1.5mg/dl, and 38.6% direct bilirubin>0.5mg/dl.

Table II summarizes the results of the analysis of correlations between the liver function tests and the hemodynamic profile in the HF and Table II in the PAH patients.

Table II. Univariate regression analysis results for investigation of relation between liver function tests and hemodynamic data in heart failure patients.

	AST	ALT	ALP	TBILI	DIRBILI	URICACID
PAP(SYS,mmHg)	0.11/0.44	0.08/0.57	0.04/0.79	0.45/0.003	0.34/0.02	0.44/0.002
PAP(DIA,mmHg)	0.07/0.58	0.08/0.56	0.08/0.62	0.38/0.01	0.34/0.02	0.52/0.000
PAP(MEAN,mmHg)	0.59/0.52	0.44/0.58	0.27/0.68	0.04/0.004	0.01/0.02	0.09/0.000
RAP(mmHg)	-0.16/0.24	-0.13/0.35	-0.02/0.9	0.33/0.03	0.22/0.15	0.22/0.13
RVP(mmHg)	0.10/0.45	0.07/0.60	0.03/0.82	0.43/0.004	0.33/0.03	0.41/0.004
PCWP(mmHg)	0.05/0.72	0.09/0.49	0.04/0.79	0.36/0.01	0.32/0.03	0.43/0.002
CI(ml/min/m2)	-0.07/0.58	0.15/0.28	-0.19/0.9	-0.3/0.05	-0.37/0.01	-0.22/0.13
PVR(wood)	-0.1/0.43	-0.1/0.47	0.07/0.67	0.18/0.26	0.29/0.06	0.13/0.36
EF%	-4.4/0.15	-4.24/0.08	-2.3/0.01	-0.04/0.002	-0.01/0.001	-0.09/0.006

Numbers are coefficient correlation)/P value, PAP: pulmonary arterial pressure,PCWP:wedge pressure,RAP:right atrial pressure,RVP:right ventricular pressure,PVR:pulmonary vasvular resistance,CI:Cardiac index,EF:Ejection Fracti

Table III. Univariate regression analysis results for investigation the relation between liver function tests and homodynamic data in PAH patients. Numbers are Pearson coefficient/p value

	AST	ALT	ALP	TBILI	DIRBILI	URICACID
PAP (SYS,mmHg)	0.1(0.6)	0.09(0.65)	-0.1(0.67)	-0.14(0.55)	-0.46(0.04)	-0.11(0.57)
PAP (DIA,mmHg)	0.03(0.88)	-0.06(0.77)	-0.18(0.46)	0.05(0.82)	-0.25(0.28)	0.05(0.78)
RVP (mmHg)	0.12(0.54)	0.11(0.59)	-0.1(0.68)	-0.13(0.57)	-0.46(0.04)	0.1(0.6)
RAP (mmHg)	-0.1(0.59)	0.26(0.18)	0.3(0.2)	0.16(0.5)	0.04(0.84)	0.09(0.65)
PCWP (mmHg)	0.18(0.36)	0.2(0.29)	0.06(0.7)	0.5(0.01)	0.3(0.17)	0.19(0.35)
PVR (wood)	0.01(0.82)	0.5(0.97)	0.17(0.49)	0.13(0.5)	0.05(0.8)	0.5(0.97)
CO (ml/min)	0.02(0.9)	0.9(0.65)	0.06(0.7)	0.2(0.26)	0.4(0.07)	0.4(0.04)

Pearson correlation, P value PAP: pulmonary arterial pressure, PCWP: wedge pressure, RAP: right atrial pressure, RVP: right ventricular pressure, PVR: pulmonary vascular resistance, CO: cardiac output, CI: cardiac index, AST, ALT: liver aminotranspherases, PAH: Pulmonary artery hypertension

Notably, the mean CI in the HF group was significantly lower than that in the PAH patients (mean difference: 1.7+-0.7 ml/min/m2, P=0.007).

In the multivariate analysis of the HF patients, we found no significant correlation between AST, ALT, and ALP and the hemodynamic indices, but there was a significant correlation between total bilirubin and sys PAP (R=0.45, P<0.003), diaPAP (R=0.38, P<0.01), RAP (R=0.33, P<0.03), RVP (R=0.43, P <0.004), and PCWP (R=0.36, P<0.01, Figure1) and direct bilirubin and uric acid levels with systolic (R=0.34, P<0.04) and diastolic PAP (R=0.34, P<0.02), RVP (R=0.33, P<0.03), PCWP(R=0.32, P<0.03), and CI (R=0.33, P<0.01).

Interestingly, in the multivariate analysis of the PAH patients, there was no significant correlation between the liver tests and the hemodynamic study except for total bilirubin level and PCWP (R=0.57, P<0.01, Figure 2). Also, there was a significant inverse association between cardiac output and uric acid levels (R=0.4, P<o.o4).

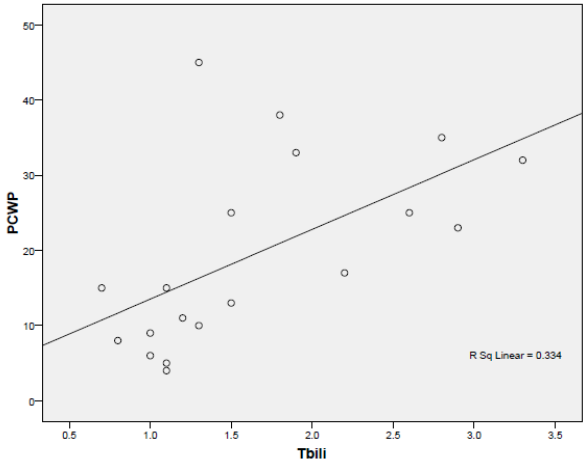

Fig. 1. Regression analysis of significant correlation between PCWP and T bilirubin serum levels in PAH patients

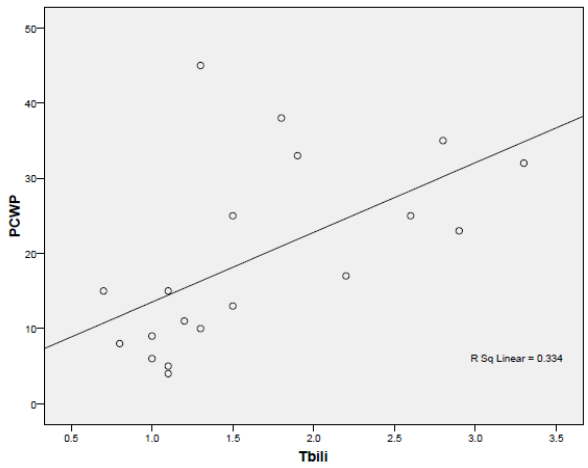

Fig.2. Regression analysis of significant correlation between PCWP and TBilirubin serum levels in PAH patients

Discussion

Heart failure itself is characterized by impaired organ perfusion resulting from both forward failure (reduced CO) and increased central venous pressure (backward failure), both of which are important determinants of renal[11] and liver dysfunction in heart failure.[1]
As systolic HF progresses, compensatory mechanisms need to maintain the cardiac output and, therefore, at the cost of worsening congestive symptoms due to elevated filling pressures, the heart tries to achieve a reasonable stroke volume [12].
Disturbances in the liver function lead to significant changes in patients with heart failure. There are two mechanisms responsible for this dysfunction in heart failure: hepatic congestion in line with systemic venous congestion (especially in those with significant right ventricular dysfunction)[13] and liver ischemia due to low cardiac output state [14].
The pathophysiology of liver failure has been attributed to either venous congestion or reduced CO, leading to hepatic hypoxic injury[15]. Low perfusion seems to be less important because oxygen consumption can easily be increased when the hepatic blood flow is decreased [16]. Almost 70% of the hepatic blood supply comes from the portal system whereas only 30% is delivered by the hepatic artery [17]. Increase in the RA and RV pressure is in parallel to CVP and hepatic vein wedge pressure, which is approximately 14.5 mmHg [18].Increased sinusoidal pressure is associated with the disruption of sinusoidal endothelium and junctions in zonula occludance and opening of biliary canaliculi to sinusoids and release of biliary enzymes into blood[19].

Hepatic dysfunction is commonly seen in HF patients and it relates to poor outcome[20]. Cogger stated that liver enzymes can be considered predictors of all-cause mortality[12]. Also, Felder asserted that liver function tests were associated with increased mortality and major cardiovascular events [6].
CHARM Trial showed the independent prognostic relation between total bilirubin with mortality due to HF. V.M. VAN DEURSEN et al. showed that direct bilirubin was in relation to poor hemodynamic state in some cases [3]. Shinagawa. H et al. demonstrated that serum total bilirubin levels were associated with high CVP and PCWP and low CO and poor prognosis and early admission of HF patients[20].
There are many studies about congestive hepatopathy which show a cholestatic pattern in HF patients[21], but the liver function test has not been evaluated in PAH patients.
Hyperuricemia also has been shown to be an independent predictor of all-cause mortality in patients with systolic heart failure[24]. Uric acid

is the end point of the metabolism of purine compounds, produced in the liver from the degradation of dietary and endogenously synthesized purine compounds via the xanthine oxidase reaction, which irreversibly oxidizes xanthase to uric acid. The Van Deuren and EWA A. Jankowska studies showed that serum uric acid elevation could predict a higher NYHA class and a lower LVEF in mild to moderate heart failure[25].

Serum uric acid levels add important prognostic information alone and when combined with the assessment of cardiac function and the patient's functional status. In recent studies, uric acid was an important predictor of in-hospital and long-term mortality independent of GFR and LVEF or other factors[5,24].

All of our patients received loop diuretic with nearly the same doses, as was the case in other studies. The correlation between uric acid serum levels and hemodynamic parameters is independent of diuretic use; consequently, it cannot be an important confounding factor in this regard. In addition, with regard to the right ventricular systolic function, there were few patients with severe right ventricular systolic function and there was no significant difference in terms of uric acid levels, PAP, and PCWP between the different right ventricular function groups in our study. It is also deserving of note that patients with severe tricuspid regurgitation were excluded from this study.

In our study, there were significant correlations between serum total and direct bilirubin level and uric acid levels with PAP (systolic and diastolic), RVP, and PCWP and significant inverse correlation between direct bilirubin and CO in the heart failure group. There was no correlation between the other liver function tests (AST, ALT, and ALP) and the hemodynamic data.

Twenty-seven PAH patients were also studied and interestingly there was no correlation between liver enzymes and pressure data. Furthermore, there was only an inverse correlation between uric acid levels and CO in this group. Pulmonary arterial hypertension puts a significant afterload on the right ventricle and PAH patients have variable degrees of right ventricular dysfunction and tricuspid valve insufficiency with high CVP and systemic venous congestion. Many studies have proved this finding by showing congested liver in abdominal ultrasonography of PAH patients[1]. Keeping in mind the mechanisms of liver dysfunction, our observation of relatively normal liver function tests in our PAH patients seems odd. As was mentioned before, the mean cardiac index levels in the PAH group in our study was significantly higher than that in the heart failure group and close to normal values. This finding might suggest that liver function and uric acid levels are deteriorated more by low cardiac output than systemic congestion since the right-sided filling pressures are much higher in PAH patients but cardiac output remains nearly normal before advanced stages. Apparently, high right-sided pressures and venous congestion cannot explain all the disturbances of liver function tests, as was mentioned later[13] , and uric acid levels in cardiac failure setting also. Our finding may also implicate that liver function tests are not useful prognostic factors in milder degrees of pulmonary arterial hypertension.

Further studies should be conducted in relation to PAH patients and other causes of

cardiac involvement in order to better understand congestive hepatopathy mechanisms.

Limitations

This is a case series study of selected patients and it cannot show the general HF and PAH population. We carried out multiple comparisons in a limited group of patients; our results should, therefore, be confirmed in other studies. Changes in liver function abnormalities were not assessed, and we could not assess whether the observed abnormalities were transient or permanent. We did not evaluate TR severity and hepatic flow and did not have an accurate estimation of the RV function, all of which could potentially influence the results. We tried to exclude liver toxic drugs and liver diseases, but there are some hepatic illnesses which we could not assess accurately like hemochromatosis, which could influence the results. Many of our patients had been fasting, albeit not for very long, before right heart catheterization. (The controls were all sampled while fasting for routine blood chemistry tests)

Conclusion

Liver function abnormalities are frequently observed in patients with heart failure. We found a significant correlation between total bilirubin, direct bilirubin and uric acid levels with RVP, PAP (sys, dia) and PCWP. We also found a significant inverse correlation between direct bilirubin and CO in our HF patients, but there was no significant correlation between AST, ALT, and ALP and hemodynamic profile. We evaluated these parameters in the PAH patients also and surprisingly could not find any significant correlation between liver enzymes and uric acid levels and hemodynamic profile. There was only a significant association between total bilirubin and PCWP and only an inverse significant relation between uric acid levels and CO. We should, therefore, consider different mechanisms influencing liver function tests and uric acid levels other than congestion and these tests cannot show hemodynamic status in PAH patients.

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