

# Effects of terlipressin on systolic pulmonary artery pressure of patients with liver cirrhosis: An echocardiographic assessment

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## Abstract

**AIM:** Portopulmonary hypertension is a serious complication of chronic liver disease. Our aim was to search into the effect of terlipressin on systolic pulmonary artery pressure among cirrhotic patients.

**METHODS:** Twelve patients (6 males and 6 females) with liver cirrhosis were recruited in the study. Arterial blood gas samples were obtained in sitting position at rest. Contrast enhanced echocardiography and measurements of systolic pulmonary artery pressure were performed before and after the intravenous injection of 2 mg terlipressin.

**RESULTS:** Of 12 patients studied, the contrast enhanced echocardiography was positive in 5, and the positive findings in contrast enhanced echocardiography were reversed to normal in two after terlipressin injection. The mean systolic pulmonary artery pressure was  $25.5 \pm 3.6$  mmHg before terlipressin injection, and was  $22.5 \pm 2.5$  mmHg after terlipressin ( $P=0.003$ ). The systolic pulmonary artery pressure was above 25 mmHg in seven of these 12 patients. After the terlipressin injection, systolic pulmonary artery pressure was  $<25$  mmHg in four of these cases (58.3% vs 25%,  $P=0.04$ ).

**CONCLUSION:** Terlipressin can decrease the systolic pulmonary artery pressure in patients with liver cirrhosis.

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## INTRODUCTION

The spectrum of pulmonary vascular disorders in liver disease and portal hypertension ranges from hepatopulmonary syndrome characterized by intrapulmonary vascular dilatations (IPVD) to pulmonary hypertension (portopulmonary hypertension), in which pulmonary vascular resistance is elevated<sup>[1]</sup>.

Hepatopulmonary syndrome (HPS) is incurable but resolves over time after liver transplantation<sup>[2]</sup>. In patients with cirrhosis, 1% pulmonary hypertension is developed<sup>[2,3]</sup>. Portopulmonary hypertension (PPH) is irreversible and there is no effective treatment<sup>[4]</sup>. Mortality of liver transplantation in patients with PPH ranges from 50% to 100%<sup>[4]</sup>. The common causes of HPS and PPH are portal hypertension and portosystemic shunting, indicating that vasoactive and angiogenic factors originating from the liver can control pulmonary circulation<sup>[4]</sup>.

So far, observational studies have examined several drugs<sup>[5-8]</sup>. No clearly effective medical therapies for PPH have been found. In the present study, we investigated the effects of terlipressin that was used in the treatment of variceal hemorrhage on systolic pulmonary artery pressure (SPAP) among cirrhotic patients.

## MATERIALS AND METHODS

### Patients

Twelve cirrhotic patients without any malignancy, heart failure, renal failure (serum creatinin  $>20$  mg/L), chronic obstructive lung disease, pneumonia, and anemia (hemoglobin level  $<100$  mg/L) were studied. All patients had portal hypertension. The presence of hepatic dysfunction or portal hypertension was assessed by the following: (1) clinical history of complications related to liver disease and portal hypertension (ascites, hepatic encephalopathy, esophagogastric varices, variceal bleeding and spontaneous bacterial peritonitis); (2) liver function tests (aspartate and alanine aminotransferase, alkaline phosphatase, total bilirubin, prothrombin time, and albumin); and (3) abdominal ultrasound evidences of cirrhosis and portal hypertension (small, nodular liver, hepatofugal portal venous flow, portosystemic collateral circulation, splenomegaly, and ascites). The severity of hepatic dysfunction was stratified according to the Pugh-Child's criteria.

### Methods

Chest X-ray and electrocardiogram were performed for all patients. Blood samples were obtained to calculate the score of Pugh-Child in the morning of study day. Arterial blood gas samples were obtained from a single radial artery puncture while the patient was breathing room air in sitting position at rest.

Transthoracic contrast-enhanced echocardiography (CEE) was performed to investigate the intrapulmonary vascular dilations. CEE was performed after the administration of 10 mL of hand-agitated normal saline solution in the supine position via an upper extremity peripheral vein. Positive results were qualitatively defined as any visual opacification of the left heart chamber more than three cardiac cycles after appearance of microbubbles in the right ventricle<sup>[9]</sup>. These findings suggested intrapulmonary passage of microbubbles through either dilated precapillary and capillary vessels or direct arteriovenous communications. Echocardiographic assessments were carried out with Wingmed system five 1.7 MHz electronic probe by an experienced cardiologist. Left lateral position was used during measurements. Left atrium, left ventricular diastolic and systolic dimensions were calculated with standard M-mode echocardiographic pictures in parasternal long axis view. Wall motions and wall thickness were also evaluated. Fractional

shortening was studied at level of chordae tendinae (left ventricular end diastolic dimension-left ventricular end systolic dimension/left ventricular end diastolic dimension  $\times 100$ ). Each parameter represented the mean value of three successive measurements. Maximum flow rates with continuous wave Doppler (CW) at level of tricuspid valves were used to calculate SPAP (modified Bernoulli equation:  $\Delta p=4V^2$ ). SPAPs were computed by adding estimated right atrial pressure (5 mmHg) to pressure gradient calculated by modified Bernoulli equation.

CEE and measurements of SPAP were performed before and after the intravenous injection of 2 mg terlipressin (Glypressin® 1 mg flacon, ERKIM Ilac AS, Istanbul, Turkey).

All statistical calculations were done using the SPSS 11.0 software. The measurements were given as the mean values. The paired sample test, Cochran's Q test, and Friedman's test were used to determine the difference of SPAP, the frequency of CEE, and the frequency of patients whose SPAP  $\geq 25$  mmHg respectively before and after terlipressin injection.  $P < 0.05$  was accepted as statistically significant.

## RESULTS

The clinical and demographical characteristics of patients are shown in Table 1. A total of 12 patients, six males and six females were studied, with a mean age of 52 years. The mean score of Pugh-Child was 5.08, and the mean value of arterial  $pO_2$  was 77.83 mmHg. Ascites was detected in two patients. Two patients suffered from dyspnea. In two patients, chest X ray films showed bilaterally reticulonodular densities at the basal areas.

Before the injection of terlipressin intravenously, a positive CEE was detected in 5 patients, and two of them were disappeared after the drug was injected. Three of the patients who had evident hypoxemia suffered dyspnea, and CEE was positive in these patients. After terlipressin injection, CEE was negative in two of the three patients. Arterial  $pO_2$  was high in the rest two patients with CEE (+), after terlipressin injection CEE positivity was continued. There was not any difference before and after the drug injection according to the frequency of the positivity of CEE (5/12 vs 3/12,  $P=0.15$  according to Cochran's Q test). This meaningless result might be due to the small number of patients. The SPAP value was  $\geq 25$  mmHg in four of five patients with positive CEE. Two patients with a negative CEE after the drug injection had the lowest SPAP value in this group, 24 mmHg and 27 mmHg respectively.

Although the value of SPAP was  $25.5 \pm 3.6$  mmHg before the drug injection, it was decreased to  $22.5 \pm 2.5$  mmHg after

terlipressin injection ( $P=0.003$ ). The value of SPAP was above the level of 25 mmHg as the limit of pulmonary hypertension in seven patients. After the injection of terlipressin, it continued to be higher above this level in three patients [7/12 (58.3%) patients versus 3/12 (25%) patients]. This difference was statistically significant ( $P=0.04$ ). CEE was positive in one of the three patients whose SPAP was  $>25$  mmHg after terlipressin injection. The positivity of CEE disappeared after terlipressin injection in one patient who had a SPAP value lower than 25 mmHg.

## DISCUSSION

The association of pulmonary hypertension with portal hypertension, also known as portopulmonary hypertension (PPH), is a complication of chronic liver disease that has been associated with high morbidity and mortality at the time of liver transplantation<sup>[2-4]</sup>. PPH has been defined as mean pulmonary artery pressure  $>25$  mmHg in the presence of a normal pulmonary capillary wedge pressure and portal hypertension<sup>[2-4]</sup>.

The presence of intrapulmonary vascular dilatations can be confirmed using one of the three imaging modalities: contrast-enhanced echocardiography, perfusion lung scan - technetium 99 m-labeled macroaggregated albumin scanning, and pulmonary arteriography<sup>[9,10]</sup>. A Doppler echocardiogram is a highly sensitive and noninvasive diagnostic modality for both measuring PAP and determining IPVD. Therefore, it should be considered as the first screening method of choice<sup>[11]</sup>.

Heretofore, therapy for chronic management of PPH is lacking. Recently, continuous intravenous infusion of epoprostenol has been demonstrated to improve symptomatology and survival in the general population of patients with PPH<sup>[5]</sup>. Anecdotal reports suggested that long-term epoprostenol therapy given by continuous infusion might be effective for patients with portopulmonary hypertension, but the efficacy of epoprostenol has not been rigorously studied in this subgroup of patients<sup>[5-7]</sup>. Kuo *et al.*<sup>[5]</sup> reported the use of epoprostenol in the more specific instance of PPH. Over a period of 6-14 mo, epoprostenol (10-28 ng/kg.min) therapy was associated with a 29-46% decrease in mean pulmonary artery pressure, a 22-71% decrease in pulmonary vascular resistance, and a 25-75% increase in cardiac output in a group of four patients<sup>[5]</sup>. These results suggest that effective chronic therapy for PPH is available. In combination with inhaled nitric oxide as acute intraoperative therapy, epoprostenol infusion represented an additional therapeutic option for treatment of PPH in the liver transplant candidate<sup>[5]</sup>.

**Table 1** Characteristics of patients. PBS: primary biliary cirrhosis, HBV: hepatitis B virus, HCV: hepatitis C virus, N: Normal, BB-Nod: bilateral basillary nodularity, (-): absent, (+): present, PAP: pulmonary artery pressure and, CEE: contrast enhanced echocardiography

Sex	Age (yr)	Etiology	Pugh-Child Score	$pO_2$ (mmHg)	Ascites	Dyspnea	Chest X-ray	PAP-0 (mmHg)	PAP-1 (mmHg)	CEE-0	CEE-1
F	60	PBS	5	89	(-)	(-)	N	28	26	(+)	(+)
F	55	HBV	4	85	(-)	(-)	N	24	24	(-)	(-)
M	54	Alcohol	4	65	(-)	(+)	BB-Nod	27	21	(+)	(-)
F	48	Cryptogenic	5	60	(-)	(+)	N	24	20	(+)	(-)
M	58	HCV	4	63	(-)	(+)	N	28	24	(+)	(+)
M	56	HBV	4	73	(-)	(-)	N	25	25	(-)	(-)
M	52	HBV	5	88	(-)	(-)	N	30	22	(+)	(+)
F	50	HBV	10	90	(+)	(+)	BB-Nod	31	26	(-)	(-)
M	48	HCV	5	85	(-)	(-)	N	21	22	(-)	(-)
M	60	HBV	7	80	(+)	(-)	N	20	19	(-)	(-)
F	55	HCV	4	71	(-)	(-)	N	27	22	(-)	(-)
F	39	HBV	4	85	(-)	(-)	N	21	19	(-)	(-)

There are no long-term studies or guidelines on the use of pharmacotherapy in PPH. In view of the rarity of this disease, much of the traditional treatment of this disease has been empirical. Inhaled NO could decrease the pulmonary artery pressures in some patients with PPH and might have some promise for long-term treatment of this disease<sup>[12]</sup>. Other medications have been reported to cause amelioration of pulmonary hypertension in patients with portal hypertension including beta-blockers, nitrates, calcium-channel blockers, prostacyclin and prostacyclin analogs, phosphodiesterase inhibitors (sildenafil), L-arginine, and, endothelin antagonists<sup>[3]</sup>. In view of the decreased incidence of variceal bleeding in patients taking beta-blockers and nitrates, we encourage the use of these medications in patients with PPH. Beta-blocking agents, which are used in the treatment for portal hypertension may have deleterious effects on the setting of pulmonary hypertension because they decrease cardiac output and increase pulmonary vascular resistance. Vasodilators are usually ineffective and poorly tolerated because these patients usually have a decreased systemic vascular resistance. Most patients with porto-pulmonary hypertension do not receive anticoagulants because the risk of bleeding is deemed to be elevated, especially when esophageal varices are present.

In patients with hepatopulmonary syndrome, supplemental oxygen and liver transplantation were the usual treatments of choice<sup>[2]</sup>. Pharmacologic approaches were limited in improving hypoxemia<sup>[2]</sup>. Outcome following liver transplantation was variable, increased cardiopulmonary mortality occurred in patients with moderate to severe pulmonary hypertension. Although a few reports have demonstrated improvement of pulmonary hypertension after liver transplantation, this procedure was a very risky one in patients with markedly increased pulmonary artery pressures<sup>[13]</sup>. Report about combined liver-lung transplantation might open a perspective for selected patients with porto-pulmonary hypertension<sup>[14]</sup>.

Terlipressin is a long-acting vasopressin analogue that has been proved useful in the treatment of variceal hemorrhage. Terlipressin could reduce portal pressure in cirrhotic patients mainly through intense splanchnic vasoconstriction that decreases portal venous inflow<sup>[15]</sup>. Hepatic blood flow might also be reduced by terlipressin<sup>[15]</sup>. The systemic haemodynamic response to terlipressin was moreover associated with the decrease in portal pressure<sup>[16]</sup>. After administration of terlipressin, the azygos blood flow decreased significantly<sup>[17]</sup>. In patients with cirrhosis, a single injection of 2 mg terlipressin significantly and markedly reduced portal pressure and azygos blood flow for up to 4 h<sup>[17]</sup>. The azygos blood flow (superior porto-systemic collateral circulation) correlated strongly with portal venous flow in patients with portal hypertension<sup>[17]</sup>. It could be expected that terlipressin could reverse the vasodilatation of dilated intrapulmonary arteries with HPS and PPH. It can also decrease SPAP by reducing the increased blood flow that may facilitate pulmonary arterial hypertension. In our study, it reduced SPAP from 25.5±3.6 mmHg to 22.5±2.5 mmHg and, this result was statistically meaningful. CEE that showed intrapulmonary vascular dilatation was positive in 5 patients, and it was reversed to normal in 2 patients after terlipressin injection. However, more studies are needed to decide whether this result is meaningful or not.

Chronic terlipressin therapy in combination with a multidisciplinary, well-planned evaluation and treatment plan, may be the answer to a heretofore untreatable disease. This one is a prestudy, because more and detailed studies are

required to show its efficiency. In the context of persisting uncertainty about the cause and treatment of PPH, future studies must focus on the pathophysiology of PPH, predicting reversibility after liver transplantation, and identifying other treatment options.

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