ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Current Status of Portopulmonary Hypertension and Hepatopulmonary Syndrome

Kazuhisa Kodama[1], Naoki Serizawa[2], Etsuko Hashimoto[1], Tomomi Kogiso[1], Takaomi Sagawa[1], Maiko Taniai[1], Katsutoshi Tokushige[1]* and Nobuhisa Hagiwara[2]

[1]*Department of Internal Medicine and Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan*

[2]*Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan*

***Corresponding Author:** Katsutoshi Tokushige, Department of Internal Medicine and Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan.

Received: August 03, 2020; **Published:** November 30, 2020

Abstract

Background: Pulmonary complications of liver cirrhosis (LC) such as portopulmonary hypertension (PoPH) and hepatopulmonary syndrome (HPS) are independent risk factors for long-term mortality in patients with LC. Several drugs that act against chronic liver diseases and pulmonary arterial hypertension (PAH) have been developed and investigated.

Patients: We treated four patients with PoPH and six patients with HPS at our hospital in 1990 - 2017. Here we evaluated the clinical characteristics and effects of the therapies administered to these patients.

Results: All four PoPH patients were female and had non-viral liver diseases (two primary biliary cholangitis, one nonalcoholic steatohepatitis (NASH), and one portal vein obstruction). Two patients died due to severe liver and respiratory conditions, and the other two survived > 5 - 10 years after being treated with several drugs for PAH. Of the six patients (5 males) with HPS and four patients had viral hepatitis (four liver cirrhosis with hepatitis C virus, two with nonalcoholic steatohepatitis). Three of the HPS patients died, but three survived. Two patients underwent liver transplantation, and in one patient, effective therapy against NASH improved the liver function and HPS.

Conclusion: Early diagnosis and effective therapy against chronic liver diseases and PAH might change the clinical course of PoPH and HPS.

Keywords: *Liver Cirrhosis (LC); Portopulmonary Hypertension (PoPH); Hepatopulmonary Syndrome (HPS); Pulmonary Arterial Hypertension (PAH)*

Abbreviations

The two major pulmonary vascular consequences of portal hypertension are hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH) [1]. PoPH is diagnosed when pulmonary arterial hypertension (PAH) exists in a patient with portal hypertension, in the absence of alternative causes of the PAH. McDonnell., *et al*. showed 0.61% prevalence of histopathologic changes of PAH in autop-

sies of patients with liver cirrhosis (LC), and PoPH was the third most common form of PAH in a population-based epidemiologic study in France [2,3]. Recent cohort studies showed a 5% - 6% prevalence of PoPH in patients presenting for liver transplant evaluation [3-5]. Patients with PoPH have an increased risk of death; their reported death rates at 1 year and 5 years were 54% and 86%, respectively [6]. In many cases, PoPH greatly complicates or precludes liver transplantation, significantly affecting the course of hepatic failure in these patients [7,8].

PAH is a disease often considered to be driven by vasoconstriction. The three key pathways, involving the endothelin, nitric oxide and prostacyclin, have been identified in the development and progression of PAH. PAH-specific therapeutic approaches concentrate on these characteristics with drugs targeting the endothelin receptor (e.g. bosentan), phosphodiesterase-5 (e.g. sildenafil), or the prostacyclin receptor (e.g. beraprost) [9,10]. The effects of these drugs on PoPH are not yet known.

HPS is defined as a defect in arterial oxygenation induced by intrapulmonary vascular dilations associated with chronic liver disease [11]. HPS was observed in 4% - 32% of adult patients with end-stage liver diseases [12]. HPS was reported to be an independent risk factor for long-term mortality in patients with liver cirrhosis [13]. Orthotopic liver transplantation is the only successful treatment for patients with HPS, but the postoperative mortality rate of patients with severe hypoxemia before transplantation is high [14]. It was recently reported that therapies for alcoholic LC and nonalcoholic steatohepatitis (NASH) improved HPS [15,16]. Those cases also indicated the possibility of therapy for HPS other than liver transplantation. We thus conducted the present study to re-assess the current status of PoPH and HPS including new therapies for chronic liver diseases and PAH.

Patients and Methods

Patient population and diagnosis

Using our hospitalized diagnostic index, we identified the cases of four patients with PoPH and six patients with HPS who were treated at our institution between January 1990 and December 2017.

In principle, both right heart catheterization and echocardiography (only echocardiography in patient #1) are performed to confirm the diagnosis of PAH and estimate its severity. The diagnosis of PoPH is confirmed when PAH was present, as indicated by elevated mean pulmonary artery pressure (mPAP) at > 25 mmHg. Portal hypertension is defined as elevated hepatic venous pressure during hepatic vein catheterization, splenomegaly, or gastro-esophageal varices [1].

The diagnosis of HPS requires the demonstration of hypoxemia, pulmonary vascular dilatation, and portal hypertension. Hypoxemia is defined as a partial pressure of oxygen < 70 mmHg or an alveolar-arterial oxygen gradient > 15 mmHg. Pulmonary vascular dilatation can be detected by contrast-enhanced echocardiography but requires a technetium-99m-labeled macroaggregated albumin scan for quantification of the shunt [1].

The present study conformed to the ethical guidelines of the Declaration of Helsinki (2000 version) and was approved by the ethics committee at our institution. Regarding informed consent, when we were able to locate and contact the patients, we obtained informed consent directly. For other patients, we showed the study plan on our institute's home page. If any patients or bereaved family members noted their disapproval of a patient's data being used in this study, we deleted the data.

Clinical data and therapy

A complete history was obtained and physical examination was performed in all patients, followed by measurement of the following the common diagnostic tests included echocardiography, electrocardiogram (ECG), chest radiography or computed tomography (CT), pulmonary function testing, polysomnography, ventilation-perfusion scanning or pulmonary angiography, autoantibody testing, brain natriuretic peptide (BNP), liver function testing (AST, ALT, γ-GTP, ALP), platelet and virus markers (HBs antigen and HCV antibody/HCV-RNA).

Several drugs and oxygen had been administered to the patients based on the guideline for PAH [17]. Treatments for chronic liver diseases including liver transplantation were also conducted in accord with the patients' diagnoses and condition of liver diseases.

Results

PoPH

Table 1 shows the four female patients with PoPH. Their ages ranged from 29 to 61 years old. The background liver diseases were primary biliary cholangitis (PBC) in two patients, NASH with hypopituitarism in one patient, and portal vein obstruction with a portosystemic shunt in the other patient.

No	Age	Sex	Based liver disease	BNP	eRVSP (mmHg) mPAP (mmHg)	Therapy	Effect	Prognosis
1	61	F	PBC	45	144.6 -	No therapy	(−)	Dead
2	39	F	NASH-LC hypopituitarism	69.7	61 45	Endothelin antagonist analog of prostacyclin	(+)	Survival
3	29	F	Portal vein obstruction Portsystemic shunt	52.2	59 34	Endothelin antagonist	(+)	Survival
4	60	F	PBC	734	106 53	Phosphodiesterase V inhibitor	(−)	Dead

Table 1: *Cases with portopulmonary hypertension.*

NP: Brain Natriuretic Peptide; eRVSP: Estimating Right Ventricular Systolic Pressure; mPAP: Mean Pulmonary Artery Pressure; PBC: Primary Biliary Cholangitis; LC: Liver Cirrhosis; NASH: Nonalcoholic Steatohepatitis.

Patient #1 was diagnosed with PBC and PoPH in 1990. At that time, there were no effective drugs for PAH. Her estimating right ventricular systolic pressure (eRVSP) was markedly increased at 144.6 mmHg. She died with both liver and heart failure at approximately 1 month after the diagnoses. By autopsy, PBC and sclerosis and obstruction of pulmonary artery was confirmed. Patient #2 was diagnosed with NASH due to hypopituitarism and PoPH. After an endothelin antagonist (bosentan), a synthetic analog of prostacyclin (beraprost), and hormone replacement therapy were administered, her condition improved. Her 6-min walk distance improved and her mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) decreased (Figure 1). Furthermore, improvement of hemodynamics and exercise tolerance have been maintained (Figure 1). Her serum BNP (Figure 2) decreased. She has remained alive for 10 years, and her serum BNP has been maintained within the normal limit.

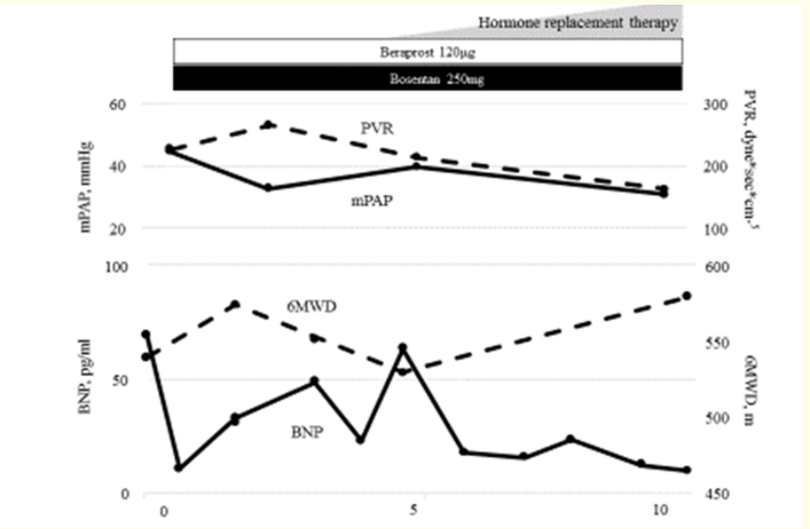

Figure 1: *Clinical course of Patient #2. After the diagnosis of PoPH, bosentan and beraprost were started. The patient's serum brain natriuretic peptide (BNP) level then decreased to within the normal limit. The 6-min walk (6MWD) improved and the pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP) decreased.*

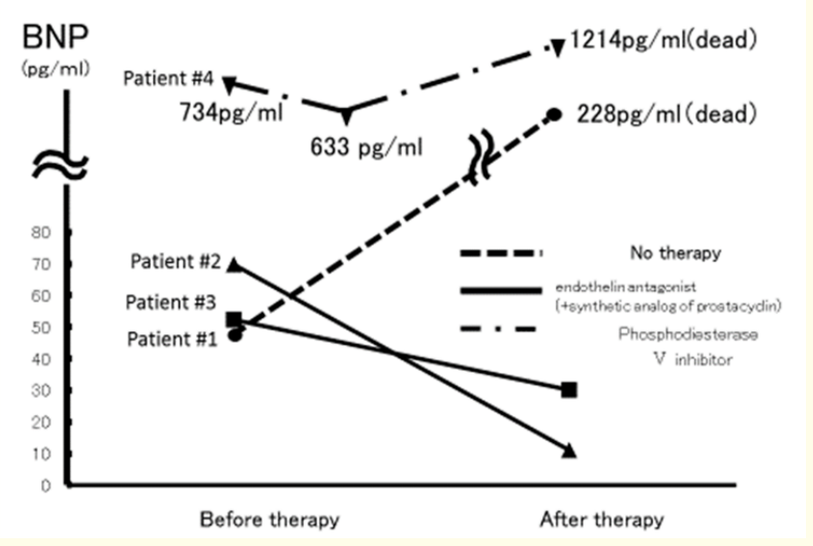

Figure 2: *The change of serum BNP levels in the four patients with PoPH. In the PoPH patients who died (Patients#1 and #4), the serum BNP level was markedly high or increased. In Patients #2 and #3, the serum BNP levels were decreased after therapy.*

Patient #3 was diagnosed with portal vein obstruction with a portosystemic shunt and PoPH. Bosentan was administered and her condition improved. Her serum BNP level improved 30.2 pg/mL from 52.2 pg/mL. She has survived for 5 years.

Patient #4 was hospitalize to undergo a liver transplantation due to late-stage PBC (Child-Pugh grade C). And her mPAP was markedly increased at 53 mmHg and serum BNP level was 734 pg/mL. PoPH was diagnosed and her condition was severe; the liver transplantation was thus considered impossible and was not performed. A phosphodiesterase-5 inhibitor (sildenafil) was administered. However, after 2 months she died due to heart and liver failure.

HPS

Table 2 summarizes the cases of the six patients (five males) with HPS. The ages ranged from 21 to 64 years. The background liver diseases were four cases of liver cirrhosis due to hepatitis C virus (HCV), and two cases of NASH with hypopituitarism. In Patients #1 and #4, Child-Pugh grade B liver cirrhosis and HPS were diagnosed. In both patients, it was judged that liver transplantation was indicated. After liver transplantation, the HPS of both patients was improved and home oxygen therapy was no longer necessary. The shunt ratios (%) calculated by TcMAA pulmonary scintigraphy improved to 7.7% from 52.0% and to 5.0.% from 23.0%, respectively.

No	Age	Sex	Based liver disease	Shunt ratio calculated by TcMAA pulmonary scintigraphy (%)	Therapy	Effect	Prognosis
1	58	F	LC-HCV	23 <after LT→5.0>	Liver transplantation	(+)	Survival
2	47	M	LC-HCV	50	Home oxygen therapy	(-)	Dead
3	64	M	LC-HCV	46	Home oxygen therapy	(-)	Dead
4	36	M	LC-NASH hypopituitarism	52 <after LT→7.7>	Liver transplantation	(+)	Survival
5	21	M	NASH hypopituitarism	45.5 <after hormone therapy→6.0>	Hormone replacement therapy	(+)	Survival
6	58	M	LC-LC Hepatocellular carcinoma	34.7	Home oxygen therapy	(-)	Dead

Table 2: *Cases with hepatopulmonary syndrome.*

TcMAA: Tc Macroaggregated Albumin; LC: Liver Cirrhosis; HCV: Hepatitis C Virus; NASH: Nonalcoholic Steatohepatitis; LT: Liver Transplantation.

Patients #2 and #3 rejected liver transplantations, and both died due to liver and respiratory failure within several months of diagnosis. Patient #5 was diagnosed with NASH (fibrosis grade 3 - 4) associated with hypopituitarism and HPS. Hormone-replacement therapy was restarted. After 5 months, a second liver biopsy revealed the amelioration of the patient's NASH (fibrosis grade 2 - 3), which improved his respiratory condition. Home oxygen therapy eventually became unnecessary. The shunt ratio improved from 45.5% to 6.0%. Patient #6 was hospitalized to undergo liver transplantation due to liver cirrhosis and HPS. The shunt ratio was 34.7 %. The size and number of hepatocellular carcinoma was without Milan criteria and pneumonia was complicated. As liver transplantation was judged as no adaptation, he died died due to liver and respiratory failure within several months of diagnosis.

Discussion

PoPH and HPS are fatal complications affecting the survival of patients with liver cirrhosis or portal hypertension, but early diagnosis and effective therapy against chronic liver diseases and PAH might change the prognosis of these diseases.

Kuwat., *et al*. reported that female gender and autoimmune liver diseases were associated with an increased risk of PoPH, whereas hepatitis C infection was associated with a decreased risk in patients with advanced liver disease [18]. Hormonal and immunologic factors may therefore be integral to the development of PoPH [18]. All four of our patients with PoPH were female, and two had primary biliary cholangitis. The results of our evaluation thus also suggest the hormonal and immunologic roles on PoPH. Two patients of the four PoPH patients died. Patient #1 died due to severe heart and liver failure, because there were no effective PAH-specific drugs at that time, and the other patient was too late for therapy. In contrast, the condition of the other two patients was not so severe and PAH-specific drugs were effective. These two patients have survived for > 5 years.

The serum BNP level is a good indicator of whether or not PAH-specific drugs are effective. It was reported that the incidence of liver function abnormality is higher in patients treated with bosentan [9]. In our patients, bosentan was relatively safe, even in LC patients. When bosentan is being administered to PoPH patients, liver function tests should be conducted frequently. It is also important to diagnose PAH and administer PAH-specific drugs at an early stage.

In our HPS patients, four had HCV and male gender was dominant. The etiology and gender distribution are similar to the etiologies and gender distribution of all LC patients [19]. Three patients had not received liver transplantation and died. As in a previous report [14], liver transplantation was effective for HPS. After the liver transplantation in Patients #1 and #4, the patients' hypoxemia was improved. The condition of the patient (#5) who suffered with NASH associated with hypopituitarism and HSP improved after hormone-replacement therapy was restarted, as the liver dysfunction, liver fibrosis grade and respiratory condition improved.

Other recent case reports [15,16] also indicated the possibility of the improvement of HPS by effective therapy for chronic liver diseases. In any case, it is important to diagnose HPS at an early stage. When liver cirrhosis combined with HPS is diagnosed, effective treatments for chronic liver diseases (such as direct antiviral agents for HCV) should be considered before liver transplantation.

Among our ten patients, hormonal abnormalities such as hypopituitarism were present in three NASH patients. In all LC patients, the prevalence of NASH with hypopituitarism is very low. Therefore, hormonal factors might play an important role in PoPH and HPS. Clinicians should check for hormonal abnormalities in patients with PoPH or HPS.

Conclusion

This study is limited as a retrospective analysis of patients treated at a single center. Prospective and multi-center studies of larger numbers of patients are needed to evaluate whether these drugs truly change the prognoses of PoPH and HPS.

PoPH and HPS were initially thought to be fatal complications when a liver transplantation was not performed, but several drugs that act against chronic liver diseases and PAH have been developed. If PoPH or HPS is diagnosed at an early stage, it may be possible to control PoPH and HPS with these drugs without the need for liver transplantation. Clinician should screen PoPH and HPS by the pulmonary function test and echocardiography in patients with chronic liver diseases in order to diagnose them at early stage.

Bibliography

1. Umeda N and Kamath PS. "Hepatopulmonary syndrome and portopulmonary hypertension". *Hepatology Research* 39 (2009): 1020-1022.

2. Humbert M., *et al*. "Pulmonary arterial hypertension in France: results from a national registry". *American Journal of Respiratory and Critical Care Medicine* 173 (2006): 1023-1030.

3. Mc Donnell PJ., *et al*. "Primary pulmonary hypertension and cirrhosis: are they related?" *The American Review of Respiratory Disease* 127 (1983): 437-441.

4. Colle IO., *et al*. "Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study". *Hepatology* 37 (2003): 401-409.

5. Krowka MJ., *et al*. "Portopulmonary hypertension: Results from a 10-year screening algorithm". *Hepatology* 44 (2006): 1502-1510.

6. Safdar Z., *et al*. "Portopulmonary hypertension: an update". *Liver Transplantation* 18 (2012): 881-891.

7. Sussman N., *et al*. "Successful liver transplantation following medical management of portopulmonary hypertension: a single-center series". *American Journal of Transplantation* 6 (2006): 2177-2182.

8. Krowka MJ., *et al*. "Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database". *Liver Transplantation* 10 (2004): 174-182.

9. Chen X., *et al*. "Bosentan therapy for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: A systemic review and meta-analysis". *The Clinical Respiratory Journal* 12 (2018): 2065-2074.

10. Feldman J., *et al*. "Oral treprostinil in the treatment of pulmonary arterial hypertension". *Expert Opinion on Pharmacotherapy* 18 (2017): 1661-1667.

11. Rodriguez-Roisin R., *et al*. "Pulmonary-hepatic vascular disorders (PHD)". *European Respiratory Journal* 24 (2004): 861-880.

12. Schenk P., *et al*. "Hepatopulmonary syndrome: prevalence and predictive value of various cut offs for arterial oxygenation and their clinical consequences". *Gut* 51 (2002): 853-859.

13. Swanson KL., *et al*. "Natural history of hepatopulmonary syndrome: impact of liver transplantation". *Hepatology* 41 (2005): 1122-1129.

14. Egawa H., *et al*. "Long-term outcome of living related liver transplantation for patients with intrapulmonary shunting and strategy for complications". *Transplantation* 67 (1999): 712-717.

15. Miyata H and Miyata S. "A case of hepatopulmonary syndrome derived from nonalcoholic fatty liver disease with severe fibrosis, in which hypoxia could be recovered by improvement of liver fibrosis". *Kazo* 55 (2014): 479-487.

16. Mastumoto S., *et al*. "Alcoholic cirrhosis associated with hepatopulmonary syndrome: Abstinence from alcohol and long term oxygen therapy improved the hepatic function and ameliorated hypoxia". *Kazo* 55 (2014): 35-239.

17. Barberà JA., *et al*. "Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Summary of Recommendations". *Archivos de Bronconeumología* 54 (2018): 205-215.

18. Kawut SM., *et al*. "Clinical risk factors for portopulmonary hypertension". *Hepatology* 48 (2008): 196-203.

19. Michitaka K., *et al*. "Etiology of liver cirrhosis in Japan: a nationwide survey". *The Journal of Gastroenterology* 45 (2010): 86-94.

Volume 7 Issue 12 December 2020