The Korean Journal of Internal Medicine
Vol. 16, No. 2, June, 2001

Hepatopulmonary Syndrome in Poorly Compensated Postnecrotic Liver Cirrhosis by Hepatitis B Virus in Korea

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Background : *Hepatopulmonary syndrome (HPS) refers to the association of hypoxemia, intrapulmonary shunting and chronic liver disease. But there is no clear data about the prevalence of HPS in postnecrotic liver cirrhosis by hepatitis B virus(HBV), the most common cause of liver disease in Korea. The aim of this study was to investigate the prevalence of HPS in poorly compensated postnecrotic liver cirrhosis by HBV, and the correlation of the hepatopulmonary syndrome with clinical aspects of postnecrotic liver cirrhosis by HBV.*

Methods : *Thirty-five patients underwent pulmonary function test, arterial blood gas analysis and contrast-enhanced echocadiography. All patients were diagnosed as HBV-induced Child class C liver cirrhosis and had no evidence of intrinsic cardiopulmonary disease.*

Results : *Intrapulmonary shunt was detected in 6/35 (17.1%) by contrast-enhanced echocariography. Two of six patients with intrahepatic shunts had significant hypoxemia (PaO_2 < 70 mmHg) and four showed increased alveolar-arterial oxygen gradient over 20 mmHg. Only cyanosis could reliably distinguish between shunt positive and negative patients.*

Conclusions : *The prevalence of intrapulmonary shunt in poorly compensated postnecrotic liver cirrhosis by HBV was 17.1% and the frequency of hepato-pulmonary syndrome was relatively low (5.7%). 'Subclinical' hepatopulmonary syndrome (echocardiographically postive intrapulmonary shunt but without profound hypoxemia) exists in 11.4% of cases with poorly compensated postnecrotic liver cirrhosis by HBV. Cyanosis is the only reliable clinical indicator of HPS of HBV-induced poorly compensated liver cirrhosis. Further studies are required to determine if the prevalence and clinical manifestations of HPS varies with etiology or with geographical and racial differences.*

Key Words : *Hepatopulmonary syndrome; Contrast echocardiography; Liver cirrhosis; Hepatitis B virus*

INTRODUCTION

The hepatopulmonary syndrome (HPS) is characterized clinically by the triad of pulmonary vascular dilation, systemic hypoxemia and the setting of advanced liver disease[1-7]. In 1956, a case report by Rydell and Hoffbauer[8] concerning a 17-year-old man with hypoxemia and juvenile cirrhosis provided the first clinical and postmortem documentation of what was to be later termed HPS by Knudsen and Kennedy in 1979[7]. The postmortem study demonstrated both precapillary dilations and direct arteriovenous communications after vascular injections with a plastic vinyl acetate solution[9,10].

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The definition of hypoxemia may vary, but several studies consider PaO_2 less than 70 mmHg in patients with liver disease as abnormal. An increased alveolar-arterial oxygen gradient ($A\text{-}aDO_2$: greater than 20 mmHg) represents a more sensitive but less practical measure of abnormal oxygenation. Patients with HPS frequently demonstrate oxygenation that become worse as one moves from the supine to standing position (orthodeoxia) breathing either room air or 100% inspired oxygen. A poor correlation exists between PaO_2 determined while breathing room air and PaO_2 determined while breathing 100% oxygen; the latter may be of additional prognostic significance. Research studies using a multiple inert gas elimination technique (MIGET) have shown the hypoxemia of HPS to be a result of shunt, diffusion-perfusion defect and excess perfusion for a given ventilation (low V/Q)[11].

Most studies about hepatopulmonary syndrome have focused on alcoholic liver disease[12-17]. There is no clear data about the prevalance of HPS in postnecrotic liver cirrhosis by hepatitis B virus (HBV). And it is unclear how the presence of HPS relates to the clinical aspects of HBV induced liver cirrhosis. So this study was done to investigate the prevalence of HPS in poorly compensated postnecrotic liver cirrhosis by HBV and the correlation of HPS with clinical aspects of HBV induced poorly compensated postnecrotic liver cirrhosis.

MATERIALS AND METHODS

1. Patients

Thirty-five cirrhotic patients were randomly recruited, from both the Gastroenterology Ward and the Gastroenterology Out-patients in Seoul Municipal Boramae Hospital (Seoul National University Hospital Affiliated Hospital), Seoul, Korea. The inclusion criteria were the followings:

Liver cirrhosis was diagnosed with histologic findings (85%), and with conventional clinical (positive evidence of chronic liver disease stigmata and physical findings of liver cirrhosis), ultrasonographic (coarse liver surface and shrunken liver on ultrasonography) and biochemical criteria (abnormal blood liver function test), and clinical presentations of portal hypertension (15%). All patients showed serum HB_sAg positve and Child C clincal findings, with absence of cardiac or pulmonary disease and absence of pulmonary vascular abnormalities not related to liver disease.

Patients were informed about the intended procedures and the aim of the study, and consent was obtained in every case, according to the specifications guidelines of the 1975 Declaration of Helsinki. Transthoraic contrast echocardiography (TTCE) was performed in all cirrhotic patients.

2. Transthoracic contrast echocardiograpy (TTCE)

We used a standard echoccardiograph (Acuson Computerized Sonography 128XP, USA), with a 3.5 MHz transthoracic probe. Studies were recorded on videotape for further analysis. For TTCE, a previously published method[2] was closely followed. Four-chamber apical image was obtained through a transthoracic approach. Then, 10 mL of saline with 0.5 mL room air, were injected through the intravenous line. The second and third injection followed. A positive result was defined when microbubbles were observed in the left atrium in one or more of the three injections. The grading method was validated by examination of its reproducibility. First, the intrinsic reproducibility was examined by comparing the results obtained after the first and the second injection of each substance. Second, intraobserver reproducibility was measured by assessing the concordance resulting from a two-step blind review of each register performed by the same observer. Third, interobserver reproducibility was assessed by blind comparison of the results obtained by both observers in the interpretation of each register. We did not compare two studies of the same patient performed at different times for ethical reasons.

3. Arterial blood gas analysis (ABGA)

A sample of arterial blood was obtained in each patient at the time of the echocardiographic study by puncture of the radial artery of the left arm, following the standard technique, in the supine position and breathing room air. PaO_2 and $PaCO_2$ were determined by selective electrodes (IL 16/40 ph/blood gas analyzer. Instrumentation laboratory SpA, Milano, Italy). $PaO_2 <$ 70 mmHg was considered as hypoxemia. $PaCO_2 <$ 35 mmHg was considered as hypocapnia.

4. Pulmonary function test

We used a standard pulmonary function test machine (Sensor Medic Model 2200, USA).

5. Diagnosis of HPS

Using saline-TTCE, we considered clinical HPS to be

present in cases with PaO_2 < 70 mmHg with bubbles in left cardiac chambers, 'subclinical' HPS in A-aDO_2 greater than 20 mmHg with bubbles in left cardiac chambers.

6. Statistical analysis

Estimation of Kappa heavy index allowed determination of the reproducibility of the procedure and intra- and inter-observer variability. Wilcoxon's test was chosen to compare results of TTCE, and correlation between ordinal variables was determined by Spearman's test. Correlation between continuous and ordinal variables was determined by ANOVA and post-hoc test (Bonferroni). The limit of significance was set at a p<0.05. For analysis purposes, we used the SPSS.

RESULTS

Thirty-five patients were studied (13 women and 22 men: mean age, 53.1± 14.5 years) All patients were classified as Child's C. (Child's classification included assessment of total bilirubin, serum albumin, clinical ascites, nutrition and existence of encephalopathy; Child's A classification represented minimal disease and Child's C classification represented the most severe liver disease). The etiologies of liver diseases of all the patients were postnecrotic liver cirrhosis by hepative B virus.

1) Symptoms and signs of study population (Table 1)

Splenomegaly and ascites were seen in all 35 patients (100%), and spider angiomas were seen in 21/35 patients (60%). Cyanosis was observed in 2 patients (6%). Esophagogastroduodenoscopy was performed before the echocardiographic studies. Thirty-two patients had esophageal varices, nine of which (25.7%) were grade Ⅰ, twenty of which (57.1%) were grade Ⅱ, three of which (8.6%) were grade Ⅲ.

Table 1. Symptoms and Signs of Study Population

Symptoms and Signs	No. of Patients (n=35)
Resting dyspnea	6 (17.1%)
Platypnea	0 (0%)
Exertional dyspnea (ATS criteria)	
grade Ⅰ	22 (62.9%)
grade Ⅱ	7 (20%)
Tachypnea	17 (48.6%)
Cyanosis	2 (5.7%)
Clubbing	1 (2.9%)
Ascites, splenomegaly	35 (100%)
Spider angioma	21 (60%)

ATS, American Thoracic Society

Japanese portal hypertension study group classification was used for esophageal varix grading (Table 2).

2) Pulmonary function test (Table 3) and arterial blood gas analysis (Table 4)

Mild ventilatory defect of the restrictive type (65-79% of predicted value) was found in 7/35 patients (20%) and decrease in diffusing capacity of carbon monoxide (below 70% of predicted value) was found in 4/35 patients (11%). Significant hypoxemia (PaO_2 < 70 mmHg)

Table 2. Laboratory Finding of Study Population

Laboratory Findings	No. of Patients (n=35)
Esophageal varix	
grade Ⅰ	9 (25.7%)
grade Ⅱ	20 (57.1%)
grade Ⅲ	3 (8.6%)
Chest PA	
small amount pleural effusion	5 (14.3%)
EKG	
non-significant arrhythmia	3 (8.6%)

Table 3. Pulmonary Function Test Result of Study Population

Parameter	Degree	No. of patient (n=35)
FVC (% of pedicted)	>80%	28 (80.0%)
	65-80%	7 (20.0%)
FEV_1 (% of predicted)	>80%	28 (80.0%)
	65-80%	5 (14.3%)
	50-64%	2 (5.7%)
DLco/VA (% of predicted)	>80%	24 (68.5%)
	65-80%	7 (20.0%)
	50-69%	4 (11.4%)

FVC, forced vital capacity
FEV_1, forced expiratory volume in one second
DLco/VA, carbon monoxide diffusing capacity/alveolar volume

Table 4. Arterial Blood Gas Analysis Result of Study Population

Parameter	No. of Patients (n=35)
PaO_2 (at room air)	
70 mmHg >	2 (5.7%)
70 mmHg ≤	33 (94.3%)
A-aDO_2 (at room air)	
20 mmHg <	4 (11.4%)
20 mmHg ≥	31 (88.6%)
Contrast-enhanced echocardiography	
intrapulmonary shunt	6 (17.1%)

A-aDO_2, Alveolar-arterial oxygen difference (gradient)

Table 5. Clinical Findings of Liver Cirrhosis Patients with Intrapulmonary Shunt

Age/Sex (years)/(M/F)	Cyanosis	Spider angioma	Varix	FVC (%)	FEV_1 (%)	DLco (%)	PaO_2 (mmHg)	$AaDO_2$ (mmHg)
65/M*	+	+	-	94	96	59	57	59
63/M*	+	+	II	117	111	66	52	68
54/M	-	-	II	106	103	101	75	32
47/M	-	-	I	77	82	70	79	32
35/M	-	-	II	82	88	73	93	33
69/F	-	-	II	91	94	74	77	34

*patients with hepatopulmonary syndrome
FVC, forced vital capacity
FEV_1, forced expiratory volume in 1 second
DLco/VA, carbon monoxide diffusion capacity/alveolar volume
A-aDO_2, Alveolar-arterial oxygen difference

was found in 2/35 patients (5.7%) and PaO_2 was below 80 mmHg in 4/35 patients (11%) and below 90 mmHg in 10/35 patients (29%), and the PaO_2 value of the remaining 19/35 patients (54%) was above 90 mmHg. A-aDO_2 were below 20 mmHg in 31/35 (88.6%) and above 20 mmHg in 4/35 patients (11.4%).

3) Clinical and laboratory findings of liver cirrhosis patients with positive shunt (Table 5)

Intrapulmonary shunt was detected by TTCE in 6/35 patients (17.1%) and these cases showed significantly lower PaO_2 than in negative intrapulmonary shunt cases (PaO_2: 72.2±15.1 vs. 90.2±7.40, p <0.05) and more increased A-aDO_2 (43.1±16.2 vs. 22.4±7.43) than in negative intrapulmonary shunt cases.

4) Comparison of clinical and laboratory findings between shunt negative and positive patients (Table 6 and Table 7)

Except cyanosis, any clinical or laboratory findings including spider angioma, esophageal varix, biochemical indicator of hepatic function and parameters of pulmonary function test, including diffusing capacity did not distinguish between positive and negative intrapulmonary shunt patients.

Table 6. Clinical Findings Relating to Intrapulmonary Shunt

Parameter	Shunt(-)	Shunt(+)	Significance
Sex (m/f)	17:12	5:1	NS
Smoking	16/29	3/6	NS
Dyspnea	6/29	2/6	NS
Dyspnea on exertion	24/29	5/6	NS
Cyanosis	0/29	2/6	p <0.05
Clubbing	1/29	0/6	NS
Tachypnea	13/29	4/6	NS
Spider angioma	19/29	2/6	NS
Esophageal varix	26/29	5/6	NS

FVC, forced vital capacity
FEV_1, forced expiratory volume in 1 second
DLco/VA, carbon monoxide diffusion capacity/alveolar volume
A-aDO_2, Alveolar-arterial oxygen difference

Table 7. Laboratory Findings Relating to Intrapulmonary Shunt

	Shunt (-)	Shunt (+)	Significance
Age	52.6± 15.0	55.2± 12.6	NS
Prothrombin time (%)	64.4±21.7	59.2±9.57	NS
Albumin	2.42±0.57	2.15±0.40	NS
Bilirubin	2.91± 1.67	2.87± 1.76	NS
FVC (%)	86.3± 1.47	94.5± 14.9	NS
FEV1 (%)	87.1±20.3	97.2± 15.5	NS
DLco/Va (%)	84.6± 16.9	73.8± 14.4	NS
PaO_2	90.2±7.40	72.2± 15.1	p<0.05
A-aDO_2	22.4±7.43	43.1± 16.2	p<0.05

DISCUSSION

The triad of liver disease, arterial hypoxemia and intrapulmonary vascular dilatation has defined an entity commonly referred to as the hepatopulmonary syndrome[1, 3, 10-11, 19, 26]. In the original description by Rydell and Hoffbauer[4], lung necropsy specimens studied using plastic vascular casts contained both precapillary/capillary dilatations and distinct anatomic arteriovenous communications which caused severe hypoxemia in the setting of chronic liver disease (juvenile cirrhosis)[14, 16-18]. Hepatopulmonary syndrome is becoming increasingly recognized as one of the most serious complications of chronic liver disease. Different workers have reported incidences of positive air-contrast echocardiography varying from 5 to 47%, and prevalence of HPS between 5 and 29%[3, 14]. Our present study,

although small, suggested a relatively lower occurrence of this condition (17.1% positive intrapulmonary shunt, 5.7% hepatopulmonary syndrome) in the Korean population, among whom hepatitis B virus is the most common cause of cirrhosis (100% in the present study), compared with alcohol and hepatitis C virus in Western countries. The results from our study were similar to those from an Indian study that the prevalence of intrapulmonary shunting in hepatitis B virus induced liver cirrhosis was 8.9% but HPS with hypoxemia was only 6.7%[2]. Further studies are required to determine if the prevalence of HPS varies with etiology of liver disease or with geographical and racial differences.

Advanced hepatic dysfunction, with associated hyperdynamic circulation, has been suggested as being the most probable setting for the development of HPS. However, the condition has also been found in cases of congenital hepatic fibrosis and portal vein thrombosis. This has given rise to the question of whether portal hypertension is a contributing factor[1, 3]. Moreover, if hepatic dysfunction was the only prerequisite, one would expect HPS to occur predominantly among Child's class C cirrhosis. However, Abrams et al. found 15 of 25 cases of HPS (60%) had Child's grade A, and only two had grade C[3]. In this study, most of HPS cases were alcoholic liver cirrhosis and hepatitis C virus (HCV)-induced liver cirrhosis. A common bile duct ligation rat model for hepatopulmonary syndrome has been developed and increased pulmonary endothelial nitric oxide synthase activities and circulating endothelin-1 levels seem to correlate with vascular dilatation and oxygen abnormalities[19, 26].

In the present study, all cases were HBV-induced Child's grade C liver cirrhosis and the prevalence of HPS is 5.7%. In this small study, the prevalence of hepatopulmonay syndrome in patients with poorly compensated (Child C) postnecrotic liver cirrhosis by HBV was 5.7%. Two of 35 cases of cirrhosis (5.7%) had positve contrast echocardiographly with hypoxemia (PO_2 < 70 mmHg) and four of 35 case of cirrhosis (11.4%) were 'subclinical' cases (positive contrast echocardiograpy without hypoxemia). Our results suggested that "subclinical hepatopulmonary syndrome" exists and maybe there were some factors, still unknown, to determine definite hepatopulmonary syndrome (hypoxemia with positive contrast echocardiograpy) and subclinical hepatopulmonary syndrome. This study suggested that there was a wide clinical spectrum of hepatopulmonary syndrome. There was one report about association of esophageal varices and hepatopulmonary syndrome in liver cirrhosis[27]. But, in this study, there was no association of the grade of esophageal varices and hepatopulmonary syndrome. Cyanosis was the only reliable clinical indicator, and there was no clear relationship with the presence of spider angioma and hepatopulmonary syndrome. Further studies are required to determine if the prevalence of HPS and clinical manifestations of HPS varies with etiology or with geographical and racial differences.

REFERENCES

1. Herve P, Lebrec D, Brenot F, Simonneau G, Humbert M, Sitbon O, Duroux P. *Pulmonary vascular disorders in portal hypertension. Eur Respir J 11:1153-63, 1998*
2. De BK, Sen S, Biswas PK, Biswas J, Maity AK. *Clinical and haemodynamic aspects of hepatopulmonary syndrome in Indian patients with cirrhosis. J Gastroenterol Hepatol 15:412-416, 2000*
3. Abrams GA, Nanda NC, Dubovsky EV, Krowka MJ, Fallen MB. *Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome, a new approach. Gastroenterology 114:305-310, 1998*
4. Rydell R, Hoffbauer FW. *Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. Am J Med 21:450-459, 1956*
5. Whyte MKB, Hughes JMB, Peters AM, Ussov W, Pathel S, Burroughs AK. *Analysis of right to left shunt in hepatopulmonary syndrome. Hepatology 29:85-93, 1998*
6. Ruff F, Hughes JB M, Stanley N, Clayton L, Aronoff A, Milic-Mili J. *Regional lung function in patients with hepatic cirrhosis. J Clin Invest 50:2403-2413, 1971*
7. Krowka MJ, Cortese DA. *Pulmonary aspects of liver disease and liver transplantation. Clin Chest Med 10: 593-614, 1989*
8. Agustic AG, Roca J, Bosch J, Rodriguoz-Roisin R. *The lung in patients with cirrhosis. J Hepatol 10(2) :251-257, 1990*
9. Krowka MJ, Dickson ER, Cortese DA. *Hepatopulmonary syndrome. Clinical observations and lack of therapeutic response to somatostatin analogue. Chest 104:515-521, 1993*
10. Duncan BW, Kneebone JM, Chi EY, Hraska V, Isik FF, Rosenthal GL, Jones TK, Starnes SL. *A detailed histologic analysis of pulmonary arteriovenous malformations in children with cyanotic congenital heart disease. J Thorac Cardiovasc Surg 117:931-938, 1999*
11. Clement B, Musso O, Lietard J, There TN. *Homeostatic control of angiogenesis; a newly identified function of the liver. Hepatology 29:621-623, 1999*
12. Krowka MJ, Cortese DA. *Severe hypoxemia associated with liver disease: Mayo Clinic experience and the*

experimental use of almitrine bimesylate. Mayo Clin Proc 62:164-173, 1996

13. Krowka MJ, Tajik AJ, Dickson ER, Wiesner RH, *Cortese DA. Intrapulmonary vascular dilatations (IPVD) in liver transplant candidates. Screening by two-dimensional contrast-enhanced echocardiography. Chest 97:1165-70, 1990*
14. Castro M, Krowka MJ. *Hepatopulmonary syndrome. A pulmonary vascular complication of liver disease. Clin Chest Med 17:35-48, 1996*
15. Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. *Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. Gastroenterology 109:1283-1288, 1995*
16. Krowka MJ, Porayko MK, Plevak DJ, Pappas SC, Steers JL, Krom RA, Wiesner RH. *Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. Mayo Clin Proc 72:44-52, 1997*
17. Lange PA, Stroller JK. *The hepatopulmonary syndrome. Ann Intern Med 122:521-529, 1995*
18. Egawa H, Kasahara M, Inomata Y, Uemoto S, Asonuma K, Fujita S, Kiuchi T, Hayashi M, Yonemura. T, Yoshibayashi M, Adachi Y, Shapiro JA, Tanaka K. *Long-term outcome of living related liver transplantation for patients with intrapulmonary shunting and strategy for complications. Transplantation 67:712-717, 1999*
19. Fallon MB, Abrams GA, Luo B, Hou Z, Dai J, Ku DD. *The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. Gastroenterology 113:606-614, 1997*
20. Dimand RJ, Heyman MB, Lavine JE, Bass NW, Lake JR, Ascher NL. *Hepatopulmonary syndrome response to hepatic transplantation[abstract]. Hepatology 14:55, 1991*
21. Krowka MJ, Cortese DA. *Hepatoplmonary syndrome, Current concepts in diagnostic and therapeutic ceansiderations. Chest 105:1528-1537, 1994*
22. Hopkins WE, Waggoner AD, Barzilai B. *Frequency and significance of intrapulmonary right-to-left shunting in end-stage hepatic disease. Am J Cardiol 70:516-519, 1992*
23. Thorens JB, Junod AF. *Hypoxaemia and liver cirrhosis; a new argument in favour of a "diffusion perfusion defect". Eur Respir J 5:754-756, 1992*
24. Andrivet P, Cadranel J, Housset B, Herigault R, Harf A, Adnot S. *Mechanisms of impaired arterial oxygenation in patients with liver cirrhosis and severe respiratory insufficiency: effects of indomethacin. Chest 103:500-507, 1993*
25. Vachiery F, Moreau R, Hadengue A, Gadano A, *Soupison T, Valla D, Lebrec D. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations. J Hepatol 27:492-495, 1997*
26. Luo B, Abrams GA, Fallon MBP. *Endothelin-1 in the rat bile duct ligation model of hepatopulmonary syndrome: correlation with pulmonary dysfunction. J Hepatol 29: 571-578, 1998*
27. Caruso G, Catalano D. *Esophageal varices and hepatopulmonary syndrome in liver cirrhosis. J Hepatol 12:262-263, 1991*