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Portopulmonary hypertension: distinctive hemodynamic and clinical manifestations

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Abstract: Portopulmonary hypertension is now recognized as one of the pulmonary complications of chronic liver disease. However, previous studies reported that the incidence ranged from 0.25% to 2%, excluding fortuitous coincidence. In this study, we aimed to determine the variant hemodynamic and clinical features of portopulmonary hypertension in an area with a high prevalence of viral cirrhosis. After reviewing the hemodynamic data of 322 patients with portal hypertension admitted to the Taipei Veterans General Hospital between 1987 and 1999, we found 10 with portopulmonary hypertension. The overall incidence was, therefore, 3.1% in all patients with portal hypertension. Most of the patients with portopulmonary hypertension experienced exertional dyspnea. The survival times ranged from 2 to 86 months. In our series, most of the patients who died, died of complications related to cirrhosis and portal hypertension, but not of complications related to pulmonary hypertension. This study suggested that portopulmonary hypertension was not a frequent complication in cirrhotic patients and was not associated with an adverse outcome.

Key words: cirrhosis, portal hypertension, primary pulmonary hypertension

Introduction

The term primary pulmonary hypertension was first coined in 1951;[1] the entity is clinically defined as precapillary pulmonary hypertension (mean pulmonary arterial pressure of 25 mmHg or greater at rest, with a pulmonary capillary wedge pressure equal to or less than 15 mmHg) in the absence of secondary pulmonary hypertension.[2] In 1979, Lebrec et al.[3] stated that primary pulmonary hypertension was a rare complication of portal hypertension that was not well known to internists or hepatologists at that time. A retrospective study from autopsy specimens showed a incidence of primary pulmonary hypertension of 0.61%–0.73% in cirrhotic patients,[4] while Hadengue et al.[5] reported a incidence of 2% in their prospective series, by hemodynamic measurement. In addition to hepatopulmonary syndrome, it is now recognized that portopulmonary hypertension (PPH) is another pulmonary complication of chronic liver disease.[6,7] Putative mechanisms for PPH include repeated microthroboembolism, the presence of unidentified vasoconstrictor substances originating from the gut that escape liver inactivation, and a hyperkinetic circulation.[8–11] As no local epidemiological studies of PPH have been reported previously in Taiwan, we would now like to present an analysis of the clinical, laboratory, and hemodyanmic findings of PPH in this area. We also review the relevant literature, and discuss the incidence, clinical presentation, diagnosis, and outcome of PPH.

Subjects and methods

Between June 1987 and July 1999, 322 patients with liver cirrhosis were admitted to the Taipei Veterans General Hospital for evaluation of the severity of portal hypertension. Their ages ranged from 32 to 78 years (mean age, 62 years). One patient had myelofibrosis; all the rest had cirrhotic portal hypertension. The causes of the cirrhosis were hepatitis B surface antigen (HBsAg) and/or anti-hepatitis C virus antibody (anti-HCV) positive in 280, alcoholic cirrhosis in 15, primary biliary cirrhosis in 2, hemochromatosis in 2, and cryptogenic in 22. The severity of liver cirrhosis was classified

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according to Pugh's modification of Child's classification.[12] There were 117 class A patients, 126 class B patients, and 79 class C patients. All patients had received abdominal ultrasound, and ascites was found in 127. Patients who had a recent variceal hemorrhage and those who had taken vasoactive drugs 7 days before the study were excluded. None of the studied patients had hepatocellular carcinoma; a previous operation for portal hypertension; or heart, renal, or lung diseases. Additionally, none of the patients had hepatic encephalopathy at the time of the study.

After an overnight fast, the patients were prepared for the hemodynamic study in the supine position. With the patients under local anesthesia, hemodynamic measurement was performed using a 7F Swan-Ganz thermodilution catheter (Gould, Cupertino, CA, USA), as previously described.[13] The pulmonary vascular resistance (dyn·s/cm^5) was calculated as follows: (mean pulmonary arterial pressure − pulmonary capillary wedge pressure) × 80/cardiac output. After we excluded secondary causes of pulmonary hypertension (e.g., chronic obstructive pulmonary disease, heart failure, chronic thromboembolic disease, and pulmonary venoocclusive disease), we found that ten patients had PPH. Their mean survival time was 40 months (range, 2 to 86 months). Six patients died; all of them died of complications related to portal hypertension, not of complications related to PPH. Four patients are still alive, and one of them has survived for more than 68 months after the diagnosis (Table 1). A brief summary of five of our patients with PPH follows.

Case reports

Case 1. A 42-year old man who presented in June 1993, with a 1-year history of progressive dyspnea and lower leg edema, was found to have had acute hepatitis in childhood. He had received a blood transfusion after a traffic accident in May 1989. Findings of his physical examination on the current admission are shown in Table 2. Abdominal ultrasound disclosed gallstones, and was compatible with cirrhosis. Upper gastrointestinal endoscopy showed esophageal varices. On June 15, 1993, hemodynamic study was performed, and mild pulmonary hypertension was noted. Further cardiopulmonary evaluation was done to confirm a diagnosis of PPH (Table 3). Over the following years, he developed refractory ascites and bleeding esophageal varices. He

Table 1. General clinical data of patients with protopulmonary hypertension

Case	Age (years)	Sex	Cause of portal hypertension	Child-Pugh class	Survival time after diagnosis (months)	Outcome/cause of death
1	42	Male	Cirrhosis (HCV)	B	24	Pneumonia with septic shock
2	64	Male	Cirrhosis (HBV)	C	66	Variceal bleeding
3	68	Male	Cirrhosis (alcoholic)	B	>68	Still alive
4	67	Female	Cirrhosis (cryptogenic)	A	>42	Still alive
5	65	Male	Cirrhosis (HBV)	C	18	Spontaneous bacterial peritonitis
6	64	Male	Cirrhosis (HBV)	A	86	Hepatorenal syndrome
7	64	Male	Cirrhosis (alcoholic)	B	65	Hepatocellular carcinoma with rupture
8	65	Male	Cirrhosis (HBV)	B	2	Variceal bleeding
9	76	Male	Cirrhosis (HCV)	A	>48	Still alive
10	70	Male	Myelofibrosis	A	>40	Still alive

HBV, Hepatitis B virus; HCV, hepatitis C virus; Pugh's modified Child score is 5–6 in class A, 7–9 in class B, ≧10 in class C

Table 2. Cardiopulmonary symptoms and physical findings in patients with protopulmonary hypertension

Case	Symptoms	Physical findings
1	Exertional dyspnea	Loud P_2, peripheral pitting edema
2	Asymptomatic	Decrease of right side breathing sounds
3	Exertional dyspnea and dizziness	Loud P_2
4	Chest pain and exertional dyspnea	Grade II/IV systolic murmur
5	Fatigability and tiredness	Shifting dullness, splenomegaly, and peripheral pitting edema
6	Exertional dyspnea	Peripheral edema and splenomegaly
7	Exertional dyspnea and orthopnea	Grade III/IV systolic murmur and peripheral pitting edema
8	Asymptomatic	Loud P_2
9	Orthopnea and productive cough	Loud P_2
10	Exertional dyspnea, fatigability, and tiredness	Grade III/IV systolic murmur, splenomegaly, and pitting edema

P_2, Pulmonary component of the second heart sound; grade II(III)/IV, grade 2 or 3 murmur

died in June 1995 of pneumonia, complicated by septic shock.

Case 3. A 68-year old man with a history of diabetes mellitus presented in October 1993 with progressive exertional dyspnea and dizziness. A year earlier, he had been diagnosed with alcoholic liver cirrhosis. After his first episode of bleeding from ruptured esophageal varices, he had received four sessions of endoscopic injection sclerotherapy. Physical examinations on admission disclosed loud P_2 (Table 2). Other findings are shown in Table 3. The abdominal ultrasound findings were compatible with liver cirrhosis. The patient was found to have PPH following hemodynamic measurement (Table 4). He is still alive, more than 68 months after the diagnosis of PPH.

Case 4. In 1996, when she was 67 years of age, a woman presented with exertional dyspnea, chest pain, and hematemesis. Physical examination and general imaging results are listed in Tables 2 and 3. All the hepatitis markers were negative. There was no antinuclear or anti-mitochondrial antibody. Liver biopsy was performed, and the histologic findings were consistent with cirrhosis. Upper gastrointestinal endoscopy revealed esophageal varies and portal hypertensive gastropathy. The hemodynamic findings supported the diagnosis of PPH (Table 4). She was discharged in February 1996, with a diagnosis of cryptogenic cirrhosis complicated by esophageal varices, ascites, and splenomegaly. She is still alive, more than 42 months after the diagnosis.

Case 7. In September 1991, a man who was alcoholic was diagnosed with liver cirrhosis. In 1993, at age 64 years, he was hospitalized because of hematemesis. He experienced exertional dyspnea and orthopnea during his daily activities. Pertinent physical findings included anemic conjunctiva, icteric sclera, peripheral edema,

Table 3. Cardiopulmonary evaluations in patients with portopulmonary hypertension

Case	Chest film	Electrocardiogram	Pulmonary function test	SaO2 (%)	Echocardiography
1	Prominent main pulmonary artery	RVH with strain	Normal ventilation	99	PH, RVH, and TR
2	Right side pleural effusion	RVH and ICRBBB	—	—	—
3	Prominent main pulmonary artery	Normal sinus rhythm	—	94	—
4	Prominent main pulmonary artery	Normal sinus rhythm	—	94	—
5	Cardiomegaly	RVH and ICRBBB	—	96	—
6	Cardiomegaly	RVH and CRBBB	—	92	—
7	Prominent main pulmonary artery	Normal sinus rhythm	—	93	PH, RVH, and TR
8	Normal	Normal sinus rhythm	—	94	—
9	Prominent main pulmonary artery	RVH with strain	Normal ventilation	95	—
10	Prominent main pulmonary artery	RVH and CRBBB	Normal ventilation	93	—

SaO2, Oxygen saturation; RVH, right ventricular hypertrophy; ICRBBB and CRBBB, incomplete and complete right bundle branch block; PH, pulmonary hypertension; TR, tricuspid regurgitation

Table 4. Hemodynamic values in patients with portopulmonary hypertension

Case	HVPG (mmHg)	MAP (mmHg)	HR (beats/min)	CO (l/min)	SVR (dyne·s/cm^5)	MPAP (mmHg)	PVR (dyne·s/cm^5)	PCWP (mmHg)
1	19	81	76	10.6	574	30	166	8
2	23	82	75	5.8	1118	25	138	15
3	20	126	74	9.9	970	30	168	9
4	22	111	67	5.9	1100	25	163	13
5	15	87	77	—	—	25	—	15
6	23	85	64	5.5	982	25	189	12
7	21	96	57	6.5	1122	30	246	10
8	15	95	75	6.8	768	29	165	15
9	22	86	65	3.2	2000	25	250	15
10	28	96	85	9.5	677	34	168	14

HVPG, Hepatic venous pressure gradient; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure

and grade III/IV systolic murmur at the left sternal border. Chest roentgenogram showed prominent main pulmonary arteries. Abdominal ultrasound revealed liver cirrhosis, splenomegaly, and ascites. Upper gastrointestinal endoscopy disclosed esophageal varices. Hemodynamic measurement was performed after clinical stabilization was achieved. During that measurement, an intravenous injection of propranolol (0.1 mg/kg) was given to determine whether he was a propranolol-responder. He was proven to be a nonresponder to propranolol, with a decreasing hepatic venous pressure gradient of less than 10% (from 21 to 20 mmHg). However, a 16.7% increase in mean pulmonary arterial pressure (from 30 to 35 mmHg) was found. Further cardiopulmonary function tests were also performed to confirm a diagnosis of PPH (Table 3). Endoscopic variceal ligation was arranged for the esophageal varices, because of his nonresponsiveness to propranolol and the PPH. Over the next 4 years, he developed hepatocellular carcinoma, massive ascites, and recurrent esophageal variceal bleeding. He died of hepatocellular carcinoma rupture in February 1997.

Case 9. A 76-year old man was admitted in August 1995 because of orthopnea and productive cough of some years' duration. In March 1991, he had been hospitalized because of pancytopenia, splenomegaly, and jaundice. Hepatitis C virus-associated liver cirrhosis with esophageal varices and splenomegaly was diagnosed. After the first episode of variceal bleeding, in January 1993, he received four sessions of endoscopic injection sclerotherapy. At this time, he was admitted for hemodynamic measurement. Loud P_2 and prominence of main pulmonary arteries were found during admission (Tables 2 and 3). Only antral gastritis was noted on upper gastrointestinal endoscopy. PPH was confirmed by the hemodynamic measurements. He is still alive, more than 48 months after diagnosis.

Results

Clinical features

Ten patients with portal hypertension were identified as having PPH, with evidence of clinically significant pulmonary hypertension. Their clinical characteristics are summarized in Tables 1 and 2. There were nine men (average age, 64 ± 3 years) and one woman in the present series. Ninety percent of our patients with PPH were older than 60 years. Exertional dyspnea (Table 2) was by far the commonest initial symptom, occurring in 60% of our patients. The other symptoms included orthopnea (2/10), chest pain (1/10), fatigability and tiredness (2/10), and dizziness (1/10); two patients were asymptomatic. More than 90% of our patients had their illness diagnosed within 3 years of presenting with symptoms. The physical findings in our patients were typical of those in patients with pulmonary hypertension. An increase in the pulmonary component of the second heart sound (P_2) was reported in 40% of our patients.

Cardiopulmonary evaluation

The chest radiographs in the ten patients showed a typical constellation of changes associated with pulmonary hypertension, with prominence of the main pulmonary artery in 60%. The electrocardiogram showed right axis deviation in 80%, right ventricular hypertrophy in 60%, and right ventricular strain in 20% of the patients. In two patients receiving echocardiogram (M mode), typical signs of pulmonary hypertension, with normal-to-small left ventricular end-diastolic internal dimension, right ventricular hypertrophy, and tricuspid regurgitation, were found. Pulmonary function tests in two of our patients showed normal ventilation with mild reduction in total lung capacity and diffusing capacity for carbon monoxide (DLco). The arterial oxygen content in our patients was greater than 90%.

Hemodynamic findings

The hemodynamic variables in our patients are summarized in Table 4. All patients with the diagnosis of PPH had elevated mean pulmonary arterial pressure (28 ± 1 mmHg; range, 25 to 34 mmHg) and pulmonary vascular resistance (184 ± 13 dyn·s/cm^5; range, 138 to 250 dyne·s/cm^5) with simultaneous elevation of cardiac output (7.4 ± 0.9 l/min; range, 3.2 to 10.6 l/min). The pulmonary capillary wedge pressure in all patients with PPH was equal to or less than 15 mmHg.

Discussion

Pulmonary hypertension secondary to cirrhotic or noncirrhotic portal hypertension (portopulmonary hypertension) has been demonstrated in sporadic case reports all over the world.[14–21] In our series, the incidence of PPH was 3%. This percentage is similar to that reported in the study by Hadengue et al.,[5] but it is higher than a previous estimate.[4] However, this rough approximation may represent an over- or under-estimation. As in the present series and that of Hadengue et al.[5] the estimation was based on hemodynamic measurements. If the patients who underwent hemodynamic measurement were severely ill at the time, the incidence of PPH may have been overestimated. On the other hand, if PPH occurred later during the course of portal hypertension, pulmonary hypertension may not

have been recognized in a number of patients with portal hypertension without regular hemodynamic measurements.

Cirrhosis was the most common cause of portal hypertension in our patients, as it was in the previously reported patients.[5] In our case 10, portal hypertension was a consequence of extramedullary hematopoiesis in the liver brought about by myelofibrosis. This is an uncommon disease that could change intrahepatic circulation in some patients.[22] The initial presentation in case 10 was pancytopenia and severe splenomegaly. Splenectomy was avoided after successful hydroxyurea administration. Complete eradication of his esophageal varices was achieved by endoscopic variceal ligation. He is still alive more than 40 months after diagnosis and is free of other complication of portal hypertension.

Most patients with PPH complained of exertional dyspnea. The main clinical sign of PPH is loud P_2 and an audible systolic murmur. Chest roentgenograms mainly show prominence of the main pulmonary artery and cardiomegaly.[23,24] Electrocardiograms always disclose right ventricular hypertrophy.[24] In our ten patients with PPH, loud P_2 (4/10) and systolic murmur (3/10) were the most common physical findings. On roentgenography, six patients had prominent main pulmonary arteries, and two had cardiomegaly. Consistent with previous reports,[21] pulmonary function tests in three patients showed normal ventilation but low diffusing capacity for carbon monoxide. Moderate pulmonary hypertension, right ventricular hypertrophy, and tricuspid regurgitation were found in the two patients who received echocardiography. The average systemic arterial oxygen saturation in room air was above 90%. In our series, the survival times ranged from 2 to 86 months and most of the patients who died, died of complications related to portal hypertension, but not of complications related to pulmonary hypertension (Table 1). One of the four living patients, case 3, is still alive more than 68 months after the initial diagnosis.

In our previous series of portal hypertensive patients without PPH,[13] the average values for mean pulmonary arterial pressure and mean pulmonary vascular resistance were around 13.7 mmHg and 75.4 dyn·s/cm,[5] respectively. In our present series, these averages were significantly higher, at 28 mmHg and 184 dyn·s/cm,[5] with a high cardiac output, of around 7 l/min, in patients with PPH. Our hemodynamics fulfilled the diagnostic criteria of PPH suggested by Krowka.[6] In contrast, the average values for mean pulmonary artery pressure and mean pulmonary vascular resistance reported by Hadengue et al.[5] were 45 mmHg and 640 dyn·s/cm,[5] and were associated with a lower cardiac output than that in our previous and present series. However, most of their patients had more severe liver disease. It has recently been suggested that the hemodynamic characteristics in cirrhotic patients with pulmonary hypertension may be divided into three types:[7] high flow/hyperdynamic circulation, volume-related, and vasoconstriction. In other words, both elevation and depression of cardiac output can be found in patients with PPH. Kuo et al.[25] have demonstrated distinct hemodynamic features in patients with PPH, including elevated pulmonary pressure and pulmonary vascular resistance, with simultaneous elevation of cardiac output and depression of systemic vascular resistance. Taken together, the hemodynamic values in the current study were typical of the hemodynamic changes in patients with PPH.

Castro et al.[26] reported that pulmonary hypertension occurred in 4% of liver transplant patients and was not found to be associated with a worse survival. Consistent with the series of Castro et al.,[26] most of our patients with PPH who died did not die of complications of pulmonary hypertension. In contrast, a number of patients reported by Hadengue et al.[5] died of complications of pulmonary hypertension, such as heart failure and pulmonary edema. This discrepancy in findings may be attributed to differences in the etiology and severity of cirrhosis. Rather than the viral cirrhosis in our patients, most of the patients reported by Hadengue et al.[5] had alcoholic cirrhosis. It is well established that chronic alcohol consumption may lead to the development of alcoholic cardiomyopathy.[27] It is known that systemic vascular resistance is one of the important modulators of cardiac contractility. In general, systemic vascular resistance is usually in inverse proportion to cardiac output.[28] This suggests that, in the series of Hadengue et al.,[5] the relatively low systemic vascular resistance may have masked left ventricular dysfunction. Left ventricular impairment is predominant only when systemic vascular resistance is increased toward normal, and there is volume or pressure overload.[29,30] It is possible that most of the patients in the series of Hadengue et al.[5] may have had subclinical left ventricular dysfunction. In fact, Estruch et al.[31] reported subclinical left ventricular impairment in patients with alcoholic cirrhosis, and such a subclinical course may be related to early compensation of the cardiovascular system. In addition, in their article, Hadengue et al.[5] suggested that low cardiac output in their patients should be considered as an indicator of a higher risk of complications related to pulmonary hypertension.

Propranolol, a nonselective beta-adrenergic blocking agent, has been proven to substantially decrease portal pressure and reduce the risk of recurrent esophageal variceal bleeding.[32,33] We observed that acute administration of propranolol increased mean pulmonary arterial pressure in one of our cirrhotic patients with portal hypertension associated with PPH (case 7). Bosch et al.[34] have also reported a similar observation

of elevated mean pulmonary arterial pressure after short-term propranolol. Therefore, the serial monitoring of hemodynamic parameters may be mandatory in patients with liver cirrhosis and portal hypertension, especially after propranolol treatment.

In conclusion, the overall incidence of portopulmonary hypertension was 3.1% in our series of patients with portal hypertension. Most of the patients with portopulmonary hypertension experienced exertional dyspnea. In our series, most of the patients who died, died of complications related to cirrhosis and portal hypertension, but not of complications related to pulmonary hypertension. The current study suggested that portopulmonary hypertension was not a frequent complication in patients with cirrhosis and was not associated with an adverse outcome.

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