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CASE REPORT

Intraoperative pulmonary hypertension occurred in an asymptomatic patient with pre-existent liver cirrhotic and portal hypertension

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Abstract

Portopulmonary hypertension (PPH) is clinically defined as the development of pulmonary arterial hypertension complicated by portal hypertension, with or without advanced hepatic disease. Physical signs may be absent in mild to moderate PPH and only appear in a hyperdynamic circulatory state. Similar signs of advanced liver disease can be observed in severe PPH, with ascites and lower extremity edema. Pulmonary hypertension is usually diagnosed after anesthetic induction during liver transplantation (LT). We present intraoperative pulmonary hypertension in a 41-year-old male patient with hepatic cirrhosis. Since this patient had no preoperation laboratory data supporting the diagnosises of pulmonary hypertension and was asymptomatic for a number of years, it was necessary to send him to the intensive care unit after operation. Further study should be focued on the diagnosis and treatment of pulmonary arterial hypertension in order to reduce its mortality.

Key words: Pulmonary hypertension; Liver transplantation; Portal hypertension; Cirrhosis; Hepatitis

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INTRODUCTION

Patients with liver disease are predisposed to develop histological changes in pulmonary vessels, which will cause pulmonary vascular disease, particularly pulmonary hypertension. Portopulmonary hypertension (PPH) is usually regarded as a severe complication of chronic liver disease with portal hypertension and occurs in 5%-10% of patients with advanced liver disease[1]. Direct measurement of pulmonary artery pressure (PAP) by right-heart catheterization (RHC) remains the gold standard for detecting pulmonary hypertension. Doppler echocardiography using trans-tricuspid valve gradient allows noninvasive estimation of pulmonary artery systolic pressure, and is mostly used for liver transplant candidates. However, echocardiography and electrocardiography are seldom performed in patients with mild or moderate PPH[2].

Patients with PPH may be asymptomatic at the time of diagnosis, and symptoms associated with advanced liver disease and portal hypertension may be indistinguishable from those of PPH of any causes[3]. The recognition of PPH requires a high degree of clinical suspicion. Treatment options for patients with PPH are few. Previous studies have shown that cirrhotic patients with moderate to severe pulmonary hypertension have a very high mortality. Patients with severe PPH who undergo liver transplant without vasodilator therapy have an extremely poor survival[4]. However, recent reports indicate that preoperative therapy can reduce pulmonary hypertension and right ventricle dysfunction, thus improving clinical status and making liver transplantation (LT) feasible[5-7]. However, pro-operative therapy is not efficient for portal hypertension (PHT). There

is no doubt that the occurrence of non-pulmonary manifestations of perioperative pulmonary hypertension presents management challenges. This report describes our new experience with the management of portal and pulmonary hypertension.

CASE REPORT

A 41-year-old male patient with end-stage liver disease secondary to alcohol and hepatitis B was referred to our department for LT. Over the previous 10 mo, the patient had ariceal bleeding, increasing jaundice, and ascites. Cutaneous spider naevi were present and his fingertips were clubbed. He refrained from smoke five years ago due to chronic active hepatitis B and denied to have prior pulmonary problems. Pulmonary and cardiac examinations were unremarkable. Chest radiography showed normal main and central pulmonary arteries. Electrocardiogram was within the normal range with no evident signs of pressure overload of the right atrium and ventricle. Lung function tests showed a mild restrictive pattern that was ascribed to ascites. Total lung capacity, FEV1 and FVC were in normal range. Urinalysis was negative. His liver function tests were as follows: 101 μmol/L total bilirubin with a direct fraction of 50 μmol/L, 113 U/L alkaline phosphatase, 112 U/L ALT and 83 U/L AST. The end-stage liver disease score was 24. PCR showed that His viral profile was HBsAg (+), anti-HBs (-), HBeAg (-), anti-HBe (+), anti-HBc (+) and HBV DNA < 10^3 copies/mL. He received 4 wk of lamivudine therapy.

Following our usual protocol for monitoring LT recipients, routine intraoperative transesophageal echocardiography was performed during LT[8]. The pulmonary artery was a moderately enlarged. His systolic PAP was higher than 53 mmHg, pulmonary capillary wedge pressure (PCWP) was 10 mmHg, cardiac output (CO) was 7.4 L/min), pulmonary vascular resistance (PVR, 201 dyn·s·cm^{-5}) was higher than the usual values observed in cirrhotic patients[9]. To reduce the increased PAP, the patient administrated nitric oxide (40 ppm) and epoprostenol (40 μg). However, no notable reduction was found in the mean PAP (mPAP). Epoprostenol therapy was continued with its dose increased from 6 to 20 ng/kg per min. One hundred percent of oxygen was then administered before liver dissection. Then the PAP came down slowly. LT was performed using the "piggyback technique", a standard procedure without venovenous bypass[8]. The anhepatic phase lasted 78 min and reperfusion was tolerated without any significant incident. Immediately after the liver was reperfused, PAP increased to a maximum of 75 mm Hg (60% of systemic level) and terribly reflow was present in the graft. About 10 min later, PAP decreased to less than 40% of systemic level (Table 1).The speed of dobutamine infusion was increased to 3-5 mg/kg per min for continuous inotropic and pulmonary vasodilator effect. The color of graft became normal after 30 min. PVR was only slightly increased, but the mean PAP was markedly increased due to a profound increase in cardiac output. After haemostasis, further surgery was completed uneventfully. At the end of surgery, haemodynamics of the patient was stable. The total operative time was 8 h. The estimated blood loss was 3346 mL, so that the patient was transfused 10 U of packed red blood cells and 30 U of fresh-frozen plasma. Immunosuppression was initiated with cyclosporin, mycophenolate mofetil, and steroid was withdrawn followed by maintenance of immunosuppression with cyclosporin and mycophenolate mofetil.

During the following 24 h in the intensive care unit (ICU), haemodynamics was mildly increased in PVR which was reduced when pulmonary vasodilators (nitroglycerin, isoprenaline, epoprostenol) were used. At this time, mPAP was 35 mmHg. The patient was extubated with dobutamine discontinued approximately 20 h after surgery. PaO_2 was 9.2 kPa, $PaCO_2$ was 6.2 kPa, and HCO_3^{-2} was 8 kPa (pH 7.36) after extubation. Graft function was remarkable following a continuous decrease in transaminases and prothrombin time (PT 50%). The post-transplant viral prophylaxis included HBIG (10 000 U/d) during the anhepatic period and lamivudine (100 mg/d) in the morning of postoperative day 1[10]. On the 7th postoperative day, the patient was transferred to the normal ward. Three weeks later, the liver function was recovered with normal transaminases and PT. In the follow-up, pulmonary function, chest X-ray and pulmonary angiography showed no evidence of pulmonary hypertension.

In January 2008, almost 2 years after LT, the patient was still in good condition and had no signs of pulmonary hypertension. A Doppler echocardiogram showed that the size right and left ventricles was normal. The viral profile of the patient was not good after transplantation with persistent positive HBsAg and negative anti-HBs and HBV DNA.

DISCUSSION

PPH is defined as mPAP ⩾ 25 mmHg and PCWP ⩽ 15 mmHg with evidence of portal hypertension. It was reported that 60% of patients with PPH are asymptomatic at the time of diagnosis, and symptoms associated with advanced liver disease and portal hypertension may be indistinguishable from those of PPH[3]. Therefore, the diagnosis of PPH is frequently established in the operating room before the transplantation procedure. Some of these patients may have mPAP exceeding 25 mmHg, but they do not have the associated pathological changes in the pulmonary vasculature that increase the mortality[11]. Some right heart catheterization information is derived from the operating room during general anesthesia[12]. Pulmonary pressure tends to increase during the initial stage of anesthesia. Our patient's pulmonary hypertension was atypical before operation and revealed pulmonary hypertension after inhaling anesthesia. Since inhalational anesthetic agents can independently increase venous return, central filling and cardiac output can be achieved in patients with portal hypertension[13].

Table 1 Intra- and post-transplantation cardiopulmonary hemodynamic data

Time	mPAP (mmHg)	PVR (dyn·s·cm^{-5})	Therapeutic agents
Before clamp	35	254	Epoprostenol, NO, 100% O_2
Anhepatic	40	340	Epoprostenol, 100% O_2
Reperfusion (15 min)	40	NA	Epoprostenol and milrinone, adrenaline
Enter ICU	30	NA	Epoprostenol
24 h-pro	35	240	Epoprostenol and isoprenaline
48 h-pro	30	211	Epoprostenol and isoprenaline

LT: Liver transplantation; mPAP: Mean pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; NO: Nitric oxide; NA: Not applicable.

Until now, the treatment options for patients with PPH are few, and the reported mean survival time of PPH patients after diagnosis is approximately 15 mo[14]. Nitric oxide, prostacyclin and isosorbide-5-mononitrate have been administered to improve PAP before and after LT[15]. Because of the association of portosystemic shunting with pulmonary hypertension, LT cannot cure both portal hypertension and PHT. LT is well tolerated in patients with only mild or moderate PPH. The mortality rates of patients with or without PPH after operation are comparable[16]. Since the risks in patients with severe PHT appear to be unacceptably high, and the affected patients deny LT, the marked reduction in PAP after epoprostenol therapy for patients with severe PPH may result in a marked decrease in perioperative mortality after LT[17]. PAP in this patient was steadily increased vasodilator therapy. This patient had a significant response to intravenous epoprostenol and the nitric oxide was also inhaled to test the reversibility of mPAP during operation. Continuous use of pulmonary vasodilators (isoprenaline, epoprostenol) reduced his PVR. Pulmonary hypertension may exacerbate after operation when patients receive no epoprostenol, and the patients may die of right ventricle failure[4]. Improvement in and de novo development of PPH may occur following LT[18-20]. The reason why transplant patients develop pulmonary hypertension following transplantation is unknown[13].

It was reported that transplant mortality is 36% (13/36) in patients with PPH[21]. Evidence from two studies suggests that preoperative mPAP is an independent predictor of mortality[6,22]. Another study showed that mPAP is not an accurate predictor of mortality and that pressure measurement does not serve as an independent surrogate of the severity of disease or outcome[23]. The marked difference in outcome suggests that single hemodynamic variables are not related with mortality in patients with PPH. In the literature, death of patients with PPH undergoing LT often occurs in the postoperative period due to cardiocirculatory stress or infectious complications[1,24,25]. Alternatively, defective hepatic metabolism and portosystemic shunting may expose the pulmonary vasculature to proliferating, vasoconstrictive, or inflammatory compounds that accelerate the progression of pulmonary arteriopathy or right ventricular failure[25]. Safer strategies for LT in patients with asymptomatic PPH can reduce the mortality rate. Our current strategies are as follows. (1) Right heart catheterization should be done pre-operation when PPH is suspected; (2) pulmonary vascular resistance should be decreased with intravenous epoprostenol therapy after diagnosis of PPH; (3) nitric oxide, epoprostenol, calcium channel blockers and other agents should be used during perioperation[26]; (4) venovenous bypass or piggy back technique that allows a more restrictive volume replacement during the anhepatic phase should be used.

In conclusion, asymptomatic PHT is not a contraindication to LT, and some of PHT patients may survive many years after LT. Patients with asymptomatic PHT who might benefit from LT need to be better characterized, and reliable screening methods to identify these patients need to be developed.

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