Hepatopulmonary syndrome (HPS) consists of a triad of liver dysfunction, intrapulmonary vascular dilatation, and hypoxemia [1, 2]. The hypoxemia is characterized by an increased alveolar-arterial oxygenation gradient of more than 20 mm Hg at rest, either in the supine or standing position [1, 2]. Many diagnostic modalities have been used to study HPS, including arterial blood gas measurements, contrast echocardiography, lung perfusion scan with $^{99m}$Tc macroaggregate albumin, and pulmonary angiography [3, 4].

The cause of hypoxemia in advanced liver disease has been attributed to several mechanisms, including right-to-left intrapulmonary shunting, alveolar-to-capillary diffusion defect, and alveolar ventilation-perfusion mismatch, although the exact etiology is unknown [5]. Severe hypoxemia resulting from HPS was previously considered a contraindication to liver transplantation [6–8]. However, recent reports have challenged the notion that HPS can be reversed after successful liver transplantation [9–14]. In this report, we describe a young girl with end-stage liver disease complicated with HPS. The hypoxemia associated with HPS resolved after successful living donor liver transplantation (LDLT). This is the first reported case of HPS successfully treated with liver transplantation in Taiwan.

**Case Report**

A 6-year-old girl with biliary atresia was admitted for pre-liver transplantation evaluation. She had undergone a Kasai procedure at the age of 56 days. After the Kasai procedure, her course was complicated with progressive hepatosplenomegaly, jaundice, ascites, and esophageal variceal bleeding. In addition, dyspnea on exertion and cyanosis were noted 6 months prior to referral for transplantation.
Discussion

HPS is a pulmonary vascular complication of liver disease. The syndrome most commonly develops in association with any cause of portal hypertension or cirrhosis. The clinical presentation of HPS includes exertional dyspnea and platypnea, digital clubbing, and apical cyanosis, concomitant with the findings of chronic liver disease, such as hepatomegaly, ascites, and cutaneous spider nevi [5]. The outcome of HPS in children without liver transplantation is poor, with a mortality of up to 48% [15]. The causes of death in these patients include multiple organ failure, respiratory failure, liver failure, infection, intracranial hemorrhage, pulmonary hemorrhage, and portal vein thrombosis [15].

HPS was initially considered a contraindication to liver transplantation, especially in patients with severe hypoxemia [6–8]. In the subset of liver recipients with a preoperative PaO₂ of less than 50 mm Hg on room air, the surgical mortality rate was 30% [9]. It has recently been reported that HPS with severe hypoxemia may resolve after successful liver transplantation. Several reports have documented complete reversibility of intrapulmonary vascular dilatation and improvement in oxygenation following liver transplantation, despite severe hypoxemia preoperatively [9–14]. However, there was still a 38% mortality rate [16], and prolonged mechanical ventilation might be required after liver transplantation [9]. In the present case, the postoperative course was uneventful except for a short period of hypoxemia, which required resumption and maintenance of oxygen supplementation until postoperative...
Fig. 2. Perfusion scan with $^{99m}$Tc macroaggregate albumin. (A) A 24% intrapulmonary shunt before liver transplantation. Uptake over brain, liver, spleen, and kidneys suggests abnormal passage through the pulmonary vascular bed. (B) Absence of extrapulmonary trapping of macroaggregate albumin 1 year after liver transplantation.

day 14. Since the main cause of death in HPS is refractory hypoxemia and/or multiple organ failure secondary to hypoxemia [9], successful management of postoperative hypoxemia is important to survival after liver transplantation.

Lung scan using technetium-99-labeled MAA is a reliable diagnostic test for intrapulmonary shunting [17]. The albumin aggregates, having a diameter greater than 20 $\mu$m, are normally trapped in the pulmonary capillaries and the lungs take up the majority of the isotope. In the presence of intrapulmonary shunting, however, the labeled isotope is not trapped totally in the pulmonary capillary bed and is taken up in other organs such as the brain, kidneys, and liver, as in the present case.

Contrast echocardiography is another useful modality for the detection of intrapulmonary shunts [18]. In patients with a cardiac septal defect, microbubbles can often be seen entering the left heart chamber immediately after their appearance in the right heart chamber, usually in one to two cardiac cycles. On the other hand, in patients with intrapulmonary shunting, microbubbles from the pulmonary veins appear in the left atrium after a time delay of at least three cardiac cycles [18].

Pulmonary angiography is helpful in delineating the pulmonary vascular abnormalities that can have a prognostic significance in HPS. There are two angiographic patterns in HPS: type I, diffuse (minimal or advanced), and type II, focal involvement [5]. The minimal type I pattern shows a normal to finely diffuse spidery vascular abnormality in the arterial phase, while the advanced type I pattern shows a diffuse, spongy, or blotchy appearance. The minimal type I pattern is usually associated with reversibility while the advanced type I or type II patterns are not [3, 19]. Thus, the anatomic variation of intrapulmonary vascular dilatation appears to be a good determinant of success after liver transplantation. However, prospective large series studies of HPS patients are needed to verify the correlation between angiographic type of lesion and reversibility of HPS after transplantation.

Other predictors of reversibility of HPS after liver transplantation are degree of hypoxemia and response to 100% oxygen. Patients with mild to moderate hypoxemia and marked increase in $\text{PaO}_2$ after 100% oxygen supplementation were associated with better outcomes than those with severe hypoxemia [20]. Therefore, it is recommended that patients with severe hypoxemia or poor response to 100% oxygen be further evaluated.
with pulmonary angiography. If pulmonary angiography demonstrates a minimal type I pattern, as in our patient, there is a greater chance that severe hypoxemia could be reversed with successful liver transplantation [21].

In summary, HPS is no longer considered a contraindication for liver transplantation. The decision to perform liver transplant in HPS patients should be based on prognostic factors including response to 100% oxygen supplementation and the angiographic picture of the intrapulmonary shunting. The minimal type I pattern is associated with better outcome than the advanced type I or type II patterns, which should probably be considered contraindications to liver transplantation, because patients with these patterns have a much worse prognosis. Early diagnosis of HPS and identification of risk factors is vital in children with end-stage liver disease, as liver transplantation may lead to complete regression of shunting and improvement in quality of life. Although complete resolution of HPS is possible after liver transplantation, such a result is by no means attainable without substantial risk.

References