CASE REPORT

Liver Transplantation in a Patient with Pulmonary Hypertension at High Altitude

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Chronic hypoxia at high altitude stresses many of the body's homeostatic mechanisms. As a consequence, the body develops alveolar hypoxia, hypoxemia, and polycythemia, which in turn causes vasoconstriction, pulmonary hypertension, and an increased risk of atherothrombotic complications. We report a successful liver transplantation in a patient with pulmonary hypertension who lives 4500 m above sea level. Pulmonary hypertension and hypercoagulable state induced by chronic hypoxia at high altitude may increase the risk of cardiopulmonary complication and perioperative mortality. The patient was discharged in good condition with normal liver function at the 34th postoperative day. After 41 months of follow-up, the patient is alive and well with a continued normalization of hepatic function and is continuing to live at 4500 m above sea level.

Key words: high altitude, liver transplantation, pulmonary hypertension, hypercoagulation, hypoxia

Introduction

Individuals living permanently at high altitude (HA) must contend with chronic hypobaric hypoxia. Some highlanders develop high pulmonary arterial pressure and chronic mountain sickness.¹ Surgical trauma at HA has a greater risk of acidosis and severe damage to the lung and brain than it does at sea level.^{2,3} Furthermore, hypoxia-mediated cell damage will generate an inflammatory response, further perpetuating the cascade of critical illness.¹ Severe pulmonary hypertension (PH) has been associated with perioperative mortality rates between 70% and 100%.^{4,5} We report a successful liver transplantation in a patient with PH who lives 4500 m above sea level. The liver graft was harvested at sea level and transferred to our surgical facility at 3658 m above sea level. Long-term hypoxemia and low blood partial pressures of oxygen (Po_2) of the patient after transplantation delayed the recovery of liver function from ischemia-reperfusion injury.

Case Report

The 45-year-old patient who presented with end-stage liver disease secondary to hepatitis B-related cirrhosis was listed for orthotopic liver transplantation (OLT) in October 2005. Symptoms and clinical signs included esophageal varices, fatigue, hyperbilirubinemia, hypoalbuminemia, and exertional dyspnea. The native Tibetan patient was B blood type, with a Model for End-Stage Liver Disease score⁶ of 21. The hemoglobin level was 168 g/L. Prothrombin time and activated partial thromboplastin time remained normal. Transthoracic echocardiogram revealed right ventricular hypertrophy. At the time of liver transplantation, pulmonary artery catheterization revealed a pulmonary artery pressure (PAP) of 62/28 mm Hg, and a mean pulmonary artery pressure (MPAP) of 39 mm Hg. The PAP decreased to 57/25 mm Hg after prostaglandin E1 ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$) infusion and 100% oxygen inhalation. As the PAP slightly decreased in response to pharmacologic treatment, the patient subsequently underwent orthotopic liver transplantation using a piggyback technique for venous outflow reconstruction to avoid caval flow disruption and potential right ventricular overload upon reperfusion. Veno-venous bypass was not used. A standard choledochocholedochostomy was used for biliary reconstruction. Prostaglandin E1 was con-

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tinued throughout the procedure. Pulmonary artery pressure throughout surgery remained manageable without right heart dysfunction or exacerbation on reperfusion. After the graft recovered blood perfusion, PAP decreased to 43/23 mm Hg, and blood pressure was 85/55 mm Hg. The patient was extubated on postoperative day 1 and continued to recover uneventfully. Pulmonary artery pressure remained in the mild to moderate range. Minor postoperative complications, including hypoxemia and mild intra-abdominal bleeding caused by heparin overdose secondary to overcorrecting for possible hypercoagulation, were successfully treated. There was no acute rejection episode during the postoperative course. The patient was eventually discharged in good condition with normal liver function on the 34th postoperative day, returning to his pretransplant daily activities. The patient tolerated daily activity well, though mild exertional dyspnea was noted at times. He continues to live at home in the Naqu region of Tibet, located at 4500 m above sea level. Up to the present, the patient is alive and well with persistent normalization of hepatic function during 41 months of follow-up.

Discussion

This report describes a liver cirrhosis patient with moderate PH who successfully underwent liver transplantation at HA. The hospital is situated at 3658 m above sea level, and the patient lived in the Naqu region of Tibet, which is more than 4500 m above sea level. Atmospheric pressure averages 448 mm Hg, and oxygen pressure in the air is only 84 mm Hg (at sea level it is generally 149 mm Hg). To our knowledge, this is the first case of a patient living more than 4500 m above sea level undergoing liver transplantation. The patient endured major abdominal surgery and rehabilitated to normal life and activity, although inhospitable HA environments and systemic changes during adaptation to hypoxia increased the risk of surgical complications and mortality.

People native to HA environments live in an environment of hypobaric hypoxia with low ambient partial pressure of oxygen. In HA environments, such as in the Naqu region of Tibet, the barometric pressure and partial pressure of oxygen are decreased and equal to only 56% of their values at sea level. Several compensatory mechanisms have evolved to enable these people to live and work in this inhospitable environment.⁷ It is estimated that between 5% and 10% of 4300-m HA inhabitants may develop chronic mountain sickness or PH.⁸ High-altitude adolescents and adults had a mean value of pulmonary artery pressure of 28 mm Hg $\pm$ 10.5 in contrast with 12 mm Hg $\pm$ 2.2 in sea-level residents.⁹ Pulmonary hypertension is also an uncommon syndrome in patients with end-stage liver disease and portal hypertension, but the exact mechanisms leading

to this vascular abnormality are unknown.¹⁰ The main factor may be release of vasoactive compounds from the splanchnic circulation, which are not metabolized by the liver, subsequently reaching the pulmonary circulation. An imbalance between pulmonary vasodilators and vasoconstrictors may promote pulmonary arterial hypertension. Whenever the constrictive factors are elevated and depart from balance, smooth muscle cell proliferation, vasoconstriction, vascular remodeling, and thrombosis are provoked. An aberrant pulmonary endothelial activity from dysfunctional regulation of the pulmonary vascular tone in the presence of a hyperdynamic state may cause PH.¹¹ Both hypobaric hypoxia and end-stage liver disease may aggravate PH. Pulmonary hypertension is classified as mild when the MPAP is between 25 and 35 mm Hg, moderate when MPAP is between 36 and 50 mm Hg, and severe when MPAP exceeds 50 mm Hg. Mild or moderate PH has been associated with an increased risk for death, particularly if right ventricular function is decreased.¹² Because of the high mortality, many liver transplantation centers consider patients with moderate or severe PH to be high-risk surgical candidates. However, when liver transplantation is the only way to save lives, it has been successfully done in patients with moderate to severe PH.^{12,13} A few therapeutic options have been proposed to manage PH in patients receiving liver transplantation. Inhaled nitric oxide or infusion of prostaglandin E1, epoprostenol, L-arginine, diltiazem, or nitroglycerin can be carefully administered to decrease PAP without causing systemic hypotension.¹⁴ Prostaglandin E1 and epoprostenol are endogenous prostaglandins with potent vasodilatory effects and similar structures and properties. Both prostaglandin E1 and epoprostenol are effective vasodilators, producing a decrease in systemic and pulmonary vascular resistance.¹⁵ In this case report, we have successfully used prostaglandin E1, via continuous intravenous infusion, with significant improvements in hemodynamic status through the course of OLT.

Hypoxia alters the coagulation cascade to create a prothrombotic milieu. Many types of thrombotic pathology have been reported at HA, including ischemic stroke, transient ischemic attack, portal system thrombosis, and deep venous thrombosis with and without pulmonary embolism.^{16–18} Erythrocytosis and hyperviscosity are known to activate platelets.¹⁹ Hypoxic stress and injury to platelets or endothelium may be the thrombogenic stimulus causing platelet activation.²⁰ Reports have shown that remaining at HA leads to an increased propensity for thrombosis. Indian soldiers exhibited a 30-times higher incidence of thrombosis after a long-term stay at HA.²¹ Our patient showed significant hypercoagulation after liver transplantation. Blood coagulation function and liver function should therefore be monitored closely. Heparin was administered after the operation to maintain both prothrombin time and acti-

vated coagulation time at around 18 to 22 seconds and 170 to 200 seconds, respectively. Although hypocoagulation and bleeding complications in liver transplant recipients are major clinical problems, the focus in OLT patients at HA should be on preventing thromboembolism.^{22,23} The balance between thrombosis and bleeding seems much more precarious in transplant patients at higher altitude than at sea level.

The liver graft was harvested at sea level and then transferred to the hospital located at 3658 m. Cold storage time was 10 hours. After extubation on postoperative day 1, the blood Po_2 of the recipient decreased to 46 mm Hg and did not rise above 60 mm Hg for 56 hours. The liver function tests showed slow decrease of transaminases and bilirubin. The graft endured long-term hypoxemia. The influence of hypoxemia on liver graft function at HA is unclear. Hepatic hypoxia during resuscitation and other critically ill conditions, such as liver transplantation, is a serious cause of acute hepatic failure. Savransky et al reported that hypoxia causes liver injury, oxidative stress, and excessive glycogen accumulation in the liver. Liver injury in the isolated perfused rat liver after hypoxia has been shown predominately in the centrilobular zone. Serum levels of hepatic enzymes may increase and ultrastructural changes appear in the centrilobular liver cells probably because the centrilobular zone of the hepatic acinus has the lowest oxygen concentration.²⁴ Cytotoxicity caused by hypoxia is generally attributed to the consequences of drastic ATP depletion.²⁵ Further studies should be performed to determine the effect of HA on the pathophysiologic changes of liver grafts.

In conclusion, we report a successful liver transplantation in a patient with PH who lives 4500 m above sea level. Follow-up over the course of 41 months revealed the patient to be tolerating daily activity quite well with normal hepatic function. A multidisciplinary, well-planned approach to the preoperative, intraoperative, and postoperative evaluation and treatment of these patients is necessary to maximize the opportunity for a favorable outcome.

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