

Pulmonary Artery Hypertension Complicating Anesthesia for Liver Transplantation

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Primary pulmonary artery hypertension is an uncommon but difficult management problem that has not been addressed in liver transplant patients. We report a case in which pulmonary arterial hypertension was associated with a fatal outcome after orthotopic hepatic transplantation.

CASE REPORT

A 41-yr-old woman was referred for orthotopic hepatic transplantation. She had end-stage liver disease due to autoimmune chronic active hepatitis that had been diagnosed over 20 yr previously. She had been receiving long-term corticosteroids for immunosuppression and propranolol prophylaxis for esophageal variceal bleeding. Because of further deterioration in hepatic function reflected by increasing ammonia levels and worsening of hepatic encephalopathy, the patient was considered a candidate for urgent transplantation.

This patient's past medical history was positive for palpitations and atypical chest pain that was not brought on by exertion or accompanied by shortness of breath. Propranolol was being taken for variceal bleeding prophylaxis and hypertension. One month prior to operation, the patient suffered a fall resulting in closed cranial trauma. Magnetic resonance imaging revealed periventricular punctate hemorrhages without mass effect. She made a good recovery with only mild left-sided hemiparesis and was alert and oriented at the time of operation. She was receiving oral penicillin for a resolving bronchitis.

General physical assessment showed a 70-kg woman who appeared slightly older than her stated age and who was in no apparent distress except for a dry cough. Physical examination was significant for clear lungs and a regular heartbeat with grade II/VI systolic murmur, loudest in the third and fourth intercostal space in the left parasternal region and radiating to the axilla, consistent with tricuspid insufficiency. Muscle weakness was noted in the left lower extremity. Preoperative pulmonary function tests showed a vital capacity of 4 l (> 100% predicted), forced expiratory volume in one second of 2.9 l (100% predicted), forced expiratory flow at 25-75% volume of 2.1 l (>100% predicted), total lung capacity of 4.6 l (83% predicted), functional residual capacity of 1.8 l (60% predicted), residual volume of 0.6 l (33% predicted), and diffusion capacity of 14 mg · min⁻¹ · mmHg⁻¹ (65% predicted). Electrocardiogram (ECG) showed small Q waves in leads II and III, unchanged in the past 3 yr. Chest radiograph revealed normal cardiac outline and clear lung fields with possibly enlarged main pulmonary arteries. Laboratory data were hematocrit 43%, prothrombin time 14.2

s (normal = 10.5-12.5 s), partial thromboplastin time 31.2 s (normal = 23.0-30.5 s), platelet count 92,000 · mm⁻³, antithrombin III level 35% (normal = 79-127), sodium 140 mEq · l⁻¹, potassium 4.8 mEq · l⁻¹, chloride 105 mM, bicarbonate 22 mEq · L⁻¹, creatinine 0.8 mg · dl⁻¹, blood urea nitrogen 11 mg · dl⁻¹, total bilirubin 3.1 mg · dl, and ammonia 110 μM (normal = 11-35 μM). A dipyridamole-thallium stress test showed normal distribution and no evidence of myocardial ischemia, and an echocardiogram demonstrated a dilated right atrium, an enlarged right ventricle, and a normal left ventricle with slight mitral and moderate tricuspid and pulmonary valve regurgitation.

Following our usual protocol for monitoring liver transplant recipients, pulmonary artery and radial artery catheters were inserted. Initial hemodynamic measurements were cardiac output of 8.0 l · min⁻¹, pulmonary artery pressure (PAP) of 80/36 mmHg, mean PAP of 53 mmHg, central venous pressure of 6 mmHg, pulmonary artery occlusion pressure (PAOP) of 9 mmHg, heart rate of 81 beats · min⁻¹, and systemic blood pressure (BP) of 131/69 mmHg. Systemic vascular resistance (SVR) was 874 dyn · s · cm⁻⁵, pulmonary vascular resistance (PVR) was 442 dyn · s · cm⁻⁵, and cardiac index was 4.4 l · min⁻¹ · m⁻².

At this time, separate consultations with the surgeon and the patient were conducted to address the increased risk of her (previously undiagnosed) pulmonary hypertension. Because this was thought to be a well-compensated chronic process based on patient history, ECG, and echocardiography findings, and because there was little hope of long-term survival without orthotopic liver transplantation, all parties agreed to proceed.

Induction of anesthesia with fentanyl and thiopental and maintenance with isoflurane and fentanyl were accompanied by hemodynamic stability. Neuromuscular blockade was accomplished with pancuronium. Venovenous bypass was established before the transplant procedure was begun. The new liver was revascularized without adverse hemodynamic effects. During this time, PVR was responsive to intravenous nitroglycerin infusion; 0.25 μg · kg⁻¹ · min⁻¹ decreased PVR to 250 dyn · s · cm⁻⁵ without affecting systemic BP.

Hemodynamic stability continued until closure of the wound, when a precipitous increase in PAP occurred, from 55-60/30-35 mmHg to > 100/60 mmHg. Systemic systolic BP decreased to < 40 mmHg with loss of carotid pulse, and ECG changes suggestive of lateral wall myocardial ischemia occurred. Cardiopulmonary resuscitation (CPR) was started, and intravenous epinephrine was administered. CPR continued for less than 2 min, at which time BP and a palpable pulse returned. Lidocaine was administered for ventricular tachycardia, which occurred after CPR, and 5 μg · kg⁻¹ · min⁻¹ dopamine was used for continued inotropic and systemic BP support along with increased nitroglycerin infusion at 0.5-1.0 μg · kg⁻¹ · min⁻¹ for pulmonary vasodilation. Approximately 5 min after CPR, the ECG showed sinus tachycardia with normal ST segment in the lateral leads. Systemic BP was 100/57 mmHg, heart rate 103 beats · min⁻¹, cardiac index 3.8 l · min⁻¹ · m⁻², PAP 79/44 mmHg, mean PAP 57 mmHg, PAOP 6 mmHg, central venous pressure 6 mmHg, SVR 746 dyn · s · cm⁻⁵, and PVR 537 dyn · s · cm⁻⁵.

The patient was transferred to the surgical intensive care unit, where she regained full consciousness within a few hours; tracheal intubation was maintained. Approximately 12 h after surgery, there was a sudden increase in PAP to 120/50 mmHg associated with a decrease in systemic BP to 70/40 mmHg and loss of consciousness. In response to 250 ml

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5% albumin and the addition of a dobutamine infusion, systemic BP increased to approximately 80/50, and PAOP increased from 6 to 9 mmHg. However, PVR increased to 800–850 $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$. Again, the patient regained consciousness. A slow, steady increase in PVR occurred that was unresponsive to nitroglycerin. Prostaglandin E_1 (PGE_1) was started and nitroglycerin gradually discontinued. At doses of PGE_1 greater than $0.05\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, the patient's systemic BP was unacceptably low. Eighteen hours after the end of surgery, PVR exceeded $1,000\ \text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$. PAP was 100–130 mmHg systolic. Throughout this period, arterial blood gas analyses and oximetry indicated adequate oxygenation. Episodes of systemic hypotension began to occur frequently, during which the patient had severe crushing chest pain and ECG evidence of myocardial ischemia. PGE_1 was stopped and epinephrine and norepinephrine infusions started, but low systemic pressures and cardiac output were unresponsive. Finally, cardiac arrest occurred, from which the patient could not be resuscitated.

Post mortem examination revealed right ventricular hypertrophy and thickened pulmonary artery walls but no evidence of pulmonary emboli.

DISCUSSION

Primary pulmonary hypertension has been reported in patients with liver failure from cirrhotic and noncirrhotic portal hypertension. McDonnell *et al.*¹ showed a 0.13% incidence of pulmonary hypertension in an unselected series of 17,901 autopsies *versus* a 0.73% prevalence among patients with cirrhosis. In a prospective study of 507 consecutive patients with portal hypertension who underwent cardiac catheterization, 2% of these patients, all asymptomatic, had evidence of primary pulmonary hypertension, defined as mean PAP ≥ 25 mmHg, PAOP ≤ 13 , and no evidence of underlying cardiac or pulmonary disorders.² Several putative mechanisms have been proposed as the cause of pulmonary hypertension in patients with portal hypertension. The major mechanisms are thought to be repeated microembolization to the pulmonary arteries,^{3,4} unidentified humoral pulmonary vasoconstrictor substances originating from the gut and escaping hepatic clearance,^{5,6} and a hyperkinetic systemic circulation.^{7,8}

Case reports suggest that anesthesia and surgery in patients with pulmonary artery hypertension are associated with a high mortality if PAP and PVR increase and right ventricular decompensation occurs.^{9,10} Patients with pulmonary artery hypertension underlying liver transplantation are at especially high risk for acute increases in PAP and PVR with sudden changes in intravascular volume from blood loss, clamping of large vessels, and use of vasoconstrictors.

Increased awareness of the association between portal hypertension and pulmonary artery hypertension is necessary because severe and even irreversible pulmonary hypertension may occur in the absence of symptoms. Routine preoperative diagnostic tests may indicate the possibility of severe pulmonary artery hypertension, despite the absence of symptomatic disease. This patient's chest radiograph and ECG had many of the findings consistent with significant pulmonary artery hypertension.

The chest radiograph will often show enlargement of the main and hilar pulmonary arteries and rapid tapering of the peripheral pulmonary arterial branches.¹¹ Large P waves in leads II, III, and AVF, with tall R waves in V1–V3 and S wave in V6, can be seen on ECG.¹¹ One common finding, not seen in this case, is a mild restrictive pattern on pulmonary function tests because of decreased pulmonary compliance from increased PAP.¹² Echocardiography can provide information on valvular pathology, pulmonary artery blood flow, and cardiac chamber size and function. This patient showed evidence of long-standing increase in PAP¹³ with an enlarged right ventricle and dilated right atrium. Tricuspid regurgitation is seen frequently, even in the absence of tricuspid regurgitation murmur or abnormality in the jugular venous pulse. Echocardiography/Doppler findings, such as pulmonary peak flow velocity, may also provide information on pulmonary resistance and compliance, although this specific examination was not performed in this case.¹⁴

If significantly increased PAP is present, an attempt should be made to decrease it as much as possible without causing systemic hypotension. Experience from the National Institutes of Health Registry on primary pulmonary hypertension¹⁵ indicates that hydralazine, nifedipine, nitroglycerin, nitroprusside, and prostacyclin (which is not clinically available) are the most frequently used vasodilators, although none is consistently effective. Prostacyclin resulted in the greatest pulmonary vasodilation with the least systemic hypotension. Nitroglycerin and nitroprusside were more likely to cause systemic hypotension, while hydralazine had the least effect on pulmonary vasodilation and resulted in the largest decrease in SVR.¹⁵ Nevertheless, Rich and Brundage¹⁶ showed enhanced survival in patients treated with nifedipine. In addition, Rich *et al.*¹⁷ showed that a $> 20\%$ reduction in PVR in response to vasodilator therapy (nifedipine and/or hydralazine) was a predictor of longer survival. Fewer than 25% of nonresponders survived as long as 4 months, whereas more than 50% of patients who responded to short-term vasodilator therapy and were subsequently placed on long-term therapy survived longer than 14 months. In addition, a national prospective registry of patients with primary pulmonary hypertension estimated median survival of 2.9 yr for untreated patients and 3.8 yr for those receiving vasodilator therapy.¹⁸ In that study, variables associated with decreased survival included a New York Heart Association functional class III or IV, presence of Raynaud's phenomenon, elevated mean right atrial pressure, elevated mean PAP, decreased cardiac index, and decreased diffusing capacity for carbon monoxide. One recent development is the use of inhaled nitric oxide in patients with pulmonary hypertension.¹⁹ Nitric oxide proved to be as effective as intravenous prostacyclin in decreasing PVR without affecting SVR.

Since the availability of livers for transplantation is not predictable, patients waiting for liver transplants with signs, symptoms, or diagnostic tests consistent with pulmonary artery hypertension should be admitted for a preoperative trial of vasodilators. The placement of a pulmonary artery catheter is necessary to monitor PAP, PAOP, and cardiac output during vasodilator trials. An intraarterial catheter is recommended because systemic pressures may change rapidly with the infusion of various vasodilators. The use of a right ventricular ejection fraction pulmonary artery catheter (Baxter Health Care Corp., Edwards Critical Care Division, Irvine, CA) may be especially helpful because it can also provide information on right ventricular volumes as well as right ventricular ejection fraction. If the patient can be tested early enough and is responsive to nifedipine or nitroglycerin, oral therapy can be initiated.

Vasodilator therapy may have limited value in patients with long-standing pulmonary artery hypertension because prolonged vasoconstriction can induce morphologic changes such as intimal proliferation and fibrosis with medial and possibly adventitial hypertrophy and result in a fixed obstruction. If increased PAP is unresponsive to vasodilator therapy, the patient should be reevaluated as a candidate for liver transplantation because of the increased intraoperative risk and high mortality rate of pulmonary artery hypertension, even without surgery.

In our patient, pulmonary artery hypertension was probably a chronic process, as evidenced by right ventricular hypertrophy and limited response to nitroglycerin and PGE₁ therapy. Also demonstrated by our patient was a marked increase in PAP shortly after liver transplantation, which may be a particular problem with this patient population. It is possible that vasoconstrictor substances that can increase pulmonary hypertension, such as serotonin, bradykinin, and histamine, are not as rapidly metabolized in the newly transplanted liver, especially if rejection is occurring.

Isoflurane is a well-accepted agent for maintenance anesthesia in patients undergoing liver transplantation.²⁰ Isoflurane has also been suggested as a safe anesthetic for patients with pulmonary artery hypertension. In one patient, Cheng and Edelist²¹ documented the ability of isoflurane to reduce mean PAP by 25% without causing systemic hypotension, increased heart rate, or depression of cardiac output. Our case also demonstrates that isoflurane can be successfully used as a maintenance anesthetic for hepatic transplantation in the patient with primary pulmonary artery hypertension. Barbiturates and opioids have minimal direct effect on PAP²² and are considered safe drugs in the presence of pulmonary hypertension. Earlier work suggested that nitrous oxide significantly increased PAP in patients with pulmonary artery hypertension.²² However, in a more recent study, Konstadt *et al.*²³

demonstrated that nitrous oxide can be administered to these patients without exacerbation of pulmonary artery hypertension.

Pulmonary vasodilators initiated before surgery, should be continued during surgery and in the postoperative period.

In summary, we present an uncommon but potentially lethal medical problem of liver failure associated with pulmonary hypertension. Signs and symptoms of primary pulmonary artery hypertension should be sought in liver transplant candidates. If pulmonary artery hypertension is confirmed by invasive studies, vasodilator therapy may be indicated. In patients with severe primary pulmonary hypertension unresponsive to pharmacologic intervention, our experience suggests that the risk associated with liver transplantation may be unacceptably high.

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