REFERENCES

1. Vervloet D, Nizankowska E, Arnaud A, Senft M, Charpin J: Adverse reactions to suxamethonium and other muscle relaxants under general anesthesia. J Allergy Clin Immunol 6:552–559, 1983

2. Moneret-Vautrin DA, Gueant JL, Kamel L, Laxenaire MC, El Kholty S, Nicolas JP: Anaphylaxis to muscle relaxants: Cross-sensitivity studied by radioimmunoassays compared to intradermal tests in 34 cases. J Allerg Clin Immunol 82(5):745–752, 1988

3. Fisher MM, Munro I: Life-threatening anaphylactoid reactions to muscle relaxants. Anesth Analg 62:559–564, 1983

4. Slater JE: Rubber anaphylaxis. N Engl J Med 320:1126–1130, 1989

5. Fisher MM: Intradermal testing in the diagnosis of acute anaphylaxis during anesthesia: Results of five years experience. Anaesth Intensive Care 7:58–61, 1979

6. Moscicki RA, Sockin SM, Corsello BF, Ostro MG, Bloch KJ: Anaphylaxis during induction of general anesthesia: Subsequent evaluation and management. J Allergy Clin Immunol 86:325–331, 1990

7. Gleich GJ, Larson JB, Jones RT, Baer H: Measurement of the potency of allergy extracts by their inhibitory capacities in the radioallergosorbent test. J Allergy Clin Immunol 53:158–169, 1974

8. Slater JE, Chhabra SK: Latex antigens. J Allergy Clin Immunol 89:673–678, 1992

9. Weiss ME, Adkinson NF Jr: Immediate hypersensitivity to penicillin and related antibiotics. Clin Exp Allergy 18:515–540, 1988

10. Gerber AC, Jorg W, Zbinden S, Seger RA, Dangel PH: Severe intraoperative anaphylaxis to surgical gloves: Latex allergy, an unfamiliar condition. ANESTHESIOLOGY 71:800–802, 1989

11. Fisher MM: Anaphylaxis to muscle relaxants: cross sensitivity between relaxants. Anaesth Intensive Care 8:211–213, 1980

12. Baldo BA, Fisher MM: Anaphylaxis to muscle relaxant drugs: Cross-reactivity and molecular basis of binding of IgE antibodies detected by radioimmunoassay. Mol Immunol 20:1393–1400, 1983

13. Axelsson IGK, Eriksson M, Wrangsjo K: Anaphylaxis and angioedema due to rubber allergy in children. Acta Paediatr Scand 77:314–316, 1988

14. Morales C, Basomba A, Carreira J, Saster A: Anaphylaxis produced by rubber glove contact: Case reports and immunological identification of the antigens involved. Clin Exp Allergy 19:425–430, 1989

15. Leynadier F, Pecquet C, Dry J: Anaphylaxis to latex during surgery. Anaesthesia 44:547–450, 1989

16. Nutter AF: Contact urticaria to rubber. Br. J Dermatol 101:597–598, 1979

17. Spaner D, Dolovich J, Tarlo S, Sussman G, Buttoo K: Hypersensitivity to natural latex. J Allergy Clin Immunol 83:1135–1137, 1989

18. Turjanmaa K: Incidence of immediate allergy to latex gloves in hospital personnel. Contact Dermatitis 17:270–275, 1987

19. Gold M, Swartz JS, Braude BM, Dolovich J, Shandling B, Gilmour RF: Intraoperative anaphylaxis: An association with latex sensitivity. J Allergy Clin Immunol 87:662–666, 1991

20. Slater JE, Mostello LA, Shaer C, Honsinger RW: Type I hypersensitivity to rubber. Ann Allergy 65:411–414, 1990

21. Slater JE, Mostello LA, Shaer C: Rubber-specific IgE in children with spina bifida. J Urol 146:578–579, 1991

22. Meeropol E, Kelleher R, Bell S, Leger R: Allergic reactions to rubber in patients with myelodysplasia (correspondence). New Engl J Med 323:1072, 1990

23. Holzman RS, Sethna NF, Sockin SM: Hypotension, flushing and bronchospasm in myelodysplasia patients (abstract). ANESTHESIOLOGY 73:A1123, 1990

24. Moneret-Vautrin DA, Laxenaire MC, Bavoux F: Allergic shock to latex and ethylene oxide during surgery for spina bifida. ANESTHESIOLOGY 73:556–558, 1990

Pulmonary Hypertension Associated with Liver Disease Is Not Reversible after Liver Transplantation

MARIE CSETE PRAGER, M.D.,* CHARLES A. CAULDWELL, M.D., PH.D.,* NANCY L. ASCHER, M.D., PH.D.,†
JOHN P. ROBERTS, M.D.,‡ CHRISTOPHER L. WOLFE, M.D.§

Pulmonary hypertension is an unusual but well-known complication of liver disease.[1] Patients with pulmonary

* Assistant Professor in Residence, Department of Anesthesia.
† Professor, Department of Surgery.
‡ Assistant Professor in Residence, Department of Surgery.
§ Assistant Professor in Residence, Department of Medicine.

hypertension are usually considered unacceptable candidates for liver transplantation because intraoperative morbidity and mortality is assumed to be high. The role of liver transplantation in reversing this form of pulmonary vascular disease is not known. We present a patient with severe pulmonary hypertension who underwent orthotopic liver transplantation.

CASE REPORT

A 23-yr-old woman with chronic active hepatitis was admitted for pre–liver transplant evaluation. The diagnosis of chronic active hepatitis was established by biopsy 12 yr prior to admission. Symptoms related

to her liver disease were fatigue and mild encephalopathy. In addition, she had laboratory evidence of thrombocytopenia. She denied gastrointestinal bleeding or ascites.

One year prior to admission she had been hospitalized for hemoptysis at another institution. Bronchoscopy was reportedly normal but echocardiography revealed right atrial and ventricular dilatation, and systolic pulmonary arterial pressure was estimated to be 75 mmHg. The patient was given no medications on discharge.

On admission, the patient was afebrile, with blood pressure 110/70 mmHg and heart rate 85 beats/min. She was obese (103.8 kg). Jugular venous pressure was estimated at 10 mmHg. The lungs were clear. Cardiac examination revealed a palpable S2 with loud P2, physiologic splitting of S2, and a right-sided S4 gallop. No murmurs were heard. The liver and spleen were not enlarged. Moderate (2–3+) pitting edema was present in the legs.

Admission laboratory values were hematocrit 45%, platelets 45,000 · mm^{-3}, fibrinogen 240 mg/dl, prothrombin time 15.1 s, partial thromboplastin time 32 s, total bilirubin 2.3 mg/dl, and albumin 2.3 mg/dl. Electrocardiography revealed normal sinus rhythm with tall R waves in V1 and V2 and inverted T waves in leads V1–V3, consistent with right ventricular hypertrophy. Chest x-ray revealed enlarged, pruned pulmonary vessels with clear lung fields. Arterial blood gas was P_{O_2} 70 mmHg, P_{CO_2} 31 mmHg, and pH 7.47 while breathing room air.

Echocardiography revealed a dilated right ventricle and decreased right ventricular ejection fraction, normal left ventricle, dilated pulmonary artery with peak pulmonary artery pressure (PAP) estimated at 70 mmHg. A saline contrast study revealed no intracardiac shunt. Pulmonary ventilation/perfusion scanning showed mild irregularities in pulmonary perfusion, especially in the left upper lobe, without evidence of pulmonary emboli.

The patient was transferred to the coronary care unit for pulmonary arterial catheterization and a trial of vasodilators for presumed pulmonary hypertension. Directly measured PAPs were 81/33 mmHg and pulmonary capillary wedge pressure 14 mmHg, right atrial (RA) pressure 2 mmHg, cardiac output (CO) 12.5 l/min, calculated systemic vascular resistance 507 dyn · s · cm^{-5}, and calculated pulmonary vascular resistance (PVR) 224 dyn · s · cm^{-5} (see table 1).

One hundred percent oxygen, delivered *via* nonrebreathing face mask, increased oxygen saturation from 93% to 100% but did not alter pulmonary pressures or PVR. Similarly, 5 mg isosorbide dinitrate sublingual and intravenous prostaglandin E₁ (maximum dose 0.48 μg · kg^{-1} · min^{-1}) did not reduce PVR. Oral nifedipine 30 mg was administered on several occasions. On one occasion, nifedipine reduced PAP by 26% and PVR by 29%. Diltiazem failed to lower PAP significantly. Because the patient's high CO was thought to contribute to her pulmonary hypertension, a trial of esmolol was instituted. Esmolol was infused in increments to a maximum dose of 250 mg · kg^{-1} · min^{-1}. CO decreased from 13.7 to 10.0 l/min, and systemic vascular resistance increased from 444 to 545 dyn · s · cm^{-5}. PAP did decrease from 95/

37 to 83/31 mmHg, but the calculated PVR increased from 274 to 337 dyn · s · cm^{-5}. Esmolol and nifedipine were then administered simultaneously, but systolic blood pressure decreased to 80 mmHg, and so this combination also was abandoned.

Despite this evidence of fixed pulmonary hypertension, the patient did not have right ventricular failure (right atrial pressure 2 mmHg), and the decision was made to proceed with liver transplantation. The patient was discharged home on nifedipine and furosemide to await organ donation.

Three months later an appropriate donor was identified, and the patient was admitted for liver transplantation. Preoperative physical examination, complete blood count, electrolytes, and chest x-ray were unchanged from the previous admission. Coagulation studies indicated deterioration of liver function since the last admission: prothrombin time 17.0 s, partial thromboplastin time 33.2 s, and fibrinogen 106 mg/dl.

Induction of general anesthesia was accomplished with 350 mg sodium thiopental, and tracheal intubation was facilitated with 100 mg succinylcholine. Anesthesia was maintained with isoflurane, a continuous infusion of fentanyl, and midazolam, and paralysis with metocurine. A radial arterial catheter and 7.5-Fr pulmonary artery catheter were placed. Initial PAP was 120/60, central venous pressure (CVP) 9 mmHg, and CO 10.4 l/min. The anesthesiologists did not obtain pulmonary capillary wedge pressure readings because of concern over the patient's coagulopathy. Simultaneous systemic pressure was 110/60 mmHg and heart rate 120 beats/min, and arterial blood gas (F_{IO_2} 100%) revealed P_{O_2} 320 mm Hg, P_{CO_2} 41 mm Hg, and pH 7.34.

After incision, PAPs were 130–140/60 mmHg. Dobutamine 3 mg · kg^{-1} · min^{-1} was started in an attempt to decrease PAP. However, the patient's systemic pressure decreased abruptly; this was treated with ephedrine, and the dobutamine was discontinued. Prostaglandin E₁ was started at 100 μg/h, and 30 mg nifedipine (liquid extracted from capsules) was placed in the nasogastric tube. Over approximately 30 min, PAP decreased to 96/63 mmHg and CVP to 9 mmHg. CO and blood pressure were unchanged, but heart rate increased to 135 beats/min. The prostaglandin E₁ infusion rate was gradually increased to 300 μg/h without further decrease in PAP, but systemic blood pressure decreased to 90/50 mmHg. In addition, 50 μg/min nitroglycerin was started, but systemic pressures decreased immediately, and the nitroglycerin was discontinued.

Immediately after vena cava cross-clamping (without veno-venous bypass), systemic blood pressure decreased precipitously and was unresponsive to an infusion of phenylephrine (40 μg/ml). Norepinephrine (about 11 μg/min) was titrated to keep systemic blood pressure at 100/50 mmHg. At this time, CO was 6.5 l/min, CVP 8 mmHg, PAP 53/36 mm Hg, pulmonary capillary wedge pressure 5 mmHg, PVR 512 dyn · s · cm^{-5}. The anhepatic period lasted 38 min.

Upon vena cava unclamping, PAPs increased to 135/50 mmHg, and CVP was 6 mmHg and CO 20.0 l/min. Vasopressors were discontinued within 15 min, and blood pressure was stable at 110/50

TABLE 1. Hemodynamic Parameters Before, During, and After Liver Transplantation

Event	MAP (mmHg)	CO (l/min)	SVR (dyn · s · cm^{-5})	MPAP (mmHg)	PVR (dyn · s · cm^{-5})
3 Months preoperative	83	12.5	507	49	224
OLTx: after induction	77	10.4	521	80	NA
Vena cava cross-clamp	73	6.5	804	42	512
Vena cava unclamp	60	20.0	208	78	NA
End transplant	73	12.3	738	66	431
3 Months postoperative	73	12.1	469	51	284

MAP = mean arterial pressure; CO = cardiac output; SVR = systemic vascular resistance; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.

mmHg; prostaglandin E_1 was continued. Nifedipine was given via nasogastric tube every 2 h. Within 1 h of reperfusion of the graft, the liver functioned well as assessed by improvement in metabolic acidosis and by bile production. At the end of surgery, which lasted 5 h, blood pressure was 110/60 mmHg, heart rate 135 beats/min, PAP 111/44 mmHg, CVP 6 mmHg, pulmonary capillary wedge pressure 10 mmHg, CO 12.3 l/min, and PVR 431 dyn·s·cm^{-5}.

On the first postoperative day, prostaglandin E_1 was infused at 500 μg/h and nifedipine continued. When the prostaglandin E_1 was transiently withheld, PVR increased by 43% to 515 dyn·s·cm^{-5}. On the second postoperative day, persistent tachycardia (heart rate 150 beats/min) prompted an esmolol infusion, which was used successfully to maintain heart rate in the 110–120-beat/min range. At this time, PAP was 80–85/40–45 mmHg.

On day 3, prostaglandin E_1 was discontinued without exacerbation of high PVR. On day 5, the patient's trachea was extubated. Hemodynamics then were blood pressure 120/70 mmHg, heart rate 100 beats/min, CO 6.5 l/min, PAP 90/43 mmHg, and CVP 12 mmHg. The patient was discharged from the hospital on day 15 and was instructed to take nifedipine and metoprolol in addition to her immunosuppressive regimen.

Because the patient continued to experience shortness of breath, pulmonary catheterization was repeated 3 months after liver transplantation (table 1). At that time, PAP was 78/37 mmHg and PVR 284 dyn·s·cm^{-5}. A trial of nifedipine did not significantly improve PAP. Upon consultation, the cardiologist recommended that the patient be considered in the future for single-lung transplant. Nine months after liver transplantation, directly measured PAP was 65/25 mmHg, mean PAP 36 mmHg, pulmonary capillary wedge pressure 7 mmHg, right atrial pressure 2 mmHg, CO 8.4 l/min, systemic vascular resistance 700 dyn·s·cm^{-5}, and PVR 256 dyn·s·cm^{-5}.

DISCUSSION

Pulmonary hypertension is generally defined as a mean PAP at rest of greater than 25 mmHg.[1] An association between liver disease and pulmonary hypertension was first noted 40 yr ago,[2] but the association is a rare one. Two studies place the prevalence of pulmonary hypertension in the setting of liver disease at about 0.25%.[3,4] Another study notes a prevalence of 0.73% in the presence of liver disease versus a 0.13% prevalence of primary pulmonary hypertension in all autopsies.[5]

The pathogenesis of pulmonary hypertension associated with liver disease is little understood. In general, three types of pathophysiologic alterations can lead to pulmonary hypertension: increased pulmonary venous pressure (as with left ventricular failure), increased pulmonary blood flow (as with ventricular septal defect), and increased PVR (as with chronic hypoxemia).[6] High CO states, and hence increased pulmonary blood flow, are characteristic of cirrhosis; hypoxemia is also common.[7] In addition, some authors have speculated that catecholamines, which in cirrhotic patients may contribute to systemic vasodilatation, may also increase susceptibility to pulmonary hypertension.[8] The association of extrahepatic portal venous obstruction (without intrinsic liver disease) and pulmonary hypertension[9,10] has led to the theory that portal–systemic shunting of unknown toxins contributes

to pulmonary vascular disease.[11] Finally, some investigators believe that microemboli from the portal circulation to the lung contribute to pulmonary hypertension.[12] None of these theories is supported by convincing evidence.

Though not discussed in the literature, both pulmonary hypertension and chronic active hepatitis may be caused by a systemic autoimmune process. Our patient's seronegative chronic active hepatitis was consistent with an autoimmune process. (The University of California, Los Angeles Liver Transplant program recently evaluated another patient with autoimmune liver disease and severe pulmonary hypertension. This patient was not accepted as a candidate for liver transplantation because of severe right heart failure.)

Various vasodilators have been tried in patients with primary pulmonary hypertension, but in the majority of these patients, PVR is unresponsive to pharmacologic intervention. Calcium-channel blockers are most likely to decrease PVR acutely[13] and may cause some long-term reduction in PAP.[14] Infusion of prostacyclin can decrease PVR,[15] but this therapy may be practical only in special situations, such as in monitored patients awaiting lung transplant.[16] Therapeutic trials of vasodilators for patients with pulmonary hypertension mandate continuous monitoring of pulmonary arterial and systemic pressures and arterial oxygenation, since vasodilator therapy may be hazardous.[17] Common complications of vasodilator trials include systemic hypotension, exacerbation of pulmonary hypertension due to increased CO, and systemic arterial desaturation.[17] β-Blocking drugs are not part of the usual treatment trials for patients with primary pulmonary hypertension. In fact, β agonists, because of their pulmonary vascular vasodilating properties, have been advocated in the treatment of primary pulmonary hypertension.[18] In our patient, a β-blocking agent was given in an attempt to decrease CO, to simulate the effect of liver transplantation on the circulation, and to assess the response of pulmonary hemodynamics. The patient's CO did indeed decrease significantly (27%); mean PAP decreased by only 10%, such that PVR increased.

Early in the intraoperative course, several vasodilators were used in an attempt to reduce the extremely high PAPs, but with little success. The patient's systemic blood pressures decreased unacceptably in response to low doses of dobutamine and nitroglycerin. Although this response is a common problem during vasodilator therapy,[17] the decrease in systemic pressures may have been exacerbated by coadministration of several anesthetics and rapid fluid shifts.

Not unexpectedly, the most extreme shifts in hemodynamics occurred at the time of vena cava cross-clamping and unclamping (table 1). The decrease in CO at the time of vena cava cross-clamping, from 9.6 to 6.5 l/min, is within the normal range for patients undergoing liver

transplantation.[19] During vena cava cross-clamping, PAPs were significantly less than baseline intraoperative values—a passive response to the lower CO—and PVR was markedly increased at 451–512 dyn · s · cm^{-5}. At the end of surgery, when CO (and pulmonary blood flow) was nearly twice that in the anhepatic period, PVR was 336 dyn · s · cm^{-5}.

When the vena cava was unclamped, the patient's pulmonary hypertension did not exceed her intraoperative baseline, and CO indicated that ventricular function was not compromised. The patient's excellent right ventricular function was the reason for her survival of this procedure.

Because patients with pulmonary hypertension are often considered unacceptable candidates for liver transplantation, the role of liver transplantation in reversing pulmonary hypertension associated with liver disease is unknown. Some secondary forms of severe pulmonary hypertension, such as that associated with mitral stenosis, are reversible when the underlying circulatory defect is surgically corrected.[20] In our patient, the pulmonary vascular process may have been a truly primary (autoimmune) process, rather than one secondary to her liver disease, and therefore not reversible after liver transplantation. Alternatively, the anatomic changes in the pulmonary vascular bed, if secondary to her liver disease, may simply have advanced to the point of irreversibility at the time of surgery.

In summary, our experience with this patient highlights the difficulty of intraoperative management and suggests that pulmonary hypertension in the setting of liver disease may not be reversible by liver transplantation.

References

1. Hancock EW: Chapter XIX, Pulmonary vascular disease and cor pulmonale. Edited by Rubenstein E, Federman DD. Scientific American Medicine, New York, 1:1–8, 1991

2. Mantz FA Jr, Craige E: Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale. Arch Pathol Lab Med 52:91–97, 1951

3. Lebrec D, Capron J, Dhumeaux D, Benhamou J: Pulmonary hypertension complicating portal hypertension. Am Rev Respir Dis 120:849–856, 1979

4. Ruttner JR, Bartschi J, Niedermann R, Schneider J: Plexogenic pulmonary arteriopathy and liver cirrhosis. Thorax 35:133–136, 1980

5. McDonnell PJ, Toye PA, Hutchins GM: Primary pulmonary hypertension and cirrhosis: Are they related? Am Rev Respir Dis 127:437–441, 1983

6. Case records of the Massachusetts General Hospital. N Engl J Med 313:1003–1012, 1985

7. Krowka MJ, Cortese DA: Pulmonary aspects of chronic liver disease and transplantation. Mayo Clin Proc 60:407–418, 1985

8. Edwards BS, Weir EK, Edwards WD, Ludwig J, Dykoski RK, Edwards JE: Coexistent pulmonary hypertension: Morphologic and clinical features. J Am Coll Cardiol 10:1233–1238, 1987

9. Cohen MD, Rubin LJ, Taylor WE, Cuthbert JA: Primary pulmonary hypertension: An unusual case associated with extrahepatic portal hypertension. Hepatology 3:588–592, 1983

10. Lockhart A: Pulmonary arterial hypertension in portal hypertension. J Clin Gastroenterol 14:123–138, 1985

11. Rich S, Brundage BH: Pulmonary hypertension: A cellular basis for understanding the pathophysiology and treatment. J Am Coll Cardiol 14:545–550, 1989

12. Sallam M, Watson WC: Pulmonary hypertension due to microthromboembolism from splenic and portal veins after portacaval anastomosis. Br Heart J 32:269–271, 1970

13. Newman JH, Ross JC: Primary pulmonary hypertension: A look at the future. J Am Coll Cardiol 14:551–555, 1989

14. Rich S, Brundage BH: High-dose calcium channel-blocking therapy for primary pulmonary hypertension: Evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. Circulation 76:135–141, 1987

15. Jones DK, Whiggenbottam TW, Wallwork J: Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin). Br Heart J 57:270–278, 1987

16. Palevsky HI, Fishman AP: The management of primary pulmonary hypertension. JAMA 265:1014–1020, 1991

17. Packer M: Vasodilator therapy for primary pulmonary hypertension. Ann Intern Med 103:258–270, 1985

18. Lee TD Jr, Roveti GC, Ross RS: The hemodynamic effects of isoproterenol on pulmonary hypertension in man. Am Heart J 65:361–367, 1963

19. Estrin JA, Belani KG, Ascher NL, Lura D, Payne W, Najarian JS: Hemodynamic changes on clamping and unclamping of major vessels during liver transplantation. Transplant Proc 21:3500–3505, 1989

20. Zener JC, Hancock EW, Shumway NE, Harrison DE: Regression of extreme pulmonary hypertension after mitral valve surgery. Am J Cardiol 30:820–826, 1972