CASE REPORTS

The Perioperative Management of Portopulmonary Hypertension with Nitric Oxide and Epoprostenol

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END-STAGE liver disease is associated with a hyperdynamic circulatory state. The pathophysiologic changes include a decreased systemic vascular resistance, an increased cardiac index, and portal hypertension together with the formation of vascular shunts.[1] These changes may be the result of an increased production of NO synthase and the resulting increase in endogenous nitric oxide (NO) causing profound vasodilation.[2] This hypothesis is further supported by the demonstration of an increased concentration of NO in the exhaled breath of patients with severe liver cirrhosis.[3,4] The pathophysiologic changes in the lung may include vascular dilatations, arteriolar wall thickening, and vascular lumen occlusion from thromboembolism. If vascular dilatations predominate in the lung, then hepatopulmonary syndrome (hypoxemia associated with hepatic dysfunction and intrapulmonary vascular shunts) may result.[5] If vascular wall thickening or occlusion predominates, then pulmonary hypertension may develop as a result of increased resistance to blood flow. All three pathologic states have been shown to exist simultaneously.[6]

Pulmonary hypertension associated with end-stage liver disease may be found in up to 8.5% of patients presenting for liver transplantation.[7] It may be defined as a mean pulmonary artery pressure (PAP) of greater than 25 mmHg with a normal pulmonary artery occlusion pressure (PAOP) and pulmonary vascular resistance (PVR) of greater than 120 dynes · s^{-1} · cm^{-5}.[8] Pulmonary hypertension may further be divided into severe (mean PAP > 45 mmHg), moderate (mean PAP > 35 mmHg), or mild (mean PAP > 25 mmHg).[7] Patients with moderate and severe pulmonary hypertension have a reduced 3-year survival after liver transplantation compared to patients presenting with normal or mild pulmonary hypertension.[7] Therefore, we endeavor to reverse pulmonary hypertension before submitting a patient to liver transplantation in an attempt to improve outcome.

Our previous experience and other reports have shown that inhaled NO does not reverse pulmonary hypertension associated with liver disease.[9,10] This is not entirely unexpected, because patients with severe cirrhosis have been reported to have increased levels of endogenously produced NO.[3,4] We now describe a patient with end-stage liver disease who responded to inhaled NO on several occasions.

This case report describes a patient in whom the combination of inhaled NO and an infusion of epoprostenol were used together to successfully control pulmonary hypertension perioperatively in a patient undergoing liver transplantation.

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Table 1. Patient Hemodynamics and Responses to Inhaled Nitric Oxide

	Arterial BP (mmHg)	PAP (mean) (mmHg)	PVR (dyne · s^{-1} · cm^{-5})	PAOP (mmHg)	CO (L · min^{-1})
1st trial					
Room air	125/62	63/18 (38)	587	5	4.5
NO (40 ppm)	154/65	47/13 (28)	383	5	4.8
2nd trial					
Room air	128/81	67/19 (39)	587	6	4.5
NO (40 ppm)	157/74	53/16 (28)	304	9	5.0
Preinduction					
Room air	166/65	46/13 (29)	193	16	5.4
NO (40 ppm)	176/68	40/13 (24)	176	13	5.0
Postreperfusion					
100% oxygen	135/55	46/23 (34)	320	10	6.0
NO (40 ppm)	114/42	40/13 (25)	267	9	4.8
2 days postoperation 2 L/min oxygen					
per nasal cannulae	125/55	64/21 (35)	432	8	5.0

PAP = pulmonary artery pressure; PAOP = pulmonary artery occlusion pressure; CO = cardiac output; NO = nitric oxide.

Case Report

The patient was a 62-yr-old, 60-kg woman with end-stage liver disease as a result of hepatitis C, the Child-Turcotte Pugh Score was 10. A liver biopsy revealed severe cirrhosis, and she had a clinical course of progressive fatigue, muscle wasting, encephalopathy, and asymptomatic esophageal varices. Prothrombin time was 13.2 s, total bilirubin concentration was 1.6 mg/dl, serum aspartate aminotransferase and serum alanine aminotransferase concentrations were 71 IU/l and 55 IU/l, respectively (normal values 5–50 IU/l and 5–40 IU/l). A chest radiograph showed a prominent pulmonary artery and the electrocardiogram (ECG) showed a right-side heart strain pattern. Therefore, echocardiography was performed and revealed evidence of pulmonary hypertension. A right-side heart catheter was placed and a PAP of 63/18 mmHg (mean 38 mmHg), a pulmonary vascular resistance of 527 dynes · s^{-1} · cm^{-5}, a PAOP of 5 mmHg, and a cardiac output of 4.5 l/min were recorded. After Institutional Review Board approval and informed patient consent, inhaled NO was administered *via* a facemask and a nonrebreathing circuit from an I-NOvent (Ohmeda, Liberty Corner, NJ) system. Nitric oxide was increased by increments of 10 ppm and at a concentration of 40 ppm inhaled NO, PAPs decreased to 47/13 mmHg (mean 28 mmHg), and the PVR decreased to 383 dynes · s^{-1} · cm^{-5}. The PAOP remained at 5 mmHg, and cardiac output was 4.8 l · min^{-1}. At cessation of the trial of NO, PAPs reverted to baseline levels during the next 30 min. The inhaled NO trial was repeated the next day with similar results (see table 1).

An infusion of epoprostenol was then started at 2 ng · kg^{-1} · min^{-1} and increased to 7 ng · kg^{-1} · min^{-1}, the highest dose tolerated by the patient because of headaches. Mean PAPs were maintained between 32–35 mmHg before removing the pulmonary artery catheter. The patient received a continuous infusion of epoprostenol for 3 weeks before a donor liver became available. At arrival in the operating room for liver transplantation, PAPs of 46/13 mmHg (mean 29 mmHg), a PVR of 193 dynes · s^{-1} · cm^{-5}, and a PAOP of 16 mmHg were noted. Inhaled NO was again instituted *via* a facemask and PAPs further decreased to 40/13 mmHg (mean 24 mmHg), PVR decreased to 176 dynes · s^{-1} · cm^{-5}, and PAOP decreased to 13 mmHg. Nitric oxide was discontin-

ued and the PAPs returned to baseline levels, but the epoprostenol infusion was continued.

At reperfusion of the liver graft, PAPs increased to 46/23 mmHg (mean 34 mmHg), PVR increased to 320 dynes · s^{-1} · cm^{-5}, and PAOP decreased to 10 mmHg. At the same time, the ST segment on lead II of the ECG was noted to be acutely increased to 5 mm. Inhaled NO at 40 ppm was administered to reverse the pulmonary hypertension, and simultaneously a rapid resolution of the ECG changes was noted. The rest of the procedure was uneventful, and the NO was weaned off with a mild elevation in PAP to a mean pressure of 32 mmHg.

Posttransplantation in the intensive care unit, the PAPs remained increased at a mean pressure of 35 mmHg; therefore, the epoprostenol infusion was continued. The patient went home on the tenth postoperative day, still receiving an epoprostenol infusion at 9 ng · kg^{-1} · min^{-1}. At 3 months postoperatively, the patient was reevaluated by echocardiography and noted to have near-normal PAPs (mean 25 mmHg). A slow weaning of the epoprostenol infusion was commenced.

Discussion

It is intriguing as to why this patient responded to inhaled NO when previous patients with end-stage liver disease have not shown a response.[9,10] However, a single case report showed an intraoperative response to inhaled NO in a patient undergoing liver transplantation who had severe pulmonary hypertension.[11]

Inhaled NO may have caused the reversal of an acute pulmonary vasoconstrictive episode after the perfusion of the lung by cold blood from the donor organ. The severe ischemia noted on the ECG may have been the result of acute right-side heart strain caused by a sudden increase in afterload to the right ventricle, although the PVR did not reach previously increased levels. The isch-

emia may have been induced by coronary vasospasm caused by the placement of the cold donor organ directly beneath the heart.[12] The rapid resolution of this episode may not be related to the NO therapy, or it may have been the result of the reduction in right ventricular afterload by NO. The transport of NO by red corpuscles combined with hemoglobin as S-nitrosohemoglobin and its release of NO on deoxygenation in the coronary artery, causing direct vasodilatation, has been suggested.[13] The concept, that inhaled NO can be delivered to the distant microvasculature, recently has been confirmed in the feline model.[14]

The positive preoperative response to inhaled NO in this patient may have been the result of a lack of increased levels of endogenous NO because the typical hyperdynamic circulation of severe liver cirrhosis did not exist in this patient. The measured cardiac outputs were in the normal range and there was mild systemic hypertension. The pulmonary hypertension may have been coincidental to the portal hypertension as opposed to being the result of it, or the patient may have had increased levels of systemic NO but decreased pulmonary microvasculature NO levels. Pulmonary hypertension may represent a collection of disease processes with diverse phenotypic expression and, therefore, differing responses to therapy.

An infusion of epoprostenol has been shown as a successful therapy in reducing pulmonary hypertension before liver transplantation.[15] For how long after transplantation should the epoprostenol infusion be maintained is unknown. More severe hypertension continues to develop postoperatively in the majority of patients with severe pulmonary hypertension at the time of transplantation, and the patients die of right ventricular failure over the next 18 months.[7] Whether remodeling of pulmonary arteriolar wall hypertrophy can occur with chronic vasodilator therapy, and over what time period, is an intriguing thought.[16,17] Whether the chronic exposure of the patient to inhaled NO *via* nasal cannulae would be equally as effective as an infusion of epoprostenol is being explored.[18] The advantage of this technique would be the avoidance of an indwelling intravenous cannula and its associated morbidity.

The role of inhaled NO and endogenous NO in end-stage liver disease deserves further evaluation. Perhaps, the presence, or absence, of an elevated exhaled NO level may indicate which patients with portopulmonary hypertension will respond to exogenous inhaled NO.

References

1. Groszmann RJ: Hyperdynamic circulation of liver disease 40 years later: Pathophysiology and clinical consequences. Hepatology 1994; 20:1359–63
2. Vallance P, Moncada S: Hyperdynamic circulation in cirrhosis: A role for nitric oxide? Lancet 1991; 337:776–8
3. Rolla G, Brussino L, Colagrande P, Dutto L, Polizzi S, Scappaticci E, Bergerone S, Morello M, Marzano A, Martinasso G, Salizzoni M, Bucca C: Exhaled nitric oxide and oxygenation abnormalities in hepatic cirrhosis. Hepatology 1997; 26:842–7
4. Rodriguez-Roisin R, Barbera JA: Hepatopulmonary syndrome: Is NO the right answer? Gastroenterology 1997; 113:682–4
5. Krowka MJ: Hepatopulmonary syndrome. Transplant Proc 1993; 25:1746–7
6. Matsubara O, Nakamura T, Uehara T, Kasuga T: Histometrical investigation of the pulmonary artery in severe hepatic disease. J Pathol 1984; 143:31–7
7. Ramsay MAE, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB: Severe pulmonary hypertension in liver transplant candidates. Liver Transpl Surg 1997; 3:494–500
8. Mandell SM, Krowka MJ: Formation of a national database on pulmonary hypertension and hepatopulmonary syndrome. ANESTHESIOLOGY 1997; 87:450–1
9. Ramsay MAE, Schmidt A, Hein HAT, Nguyen AT, Lynch K, East CA, Ramsay KJ: Nitric oxide does not reverse pulmonary hypertension associated with end-stage liver disease: A preliminary report. Hepatology 1997; 25:524–7
10. De Wolf AM, Scott V, Bjerke R, Kang Y, Kramer D, Miro A, Fung JJ, Dodson F, Gayowski T, Marino IR, Firestone L: Hemodynamic effects of inhaled nitric oxide in four patients with severe liver disease and pulmonary hypertension. Liver Transpl Surg 1997; 3:594–7
11. Mandell MS, Duke J: Nitric oxide reduces pulmonary hypertension during hepatic transplantation. ANESTHESIOLOGY 1994; 81:1538–42
12. Ramsay MAE, Takaoka F, Brown MR, Rosenlof P: Coronary artery vasospasm following placement of a cold liver graft during orthotopic liver transplantation. Anesth Analg 1989; 69:854–5
13. Jia L, Bonaventura C, Bonaventura J, Stamler JS: S-nitrosohaemoglobin: A dynamic activity of blood involved in vascular control. Nature 1996; 380:221–6
14. Fox-Robichaud A, Payne D, Hassan SU, Ostrovsky L, Fairhead T, Reinhardt P, Kubes P: Inhaled NO as a viable antiadhesive therapy for ischemia/reperfusion injury of distal microvascular beds. J Clin Invest 1998; 101:2496–505
15. Plotkin JS, Kuo PC, Rubin LJ, Gaine S, Howell CD, Laurin J, Njoku MJ, Lim JW, Johnson LB: Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. Transplantation 1998; 65:457–9
16. Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ: Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. Transplantation 1997; 63:604–6
17. Horstman DJ, Frank DU, Rich GF. Prolonged inhaled NO attenuates hypoxic, but not monocrotaline-induced, pulmonary vascular remodeling in rats. Anesth Analg 1998; 86:74–81
18. Channick RN, Newhart JW, Johnson FW, Williams PJ, Auger WR, Fedullo PF, Moser KM: Pulsed delivery of inhaled nitric oxide to patients with primary pulmonary hypertension: An ambulatory delivery system and initial clinical tests. Chest 1996; 109:1545–9