Hemodynamic Effects of Inhaled Nitric Oxide in Four Patients With Severe Liver Disease and Pulmonary Hypertension

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Patients with moderate and severe pulmonary hypertension have a very high mortality rate when undergoing orthotopic liver transplantation. Because nitric oxide has been successful in reducing pulmonary artery pressures in certain patients with pulmonary hypertension, the efficacy of NO inhalation (40 and 80 ppm) in 4 patients with pulmonary hypertension associated with liver disease was determined. No clinically significant changes in pulmonary artery pressures or other hemodynamic parameters were observed using either concentration of NO. In conclusion, no pulmonary vasodilatory response from inhalation of NO in 4 patients with severe liver disease and pulmonary hypertension was found.

Pulmonary hypertension (PH) is more common in patients with severe liver disease (0.73%) than in the general population (0.13%).[1] PH is defined as mean pulmonary artery pressure (PAP_M) of >25 mm Hg with a pulmonary capillary wedge pressure of <15 mm Hg; PAP_M between 25 and 35 mm Hg is defined as mild PH; PAP_M between 35 and 50 mm Hg is defined as moderate PH, and PAP_M of >50 mm Hg is defined as severe PH. Although portal hypertension and not cirrhosis itself appears to be the necessary prerequisite,[2] the exact etiology remains unknown. With increasing numbers of patients being considered for orthotopic liver transplantation (OLT), a corresponding increase in liver transplant candidates with PH is expected. Although successful OLT is possible in patients with mild PH,[3] OLT in patients with moderate or severe PH is associated with a very high perioperative mortality.[4-6] In general, patients with at least moderate PH who undergo OLT develop intraoperative and/or immediate postoperative exacerbation of PH and right ventricular failure, which is not responsive to pulmonary vasodilators and inotropic agents.[4-6] Therefore, there seems to be a relationship between the degree of PH and outcome, and consequently, patients with moderate or severe PH are usually denied OLT.[4-6] The intravenous administration of conventional pulmonary vasodilators, such as prostacyclin, prostaglandin E_1, nitroglycerin, sodium nitroprusside, and calcium channel antagonists, has not resulted in a clinically significant reduction in pulmonary artery pressure (PAP) and is associated with unacceptable side effects such as systemic hypotension (a result of systemic vasodilation or venous pooling).[6]

Inhalation of nitric oxide (NO) directly dilates the pulmonary vasculature and has limited effects on the systemic circulation because of its very short half-time.[7,8] Because NO may have the potential to selectively decrease PAP in patients with PH associated with severe liver disease, possibly allowing OLT to be performed, we determined the efficacy of NO inhalation in these patients.

Materials and Methods

With institutional approval, Food and Drug Administration approval (IND no. 39,733), and informed consent, the response to NO inhalation was determined in 4 unselected patients with moderate or severe PH associated with severe liver disease (Table 1). There were no known causes for the PH, such as pulmonary embolism, significant pulmonary parenchymal disease, or cardiac disease. No patient was being treated with pulmonary artery vasodilators.

Hemodynamic measurements were obtained from

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Table 1. Demographic and Individual Hemodynamic Information in Four Patients

	L.M.	R.V.K.	L.B.	W.T.
Age (yr); sex	49; M	39; M	56; M	34; M
Weight (kg)	76	90	60	95
Diagnosis	PNC-E	Hepatitis C	Hepatitis C + PNC-E	Hepatitis C + hemochromatosis
PT (s)	17.0	20.2	17.2	13.3
Albumin ($g \cdot dL^{-1}$)	3.1	3.4	1.9	1.6
Bilirubin ($mg \cdot dL^{-1}$)	8.8	4.6	4.7	0.7
CVP (mm Hg)	6	19	4	4
PAP* (mm Hg)	64/30/43	86/38/58	53/18/29	72/28/44
PCWP (mm Hg)	21	13	10	9
BP† (mm Hg)	97/50/65	141/72/91	139/53/81	147/69/95
CO ($L \cdot min^{-1}$)	6.2	7.8	6.5	7.5
SVR ($dyne \cdot s \cdot cm^{-5}$)	764	741	948	973
PVR ($dyne \cdot s \cdot cm^{-5}$)	285	463	234	374

Abbreviations: BP, systemic blood pressure; CVP, central venous pressure; PNC-E, alcohol-induced postnecrotic cirrhosis; PT, prothrombin time; PCWP, pulmonary capillary wedge pressure.
*PAP is expressed as systolic/diastolic/mean.
†BP is expressed as systolic/diastolic/mean.

radial arterial and pulmonary arterial catheters, inserted using local anesthesia without sedation. Cardiac output (CO) was determined by the thermodilution technique, averaging three separate measurements (Explorer; Baxter, Irvine, CA). All pressure transducers were leveled to the midthoracic level. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated using a standard formula (pressure gradient $\times 80/CO$).

NO was delivered by a low-flow blender into the gas inlet of a Siemens Servo 900C ventilator/anesthesia machine (Siemens Elema, Stockholm, Sweden) from an aluminum tank containing 2200 ppm NO in N_2 (Scott Medical Gases, Plumsteadville, PA). The NO (20-50 mL/min) was combined with diluent gas (typically 5 L/min of oxygen) upstream from the standard oxygen monitor, and 10-80 ppm of NO can be delivered to within 5% accuracy.[9] The concentration of delivered NO in the nonrebreathing system was monitored continuously online at the face mask by direct chemiluminescence technique using a Sievers 10A (Sievers, Boulder, CO) instrument.[10] Calibrations of this unit conducted in our laboratory with a commercial standard indicate the high level of accuracy ($<$1% error) with minimal drift over time ($<$2% error at 2 hours). Humidification of the fresh gases was avoided to diminish the chance of nitric acid formation.

NO (40 and 80 ppm) was administered by face mask for 10 minutes, with the patient awake in a 30° semisitting position, and its hemodynamic effects were determined. The first control data were obtained before the administration of 40 ppm NO, and the second control data were taken before the administration of 80 ppm NO and at least 15 minutes after discontinuing 40 ppm NO.

All patients served as their own controls, and paired *t*-tests were used to determine the physiological effects of NO (one-tailed *t*-tests for comparison of PAP and PVR, and two-tailed *t*-tests for all other parameters). All results are expressed as means $\pm$ SD. Statistical significance was assumed at a value of $P < .05$.

Results

Four patients with PH were studied (Table 1). Three patients had severe PH, and 1 had moderate PH. All had increased PVR. There was no evidence of left ventricular dysfunction, as determined by transthoracic echocardiography. All patients had hemodynamic changes typically associated with severe liver disease, such as increased CO and decreased SVR.

PAP_M decreased from 43 $\pm$ 12 to 40 $\pm$ 11 mm Hg after inhalation of 40 ppm NO but did not change after inhalation of 80 ppm NO (Table 2). SVR increased from 909 $\pm$ 129 to 977 $\pm$ 166 $dyne \cdot s \cdot cm^{-5}$ after inhalation of 80 ppm NO. None of the 4 patients experienced a decrease in PAP_M of $>$9% at either of the NO concentrations. No other hemodynamic changes were observed at either level of NO inhalation, and no complications were noted.

Table 2. Hemodynamic Responses to NO Inhalation (40 and 80 ppm) in Four Patients*

	Control 1	NO 40 ppm	Control 2	NO 80 ppm
CVP (mm Hg)	8 ± 7	7 ± 6	7 ± 6	7 ± 5
PAP_S (mm Hg)	69 ± 14	66 ± 10	63 ± 11	64 ± 10
PAP_D (mm Hg)	28 ± 8	27 ± 6	26 ± 7	28 ± 6
PAP_M (mm Hg)	43 ± 12	40 ± 11†	40 ± 11	41 ± 9
PCWP (mm Hg)	13 ± 5	15 ± 8	14 ± 4	14 ± 5
BP_M (mm Hg)	83 ± 13	82 ± 18	85 ± 17	85 ± 17
CO ($L \cdot min^{-1}$)	7.0 ± 0.8	6.8 ± 0.8	6.8 ± 0.7	6.4 ± 0.4
SVR ($dyne \cdot s \cdot cm^{-5}$)	857 ± 121	869 ± 121	909 ± 129	977 ± 166*
PVR ($dyne \cdot s \cdot cm^{-5}$)	339 ± 101	291 ± 142	305 ± 106	335 ± 96

Abbreviations: BP_M, mean systemic blood pressure; CVP, central venous pressure; PAP_D, diastolic pulmonary artery pressure; PAP_S, systolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.
*Data are expressed as means ± SD.
†$P < .05$ compared with respective control.

Discussion

The physiology and pharmacology of NO have been reviewed recently.[7] Its vasodilatory effects are mediated by activation of guanylate cyclase in smooth muscle, which increases intracellular guanosine 3′,5′-cyclic monophosphate.[11] Inhaled NO has significant beneficial effects under conditions of acute[12,13] and chronic[14-16] PH; however, results in chronic PH are more variable and less predictable.

Although 1 patient had an increased pulmonary capillary wedge pressure of 21 mm Hg and therefore did not strictly meet the criteria of primary PH, we do not believe that his PH was solely the result of this increased pulmonary capillary wedge pressure, and therefore, we included this patient in this series. In this study, no clinically significant changes in PAP, PVR, or other hemodynamic parameters were noted after the inhalation of either 40 or 80 ppm of NO. Although there was a statistically significant reduction in PAP_M from 43 to 40 mm Hg after administration of 40 ppm NO, we do not believe that this small reduction is clinically significant. Thus, we did not observe a vasodilatory effect of NO inhalation on the pulmonary circulation under controlled circumstances in patients with PH associated with severe liver disease.

It is unclear why the 4 patients in our study did not respond to NO inhalation. This may be partially related to the incomplete understanding of the pathophysiology of PH associated with liver disease. PH associated with liver disease is a chronic type of PH, and in these patients NO has more variable and less predictable results. Thus, it is possible that patients with PH associated with liver disease have little or no ongoing vasoconstriction of pulmonary arterioles, and therefore even a potent vasodilator would not affect PVR. In that case, the PH would be mostly the result of anatomic changes in the pulmonary vasculature (plexogenic vascular lesions), and such lesions are typically present in patients with PH and severe liver disease.[17] However, it is also possible that patients with PH associated with liver disease are unresponsive to NO because they have very high plasma concentrations of a very potent vasoconstrictor, overriding the vasodilatory effects of NO. Indeed, increased arterial plasma concentrations of endothelin have been documented in patients with severe liver disease (mean ± SD, 1042 ± 373 pg/100 mL vs. 406 ± 162 pg/100 mL in control patients).[18] Furthermore, 1 patient with severe liver disease and PH had even higher arterial plasma concentrations of endothelin (2100 pg/100 mL) (C. Gandhi, unpublished observations, Pittsburgh, PA, June 1996), suggesting that increased endothelin concentrations may play a role in the pathophysiology of PH associated with liver disease. Increased endothelin concentrations have been implicated to contribute to the vascular abnormalities seen in PH in patients without liver disease.[19] This may suggest that pulmonary vascular endothelial receptors or postreceptors respond differently than systemic receptors. Another possible explanation relates to the abnormal NO metabolism in patients with liver disease: NO synthesis is increased in patients with advanced liver disease and may play a role in the pathogenesis of vasodilation and hyperdynamic circulation.[20,21] It is unclear, however, what role the increased NO production plays in the pathophysiology of PH in these pa-

tients. Other indicators (e.g., muscarinic type 3 receptors and hepatocyte growth factor) have also been implicated. It is also unknown whether even higher concentrations of inhaled NO (>80 ppm) would achieve pulmonary vasodilation in patients with PH associated with liver disease.

Although our results suggest that NO inhalation does not result in clinically significant pulmonary vasodilation in patients with PH associated with liver disease, the small number of patients in our study does not rule out a vasodilatory effect in other patients. Our observations are in contrast with a case report, which suggested that NO inhalation (40 ppm) resulted in a reduction in PAP in 1 patient during OLT.[22] However, conditions were not well controlled, and therefore, the effects of NO in that patient remain unclear. Nevertheless, we believe that a clinically significant reduction in PAP should not be expected from inhalation of NO in the majority of patients with severe liver disease and PH. Preliminary results indicate that chronic administration of pulmonary vasodilators (e.g., prostaglandins) may be promising.

In conclusion, NO inhalation (40 and 80 ppm) did not affect PAP and PVR in 4 patients with severe liver disease and moderate or severe PH, and therefore, such patients remain at high risk for undergoing OLT.

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