Inhaled nitric oxide improves the hepatopulmonary syndrome: a physiologic analysis

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ABSTRACT

The hepatopulmonary syndrome (HPS) is defined by liver dysfunction, intrapulmonary vasodilatation and abnormal oxygenation. Hypoxaemia is progressive and liver transplant is the only effective treatment. Severe hypoxaemia is a life-threatening HPS complication, particularly after transplant. We evaluated gas-exchange and haemodynamic effects of invasive therapies in a consecutive sample of 26 pre-transplant patients. Inhaled nitric oxide significantly improved partial pressure of oxygen (12.4 mm Hg; p=0.001) without deleterious effects on cardiac output. Trendelenburg positioning resulted in a small improvement, and methylene blue did not, though individual responses were variable. Future studies should prospectively evaluate these strategies in severe post-transplant hypoxaemia.

INTRODUCTION

The hepatopulmonary syndrome (HPS) is defined by liver dysfunction, intrapulmonary vasodilatation and abnormal oxygenation.[1] It occurs in up to 32% of people with cirrhosis[1 2] and carries a poor prognosis.[3] Liver transplantation is the only established therapy.[1 4] However, some patients develop refractory hypoxaemia precluding transplant, and severe post-transplant hypoxaemia (requiring 100% fraction of inspired oxygen to maintain oxygen saturation ≥85%) occurs in 12% of patients, carries a 45% mortality and accounts for 68% of post-operative HPS deaths.[5] This complication is thought to be caused by a transient post-transplant exaggeration of underlying HPS pathophysiology.[5] Reports of strategies to manage severe hypoxaemia in HPS are limited to case reports and small case series.[2] We sought to formally evaluate possible strategies in a cohort of stable pre-transplant patients with HPS.

METHODS

We retrospectively analysed consecutive patients from the Canadian HPS Programme (Toronto, Ontario) with moderate to very severe HPS (PaO_2 <70 mm Hg with $AaDO_2$ ≥20 mm Hg)[1] who had physiologic testing between November 2013 and June 2018. The study was approved by St. Michael's Hospital's Research Ethics Board (Toronto).

We inserted an indwelling radial artery catheter and a pulmonary artery catheter and serially evaluated effects of position change, inhaled nitric oxide (iNO), methylene blue (MB) and combinations thereof (figure 1). We waited a minimum of 10 min after each position change and 20 min after any change in FiO_2 and/or administration of iNO before starting measurements. We measured MB effects hourly after completion of the infusion, up to its reported peak effect at 5 hours (used as the main time point for MB effect reporting).[6] Our primary outcome was PaO_2. We also calculated the $AaDO_2$, pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR), and assessed changes in these variables, and in mean systemic arterial pressure, mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO).

Additional methodological details are provided in the online supplemental information.

RESULTS

We included 26 participants (15 (58%) female, mean (SD) age 54.6 (10.5) years, PaO_2 46.2 (9.6) mm Hg, see online supplemental table 1 for patient characteristics).

All patients received iNO and 18 patients also received MB. Physiologic measurements at baseline and with each intervention are reported in table 1. Changes in key measurements (oxygenation and CO), and the proportion of patients exhibiting PaO_2 improvements of at least 10% and 20%[2] are shown in table 2 (also see online supplemental figure 1). Significantly higher PaO_2 was seen in the supine compared with the seated position, in the Trendelenburg compared with the supine position, and with iNO (table 2). Addition of MB to iNO did not produce a significant incremental benefit (table 2). There was no significant improvement in PaO_2 5 hours after MB administration (similar results were seen at intervening time points—online supplemental table 2). CO increased in the supine position (as expected due to increased venous return), was unchanged with iNO and increased with MB administered alone, in combination with iNO (compared with no intervention) and when added to iNO (compared with iNO alone) (table 2).

Changes in SVR, PVR and MPAP with each intervention are reported in online supplemental table 3. We found no relationships between baseline characteristics (age, sex, time since HPS diagnosis, PaO_2 (standing), orthodeoxia value, macroaggregated albumin (MAA) shunt fraction or non-invasive shunt fraction) and PaO_2 response to each intervention (online supplemental tables 4, 5).

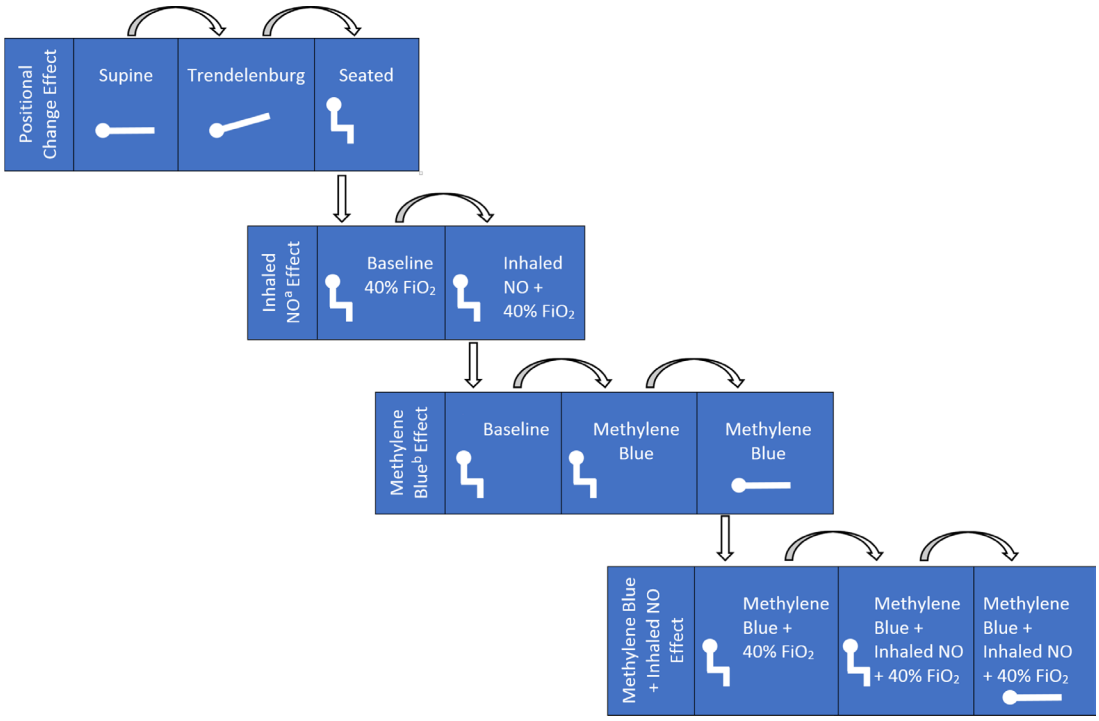

Figure 1 Intervention protocol. Each intervention is shown in order of occurrence. Stick figures represent patient position. Tests were performed on room air unless otherwise specified. [a]Inhaled NO administered at 20 parts per million. [b]Methylene blue effects measured hourly while seated up to 5 hours postintravenous infusion. FiO_2, fraction of inspired oxygen; NO, nitric oxide.

DISCUSSION

In this physiologic study of 26 patients with moderate to very severe HPS, supine positioning, Trendelenburg positioning and iNO significantly improved oxygenation without negative impacts on CO. To our knowledge, this is the largest report of any of these interventions.

The PaO_2 was 3.3 mm Hg higher in the supine compared with the seated position, and 0.9 mm Hg higher in the Trendelenburg position compared with the supine position (table 2). These position changes are theorised to work through diversion of pulmonary blood flow away from pathologically dilated pulmonary vessels at lung bases, reducing shunt and V/Q mismatch.[2 7] Although improvements in PaO_2 were small, it is more relevant to consider the potential impact on tissue oxygen delivery (DO_2). DO_2 is proportional to oxygen saturation, which is dependent on PaO_2 through the sigmoidal oxyhaemoglobin dissociation curve. Patients with severe post-transplant hypoxaemia have saturations of 80%–85% or lower,[5] corresponding to a baseline PaO_2 ≤45 mm Hg. On this steep portion of the oxyhaemoglobin dissociation curve, even small positional PaO_2 improvements could result in clinically significant improvements in saturation and DO_2. These benefits would need to be weighed against the risk of aspiration and ventilator-associated pneumonia. In routine care, Trendelenburg positioning might also be considered in an HPS exercise programme and/or as a sleep positional strategy to reduce overnight oxygen requirements.

Inhaled NO was the most effective intervention, demonstrating a mean PaO_2 improvement of 12.4 mm Hg and responses of ≥10% in over half of patients (table 2). Given that basilar lung vessels may already be maximally dilated,[8] vasodilatory effects of iNO are thought to be more effective in mid and upper lung units, whereby flow is redistributed away from basilar lung units, improving V/Q matching and oxygenation. The same mechanism likely explains observed benefits of garlic in HPS, the active compound of which (allicin) is a potent vasodilator.[9] Unfortunately, we were not able to formally assess regional changes in lung perfusion in order to prove this theory. Overall, our findings suggest that a trial of either iNO or a comparable inhaled vasodilator for severe post-transplant hypoxaemia[2] (and/or for intraoperative hypoxaemia or as a bridge to transplant) would be reasonable. Ambulatory iNO, longer-acting inhaled vasodilators such as inhaled iloprost,[10] and systemic vasodilators might also be evaluated as chronic medical therapies for HPS.

MB infusion did not produce changes in PaO_2 (table 2). As a potent vasoconstrictor, MB is thought to act by directly vasoconstricting dilated vessels at lung bases to improve V/Q matching, and by restoring impaired hypoxic vasoconstriction in poorly ventilated areas.[2] There was a significant increase in MPAP but no significant increase in PVR with MB (table 1, online supplemental table 3). In a previous study of seven subjects, Schenk *et al*[6] reported improvement in oxygenation from 58 mm Hg to 74 mm Hg with MB.[6] Divergence in our results may be attributable to our more severe disease population (baseline PaO_2 46 mm Hg), which may have been less MB responsive due to end-stage vascular remodelling with resulting vasoplegia of dilated HPS vessels.[11] This is supported by Schenk, *et al*'s reported significant PVR increase with MB,[6] compared with a non-significant change in our cohort. Furthermore, this group reported a significant correlation between improvement in oxygenation and increase in PVR.[6] However, both Schenk, *et al*'s report and our own demonstrate variable PaO_2 responses, likely reflective of a heterogeneous population, with some but not all patients having preserved

Table 1 Physiologic measurements at baseline and with each intervention

	Room air							
		Position change						
	Baseline (upright)* n=26	Supine n=26	P value	Trendelenburg n=21	P value	Baseline (upright)* n=18	MB† (upright) n=18	P value
Oxygenation								
PaO_2 (mm Hg)	48.9 (9.6)‡	52.2 (9.0)‡	0.003	52.4 (9.5)	0.002	49.9 (9.1)	51.0 (9.9)	0.34
$AaDO_2$ (mm Hg)	67.4 (31.6)‡	62.3 (27.9)‡	<0.0001	56.7 (8.3)	<0.0001	62.5 (10.6)	61.7 (12.4)	0.62
Pulmonary haemodynamics§								
CO (L/min)	7.6 (2.1)	8.5 (2.5)	0.0008	8.4 (2.2)	0.005	7.6 (2.3)	8.5 (2.5)	0.01
MPAP (mm Hg)	14.6 (6.5)	17.8 (5.5)	0.02	20.0 (7.0)	0.001	13.6 (5.2)	17.6 (6.9)	0.0002
PCWP¶ (mm Hg)	7.7 (5.4)	10.5 (4.4)	0.01	12.6 (5.1)	0.001	7.5 (5.1)	10.1 (5.6)	0.002
PVR¶ (dyn·s·cm^{-5})	77.6 (48.0)	76.4 (43.4)	0.88	73.9 (35.5)	0.99	68.5 (42.2)	74.0 (47.5)	0.49
Systemic haemodynamics§								
CVP (mm Hg)	6.8 (4.3)	7.1 (3.3)	0.92	8.8 (4.3)	0.14	7.0 (4.0)	8.3 (4.3)	0.01
MAP (mm Hg)	92.1 (12.4)	81.7 (13.5)	0.0002	79.0 (12.3)	<0.0001	93.9 (12.6)	101.9 (13.8)	0.007
SVR (dyn·s·cm^{-5})	977.9 (347.7)	785.9 (344.0)	<0.0001	718.9 (225.8)	<0.0001	999.5 (352.2)	967.2 (332.4)	0.31
	40% FiO_2 Baseline (upright)* n=26	Inhaled NO (upright) n=26		P value	Inhaled NO + MB† (upright) n=18			P value
Oxygenation								
PaO_2 (mm Hg)	85.8 (28.8)	98.2 (39.3)		0.0006	103.0 (30.9)			0.001
$AaDO_2$ (mm Hg)	157.8 (29.6)	145.2 (40.1)		0.0009	140.7 (33.6)			0.0005
Pulmonary haemodynamics§								
CO (L/min)	7.0 (1.9)	6.9 (1.9)		0.71	8.1 (2.6)			0.04
MPAP (mm Hg)	15.4 (5.5)	14.6 (5.6)		0.23	17.3 (5.6)			0.0004
PCWP¶ (mm Hg)	7.8 (4.9)	8.3 (4.9)		0.30	9.8 (5.5)			0.03
PVR¶ (dyn·s·cm^{-5})	103.3 (91.0)	76.9 (43.9)		0.12	81.1 (57.3)			0.41
Systemic haemodynamics§								
CVP (mm Hg)	5.9 (3.9)	5.7 (3.8)		0.65	8.3 (5.3)			0.02
MAP (mm Hg)	93.5 (15.9)	97.5 (11.5)		0.07	107.4 (14.4)			0.001
SVR (dyn·s·cm^{-5})	1093.8 (413.5)	1135.0 (334.2)		0.22	1101.4 (450.1)			0.59

Values reported as mean (SD) and p values calculated using paired t-tests for each intervention; note that some interventions were tested in a smaller number of patients than the baseline comparator; in these cases, only data from patients providing both baseline and intervention data could be compared statistically.
*Although the procedure was started in the supine position, the upright (seated) position is taken as the baseline for each comparison in this table.
†Measured at least 5 hours after MB infusion.
‡Includes one patient on 40% FiO_2 (could not tolerate room air); baseline upright, supine and inhaled NO data points were collected on 40% FiO_2 in this patient; the patient did not undergo Trendelenburg position nor MB testing.
§Two patients did not contribute to haemodynamic data because the pulmonary artery catheter could not be inserted due to recent central venous thrombosis (n=1); and the pulmonary artery catheter malfunctioned (n=1).
¶One additional patient did not contribute pulmonary capillary wedge pressure or PVR data in the Trendelenburg position due to transient catheter malfunction; in an additional two patients, reliable PCWP was not attainable, and we used the diastolic pulmonary artery pressure (PAD) to approximate the PCWP across interventions.
$AaDO_2$, alveolar–arterial oxygen gradient; CO, cardiac output; CVP, central venous pressure; FiO_2, fraction of inhaled oxygen; MAP, mean arterial pressure; MB, methylene blue; MPAP, mean pulmonary artery pressure; NO, nitric oxide; PaO_2, arterial partial pressure of oxygen; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

vasoconstrictor responses. Accordingly, a trial of MB may still be merited in severe post-transplant hypoxaemia, as long as impact on CO (and thus DO_2) is monitored. We also note that adding MB to iNO did not significantly improve PaO_2 compared iNO alone. However, responses were again variable and there was a 13% increase in CO compared with iNO alone, suggesting a DO_2 benefit. Accordingly, we believe that a trial of combined inhaled vasodilator and MB may be merited in severe situations.

Our study has several limitations. The iNO was delivered with FiO_2 of 0.4 as opposed to room air. However, this more closely approximates the real-world scenario in which this salvage therapy would be used, and effects of all interventions were determined based on comparison to a baseline on the same FiO_2. Although much larger than any prior reports, our sample size remains small and may have been underpowered to detect a small MB effect. We did not pursue molecular biomarker testing to confirm or refute the proposed mechanisms of action of reported agents. We also have not prospectively evaluated the effectiveness nor sustainability of these strategies in the post-transplant context.

In summary, we demonstrated that iNO significantly improves oxygenation in severe HPS, without deleterious effects on CO. Although more data are needed, it may be

Table 2 Change in PaO_2 and CO, by intervention

Intervention	N	Change in PaO_2 (mm Hg)	Change in PaO_2 (%)	P value	N (%) with ≥10% PaO_2 increase	N (%) with ≥20% PaO_2 increase	Change in CO (L/min)	Change in CO (%)	P value
Positional effects									
Supine vs seated (orthodeoxia)	26	3.3 (1.3, 5.3)	8 (2.8, 13.1)	0.003	9 (35)	3 (12)	0.8 (0.4, 1.2)	11 (5.5, 16.4)	0.0008
Trendelenburg vs supine	21	0.9 (0.4, 1.5)	2 (0.6, 2.9)	0.02	0	0	0.1 (–0.2, 0.4)	2 (–2.0, 5.0)	0.56
MB									
MB* (seated)	18	1.1 (–1.1, 3.2)	2 (–2.4, 7.1)	0.34	3 (17)†	1 (6)	0.8 (0.3, 1.4)	12 (5.7, 18.5)	0.01
MB* (supine)	18	2.3 (0.1, 4.6)	5 (0.5, 9.3)	0.06	6 (33)†	1 (6)	0.6 (–0.1, 1.4)	8 (–0.4, 17.2)	0.13
Inhaled NO									
Inhaled NO (seated)	26	12.4 (6.2, 18.6)	13 (8.0, 18.7)	0.0006	14 (54)	6 (23)	0.0 (–0.3, 0.2)	0 (–3.6, 3.6)	0.71
Inhaled NO + MB									
Inhaled NO + MB* vs Inhaled NO alone (seated)	18	0.8 (–11.5, 13.1)	6 (–3.8, 15.8)	0.90	7 (39)‡	5 (28)	0.9 (0.2, 1.6)	13 (3.7, 21.4)	0.03

Values reported as mean (95% CI) and p values calculated using paired t-tests for each value.
All comparisons are to no intervention, in the same position, on the same fraction of inspired oxygen, unless stated otherwise.
*Measured 5 hours after MB infusion.
†One patient had a ≥10% drop in PaO_2 with each of the following interventions: 17% drop in PaO_2 with MB (seated), 11% drop in PaO_2 with MB (supine), 13% drop in PaO_2 with inhaled NO + MB (seated) (a different patient experienced each of these drops across interventions).
‡Four patients had a ≥10% drop in PaO_2, as follows: drop in PaO_2 of 10%, 13%, 33%, 36%.
CO, cardiac output; MB, methylene blue; NO, nitric oxide; PaO_2, arterial partial pressure of oxygen.

considered early in the management of severe hypoxaemia, whether as a bridge to transplant, during transplant or after. Longer-acting vasodilators require study as possible maintenance therapy for HPS. Small but significant effects were seen with Trendelenburg positioning, but not with MB. However, observed individual variability in effects suggests that pre-transplant testing of all agents in high-risk patients may be helpful in guiding post-transplant management in the event of severe hypoxaemia. Future studies are required to prospectively evaluate the effect of iNO in patients with severe post-transplant hypoxaemia and measure correlations between pre-transplant and post-transplant responses.

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