

Nitric oxide has little effect on acute pulmonary hypertension and right ventricular function during acute respiratory distress syndrome

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Objective. To evaluate the effect of nitric oxide (NO) on acute pulmonary hypertension and right ventricular function in patients with acute respiratory distress syndrome.

Design. A prospective clinical study.

Patients. Ten patients in the respiratory and surgical intensive care units were used. They met the criteria for acute respiratory distress syndrome and were significantly hypoxic. They were all ventilator-dependent at the time of the study.

Intervention. NO was delivered to the patients in 5, 10, 20 and 30 ppm doses for 30 minutes at each concentration. The dosing was not randomised.

Measurements and results. The general and central haemodynamics were measured. Right ventricular function and interaction with the pulmonary artery impedance (Ea) were quantified with the ratio of right ventricular stroke work index/Ea.

NO did not decrease the raised pulmonary artery pressure found in all of the patients. Right ventricular coupling to the circulation did not improve during the administration of NO.

Conclusion. NO did not relieve the acute pulmonary artery hypertension associated with acute respiratory distress syndrome. As a consequence of this, right ventricular function failed to improve during the administration of NO.

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In 1970 Clowes *et al.* documented right ventricular (RV) dysfunction as the result of pulmonary hypertension occurring in patients with peritonitis.¹ However, it was not

until the report by Zapol and Snider in 1977 that the incidence and severity of pulmonary hypertension during acute respiratory distress syndrome (ARDS) were finally established.²

In a recent prospective study we documented severe acute pulmonary hypertension (APHT) in 20 patients with ARDS³ (patients with a Murray score in excess of 2.5 points⁴). In this study every patient had a significantly raised mean pulmonary artery pressure (PAP) at the time of admission to the intensive care unit and thereafter the PAP did not change much during the course of the illness. In addition our data showed that RV failure occurred in each of the patients. This published report supported a previous retrospective analysis of 60 patients with ARDS who had significant hypoxia (arterial haemoglobin saturation (SaO₂) < 90% while breathing an inspired oxygen fraction (FiO₂) > 0.8). In this analysis we found that 50% of patients had significant RV failure in the presence of APHT (A Coetzee, J Swanevelder — unpublished data).

If APHT causes RV failure, the resultant mixed venous blood haemoglobin desaturation will aggravate arterial hypoxaemia associated with the pulmonary shunt of ARDS. In addition, the raised PAP and pulmonary capillary pressure will increase lung water and further increase the pulmonary shunt.^{5,7} It is therefore clear that the reduction in PAP in the presence of ARDS is of some importance in the management of these critically ill patients.

The aim of this study was to examine the effect of various doses of nitric oxide (NO) on PAP, RV function and the circulation in patients with ARDS.

Methods

Permission for this study was obtained from the Ethics Committee of the University of Stellenbosch Medical School. Whenever possible, informed consent was obtained from patients or from close relatives.

Patients with ARDS admitted to the surgical and respiratory intensive care units were selected according to the criteria of Murray.⁴ All the patients had arterial lines and pulmonary artery catheters *in situ* as part of their clinical management. They were ventilated with intermittent mandatory ventilation (IMV) and pressure support (PS). The FiO₂ and positive end-expired pressure (PEEP) were adjusted in order to maintain an SaO₂ > 90%. Permissive hypercapnia was used when necessary to limit the risk of volume trauma to the lung and the pressure control mode was usually used, allowing peak airway pressures up to 40 cm H₂O. A capnograph monitored expired CO₂.

For the study, NO (900 ppm NO in N₂ in a 10-litre aluminium cylinder) was administered with the Pulmonox system (Messer Griesheim, Austria), which was loaned to the researchers by the Fedgas Co. of South Africa. NO was blended into the respiratory circuit of the ventilator while the concentrations of NO in the endotracheal tube were monitored. The generation of the toxic higher oxide of nitrogen (NO₂)⁸ was constantly measured and remained below 0.5 ppm during the study.

For the duration of the study, FiO₂ and ventilator settings were left unaltered and 5, 10, 20 and 30 ppm of NO were administered for 30 minutes each. Because of the very short half-life of NO, it was not thought necessary to randomise

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the doses. At the end of each test period, arterial and mixed venous blood gases (including the methaemoglobin concentration) and ventilator settings were recorded.

Haemodynamic data recorded included: arterial pressure and PAP, central venous pressure (CVP), pulmonary artery wedge pressure (PAWP) and heart rate (HR). The cardiac output (CO) was obtained with thermodilution performed in triplicate with the injections performed throughout the respiratory cycle. The CVP and PAWP were measured at the end of expiration with the aid of an immobilised monitor screen and cursor. For the pressure measurements, zero was taken at the mid-axillary level.

The FiO_2 , inspired and expired tidal volumes, PEEP, auto-PEEP (dynamic hyperinflation), peak and plateau pressures were recorded.

The following indices were calculated using standard equations: mean arterial/pulmonary artery pressure (MAP, PAP); cardiac index (CI); stroke index (SI); left and right ventricular stroke work index (LVSWI and RVSWI); systemic and pulmonary artery vascular resistance; alveolar arterial oxygen tension; arterial, mixed venous and capillary blood oxygen content; pulmonary shunt; and pulmonary artery elastance (Ea). The latter was calculated as the ratio of systolic PAP/stroke volume and represents pulmonary artery impedance, which is a measure of RV afterload.⁹ Oxygen delivery and oxygen consumption data from the various patients were pooled, and the average and standard deviation (SD) of the mean obtained. Data were analysed by comparison of results obtained from the various concentrations of NO (including zero NO, i.e. control) using ANOVA and the multiple range test to define homogeneous groups. For correlations the Pearson's *r*-method was used. A probability of 0.05 was accepted as indicative of a significant difference or association.

Results

Data on 1 patient were incomplete and were not included in the haemodynamic and gas exchange data. The demographics of the patients and aetiology of the ARDS are summarised in Table I. The mean ARDS score (Murray) was 3.11 ± 0.67 . Two of the patients survived their ARDS (20%).

Table I. Demographic data, initial pathology and severity of the patients included in the study

Gender	Age	Died (D)/ survived (S)	Initial pathology	Murray score ⁴
1 F	47	D	Mitral valve replacement	2.0
2 F	41	D	Diaphragm rupture	4.0
3 F	48	S	Multitrauma/MVA	3.5
4 F	26	D	Knife wound (abdomen); massive blood transfusion	3.25
5 F	34	S	Multiple fractures; pneumonia	3
6 F	26	D	Aspiration pneumonia	3.5
7 M	43	D	Perforated peptic ulcer	3.7
8 F	54	S	Pneumonia	2.75
9 F	46	D	Diabetes, cardiac failure	2.25
10 M	53	D	Bilateral pneumonia/ tuberculosis	3.0

MVA = motor vehicle accident.

Table II summarises the **systemic and central haemodynamic data**. The patients all had significant pulmonary artery hypertension. The PAP did not decrease significantly after the administration of NO although there was a trend towards lower PAP values after the initial dose of NO was administered (Fig. 1). In addition, no dose-related change in the PAP could be demonstrated and little change in the PAP was observed after the initial 5 ppm NO. The CVP tended towards lower values after NO was initiated but this failed to reach statistical significance. The CI also showed a tendency to increase after the administration of NO but, as with the other variables, this numerical trend failed to reach statistical significance.

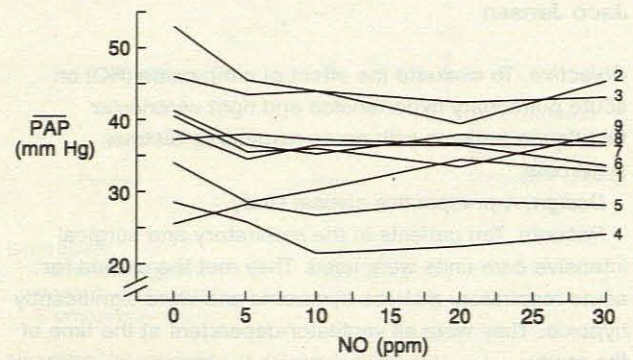


Fig 1. Mean PAP changes for each of the 10 patients exposed to NO.

In 2 patients there was no response in PAP and on average the initial decrease therein was 2.9 ± 3.0 mmHg (mean \pm SD) at 5 ppm. At higher doses very little change, over and above the initial reduction, could be demonstrated (Table II).

Pulmonary gas exchange data are summarised in Table III. The PEEP and FiO_2 were kept constant for the duration of the study. The pulmonary shunt did not improve and, as expected, the PaO_2 did not change. Any change occurred at the 5 ppm step with little change thereafter.

In order to decide on the best index that could be used to define RV function, correlations were attempted with SI as the dependent variable. The following results were obtained: SI/RVSWI — $r = 0.37$, SEE 8.67; SI/PVR — $r = -0.62$, SEE 7.39; SI/PAP — $r = -0.70$, SEE 6.67; SI/Ea — $r = -0.82$, SEE 5.43; SI/(RVSWI/Ea) — $r = 0.95$, SEE 3.11.

On the basis of these results it was decided to use the ratio of RVSWI/Ea as the most suitable index to define the RV-afterload interaction (ventricular-arterial coupling). This ratio and the dose of NO demonstrated a poor correlation ($r = 0.09$, $r^2 = 0.88\%$) and the ratio recorded during control (zero NO) did not change with the administration of the various doses of NO (Table III).

Discussion

There is some scientific justification for the treatment of APHT that occurs in association with ARDS. RV function should improve¹⁰⁻¹² and fluid transudation into the lungs should diminish if the PAP is reduced.⁵⁻⁷ Reduction of APHT

Table II. Systemic and central haemodynamics (mean ± SD) before and during the administration of NO (N = 9)

	HR (/min)	MAP (mmHg)	PAP (mmHg)	CVP (mmHg)	PAWD (mmHg)	CI (l/min/m ²)	LVSWI (g.m/m ²)	RVSWI (g.m/m ²)	SVR (d.sec/cm ²)	PVR (d.sec/cm ²)	VO ₂ (ml/min)	DO ₂ (ml/min)	EA (mmHg/ml)	RVSWI/Ea
Control	122.10 ±10.54	81.04 ±10.18	41.24 ±11.68	15.00 ±4.12	14.60 ±7.43	4.61 ±1.09	35.54 ±12.31	12.81 ±3.01	701.32 ±143.68	297.90 ±133.17	236.69 ±41.59	1 117.91 ±258.75	1.68 ±1.12	9.79 ±4.51
NO 5 ppm	122.40 ±14.59	81.71 ±11.72	38.28 ±11.32	14.70 ±4.00	14.20 ±7.01	4.70 ±1.15	36.64 ±13.74	11.75 ±2.77	684.63 ±123.92	258.78 ±105.11	253.75 ±48.23	1 210.85 ±202.73	1.57 ±1.00	9.37 ±4.31
NO 10 ppm	120.80 ±14.97	78.69 ±11.62	37.84 ±11.76	14.10 ±3.88	14.90 ±8.08	4.72 ±1.05	35.61 ±13.42	11.99 ±2.90	659.58 ±109.54	242.86 ±93.45	250.96 ±56.89	1 223.50 ±203.62	1.51 ±0.99	9.76 ±4.23
NO 20 ppm	121.90 ±13.73	79.86 ±13.50	37.76 ±10.67	13.40 ±3.58	14.90 ±8.51	4.85 ±1.14	36.89 ±14.72	12.57 ±2.84	664.42 ±115.94	235.29 ±74.76	250.05 ±56.76	1 232.59 ±240.69	1.48 ±0.99	10.75 ±5.25
NO 30 ppm	121.60 ±13.73	80.50 ±13.10	37.56 ±8.82	13.50 ±3.61	15.80 ±8.61	4.77 ±1.07	36.23 ±14.08	12.54 ±3.33	679.42 ±128.09	221.79 ±56.72	247.73 ±66.70	1 235.05 ±255.65	1.41 ±0.69	10.62 ±5.37
Signifi- cance level	0.999	0.993	0.948	0.87	0.995	0.993	0.994	0.937	0.957	0.512	0.970	0.978	0.982	0.966

Significance level: ANOVA between various NO concentrations.

HR = heart rate; MAP = mean arterial pressure; PAP = mean pulmonary artery pressure; CVP = central venous pressure; PAWP = pulmonary artery wedge pressure; CI = cardiac index; LVSWI/RVSWI = left and right ventricular stroke work index; SVR/PVR = systemic and pulmonary vascular resistance; VO₂ = oxygen consumption; DO₂ = oxygen delivery; Ea = pulmonary artery elastance.

Table III. Pulmonary function (mean ± SD) during control and various concentrations of NO (N = 9)

	Temp (°C)	FiO ₂	PaO ₂ (kPa)	SaO ₂ (%)	PaCO ₂ (kPa)	pH _{art}	PvO ₂ (kPa)	SvO ₂ (%)	Qs/Qt (%)	PEEP (cmH ₂ O)
Control	37.9 ±1.21	0.68 ±0.21	9.97 ±2.51	91.63 ±6.11	7.05 ±1.64	7.37 ±0.08	5.43 ±0.57	72.61 ±8.30	39.10 ±12.14	9.50 ±2.58
NO 5 ppm	37.92 ±1.26	0.68 ±0.21	11.15 ±3.09	93.56 ±4.10	7.25 ±1.41	7.35 ±0.07	5.75 ±0.54	73.83 ±5.88	35.00 ±13.15	9.50 ±2.58
NO 10 ppm	37.93 ±1.27	0.68 ±0.21	10.78 ±2.87	93.77 ±2.93	7.06 ±1.36	7.36 ±0.08	5.76 ±0.56	74.22 ±6.33	36.00 ±10.03	9.50 ±2.58
NO 20 ppm	37.99 ±1.23	0.68 ±0.21	10.67 ±4.04	92.85 ±4.05	7.21 ±1.35	7.36 ±0.08	5.63 ±0.56	73.54 ±5.36	38.10 ±15.15	9.70 ±3.03
NO 30 ppm	37.98 ±1.24	8.80 ±24.42	10.98 ±3.55	93.93 ±3.12	6.91 ±1.22	7.37 ±0.08	5.69 0.55	74.92 ±6.73	36.50 ±10.54	9.70 ±3.03
Significance level	0.992	0.998	0.951	0.771	0.986	0.986	0.714	0.962	0.957	0.999

Significance level: ANOVA between various concentrations of NO.

FiO₂ = inspired oxygen fraction; PaO₂, PaO₂/PvO₂ = arterial and mixed venous oxygen partial pressure; SaO₂/PvO₂ = arterial and mixed venous haemoglobin saturation; PaCO₂ = partial pressure for CO₂; Qs/Qt = pulmonary shunt; PEEP = positive end-expiratory pressure.

with direct vasodilators such as sodium nitroprusside, nitroglycerine and prostaglandins are associated with systemic hypotension and the risk of ischaemic RV failure. In addition, because of interference with the pulmonary vasoconstrictor response, they increase the pulmonary shunt and this aggravates the existing difficulty in oxygenating the patient.¹³⁻¹⁶

The pharmacological profile of NO is theoretically ideally suitable for the treatment of the problems of APHT.⁸ Because of its short half-life *in vivo*, its vasodilatory effect is terminated by the time it reaches the systemic circulation. It therefore has little, if any, potential to cause systemic hypotension if administered through the lung. Furthermore, when NO is inhaled, it will only reach the alveoli with effective ventilation and its effect will therefore be limited to the capillaries of those alveoli. There is therefore little risk of an increased pulmonary shunt.

The hypothesis for this study was that NO, because of its known ability to dilate the pulmonary vascular bed,⁸ will reduce the PAP and thereby reduce the ejection pressure of the RV. However, our data failed to show a significant reduction in PAP when NO was administered. Neither the change in absolute PAP, nor the difference in PAP associated with the administration of NO, reached statistical significance. We also failed to show a dose-related effect on PAP and this suggests that increasing the number of patients is unlikely to show a significant difference. As a consequence of the failure to reduce PAP pressure and Ea (the effective RV afterload), RV coupling to the pulmonary circulation did not benefit from the administration of NO.

The average (insignificant) change we demonstrated in PAP was of the order of 3 mmHg and 2 patients did not respond when NO was administered. Previous reports have also shown some patients to be non-responders to NO.¹⁷⁻²⁰

Our data are in contrast to those of Roissant *et al.*, who showed an improvement in RV ejection and RV end-diastolic volume once the PAP was reduced by a mean of 5 mmHg. This reduction in PAP was obtained with the administration of 18 ppm NO to patients with ARDS.²¹ However, in their study, despite the increase in RV ejection, the CO failed to improve. In view of the fact that the CO was measured directly as a function of RV function (thermodilution), the constant CO in the face of an improved RV ejection fraction cannot easily be explained. The authors speculate that the absence of a reduction in SVR is responsible for the failure of the CO to increase and refer to the increased CO that occurred when, in their study, prostacycline was used.

Previous studies, conducted in animals with thromboxane-induced pulmonary artery hypertension⁸ and human volunteers with pulmonary hypertension induced with alveolar hypoxia,²² demonstrated that NO reduces PAP. Studies in human ARDS have also suggested a reduction in PAP when patients were exposed to NO.¹⁷⁻¹⁹ The study by Roissant *et al.* evaluated the effect of NO on gas exchange and PAP in 30 patients with ARDS.¹⁹ They confirmed improvement in gas exchange and in 63% of their patients PAP was reduced by more than 3 mmHg (regarded as responders). In absolute values, the mean decrease in PAP they recorded was 4 mmHg but they failed to demonstrate an improvement in cardiac output associated with this small change in PAP. In another study by Roissant *et al.*¹⁷ the authors showed a mean reduction in PAP of 7 mmHg while Bigatello and colleagues demonstrated an average reduction in PAP of only 4 mmHg.¹⁸ Gerlach *et al.* suggested that only in ARDS patients with an initial mean PAP in excess of 45 mmHg was there a significant reduction in the PAP once NO was given.²⁰

In our study we only used up to 30 ppm. This decision was taken in light of the USA Occupation Safety and Health Administration Standards which set the maximal working exposure level for NO at 25 ppm (8 hours).²² In addition, there is little data which supports the use of higher doses of NO to improve outcome of these critically ill patients and it was therefore decided not to use high concentrations of NO.

On re-evaluation of the initial hypothesis it can justifiably be asked whether there was sufficient reason to expect a significant reduction in pulmonary artery pressure in patients with ARDS. Although it is accepted that there is an element of pulmonary vasospasm associated with the pulmonary artery hypertension during ARDS, there is also evidence of intravascular obstruction caused by clot formation in the pulmonary arterial bed in patients with ARDS.²³ NO will only relieve arterial spasm and will not modify the intravascular mechanical obstruction. How much of the raised PAP is due to the clot formation and how much can be ascribed to vasospasm has not been elucidated. Studies showing the biggest reduction in PAP on the administration of NO were obtained in experiments where the pulmonary artery hypertension was caused solely by pulmonary arterial vasospasm such as thromboxane- and alveolar hypoxia-induced pulmonary artery hypertension.^{8,24} There is probably little reason to extrapolate these findings directly to human ARDS.

In conclusion, we failed to demonstrate a significant reduction in PAP in patients suffering from ARDS when administering NO in concentrations of 5 - 30 ppm.

Because of this, there was also no improvement in RV function or cardiac output. These results, seen against the background of previous results which have shown unpredictable and, at best, only small changes in PAPs when NO was administered, make the role of NO in the treatment of APHT during ARDS doubtful. In addition, studies to date have not demonstrated improved outcome in patients with ARDS who received NO. There is therefore currently little evidence to support the routine use of NO in ARDS.

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