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Inhaled nitric oxide and arterial oxygen tension in patients with chronic obstructive pulmonary disease and severe pulmonary hypertension

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Abstract

***Background* – Inhaled nitric oxide (NO) is a selective pulmonary vasodilator which can improve gas exchange in acute lung injury. However, it is uncertain that this effect on arterial oxygenation can be generalised to all lung diseases.**

***Methods* – The effects of inhaled NO on gas exchange were studied in nine patients with chronic obstructive pulmonary disease (COPD), 11 patients with severe pulmonary hypertension, and 14 healthy volunteers. A randomised sequence of 40 ppm of NO or air was inhaled for 20 minutes through an orofacial mask.**

***Results* – Inhaled NO reduced mean (SE) transcutaneous arterial oxygen tension ($TcPO_2$) from 9.6 (0.3) to 8.9 (0.4) kPa in healthy volunteers and from 7.4 (0.6) to 7.0 (0.5) kPa in patients with COPD. There was no change in $TcPO_2$ in patients with severe pulmonary hypertension. During inhalation of NO and air no change occurred in transcutaneous arterial carbon dioxide tension ($TcPCO_2$), arterial oxygen saturation (SaO_2) measured by pulse oximeter, or cardiac output determined by the transthoracic impedance method.**

***Conclusions* – Inhaled NO does not improve $TcPO_2$ nor increase cardiac output in normal subjects and patients with COPD, suggesting that inhaled NO worsens gas exchange. This could represent inhaled NO overriding hypoxic pulmonary vasoconstriction in COPD. The finding that $TcPO_2$ also fell when normal subjects inhaled NO suggests that a similar mechanism normally contributes to optimal gas exchange. Whilst inhaled NO can improve oxygenation, this effect should not be considered to be a general response but is dependent on the type of lung disease.**

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Keywords: nitric oxide, chronic obstructive pulmonary disease, pulmonary hypertension.

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Nitric oxide (NO) is endothelium-derived relaxing factor.[1 2] Vasorelaxation is caused by activation of soluble guanylate cyclase which increases the concentration of cyclic GMP in vascular smooth muscle.[3] Inhaled NO in low concentration (40 parts per million (ppm)) is a selective pulmonary vasodilator.[4] It improves the arterial oxygenation of infants with persistent pulmonary hypertension of the newborn.[5] In many patients with acute respiratory distress syndrome (ARDS) inhaled NO reduces the pulmonary artery pressure and increases arterial oxygenation by lessening intrapulmonary shunt.[6] Experimentally, inhaled NO reverses hypoxic pulmonary vasoconstriction.[7] Inhaled NO, however, can worsen gas exchange by overcoming the usual physiological mechanisms of matching ventilation (VA) and perfusion (Q). Whilst inhaled NO acts as a selective pulmonary vasodilator in some patients with chronic obstructive pulmonary disease (COPD), it fails to improve oxygenation.[8 9] It is important to establish in which diseases inhaled NO fails to improve gas exchange. We have studied the change in arterial oxygenation during NO inhalation in patients with COPD and compared it with normal volunteers and patients with severe pulmonary hypertension.

Methods

Nine patients with COPD, 11 with severe pulmonary hypertension, and 14 healthy volunteers were studied. All gave their informed consent and the study was approved by the local hospital ethics committee. The diagnosis of COPD was established from a history of clinical and physiological evidence of irreversible airway obstruction. All patients with COPD ceased bronchodilators 12 hours before the study. The diagnosis of severe pulmonary hypertension was established by previous right heart catheterisation. All patients with severe pulmonary hypertension were receiving vasodilator therapy.

Measurements were made after breathing normal air or after breathing air with 40 ppm NO, both for 20 minutes. The order of giving the treatments was randomised and delivered in a single blind fashion.

The NO (British Oxygen Company Ltd, London, UK) was supplied in cylinders in a concentration of 10 000 ppm NO in nitrogen. The inspired gas mixture of NO in air (40 ppm) was prepared using an NO delivery system[10] (PneuPAC Ltd, Luton, UK) which was delivered to the patients using a close fitting nasal mask (Nasal CPAP mask, Puritan-Bennett Corporation, Indianapolis, Indiana, USA) fitted with two one-way valves (fig 1). Continuous monitoring of the NO and nitrogen dioxide (NO_2) concentration in the inspirate was made by fuel cell monitors (Models EC90 and EC40,

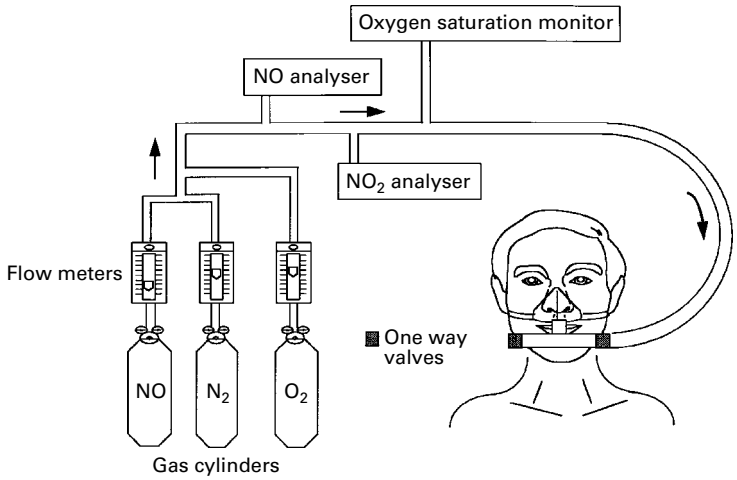

Figure 1 Nitric oxide delivery system.

Bedfont Scientific Ltd, Kent, UK). Each analyser was calibrated with a standard gas of 80 (1) ppm NO in nitrogen and 10 ppm NO_2 (British Oxygen Company Ltd, London, UK). The fractional inspired oxygen concentration (Fio_2) of the inhaled gas was monitored continuously using a portable oxygen monitor (TED 200-T, Teledyne Electronic Devices, City of Industry, California, USA). Air was supplied to the nasal mask by the same delivery system.

The venous blood methaemoglobin (Met-Hb%) formed from inhaled NO was measured from samples collected from an antecubital vein before and after each inhalation period using a multiple wavelength spectrophotometric CO oximeter (IL282 CO-Oximeter, Instrumentation Laboratory, Lexington, Massachusetts, USA). Total lung capacity (TLC) was measured by whole body plethysmography, and dynamic lung volumes (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)) were measured with a dry wedge spirometer. Transcutaneous arterial oxygen and carbon dioxide tensions ($TcPo_2$, $TcPco_2$) were measured, respectively, by Servomed Oxymonitor and Servomed Kapnomonitor (Hellige GmbH, Freiburg im Breisgau, Germany). Arterial oxygen saturation (Sao_2) was measured by pulse oximeter (Pulsox-DP7, Minolta, Tokyo, Japan) and cardiac output by the transthoracic impedance method (NCCOM 3 cardiovascular monitor, BioMed Medica Manufacturing Inc, Irvine, California, USA).[11]

STATISTICAL ANALYSIS

Two way analysis of variance was used together with a paired Student's *t* test to assess differences between treatments. p values of less than 0.05 were considered significant. The results are expressed as mean and standard error.

Results

The FEV_1 was 26 (9)% predicted and the FEV_1/FVC ratio was 38 (7)% in patients with COPD (table 1). Most patients with severe pulmonary hypertension took calcium antagonists or angiotensin converting enzyme inhibitors. No patient was receiving treatment with continuous intravenous infusion of prostacyclin (table 2). The patients with severe pulmonary hypertension had high values of pulmonary vascular resistance (PVR). Inhaled NO reduced mean $TcPo_2$ from 9.6 (0.3) kPa to 8.9 (0.4) kPa ($p < 0.05$) in healthy volunteers and from 7.4 (0.6) kPa to 7.0 (0.5) kPa (p

Table 1 Mean (SE) data for patients and volunteers

	Number	*Age (years)*	*M:F*	*FEV_1 (% pred)*	*VC (% pred)*	*FEV_1/FVC (%)*	*Mean arterial pressure (mm Hg)*
Volunteers	14	32.2 (2.1)	10:4	101 (5)	98 (4)	94 (4)	–
COPD	9	69.0 (2.0)	5:4	26 (9)	50 (10)	38 (7)*	–
Pulmonary hypertension	11	32.4 (2.0)	4:7	73 (7)	77 (7)	86 (5)	59.1 (5.0)

FEV_1 = forced expiratory volume in one second; VC = vital capacity; FVC = forced vital capacity; COPD = chronic obstructive pulmonary disease.
* FEV_1/FVC was significantly lower in patients with COPD than in the other two groups ($p<0.01$).

Table 2 Haemodynamic data of the patients with pulmonary hypertension

Age	*Diagnosis*	*Ppa (mm Hg)*	*PVR (dynes.s.cm^{-5})*	*SVR (dynes.s.cm^{-5})*	*CI l.m^{-2}.min^{-1})*	*PaO_2 (kPa)*	*SaO_2 (%)*	*Treatment*
34	PPH	54	18.8	31.3	1.3	8.5	–	W, Heparin
22	PPH	53	15.9	26.9	1.35	9.1	96	W, Dil, Frusemide,
61	PPH, thrombo	47	16.6	37.9	1.3	8.0	95.2	W, Dil, Frusemide,
32	PPH	54	23	31.5	–	7.7	87	W, Dil, Frumil, Digitoxin
51	PPH	40	8.3	30.5	2	8.8	94	W, Dil, Frumil, Bendrofluazide, Thyroxine, Dothiepin
58	PPH, thrombo	72	20	32.8	1.65	8.3	91	W, Dil, Frumil
24	PPH	75	17.6	22.4	2.2	9.6	94	W, Dil
26	PPH	80	16.2	21.4	1.8	9.7	96	W, Dil
29	PPH	83	17.9	23.5	2.55	9.5	88	W, Dil
36	SPH, sarcoidosis	53	9.7	21.1	2.9	9.6	92	W, Dil, Frusemide, Frumil, Prednisolone
42	SPH, CFA	39	8	17.8	2.1	8.8	89	Nasal oxygen
37.7 (4.1)		59.1 (4.7)	15.6 (1.5)	27.0 (1.9)	1.9 (0.2)	8.86 (0.21)	92.2 (1.1)	

Ppa = pulmonary arterial pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CI = cardiac index; Pao_2 = arterial oxygen tension; Sao_2 = arterial oxygen saturation; PPH = primary pulmonary hypertension; SPH = secondary pulmonary hypertension; thrombo = secondary to pulmonary thromboembolism; CFA = cryptogenic fibrosing alveolitis; W = warfarin; Dil = diltiazem.

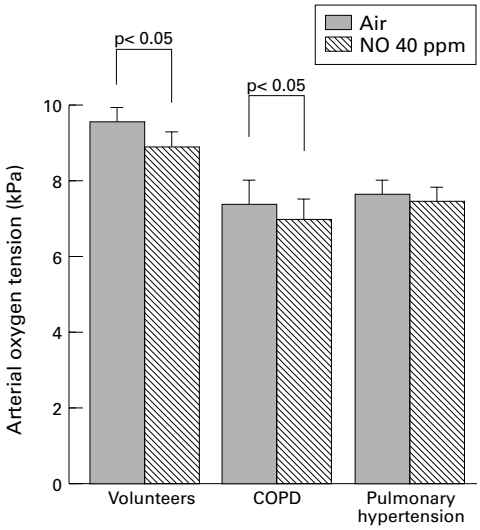

Figure 2 Transcutaneous arterial oxygen tension during 20 minutes breathing 40 ppm nitric oxide (NO) and a similar period of breathing air in patients with chronic obstructive pulmonary disease (COPD), severe pulmonary hypertension, and in volunteers. No change was observed in the arterial oxygen tension in patients with severe pulmonary hypertension, but it was reduced in the normal subjects and the patients with COPD (both p<0.05) following inhalation of NO.

<0.05) in patients with COPD. In patients with severe pulmonary hypertension $TcPo_2$ was 7.6 (0.4) kPa with air and 7.4 (0.4) kPa with inhaled NO ($p = 0.68$; fig 2). No changes occurred in the $TcPco_2$, Sao_2, or cardiac output in patients or volunteers with inhaled NO (table 3). No significant changes in venous MetHb% level were observed during inhaled NO (table 3).

Discussion

In patients with COPD and in normal subjects the $TcPo_2$ fell during the 20 minute period of breathing 40 ppm of NO in air; no change in $TcPo_2$ occurred in patients with severe pulmonary hypertension. These observations support the idea that inhaled NO appears to worsen gas exchange in those patients where the change in pulmonary haemodynamics is small.[4 8 9]

A concentration of 40 ppm inhaled NO was chosen on the basis of an isolated lung experiment in which pretreatment with the NO synthase inhibitor N^G-nitro-L-arginine caused a fall in PVR which was normalised by 40 ppm and 80 ppm inhaled NO but not by 10 ppm.[12] To ensure that the correct concentration of NO was administered a nasal CPAP mask was used which is more airtight than a face mask. Moreover, the use of two one-way valves ensured that patients were unable to re-breathe expired air. The Sao_2 and NO and NO_2 concentrations were monitored to avoid the development of hypoxia and NO and NO_2 toxicity. NO reacts with oxygen and forms NO_2 which can cause airway injury so NO was first mixed with nitrogen and then oxygen (fig 1).

The study was dependent on the accuracy of the non-invasive measurements which were chosen to involve minimal disturbance to the haemodynamics of the study participants. The measurement of $TcPo_2$ was first reported in 1969 by Huch *et al*.[13] The sensor allows measurement of $TcPo_2$ which reflects the arterial oxygen pressure (Pao_2)[14] in many clinical conditions. We allowed 20 minutes exposure to each gas mixture which is sufficient for the fall in Pao_2 to be detected by the $TcPo_2$.[13] The low cardiac output and poor tissue perfusion in the patients with severe pulmonary hypertension could have decreased the accuracy of the $TcPo_2$ measurement. However, inhaled NO does not necessarily increase the Pao_2 in patients with severe pulmonary hypertension. This is partly explained by the fact that, although the pulmonary artery pressure falls, cardiac output does not increase with inhaled NO.[4 6 7] As previously reported, cardiac output did not change in any of our patient groups (table 3). The transthoracic impedance method of measuring cardiac output is valid in many patient groups[11] and in normal subjects[15 16] and reliably follows the changes in cardiac output seen with exercise.[11] An additional explanation for the failure to improve $TcPo_2$ in patients with severe pulmonary hypertension could be the existing vasodilator treatment which will lessen the vasodilator effects of inhaled NO.

Inhaled NO is a selective pulmonary vasodilator,[4–7] causing relaxation of smooth muscle cells of the pulmonary precapillary resistance arteries.[17] These vessels are found within the pulmonary acini and the distance of diffusion of inhaled NO into the smooth muscle of these vessels is no greater than into the alveolar capillaries. Most of the inhaled NO is taken up in alveolar capillaries where it combines rapidly with oxyhaemoglobin within red blood cells to form methaemoglobin and nitrate.[18 19] The formation of methaemoglobin effectively inactivates NO which has no subsequent action on the systemic circulation. Our failure to demonstrate a change in venous MetHb% agrees with earlier work on short term exposure to NO[5–7] and reflects the efficiency of the red blood cell methaemoglobin reductase in restoring iron II haemoglobin.[19]

Table 3 Mean (SE) haemodynamic and gas exchange data on air and after 20 minutes of 40 ppm nitric oxide (NO) inhalation

	Volunteers		*COPD*		*Pulmonary hypertension*	
	Air	*NO*	*Air*	*NO*	*Air*	*NO*
Cardiac output (1/min)	5.2 (0.4)	5.1 (0.4)	4.3 (0.6)	4.4 (0.6)	3.3 (0.4)	3.4 (0.3)
$TcPco_2$(kPa)	6.6 (0.3)	6.5 (0.4)	8.1 (0.4)	8.0 (0.5)	6.3 (0.4)	6.3 (0.4)
$TcPo_2$(kPa)	9.6 (0.3)	8.9 (0.4)*	7.4 (0.6)	7.0 (0.5)*	7.6 (0.4)	7.4 (0.4)
Sao_2(%)	97.6 (0.2)	97.4 (0.3)	87.2 (2.1)	87.6 (1.7)	93.2 (0.9)	92.5 (1.0)
Methaemoglobin (mg/dl)	0.8 (0.1)	0.8 (0.1)	1.0 (0.2)	0.8 (0.1)	0.4 (0.1)	0.7 (0.1)

* p<0.05 versus air inhalation.

Inhaled NO improves Pa_{O_2} in certain lung diseases. In ARDS inhaled NO is distributed to ventilated regions of the lung where it increases perfusion. Probably by a "steal" phenomenon, the inhaled NO lessens blood flow in regions of intrapulmonary shunt by diverting it from the unventilated regions[6] to ventilated regions. On the other hand, the effect of aerosolised prostacyclin in ARDS has been reported to be the same as inhaled NO.[20] However, there was still a larger decrease in systemic vascular resistance during aerosolised prostacyclin than during inhaled NO. In persistent pulmonary hypertension of the newborn the Pa_{O_2} is also increased by inhaled NO. This is simply by reducing the pulmonary artery pressure which reverses the amount of right to left shunt through the patient's ductus arteriosus.[5]

Patients with COPD do not have high values of pulmonary vascular resistance[8 9] and have normal or even raised cardiac output.[21] Inhaled NO will be expected to have only a minimal haemodynamic effect in these patients. One of the major abnormalities in patients with COPD is the disturbance of the distribution of ventilation. The homogeneity of the distribution of ventilation is reflected by the wide range of time constants.[22] Conventional NO inhaled at a fixed concentration can be expected to reach regions with both slow and fast ventilation. Furthermore, in diseases such as emphysema collateral ventilation occurs.[23] We do not know the minimum alveolar concentration of inhaled NO needed to cause pulmonary vasodilation in humans, although concentrations as low as 1 ppm in the inhaled gas mixture can cause vasodilatation.[24] Alveolar concentrations are likely to be well below this level and yet are effective, so even slow ventilated regions of the lungs in patients with COPD are likely to receive sufficient NO to overcome hypoxic vasoconstriction.[6] This, in turn, will lead to poorer matching of VA/Q and worsening gas exchange. The pulmonary endothelial production of NO is dependent on alveolar partial pressure of oxygen.[25] Hypoxia inhibits endothelial NO production[26] which suggests that it might play a parallel role to the direct action of hypoxia on pulmonary artery tone[27] in regulating pulmonary blood flow. In diseases such as COPD alveolar hypoxia enhances the matching between the distribution of ventilation and perfusion by reducing perfusion of unventilated regions. Overriding of this effect by inhaled NO may account for the fall in $TcPo_2$ seen in the patients with COPD and is supported by the observed widening of the distribution of the VA/Q in these patients when NO is inhaled.[28]

It is interesting that a similar fall in $TcPo_2$ with inhaled NO was also seen in normal volunteers. As the cardiac output was unchanged it can be concluded that, under resting conditions, matching of ventilation and perfusion is an active process even in healthy subjects. It is possible that pulmonary artery vasoconstriction occurs even in normal subjects and that this is a cause of close matching of VA/Q. This idea is supported by the fact that, in normal volunteers, inhalation of hyperoxic gas mixtures can cause an increased inequality in VA/Q.[29] In other words, there is evidence that hypoxic vasoconstriction contributes to the matching of VA/Q even in normal subjects.

It can be questioned whether pulmonary endothelial NO subserves a similar function. Whilst inhaled NO does not necessarily improve Pa_{O_2} in patients with COPD, it is still effective in other chronic lung diseases. In patients with pulmonary fibrosis[30] inhaled NO improves arterial oxygenation. These patients, however, behaved like the patients with severe pulmonary hypertension, with marked improvement of pulmonary haemodynamics as well as a rise in Pa_{O_2}. This serves to emphasise the fact that important differences in the response of patients to inhaled NO depend upon the underlying pathophysiology of the lung disease.

In conclusion, inhaled NO is a selective pulmonary vasodilator with considerable therapeutic potential. In many diseases it can also improve gas exchange, lessening hypoxaemia. In patients with COPD the gas exchange is not necessarily improved. Existing delivery systems for inhaled NO do not selectively distribute NO to fast ventilated regions alone and so the benefits of hypoxic vasoconstriction are overridden. The same effect of inhaled NO in our volunteers suggests that an element of mismatching between VA/Q driven by hypoxic vasoconstriction occurs even in the normal lung.

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