NO: COPD and beyond

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Introductory article

Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease

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Background. Inhalation of nitric oxide (NO) causes selective pulmonary vasodilation and improves arterial oxygenation in acute respiratory distress syndrome. But some patients do not respond or gas exchange worsens when inhaling NO. We hypothesised that this detrimental effect might be related to the reversion of hypoxic vasoconstriction in those patients where this mechanism contributes to ventilation-perfusion (VA/Q) matching. **Methods.** We studied 13 patients with advanced chronic obstructive pulmonary disease (COPD). We compared their responses to breathing room air, NO at 40 parts per million in air, and 100% O₂. Changes in pulmonary haemodynamics, blood gases, and VA/Q distributions were assessed. **Findings.** NO inhalation decreased the mean (SE) pulmonary artery pressure from 25.9 (2.0) to 21.5 (1.7) mm Hg (p=0.001) and PaO₂ from 56 (2) to 53 (2) mm Hg (p=0.014). The decrease in PaO₂ resulted from worsening of VA/Q distributions, as shown by a greater dispersion of the blood-flow distribution (logSD Q̇) from 1.11 (0.1) to 1.22 (0.1) (p=0.018). O₂ breathing reduced the mean pulmonary arterial pressure to 23.4 (2.1) mm Hg and caused greater VA/Q mismatch (logSD Q̇, 1.49 [0.1]). The intrapulmonary shunt on room air was small (2.7 [0.9]%) and did not change when breathing NO or O₂. **Interpretation.** We conclude that in patients with COPD, in whom hypoxaemia is caused essentially by VA/Q imbalance rather than by shunt, inhaled NO can worsen gas exchange because of impaired hypoxic regulation of the matching between ventilation and perfusion. (Lancet 1996;347:436–40)

The increasing use of inhaled nitric oxide (NO) as a pulmonary vasodilator has stimulated intense research interest in recent years. Nevertheless, as shown by the introductory article by Barberà *et al*,¹ NO may not be beneficial in all pulmonary conditions complicated by elevated pulmonary vascular resistance. In this review the basic properties of NO are described, and the general problems surrounding the use of pulmonary vasodilators in the treatment of respiratory failure are discussed.

Nitric oxide

In 1980 Furchgott and Zawadzki first demonstrated the ability of mammalian cells to synthesise an endothelially-derived relaxant factor (EDRF).² In 1987 two independent groups suggested that EDRF and nitric oxide (NO) were the same substance,^{3,4} an hypothesis that has since gained widespread acceptance. Subsequently, NO has been the subject of intense investigation, and a substance that had long been considered as nothing more than an environmental pollutant is now acknowledged to be an almost ubiquitous biological mediator, involved in processes as diverse as the regulation of blood flow, neurotransmission, inflammatory and

immunological defence mechanisms, coagulation and, possibly, cell growth.⁵

Nitric oxide is synthesised from the terminal guanidino nitrogen of the semi-essential amino acid L-arginine and molecular oxygen in a stereospecific reaction catalysed by a family of nitric oxide synthases (NOS), citrulline being the co-product (fig 1).⁶ Three major isoforms of these complex haemoproteins have been identified. Two, neuronal NOS (nNOS or type 1) and endothelial NOS (eNOS or type 3), are expressed constitutively and are collectively termed constitutive NOS (cNOS). Expression of a third isoform (iNOS or type 2) can be induced by various cytokines in macrophages and a number of nucleated mammalian cells, including smooth muscle and vascular endothelial cells. All forms of the enzyme are highly regulated, requiring numerous cofactors. The constitutive form is also calcium dependent.⁷ Nitric oxide is a small, uncharged molecule with water and lipid solubility properties similar to carbon monoxide and oxygen. In the circulation it acts as a vasodilator, diffusing rapidly from the endothelium to neighbouring smooth muscle cells where it activates soluble guanylate cyclase, binding directly to its haem moiety, leading to an increase in the second messenger

Figure 1 Synthesis and action of nitric oxide. cNOS= constitutive nitric oxide synthase; NO= nitric oxide; GTP= guanosine triphosphate; cGMP= cyclic guanosine monophosphate; sGC= soluble guanylate cyclase; $[Ca^{2+}]_i$ = intracellular calcium.

cyclic guanosine monophosphate (cGMP), resulting in relaxation. The mechanism by which cGMP causes relaxation has yet to be fully determined. Nitric oxide is a free radical, by virtue of its unpaired electron, and is highly reactive, its physiological half life being measured in seconds. Its fate depends upon the prevailing metabolic conditions, but several of its metabolites are toxic. Nitric oxide also binds avidly to haemoglobin, resulting in methaemoglobinaemia, this being one of the pathways by which it is inactivated, particularly on the luminal surface of the endothelium.^{6,8}

Nitric oxide and the pulmonary circulation

The existence of NO has been confirmed in the mammalian pulmonary circulation,⁹ including that of man.¹⁰ Under physiological conditions the pulmonary vasculature exhibits a low degree of resting tone, despite receiving the whole of the cardiac output, and operates at pressures approximately 20% of those in the systemic circulation. Even when cardiac output rises markedly, pulmonary artery pressure (Ppa) does not increase significantly. It has been suggested that these characteristics are attributable to the continuous release of NO stimulated by changes in wall shear stresses. Scientific evidence for this hypothesis is contradictory. Thus, NOS inhibitors enhance pulmonary vascular tone in some models, but have no effect in those that attempt to keep cardiac output constant, thereby avoiding passive, flow-dependent changes in pulmonary vascular tone.¹¹ Chronic inhibition of NOS in rats causes systemic, but not pulmonary, hypertension.¹² Controversy also surrounds the role of NO in the response of the pulmonary circulation to hypoxia. Hypoxic vasoconstriction (HPV) is considered, teleologically, to be a protective response, diverting blood away from less well ventilated areas of lung, thereby maintaining ventilation-perfusion ($\dot{V}/\dot{Q}$) matching. The mechanism underlying HPV has been the subject of intense investigation since the phenomenon was first described in 1947.¹³ Many vasoactive mediators, including NO, have been proposed as putative mediators of HPV,¹⁴ although it is now believed to be an inherent property of the vascular myocyte¹⁵ related to the direct action of hypoxia on membrane potassium channels.^{14,16} Inhibition of NO under hypoxic conditions leads to an enhanced hypoxic pressor response,¹⁷ and increased levels of NO and its metabolites are produced by bovine

endothelial cells under hypoxic conditions.¹⁸ This suggests that NO activity is potentiated under conditions of acute hypoxia, possibly modulating the pulmonary vasoconstrictor response. In chronic hypoxia remodelling of the peripheral pulmonary arterial tree occurs, with intimal and smooth muscle cell proliferation. Nitric oxide is known to inhibit smooth muscle cell¹⁹ and fibroblast proliferation.²⁰ Furthermore, decreased endothelially-dependent vascular contraction has been identified under conditions of chronic hypoxia,²¹ which may therefore represent a NO-deficient state. However, others have found that endothelially-dependent vasorelaxation is normal or even potentiated under conditions of chronic hypoxia,¹¹ inferring that, as in acute hypoxia, NO activity is actually augmented.

Pulmonary hypertension in chronic obstructive pulmonary disease (COPD)

Pulmonary hypertension can complicate most chronic lung diseases, but in contrast to the gross increases in Ppa (>50 mm Hg) seen in primary pulmonary hypertension or recurrent thromboembolic disease, those seen secondary to COPD are relatively mild (30–40 mm Hg).²² However, although Ppa may be normal or only slightly increased at rest in such patients, it may rise markedly during exercise²³ in association with acute infective exacerbations²⁴ and during episodes of arterial desaturation associated with rapid eye movement (REM) sleep.²⁵ Many factors are thought to contribute to the increase of Ppa in COPD, including hypoxia, hypercapnia, mechanical distortion of the pulmonary vascular bed, elevation of the cardiac output, and increased blood viscosity.²⁶ However, hypoxia is clearly significant, the rise in Ppa correlating with its severity. The rate of progression of pulmonary hypertension in COPD is slow, of the order of 3 mm Hg/year,²⁷ and correlates well with deterioration in arterial blood gas tensions.^{27,28} Despite this slow progression the presence of pulmonary arterial hypertension in patients with COPD is probably a poor prognostic sign. Thus, patients with a normal Ppa had a four year survival of 72% compared with 49% in those in whom Ppa was raised²⁹ although, in the same study, survival also correlated strongly with forced expiratory volume in one second (FEV₁). Others have found survival to correlate with arterial oxygen and carbon dioxide tensions (Pao₂, Paco₂), FEV₁, and the presence of peripheral oedema,³⁰ suggesting that the degree of pulmonary hypertension simply reflects the severity and progression of the underlying disease process.

Vasodilators in the treatment of pulmonary vascular disease

Studies using the multiple inert gas technique (MIGET)³¹ have confirmed that hypoxaemia in COPD can be entirely explained by the degree of ventilation ($\dot{V}$)/perfusion ($\dot{Q}$) mismatch.³² Such abnormalities, present even in mild disease,³³ worsen as the disease progresses, and also (reversibly) during exercise³⁴ and acute exacerbations.³⁵ In patients with COPD two distinct, abnormal patterns of $\dot{V}/\dot{Q}$ have been identified, often occurring simultaneously in the same patient. An increase in lung units with high $\dot{V}/\dot{Q}$ ratios represents areas that are ventilated but underperfused – for example, regions of emphysema; similarly, an increase in units with low $\dot{V}/\dot{Q}$ ratios is identifiable, representing areas that are perfused but underventilated.

The belief that pulmonary hypertension in COPD is

associated with a worse prognosis has provoked attempts to use vasodilator agents to reduce right ventricular afterload, increase cardiac output, and improve oxygen delivery and tissue oxygenation. The proven benefits of using vasodilators in primary pulmonary hypertension³⁶ have also led to their application in patients with COPD. Many agents have been evaluated but results have been uniformly disappointing. All such agents are non-selective vasodilators, causing systemic as well as pulmonary hypotension. Although an acute reduction in Ppa may be detectable, long term studies have failed to demonstrate any consistent improvement in pulmonary haemodynamics or a reduction in mortality. Some agents induce a worsening of peripheral oedema due to negative inotropy and a fall in cardiac output.^{37,38} Secondly, vasodilators are usually given systemically (oral or intravenously) and affect arteries serving well ventilated and poorly ventilated lung units equally. This results in a reversal of HPV in poorly ventilated regions,³⁹ although the resultant fall in arterial saturation and Pao₂ may be offset by increased oxygen delivery if cardiac output improves.

Until recently the only selective pulmonary vasodilator available for clinical use has been oxygen, the only therapy for patients with severe COPD that has been shown to improve long term survival in controlled trials.^{28,40} Studies with repeated haemodynamic assessment have shown that in some patients long term oxygen therapy (LTOT) administered for more than 15 hours/day may improve, or at least attenuate, the deterioration in pulmonary hypertension.^{41,42}

Inhaled NO

The use of inhaled NO as a selective pulmonary vasodilator is intellectually appealing and seems to be a role for which it is well suited. Nitric oxide is preferentially a gas and, with certain monitoring and safety practices, can be easily administered in a controlled fashion as an air/NO/oxygen mixture. In theory, administration by the inhaled route should result in selective vasodilation in ventilated alveolar units only, thereby minimising any detrimental effect on $\dot{V}/\dot{Q}$ of the reversal of hypoxic vasoconstriction. Avid binding to haemoglobin ensures that NO is rapidly inactivated, thereby obviating any systemic vasodilator effect. Nitric oxide may also have a bronchodilatory action.⁴³ Inhalation of NO has no effect on pulmonary or systemic haemodynamics, nor on gas exchange in awake lambs⁴⁴ or humans⁴⁵ breathing air, but completely reversed HPV induced in the same studies by inspiring 12% oxygen. In mechanically ventilated sheep this response has been attributed to redistribution of blood flow to better ventilated lung units.⁴⁶

There has been an explosion in the application of this novel therapy in many pulmonary diseases complicated by pulmonary hypertension. Reports have been made of its successful use in primary pulmonary hypertension,⁴⁷ respiratory failure in the newborn,⁴⁸ persistent pulmonary hypertension of the newborn,^{49,50} and pulmonary hypertension associated with congenital heart disease.⁵¹ In patients with acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) inhaled NO causes selective pulmonary vasodilation, reducing Ppa and improving oxygenation in a proportion of cases.⁵² Indeed, inhaled NO is now employed extensively in this context, despite a lack of randomised controlled trials to show efficacy. However, the hypoxaemia in ALI/ARDS can be completely explained by shunt,⁵³ there being some evidence that HPV is impaired in such

patients.⁵⁴ Under such conditions inhaled NO preferentially vasodilates arterioles supplying ventilated regions, improving oxygenation and lowering pulmonary vascular resistance (PVR). In other pulmonary conditions shunt is a less significant problem, and the preservation of adequate gas exchange depends on the integrity of HPV. In these conditions inhalation of NO, with the subsequent reversal in HPV, might be detrimental to $\dot{V}/\dot{Q}$ matching and gas exchange.

The study by Barberà *et al*⁵ is the most comprehensive of several recent investigations into the effects of inhaled NO in patients with COPD-associated pulmonary hypertension.⁵⁵⁻⁵⁷ Changes in haemodynamics and gas exchange were investigated in patients with advanced COPD in response to breathing room air, NO at 40 parts per million in air, and 100% oxygen. In common with other studies where direct haemodynamic measurements have been made, inhaled NO led to a significant decrease in Ppa (from 25.9 (2.0) to 21.5 (1.7) mm Hg) with no significant change in cardiac output or pulmonary artery occlusion pressure, representing a 22% fall in PVR. A less marked but significant fall in Ppa was also seen following inhalation of 100% oxygen (Ppa decreasing to 23.4 (2.1) mm Hg), although this was associated with a decrease in cardiac output so that, although the 9% fall in PVR was not statistically significant, no effect on the systemic circulation was noted with either vasodilator. Nitric oxide induced a significant fall in Pao₂ (from 56 (2) to 53 (2) mm Hg), with an increase in the alveolar-arterial (A-a) oxygen gradient. Inhalation of NO also worsened $\dot{V}/\dot{Q}$, as shown by broadening of perfusion distribution and a rise in the overall index of $\dot{V}_A/\dot{Q}$ heterogeneity estimated using MIGET with a 3% increase in blood flow to poorly ventilated alveolar units. Intrapulmonary shunt fraction, dead space ventilation, and distribution of alveolar ventilation remained unaltered. Similar but more marked changes in $\dot{V}/\dot{Q}$ inequality were seen following 100% oxygen (fig 2).

These findings are both in agreement and at odds with previously and subsequently published studies. In an earlier study inhaled NO induced a rise in Pao₂ and a fall in venous admixture in patients with COPD.⁵⁵ In the same study intravenous acetylcholine, a known stimulant of NO production from endothelial cells, worsened both indices. In a study in similar patients, comparing NO and 100% oxygen, no significant overall effect was seen on Pao₂ or $\dot{V}/\dot{Q}$ following inhaled NO (15 ppm).⁵⁶

However, a follow up study from the group of Barberà and colleagues using non-invasive measurements of arterial oxygenation and cardiac output confirmed worsening gas exchange following inhalation of NO (40 ppm), not only in patients with severe COPD but also in normal individuals.⁵⁸ The answer to these seemingly contradictory results probably lies in the analysis of changes occurring within individual patients. In the study under review, although the overall effect was of worsening gas exchange, three of 13 patients actually improved (fig 3). Similarly, when individual patient responses are analysed in the previously published studies^{56,57} both improvement and deterioration can be identified, with no obvious predictors of response.

Should we be surprised by the results of such investigations? It is known that hypoxaemia in COPD can be explained in terms of $\dot{V}/\dot{Q}$ mismatch alone, and that intrapulmonary shunt is minimal.³² Although intravenous vasodilators lower Ppa, they worsen gas exchange due to non-selective reversal of HPV.^{37,38} Oxygen also worsens $\dot{V}/\dot{Q}$ matching,⁵⁸ even when inspired in

Figure 2 Ventilation-perfusion ($\dot{V}/\dot{Q}$) distributions during inhalation of (A) room air, (B) nitric oxide, and (C) oxygen in a patient with COPD. NO worsened $\dot{V}/\dot{Q}$ distribution, as reflected by broadened blood flow distribution with increased dispersion (log SD $\dot{Q}$). During 100% oxygen breathing $\dot{V}/\dot{Q}$ mismatch increased further, giving a bimodal pattern to blood flow distribution with substantial perfusion in areas with low $\dot{V}/\dot{Q}$ ratios. Shunt did not change significantly on nitric oxide or oxygen. Reproduced with permission from reference 1.

low concentrations (26%),⁵⁹ presumably due to the reversal of HPV in poorly ventilated areas of lung which increases perfusion to alveolar units with low $\dot{V}/\dot{Q}$ ratios. Nitric oxide reverses HPV in both experimental animals⁴⁴ and humans,⁴⁵ and the selective pulmonary vasodilatation it causes (as with oxygen) is associated with worsening $\dot{V}/\dot{Q}$ matching, gas exchange, and increasing hypoxaemia. This explanation is supported by the finding that nebulised prostacyclin (PGI_2) worsens hypoxaemia in patients with severe pneumonia in the presence of pre-existing pulmonary fibrosis. Intrapulmonary shunt due to loss of HPV is known to account for a considerable degree of hypoxia in pneumonia, and in patients with otherwise normal lungs aerosolised PGI_2 led to an improvement in gas exchange.⁶⁰

Is there a future for the use of inhaled NO in COPD complicated by pulmonary hypertension? The answer depends in part on whether pulmonary hypertension is

Figure 3 Effect of NO inhalation on arterial oxygen tension (Pao_2) in patients with COPD. Open symbols = mean (SE). Pao_2 decreased significantly ($p < 0.05$) during NO inhalation. Reproduced with permission from reference 1.

truly an independent risk factor for morbidity or mortality, and should therefore be treated in its own right. However, if it is purely a marker of the severity of the underlying lung disease and resultant hypoxaemia, such directed therapy is probably not warranted. In ARDS much lower doses of NO have been employed (1–10 ppm),⁶¹ at which gas exchange is preferentially improved over Ppa. Low dose NO is therefore unlikely to be beneficial in COPD, as worsening of $\dot{V}/\dot{Q}$ matching will occur at doses lower than those required to improve pulmonary hypertension. Is there a possible role for combined therapy with NO and oxygen? This is theoretically an attractive option, combining the superior vasodilator effects of NO⁵⁵ with the ability to preserve oxygenation, and thus tissue oxygen delivery. In a recent study the effects of NO or oxygen on haemodynamics and gas exchange were compared with the combined inhalation of NO and oxygen, in spontaneously breathing subjects with COPD.⁶² Pulmonary haemodynamics and blood gas tensions were measured after room air, oxygen (1 l/m), NO added to air, and NO and oxygen. The inhalation of NO (2 ppm) was associated with a significant fall in Ppa and PVR and a minor fall in Pao_2 compared with room air. Breathing oxygen alone had no significant effect on pulmonary haemodynamics, but obviously improved oxygenation. However, NO and oxygen combined not only led to a significant fall in Ppa and PVR, but also to a remarkable improvement in Pao_2 compared with values obtained with oxygen alone. Whilst these findings may have exciting implications with regard to the future long term treatment of COPD, at present there are several practical difficulties in using this approach. Nitric oxide reacts avidly with oxygen to form nitrogen dioxide which is highly toxic to human cells, the reaction being increasingly vigorous at higher oxygen concentrations. Present delivery systems for NO are cumbersome and complicated,

LEARNING POINTS

- * Nitric oxide is a ubiquitous mediator, involved in many biological systems.
- * Although its role in the systemic circulation is well described, its role in the pulmonary circulation, particularly in modulating the response to hypoxia, is less well understood.
- * When inhaled, NO acts as a selective pulmonary vasodilator, decreasing Ppa, with no effects on the systemic circulation.
- * In cases of respiratory failure where shunt is the predominant cause of hypoxia, inhaled NO is likely to improve gas exchange. In the presence of pre-existing lung disease, where HPV is important in maintaining adequate V/Q matching, its use is likely to be detrimental.
- * Despite encouraging results in some conditions, concerns still exist with regard to the safety of its application, and it remains unlicensed for general therapeutic use in the UK.

making combination with domiciliary oxygen therapy impractical, inaccurate, and potentially dangerous. However, in patients with COPD and acute respiratory failure requiring high dependency or intensive care, it may be possible to manipulate both Ppa and gas exchange with this combination.

Almitrine, a selective peripheral chemoreceptor stimulant, has been shown to improve oxygenation in patients with COPD⁶³ to a greater than expected extent for the degree of increased ventilatory drive, suggesting that almitrine may improve V/Q. Several studies have subsequently confirmed that almitrine is associated with increases in Ppa and PVR with an increased proportion of higher V/Q units, even when ventilation remains constant, presumably due to enhanced HPV diverting the circulation from poorly to well ventilated lung units.^{64 65} Theoretically, a combination of almitrine and NO therapies in COPD would enhance HPV in poorly ventilated alveolar units whilst selectively vasodilating well ventilated alveolar units. Such an approach has been studied in patients with ARDS⁶⁶ and was found to have additive effects on oxygenation whilst decreasing Ppa. However, there are fundamental pathophysiological differences in both the mechanisms of hypoxia and pulmonary hypertension between ARDS and COPD. The use of a therapeutic agent known to cause pulmonary vasoconstriction, even with concomitant application of a pulmonary vasodilator, may be undesirable in patients with COPD. However, long term studies have shown that, with low dose almitrine therapy at least, the effects on pulmonary haemodynamics may be transient, with no significant worsening in Ppa at rest or on exercise, whilst improvements in gas exchange are maintained after 12 months.^{67 68}

The results of the investigation by Barberà *et al* and similar studies have a message that extends beyond the therapeutic use of inhaled NO in patients with COPD. Following the seemingly successful application of this treatment in patients with ARDS there has been a tendency to consider its use in other forms of respiratory failure complicated by pulmonary hypertension. However, the only randomised controlled trials performed to date have been in neonates with hypoxaemic respiratory failure⁴⁸ and persistent pulmonary hypertension of the newborn.⁵⁰ In both studies inhaled NO improved oxygenation and decreased the need for more invasive procedures, but in neither study was an effect on mortality shown. Secondly, NO remains an unlicensed therapy in the UK. Its possible side effects are incompletely understood, resulting in concerns over the safety of its use.⁶⁹ Inhaled NO and similar therapies are only likely

to be of benefit in improving gas exchange in respiratory failure when there is no evidence of pre-existing lung disease and the principal mechanism of hypoxia is increased intrapulmonary shunt. In other conditions HPV is likely to be an important mechanism in the preservation of V/Q matching, and inhaled vasodilators – even if specific for the pulmonary circulation – are likely to cause a deterioration in gas exchange.

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