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 vasconstriction 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 Q) 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 Q, 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 Barberá et al, 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). In 1987 two independent groups suggested that EDRF and nitric oxide (NO) were the same substance, an hypothesis that has since gained widespread acceptance. Subsequently, NO has been the subject of intense investigation, and a substance that has 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. Nitric oxide is synthesised from the terminal guanino dinitrogen 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). 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. 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.
The existence of NO has been confirmed in the mammalian pulmonary circulation, including that of man. 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. However, NO activity is potentiated under conditions of chronic hypoxia, suggesting that 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 secondary to COPD are relatively mild (30-40 mm Hg). However, although Ppa may be normal or only slightly increased at rest in such patients, it may rise markedly during exercise in association with acute infective exacerbations and during episodes of arterial desaturation associated with rapid eye movement (REM) sleep. Any 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. 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 and correlates well with deterioration in arterial blood gases.

Vasodilators in the treatment of pulmonary vascular disease

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

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 vasodilator agents in primary pulmonary hypertension 

\[ Ppa \]

41 42 (A±a) oxygen gradient. Inhalation of NO also worsened ARDS can be completely explained by shunt, there was change due to non-selective reversal of HPV. 37 38 Oxygen tension, respiratory failure in the newborn, persistent worsening gas exchange, three of 13 patients actually by pulmonary hypertension. Reports have been made of changes occurring within individual patients. In the studies by inspiring 12% oxygen. In mechanically ventilated 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. 44 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 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 V/Q mismatch alone, and that intrapulmonary shunt is minimal. 45 Although intravenous vasodilators lower Ppa, they worsen gas exchange due to non-selective vasodilation. 46 Change was also worsens V/Q matching, even when inspired in
Figure 3 Effect of NO inhalation on arterial oxygen tension (PaO₂) in patients with COPD. Open symbols = mean (SE). PaO₂ 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), at which gas exchange is preferentially improved over Ppa. Low dose NO is therefore unlikely to be beneficial in COPD, as worsening of V/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 NO 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. Pulmonary haemodynamics and blood gas tensions were measured after room air, low concentrations (26%), presumably due to the reversal of HPV in poorly ventilated areas of lung which increases perfusion to alveolar units with low V/Q ratios. Nitric oxide reverses HPV in both experimental animals and humans, and the selective pulmonary vasodilatation it causes (as with oxygen) is associated with worsening V/Q matching, gas exchange, and increasing hypoxaemia. This explanation is supported by the finding that nebulised prostacyclin (PGI₂) 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 PGI₂ led to an improvement in gas exchange.

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
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, inaccuracy, and potential danger. However, in patients with COPD and acute respiratory failure requiring high dependency or intensive care, it may be possible to manipulate both 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.4,45 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 ARDS46 and was found to have additive effects on oxygenation whilst decreasing Ppa. However, there are fundamental pathological 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 concurrent 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.46,47

The results of the investigation by Barberá 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.49 In both studies inhaled NO improved oxygenation and decreased the need for more invasive procedures, but in neither study was an effect on morbidity or mortality shown. Secondly, NO remains an unlicensed therapy in the UK. Its possible side effects are incompletely understood, rendering in concerns over the safety of its use.49 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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