Chronic lung disease and pulmonary hypertension: yes or no to NO?

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Nitric oxide (NO) is synthesised *in vivo* from the semi-essential amino acid, L-arginine. It is a small uncharged molecule with an unpaired electron, making it rapidly diffusible through cell membranes but highly reactive. It is a vasodilator, this effect being achieved following activation of soluble guanylyl cyclase after binding to its haem moiety, with a resultant increase in intracellular cyclic guanosine monophosphate (cGMP).¹ Endogenous NO appears to make an important contribution to the maintenance of vascular tone in many species, including man. In particular, infusion of the nitric oxide synthase inhibitor, L-NMMA, in man leads to an increase of approximately 40% in pulmonary vascular resistance (PVR) and a 60% increase in systemic vascular resistance (SVR).² NO is, in many ways, well equipped to be employed as a selective vasodilator in the lung. The ability to administer NO/air/oxygen mixtures in a controlled fashion has led to an ever expanding utilisation of this agent both as a research tool and as a treatment. In particular, the administration of NO by inhalation to patients with sepsis complicated by acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) has proved to be an elegant concept by which dilatation of pulmonary vasculature only occurs in areas of the lung that are ventilated.³ The improved blood flow through the lungs can therefore be targeted to areas that were best able to oxygenate it, hence reducing ventilation/perfusion (VA/Q) mismatch whilst simultaneously reducing PVR and often improving right ventricular performance.⁴ Perhaps most elegant of all, upon reaching the blood NO is rapidly inactivated by its avid binding to haem, thereby removing its potential for deleterious systemic vasodilation. Inhaled NO is now being employed extensively in this context with considerable reported success, despite the lack of hard evidence in the form of randomised controlled trials, as well as concerns over safety.⁵ Although the results of the first clinical trials assessing inhaled NO therapy in the context of persistent pulmonary hypertension of the newborn are due to be published within the next 12 months,^{6,7} similar trials are awaited in adults.

The intellectual appeal of the therapeutic use for NO in ALI overshadows our lack of a clear understanding of the role of endogenous NO in fundamental physiological and pathophysiological reactions, central to which is hypoxic pulmonary vasoconstriction (HPV). In teleological terms we assume HPV is a beneficial reaction by which VA/Q matching is continuously maintained, but as yet the underlying mechanism is incompletely understood. The role of NO in HPV is gradually becoming clearer. Theoretically, a reduction in NO production or a decrease in its target receptor sensitivity could cause or exacerbate vasoconstriction during hypoxia. Certainly, the contraction induced by hypoxia in isolated human lobar arteries is potentiated by endothelial removal.⁸ Further, in isolated perfused lung preparations inhibition of NO release under hypoxic conditions potentiates pressor responses.⁹ These results are consistent with observations suggesting that endothelium-derived relaxing factor (EDRF) activity^{10,11} and NO synthesis¹² are enhanced in hypoxia. Thus, whilst

we have a reasonable understanding of the mechanism of HPV¹³ and the interaction between NO and HPV,¹⁴ the paper by Katayama *et al*¹⁵ in this issue of *Thorax* raises important questions as to the role of HPV in normal and abnormal lungs. They found that inhaled NO at a concentration of 40 ppm precipitated small but significant reductions in arterial oxygen tension (TcPo₂) in both healthy volunteers and in patients with chronic obstructive pulmonary disease (COPD). There was no effect on TcPo₂ in patients with pulmonary hypertension unrelated to lung disease.

The study raises some interesting issues, but there are some concerns regarding the methods. All the changes observed were of a small magnitude and were obtained in small numbers of subjects using a non-invasive technique that may be more fallible than direct measurement of arterial blood gas tensions. Nevertheless, the authors speculate that the results from the first two groups indicate that inhaled NO may be "overriding" HPV in both patients with COPD and in normal subjects. These results are consistent with those of prior studies. In one previous report a group of patients with COPD whose pulmonary artery pressures (Ppa) were raised were found to respond to 40 ppm of NO with a decrease in their Ppa together with a fall in SaO₂.¹⁶ The latter observation was explained by a demonstrable deterioration in VA/Q distributions following the NO. In another study on 14 patients with COPD who were chronically hypoxic and whose resting PVR and Ppa were raised, 15 ppm NO produced a reduction in both of these parameters that was proportional to the baseline Ppa.¹⁷ Whilst there were no overall changes in the blood gas tensions or dispersion of ventilation and blood flow distributions during NO therapy, there was an increase in the percentage of ventilation in poorly and unperfused areas. Taken together, these studies imply that inhaled NO is unlikely to be of benefit in patients with COPD, although the precise explanation for the lack of benefit is not yet clear. The most logical explanation, supported by at least some of the data, is that NO upsets the abnormal VA/Q balance that is achieved in the lungs of these patients, perhaps by vasodilation in partially constricted areas with reduced ventilation and possibly also by dilation of airways in underperfused areas, as suggested by the paper of Moinard *et al*.¹⁷ In fact, this explanation probably extends to other types of vasodilator. For example, a recent study on patients who were on assisted ventilation for COPD demonstrated that prostacyclin also produced detrimental changes in Pao₂.¹⁸ In contrast to the trials of NO therapy in patients with COPD mentioned above, a study of 13 patients with COPD and pulmonary hypertension found not only a reduction in Ppa with 40 ppm NO, but also a significant *increase* in Pao₂ at the same Fio₂.¹⁹ It is tempting to speculate that the reason for these discrepant results is that the population being studied under the collective label of chronic obstructive pulmonary/airways disease are in fact a highly heterogeneous group. In contrast to the statement by Katayama *et al* that "patients with COPD do not have high values of PVR...", some

of the patients in the other studies, whose pulmonary haemodynamics were actually measured, did have increased Ppa and PVR, although this was often mild. These differences are likely to reflect variable pathophysiological responses, both in terms of ventilation and pulmonary vascular tone and structure, to the same chronic hypoxic insults. There can, however, be no doubt that the initial VA/Q relationships in these patients with COPD are entirely dissimilar from those of patients with acute respiratory failure and lung injury.

The results in normal volunteers are harder to explain. Whilst it is easy to accept the hypothesis that a degree of HPV is present even in healthy individuals, it is more difficult to understand why the NO could worsen VA/Q matching. One interesting possibility is that there are regions even in the normal lung where there is partial ventilation and (appropriately) reduced perfusion. In these areas, the arrival of NO could effectively worsen shunting by increasing blood flow without increasing ventilation. In another study in which healthy volunteers were subjected to an inspired oxygen concentration of 12% the PVR was increased, presumably due to HPV.²⁰ The addition of 40 ppm NO to this inhaled gas mixture reduced the Ppa to baseline without changing the Pao₂. In the study by Katayama *et al.*, however, 40 ppm NO in 21% Fio₂ had no effect on PVR or Pao₂. We appear to have only an incomplete understanding of the relationship between inspired gas concentrations, ventilation, and blood flow distribution in the lung.

In the case of patients with pulmonary hypertension not caused by lung disease we are again looking at a highly heterogeneous group. It seems clear that in patients with primary pulmonary hypertension and in those with pulmonary hypertension secondary to cardiac disease there is a subgroup who respond to inhaled NO with a reduction in Ppa and a second subgroup who are non-responders.²¹ In these patients there are two main treatment objectives in the use of inhaled NO – firstly, to reduce PVR in order to prevent a terminal decline into cardiac failure and, secondly, to improve Pao₂. In this sense they are therefore similar to the patients with ALI with raised PVR, and dissimilar to patients with COPD without pulmonary hypertension, in whom improved gas exchange is the sole objective of inhaled NO therapy. A lack of effect on gas exchange in patients with pulmonary hypertension suggests that the underlying problem is not one of VA/Q mismatching or that NO cannot reverse existing pulmonary constriction.

Through our considerable enthusiasm for the (still preliminary) results of inhaled NO in patients with ALI/ARDS and raised PVR, we have realised that we now hold a powerful therapeutic weapon. However, it is clear that, even in the normal lung, our understanding of the interaction between ventilation and perfusion of the lung is incomplete. In patients with COPD and pulmonary hypertension, in whom evidence suggests that these VA/Q relationships are

altered and are even more complex, we require further data to distinguish on which subgroups this therapeutic tool should be used and those in whom it may prove detrimental.

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