Pulmonary hypertension in COPD

Pulmonary hypertension in patients with COPD: NO treatment?

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The application of "pulsed" NO combined with LTOT may have a role in treating pulmonary hypertension secondary to COPD.

Following the identification of nitric oxide (NO) in 1986 as "endothelium derived relaxing factor", there has been an exponential growth in our understanding of the physiological role of NO culminating in the award of a Nobel Prize, and the naming of NO as "molecule of the decade".[1] Considerable research has subsequently been devoted to understanding the role of this molecule in vascular biology in general, and the pulmonary vascular system in particular.

NO is an unstable radical with a low blood gas partition coefficient. For decades NO was considered an environmental contaminant produced by bacteria and internal combustion engines. Believed to be highly toxic, it appeared an unlikely candidate for a major role as a biological mediator. However, within the last 15 years it has become clear that endogenously produced NO is ubiquitous in mammalian systems, playing an important role in both health and disease: in the regulation of blood pressure and flow, inflammatory responses, and neurotransmission. Insight into these physiological roles has led to its use as a therapeutic agent in a number of clinical settings.

There are ample data to support a major role for NO in the regulation of tone and vascular remodelling in the normal and diseased pulmonary circulation. Endothelial NO contributes significantly to the normally low pulmonary vascular tone,[2] and dysfunction of endothelial NO release has been documented in patients with chronic obstructive pulmonary disease (COPD).[3 4] Although nitro-vasodilatation (acting through the intracellular generation of NO) has been used effectively since the 1800s for systemic arterial dilatation (delivered sublingually, orally, and intravenously), the prospect of selective pulmonary nitro-vasodilatation only became evident in the early 1990s.[5] Treatment with inhaled NO has subsequently been applied in a variety of lung diseases which have in common a degree of pulmonary vascular endothelial dysfunction and/or abnormalities of gas exchange based on low ventilation/perfusion (V/Q) ratios. This includes the use of NO in patients in intensive care, neonates with persistent pulmonary hypertension, and in postoperative settings where NO is used to reduce pulmonary vascular resistance and/or improve oxygenation—for example, pulmonary thromboendarterectomy, heart and lung transplantation, acute lung injury.

In the lungs, one important molecule with which NO reacts is oxyhaemoglobin (HbO_2). The affinity of HbO_2 for NO is 10^6 times greater than its affinity for oxygen.[6] Oxidative reactions of NO with haemoglobin largely limit the effects of inhaled NO to the lung vasculature. However, there are reports that high concentrations of inhaled NO have peripheral vascular effects when peripheral endothelial NO synthesis is blocked, suggesting that at least a portion of inhaled NO survives long enough to reach tissue remote from the lungs.[7] The major immediate breakdown products of NO in human plasma are inactive nitroxides such as nitrite (NO_2^-). The rate of this reaction increases exponentially with the concentration of both oxygen and NO.[8] This has several consequences. Firstly, low NO concentrations or oxygen free environments permit relatively long term persistence of NO. Secondly, the therapeutic efficacy of inhaled NO may not rise dramatically with increased doses as the more NO given, the faster it is oxidised.[9] In fact, higher doses of NO result in a relatively greater proportion of toxic products with little incremental yield of intact NO. Finally, the rapid inactivation of inhaled NO in an oxygen rich environment is what makes NO a selective pulmonary vasodilator. Inhalation delivers NO to the pulmonary resistance vessels before it is oxidised. The seconds before the inhaled NO enters the systemic circulation are enough for its breakdown by interaction with oxygen and haemoglobin.

Pulmonary hypertension secondary to COPD is probably more common than is generally appreciated. Right heart catheterisation studies suggest a prevalence of up to 40% in selected series of patients with severe COPD.[10 11] A degree of pulmonary hypertension was observed in 55% of consecutive respiratory outpatients using Doppler echocardiography.[12] The presence of pulmonary hypertension in patients with COPD is associated with increased mortality[11 13] and an increase in exacerbation rate and length of hospital stay, independent of the degree of airflow obstruction.[14] Although often inferred, the precise contribution of pulmonary hypertension to exercise limitation or quality of life in stable COPD patients is unknown. Mean pulmonary artery pressure in patients with COPD is typically mild (in the region of 25 mm Hg) at rest but can rise to abnormally high levels on exercise.

At present there are no specific treatments recommended for the reduction of pulmonary artery pressure in COPD. Although long term oxygen therapy (LTOT) improves survival in hypoxaemic patients with COPD, it has a negligible effect on pulmonary haemodynamics. Clearly, other factors in addition to alveolar hypoxia contribute to the development of pulmonary hypertension in COPD. For example, remodelling of the pulmonary vessels is present in many patients with mild COPD who are not hypoxaemic and appears to be related to cigarette smoking.[15]

There are several reports of the use of inhaled NO in patients with stable COPD.[16–19] NO inhalation alone may worsen V/Q relationships and exacerbate systemic hypoxaemia while lowering pulmonary vascular resistance. However, when NO is delivered to well ventilated alveolar units with fast time constants, the deleterious impact on gas exchange is avoided.[19] This effect can also be achieved by using "pulsed" delivery of NO where spikes of NO are added at the beginning of inspiration. The addition of oxygen to NO further prevents hypoxaemia.

The study reported in this issue of *Thorax* by Vonbank *et al*[20] shows that long term use of pulsed NO with oxygen leads to sustained improvement in pulmonary haemodynamics without worsening hypoxaemia in patients with stable COPD. Benefits of the pulsed method include the reduced formation of nitrogen dioxide and methaemoglobinaemia. A further safety issue that needs to be addressed is whether discontinuation of long term inhaled NO can lead to severe rebound pulmonary hypertension. Although the results presented by Vonbank *et al* show promise, it remains to be determined whether pulsed NO/oxygen treatment will lead to an improvement in exercise tolerance, quality of life, and survival in patients with hypoxaemic COPD. Potential disadvantages of the approach include the delivery system and monitoring systems necessary to ensure accurate dosing and safety. In addition, long term gas therapies are far

from convenient for the patient. NO reduces pulmonary vascular resistance by increasing cyclic GMP levels in vascular smooth muscle cells. This effect can also be achieved by inhibition of the enzymes that metabolise cyclic GMP. Inhibitors of the type 5 cyclic GMP phosphodiesterase such as sildenafil may have some selectivity for the pulmonary circulation, and it remains to be seen whether these drugs administered orally may have an effect equivalent to inhaled NO.

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Childhood asthma

Second line treatment for severe acute childhood asthma

M South

The choice of treatment for a child with severe acute asthma unresponsive to high dose inhaled bronchodilators and oral or intravenous corticosteroids is still the subject of debate. Although both salbutamol and aminophylline have been around for a long time and have been the subject of many studies, it is still not possible unreservedly to recommend one of these agents over the other as second line treatment.

Most physicians would agree that first line treatment for an acute exacerbation of childhood asthma should be the administration of high dose inhaled bronchodilators[1] and corticosteroids administered either orally or intravenously,[2] but when a child with severe acute asthma is unresponsive to such treatment—what should come next? This is an important question that is faced by doctors every day in emergency departments, paediatric wards, and intensive care units the world over. Most commonly, physicians will reach next for intravenous salbutamol or intravenous aminophylline, although some will consider other treatments.

Salbutamol and aminophylline have been shown to be individually better than placebo in severe acute asthma.[3 4] Although a recent Cochrane systematic review appeared to cast doubt on this statement for salbutamol,[5] many suspect that this is a flaw caused by the inclusion of several very weak early studies of salbutamol in the analysis. A large study of aminophylline[6] and another Cochrane systematic review[7] have confirmed its efficacy in improving a number of important outcomes including the need for, and duration of, mechanical ventilation in acute childhood asthma.

A study by Roberts *et al*[8] in this edition of *Thorax* is the first to compare the two agents using a good trial design. The authors have attempted to study these second line treatments in a randomised controlled trial to compare an intravenous bolus of salbutamol with a loading dose of aminophylline followed by an intravenous infusion. They have inevitably come across two of the major obstacles faced by anyone studying acute asthma episodes in children: (1) how to study such very sick children and (2) what outcomes are both measurable and important in this context? Improvement in severity score and reduced length of hospital stay are clearly of interest but are not the main goals of treatment. Unfortunately, despite the inclusion of five hospitals in the study, their sample size is still relatively small with only 44 subjects. Although this was the required number from the calculations, it is too small to address important outcomes such as the need for intensive care admission or mechanical ventilation, and much too small to examine an impact on long term morbidity or mortality from severe asthma exacerbations. In their salbutamol group 11% of patients required intubation and ventilation, while only 4% in the aminophylline