

Inhaled nitric oxide for hypoxemic respiratory failure: Passing bad gas?

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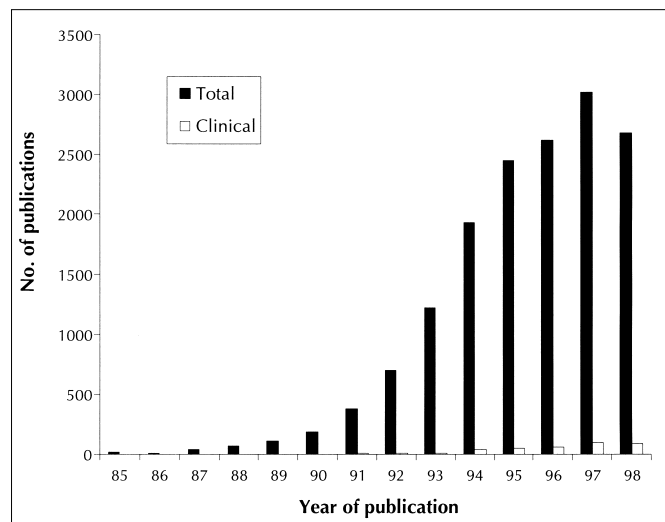
Technology: Inhaled nitric oxide for the treatment of hypoxemic respiratory failure

Use: Nitric oxide (NO) has been rapidly embraced by critical care physicians to treat hypoxemic lung diseases such as acute respiratory distress syndrome¹ and, perhaps more rationally, persistent pulmonary hypertension in newborn infants.² NO's ultrashort half-life and its properties as a vasodilator make it a very good candidate, when inhaled, to improve ventilation-perfusion matching and reduce pulmonary artery pressures.

History: The past decade has seen an explosion of studies related to NO. Previously seen as a noxious pollutant and graded as a Class A poison, NO is now thought to play a vital role in many physiologic processes, including vasodilation, neurotransmission and inflammation. The discovery of NO's biological functions arose from speculations of Robert Furchgott in 1980 regarding a circulating signal molecule, which he called endothelium-derived relaxation factor, that caused vascular smooth muscle to relax. Subsequent to Ferid Murad's discovery that a gas was capable of regulating important cellular functions, Louis Ignarro confirmed that Furchgott's endothelium-derived relaxation factor was, in fact, NO. Work by Salvador Moncada is central to further defining the biological relevance of NO. With these revelations, the use of NO spread from that of calibrating emissions-testing equipment to clinical practice virtually overnight.

Since being named "Molecule of the Year" by *Science*³ in 1992, the number of NO-related publications has risen exponentially and has only recently reached a plateau (see Figure). Interestingly, it was a century after Alfred Nobel's invention of dynamite that nitroglycerin's beneficial effects for chest pain were linked to the release of NO gas. In 1998 Furchgott, Murad and Ignarro received the Nobel Prize in Physiology or Medicine for their discoveries concerning NO as a signalling molecule in the cardiovascular system (see www.as.nobel.se/laureates/medicine-1998.html).

Promise: Inhaled NO appears to be an ideal treatment for hypoxemia in patients with acute respiratory distress syndrome because it selectively increases perfusion to portions of the lung receiving ventilation. However, because most patients with acute respiratory distress syndrome do not die from hypoxemic respiratory failure, but from multisystem organ failure, inhaled NO may not improve final outcome. Randomized clinical trials have reported temporary improvements in arterial oxygenation but no significant differences in outcome



Total number of publications related to NO and number of clinical publications related to NO between 1985 and 1998.

between patients who received inhaled NO and those who received placebo gas.^{4,5} Despite these observations, inhaled NO may allow clinicians to use less-injurious ventilatory strategies (e.g., by reducing the inspired oxygen concentration), and this may reduce toxic effects and morbidity. In addition, inhaled NO may prove invaluable for the minority of patients in whom severe oxygenation defects are the primary cause of death. The only area where NO has proven efficacy is in infants with persistent pulmonary hypertension, where it has been found to improve systemic oxygenation and decrease the need for extracorporeal membrane oxygenation.²

The benefit (or harm) of NO will most likely be secondary to its immunological effects. Inhaled NO is capable of modulating neutrophil chemotaxis, adherence and activation,⁶⁻⁸ both locally and in nonpulmonary vascular beds after reperfusion injury;⁹ therefore, future studies will likely evaluate its immunomodulating potential in patients who are at risk for acute lung injury and reperfusion injury syndromes. In this regard, we are currently evaluating the efficacy of inhaled NO for attenuating reperfusion injury after lung transplantation, and because NO production in the lung is altered by inflammatory conditions, it is also being evaluated as a diagnostic tool to assess pulmonary disease activity.

Problems: There are a number of potential concerns regard-

ing the use of inhaled NO. Initially, its use was reserved for extreme cases of respiratory failure, but its initial promise and ready availability quickly led to a more widespread clinical use, despite the paucity of clinical studies (see Figure). Thus, NO was not subjected to the rigorous evaluation or the usual regulatory pathways for drug development; it was being used to treat respiratory conditions before an understanding of its biology, let alone clinical efficacy was achieved. Seemingly simple questions, such as optimal doses, are still being addressed. Recent data suggest that lower doses (e.g., 1 ppm) may be safer and more effective than the higher doses used previously.⁴

There is insufficient data at present to be confident about the safety of inhaled NO, however — the possibility remains that NO may actually be harmful. Although its use as an inhalant likely limits its systemic effects, inhaled NO may actually worsen lung injury, especially at higher doses. Its use as a diagnostic tool has also been hampered by difficulties with measurement techniques and a lack of uniform standards.¹⁰

Prospects: Clearly, further clinical studies on the use of NO are urgently needed. Only when well-designed clinical trials are completed will we be confident in the best procedures to use to administer NO and be able to predict which patients will benefit most from its administration. Until these data are available our only reassurance comes from anecdotal evidence of utility and a few clinical trials in children that suggest its use is safe. As both clinicians and scientists, however, this level of imprecision and uncertainty is unacceptable for the long-term.

Competing interests: None declared by Dr. Ferguson. Dr. Granton is currently conducting a clinical trial, supported by

the Canadian Cystic Fibrosis Foundation, to evaluate the effectiveness of inhaled NO in preventing reperfusion injury after lung transplantation.

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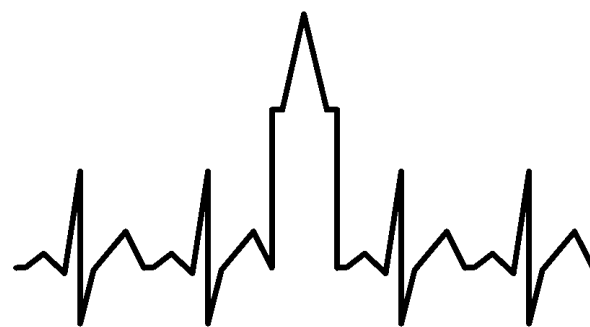
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