Endogenous Nitric Oxide in Exhaled Human Breath

A New Means of Monitoring Airway Disease Activity or Another NO-NO?

The endogenous vasodilator nitric oxide (NO) is synthesized enzymatically from the amino acid L-arginine by three isoforms of NO synthase (NOS). Two are expressed constitutively in neuronal (nNOS) and in endothelial cells (eNOS), but the expression of the third is induced (iNOS) by cytokines and inflammatory mediators in macrophages and other nucleated mammalian cells, including vascular smooth muscle and hepatocytes. It is now clear that NO is a constituent of normal exhaled human breath,1,2 but the biologic significance of this phenomenon remains unclear. Thus, although the modulation of pulmonary3 and systemic4 tone may depend in part upon eNOS under physiologic circumstances, and be modulated by iNOS expression during conditions such as systemic sepsis,5,6 how such activity relates to variations in expired NO concentration is uncertain. Moreover, whether the quantification of exhaled NO is likely to prove clinically useful depends in part upon the origin of the gas.

Details of a variety of experiments designed to locate the source of exhaled NO have now been published,7-10 and a picture is beginning to emerge. The article by Dillon and colleagues published in this issue of CHEST (see page 930) represents a significant addition to this literature. The investigation was designed to locate the sites of NO formation in the respiratory system, and to assess the contributions of iNOS and respiratory tract bacterial flora to its production. Exhaled gas was sampled from a variety of sites in the respiratory system using chemiluminescence. Many workers have expressed concern regarding the accuracy of such measurements of airway-derived NO; to this end, Dillon and colleagues included a conscientious validation of methods in their investigation. Topical steroids and systemic antibiotics were employed to influence iNOS formation and the contribution of bacterial-derived NO respectively. The results support the hypothesis that iNOS is at least partially responsible for the production of exhaled NO. Furthermore, the data are in accord with other published works showing that while NO is undoubtedly present in the lower respiratory tract, most of the exhaled gas originates from the nasal or paranasal structures.7-10 Some reservations should be expressed regarding this generally excellent study. First, the lack of a detectable effect of antibiotic therapy on exhaled NO concentrations may reflect incomplete sterilization of the upper respiratory tract. Second, it should be possible to employ selective pharmacologic agents administered by inhalation to block NOS activity in a more specific fashion than can be achieved by using antibiotics alone, thereby teasing out the potential contributions of constitutive and inducible forms of NOS to NO production.11,12

Despite these limitations, such data suggest that iNOS localized to epithelial cells is an important source of airway NO, both constitutively and in conditions of bronchial inflammation,13,14 although whether it plays a part in modulating airway physiology, or merely represents a by-product of neurotransmission or bronchial vascular control mechanisms is unknown. Alternatively, NO inspired from such sources may be important as an endogenous inhaled vasodilator modulating pulmonary ventilation/perfusion matching. NO may be important in a host defense. The high levels apparently produced by the nasal sinuses are some three orders of magnitude greater than the concentrations estimated to be detectable in the distal airways. At these levels NO has bacteriostatic15 and antiviral16 properties, which may explain the fact that the sinuses are normally sterile. NO also alters ciliary beat frequency.17 Patients with immotile cilia syndrome/pri¬mary ciliary dyskinesia8 have very low levels of nasal NO and are prone to chronic sinusitis.

The induction of iNOS in inflammatory states is now established, and elevated levels of exhaled NO have been reported previously in asthmatics,18,19 These levels then fall following the administration of inhaled corticosteroid therapy.20 The iNOS mRNA expression is transcriptionally regulated and has been shown to be suppressed by steroid administration.5 In this sense, if the measurement of exhaled NO proves to be practical in the clinical setting, it may represent a useful tool in monitoring the response to therapy of patients with inflammatory airway diseases. Unfortunately, the measurement of endogenous airway NO that is most reproducible and representative of disease activity is uncertain. NO concentrations in nasal air, peak or plateau expired NO concentrations, and end-tidal NO concentrations may provide differing and even conflicting information about the same pathologic process or coexisting disease states such as asthma and airway infection.

The work of Dillon and colleagues represents an important advance in our understanding of the clinical significance of measurements of exhaled NO concentrations. Much work remains to be done before a new and exciting means of monitoring airway disease activity can be announced.21

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REFERENCES


ICU Stay After Single Lung Transplantation

In this issue of CHEST (see page 1014), Lee and colleagues examine factors that may impact upon the length of stay (LOS) of single lung transplant (SLT) patients in the ICU after transplantation. They determined retrospectively that the immediate postoperative PaO2/FIO2 ratio was superior to other measures in predicting ICU LOS and that the median ICU LOS was highly correlated with duration of mechanical ventilation. A low transpulmonary gradient and reduced extent of perfusion mismatch between the two lungs were also associated with a significantly shorter ICU LOS, while an APACHE II score ≤10 was not. While these findings are interesting, perhaps the crux of the matter lies in determining why patients have significant postoperative hypoxemia and prolonged ventilator dependence. A number of preoperative, intraoperative, and early postoperative factors may potentially influence oxygenation as well as the need for mechanical ventilation and in turn ICU LOS. Both donor lung and recipient characteristics may be implicated. There are data supporting some of these potential influences.

The Pittsburgh group previously determined that patients with preoperative pulmonary hypertension undergoing SLT have significantly increased mortality and a more prolonged ICU stay than patients without pulmonary hypertension.1 In patients with pretransplant pulmonary hypertension, nearly all of the cardiac output perfuses the transplanted lung resulting in edema and reduced compliance after transplantation favoring ventilation to the native lung and worsening ventilation perfusion mismatch. Davis and colleagues concluded retrospectively that gas exchange was worse and pulmonary artery pressure higher following SLT for idiopathic pulmonary fibrosis or primary pulmonary hypertension than when obstructive lung disease was present. Patients with pulmonary fibrosis required more intensive and prolonged ICU stays as well as more prolonged mechanical ventilation. Higher ventilator pressures were also required in the patients with pulmonary fibrosis, presumably as a result of decreased compliance in the remaining native lung. Patients with COPD often have relatively benign postoperative courses after SLT. However, significant native lung herniation after SLT for obstructive disease, particularly in the setting of infection or edema, may affect lung function and potentially ICU LOS. Clearly, the cause and severity of native lung disease can impact upon the postoperative course.

Preoperative ventilator dependence might be expected to prolong duration of mechanical ventilation after transplantation, and therefore, ICU LOS.