treat ing a disease that has been considered in a nihilist manner for too many years.

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References

19 Petticrew M. Why certain systematic reviews reach uncertain conclusions. BMJ 2003; 326:756–758

Exhaled Nitric Oxide in Pathophysiologic States

The Substance Behind the Gas

Nitric oxide (NO) is a readily diffusible, small molecule that has a huge variety of effects, both physiologic and pathophysiologic. The field of research into NO is exceedingly large, with >56,000 references regarding this molecule in the medical literature. NO is produced by several different isoforms of NO synthase (NOS). These isoforms include both enzymes that produce NO in a constitutive fashion (endothelial NOS [eNOS] and neuronal NOS), and those that produce NO in response to a stimulus (inducible NOS [iNOS]). NO has a variety...
of physiologic roles, including vasodilation and control of cellular respiration.1,2

Studies of endothelial cells in vitro have suggested that the constitutive generation of NO via eNOS and/or mitochondrial NOS produces a specific NO: oxygen ratio that exists to control cellular respiration.3–5 The proposed mechanism for this control is via competition between NO and oxygen for cytochrome c oxidase, the final oxygen acceptor in the oxidative phosphorylation pathway.3,5

A host of pathophysiologic states have been shown to be associated with increased levels of NO and induction of iNOS, including a variety of inflammatory states,6,7 trauma,8 neurodegenerative disease,9 pulmonary disease,10 and others. This has led to the obvious next step at attempts to limit the pathophysiology of illnesses by manipulating production of NO. A number of experiments have shown a beneficial effect of iNOS inhibition in shock states,11–13 suggesting that an overproduction of NO may play a key role in the pathophysiology of shock states. However, several investigators14–17 have observed increased tissue damage during shock states when NO production was inhibited prior to resuscitation. Interestingly, this may be a contributing factor in the increased mortality demonstrated in human trials of N(G)-methyl-L-arginine hydrochloride, an NOS inhibitor, in patients with septic shock.18 Because there are multiple reports of both beneficial and detrimental effects of NO on tissue damage and survival in pathophysiologic states, it is plausible that a small amount of NO (likely the amount produced constitutively) is beneficial and necessary for normal function, while an overproduction (likely induced and more regionally distributed) is harmful, potentially through increased production of oxygen radicals such as peroxynitrite and superoxide anion.19 It is obvious from the vast amount of basic and clinical research performed that this ubiquitous, multifunctional molecule is part of an elegant set of signaling mechanisms whose effects are closely related to the levels of NO produced, the location where NO is produced, and the environment in which it is produced (eg, other products of inflammation).

Qureshi and coauthors report their experience with measurement of exhaled NO in this issue of CHEST (see page 281). In this study, the authors measured exhaled lower respiratory tract concentrations of NO in patients before and after autologous peripheral hematopoietic stem-cell transplantation, which is associated with idiopathic pneumonia syndrome (in the authors’ series, 100% of the 17 patients completing all measurements). The authors noted increased NO levels in exhaled breath as compared to baseline levels in all patients after stem-cell transplantation, and a good correlation of these increased levels with decreased diffusion capacity of the lung for carbon monoxide.

Analysis of exhaled gases for a number of biomarkers has allowed a window, albeit a cloudy one, to noninvasively measure the status of the lung in a variety of diseases. This topic has been recently reviewed.20,21 Measurement of NO in exhaled gas relies on its poor solubility in aqueous solutions and good stability in the gaseous phase. This results in diffusion of NO into hollow, gas-filled structures such as the lung, allowing detection. The described chemiluminescent technique has been well described and standardized. A number of studies, summarized in the reviews above, have demonstrated increased levels of NO in patients with asthma, COPD, after allergen challenge, and in interstitial lung disease.

What do increased levels of NO in exhaled gases imply? It has been suggested that NO in exhaled gases may reflect either oxidative stress or inflammation in the airways. The evidence in support of elevated NO being related only to inflammation is unclear, since exhaled NO has not been shown to be elevated in patients with cystic fibrosis.22 Additionally, Qureshi and coauthors showed no decrease in NO levels after treatment with steroids, a finding that has also been demonstrated in patients with COPD.23 These elevated levels may also be related to increased oxidative stress due to chemotherapeutic agents or decreased metabolism of NO in the airways. Careful study is necessary to understand the complex interplay of interactions of the cells of the respiratory system resulting in the observed increase in NO in the reported study and others.

It is not infrequent for scientists and clinicians to make the understandable error that because a factor changes during a pathophysiologic process, the factor is the cause of the pathophysiologic process. The medical literature is full of expensive examples of this error. Qureshi and coauthors make the interesting observation that NO levels are elevated in exhaled gases from patients with post–stem-cell transplantation idiopathic pneumonia syndrome. Before we conclude that NO is the causative agent in this process, further study is necessary to tease out the complex interplay of events in this and other pulmonary processes.

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A Proper Balance

Fiberoptic bronchoscopy should be performed in a safe, efficient, and reasonably comfortable manner. Maximal comfort can be obtained in the operating theater using general anesthesia. This sacrifices efficiency, increases cost, and exposes the patient to the risks of general anesthesia. Bronchoscopy also can be performed solely with local anesthesia. Obviously, this does not optimally alleviate pain and anxiety. If the patient’s cough and pain are not controlled, the yield of the procedure can decrease. The use of IV sedation and analgesia (conscious or moderate sedation) provides a middle ground between these two approaches. It is a compromise between general anesthesia and a “bite-the-bullet” approach. The goal of moderate sedation is to achieve a proper balance among comfort, efficiency, cost, efficacy, and safety.

Controlled studies provide the most useful information in developing techniques to refine bronchoscopy. Such studies show that bronchoscopists and endoscopic nurses can distinguish patients receiving sedation from those receiving placebo. These studies show that there is a better yield with sedation.1,2 Hypoxemia and tachycardia are common during fiberoptic bronchoscopy. In one study,3 a surprising number of patients showed evidence of myocardial ischemia. A study also revealed that nasal insertion is associated with pain.4 The same study showed that patients with poor health and lower educational levels experience more pain than better educated patients who are in better health.4 In one study, despite the use of “adequate sedation and analgesia,” 10% of patients experienced inadequate control of pain.4

In many respects, the pediatric population represents the most difficult challenge for the bronchoscopist. Some advocate that all pediatric fiberoptic bronchoscopy be performed in the operating room with the help of the anesthesia department.5 In this issue of CHEST (see page 315), Fauroux et al report

References

20. van Beurden WJ, Dedhuizjen PN, Smeenk FW. Exhaled biomarkers in COPD: their potential role in diagnosis, treatment and prognosis. Monaldi Arch Chest Dis 2002; 57:258–267