Present utility of cardiac troponin is outlined in Table 1. The only disadvantage of cardiac troponin is in its utility for the diagnosis of reinfarction. Due to its long half-life, a second myocardial infarction within 7 to 10 days of the first may be difficult to diagnose using cardiac troponin assays alone.

**Cardiac Troponin T vs Troponin I**

No head-to-head comparison studies have been performed; however, the assay for cardiac troponin I appears to have several advantages over cardiac troponin T. The assay for cardiac troponin T has been positive in patients with diseased skeletal muscles. One such example is that of a patient with polymyositis and no apparent cardiac disease. Also, troponin T has been shown to be elevated in patients with regenerating skeletal muscles. The other disadvantage is the observance that cardiac troponin T is elevated in patients with chronic renal insufficiency. In a preliminary report, 26 blood samples from chronic dialysis patients without evidence of acute myocardial injury were elevated. Sixty-nine percent had elevated troponin T, and none had elevated troponin I levels. Some hypothesize that the cardiac troponin T levels are elevated in these patients due to a myopathy with muscle regeneration, which is known to occur with uremia.

In conclusion, cardiac troponin has been shown to be a more sensitive and specific marker of myocyte injury than myoglobin or CK-MB. The assay for cardiac troponin I currently seems to be the most sensitive and specific biochemical marker for the diagnosis of myocardial injury; however, in the absence of muscle disease or renal failure, the assay for cardiac troponin T seems to be adequate. It is now time for CK-MB to take its place in history along with SGOT and LDH. Cardiac troponin will certainly become the most reliable biochemical aid in the diagnosis of cardiac injury.

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**Just Say NO**

Just 10 years ago, who would have thought that a lethal gas that was “...found in unsavory places as cigarette smoke and smog...” and was a “...destroyer of ozone, suspected carcinogen and precursor of acid rain...”1 would one day be recognized...
as playing a crucial role in mammalian physiology. Since 1987 when Palmer et al2 and Ignarro et al3 independently identified nitric oxide (NO) as the endothelium-derived relaxing factor, this gas has generated a phenomenal amount of interest.4 Many excellent reviews of the biochemical, physiologic, and clinical aspects of NO have appeared,5-7 including a review by Mitzutani and Layon8 and an editorial by Brett and Evans9 in recent issues of CHEST.

The role of NO in human physiology can be briefly summarized as follows. NO is synthesized by the enzyme, NO synthase (Nos), from the amino acid L-arginine. The two major isoforms of constitutive Nos (cNos) are present in the vascular endothelial cells (Nos3) and neurons (Nos1). These isoforms release NO in rapid short bursts with potent vasodilator and neurotransmitter actions. NO thus released also possesses antithrombotic properties10-12 and inhibits the proliferative response of the intima to vascular injury.13 A second category of Nos, known as inducible (iNos), is formed de novo under the influence of cytokines released in immunologic or inflammatory reactions.5-7 Release of NO by iNos occurs for prolonged periods and has antimicrobial, immunologic, and inflammatory activities.

The lung contains all three isoforms of Nos. Nos3 is present in vascular endothelium and plays a key role in the maintenance of vascular tone through the release of NO in response to increase in intracellular calcium.14 Exercise or volume overload or biochemical mediators like thrombin, bradykinin, or adenosine diphosphate activate Nos3. NO is released and rapidly diffuses to the smooth muscles, producing relaxation. Nos1, the primary neurotransmitter, is in nonadrenergic, noncholinergic nerves,15 whose stimulation also leads to increased NO production. Finally, iNos (Nos2) is present in alveolar macrophages, airway cells, Clara cells, neutrophils, bronchial epithelium, and alveolar pneumocytes, and is activated in immunologic, inflammatory, or irritant reactions.16,17

With the advent of chemoluminescence analyzers to allow rapid, accurate measurement of NO in exhaled air,18 the study of NO in expired air has been an active area of research. The major sources of NO in expired air are the nose19 and sinuses,20 although measurements after orotracheal intubation and bronchoscopic sampling from the lobar and segmental bronchi have shown conclusively that expired air contains the NO produced in the lung and airways.21 Higher concentrations are recorded during nasal breathing due to contamination with NO produced in the paranasal sinuses and nasopharynx.22 The use of a mouthpiece and noseclip for collection of expired air reduces the contribution of nasopharyngeal air to the expired air, but some contamination by nasopharyngeal air still occurs.23 NO is also increased on breath-holding and forced expiration.24 Therefore, close attention to the technical details of sampling of the expired air and the equipment is essential to the interpretation of expired NO.

Release of NO in the exhaled air per unit of time (VNO) could yield important information on pulmonary vascular endothelial function. Changes in VNO occur under many physiologic stimuli. VNO increases during exercise in normal human subjects,25-27 and positive correlation exists between diffusing capacity of carbon monoxide and exhaled NO.28 A rise in VNO has also been observed in women during the middle of the menstrual cycle.29 These changes are generally attributed to the activation of Nos3 in endothelial cells in response to increased capillary blood volume.

An increase in the fractional concentration of NO is seen in such disease conditions as sinusitis, and vasomotor and allergic rhinitis due to the release of NO by the inflammatory cells.30 VNO increases during an asthma attack,31 late asthmatic reactions,32 and antigen-induced bronchospasm, and decreases after treatment with steroids.33 However, no rise in VNO is observed during early asthmatic response or bronchospasm after histamine challenge.34 The increased VNO in the expired air in these instances and in ARDS is attributed to activation of Nos2 in the inflammatory cells, although nonadrenergic, noncholinergic nerves also could be a source of NO in asthma.

A decrease in VNO is noted in conditions with poor endothelial cell function. VNO is decreased in many subjects with coronary artery disease.35 Reduced endothelial Nos in the lungs of patients with pulmonary hypertension has been reported.36 Similarly, decreased VNO is noted in patients with pulmonary fibrosis37 and in smokers.38

In this issue of CHEST (see page 44), Riley and colleagues report their findings on VNO in exhaled air in patients with primary pulmonary hypertension (PPH) and pulmonary fibrosis (PF). They noted a lower VNO at rest in PF subjects compared with normal subjects. In subjects with PPH, although the VNO at rest was the same as in normals, it failed to rise with exercise. Destruction of vascular endothelial cells in PF and deficiency of endothelial Nos3 or reduced capillary blood volume in PPH appear to be the most likely explanations for these findings, as postulated by the authors. Although they used an NO analyzer with a slower response time, which led to a delay between sampling and measurement, their results are compatible with known actions of NO in maintaining normal vascular tone and preventing microvascular proliferation. Similar results have been reported by others, but the present work is...
unique in comparing normal subjects and those with PPH and PF under similar settings.

Riley and colleagues have contributed to the growing body of work suggesting a possible clinical role for measurements of NO in expired air. However, this will have to await the availability of accurate and relatively inexpensive analyzers with fast response and recording capabilities. Even when such equipment is available, the technique to avoid nasopharyngeal contamination would need to be standardized. The normal ranges of VNO and FNO in expired air and their response to exercise and other physiologic states and illnesses also must be clarified before measurements of NO can be used clinically. Nevertheless, this is an area of intense ongoing research and NO measurement may eventually become a useful pulmonary function test for airway inflammation, delayed type of hypersensitivity, non-adrenergic, noncholinergic nerve and endothelial cell function, and response to treatment.

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Pulmonary Function Tests and Idiopathic Pulmonary Fibrosis

Simple May Be Better

"God made man simple; man's complex problems are of his own devising." Ecclesiastes 7:39

In idiopathic pulmonary fibrosis (IPF), pulmonary function tests (PFTs) provide a noninvasive quantitative measure of the severity of the disorder, and repeated testing to monitor the disease course has become a cornerstone of current practice. However, the ability of PFTs to predict natural history, prognosis, and histology in IPF is tenuous. IPF is a heterogeneous disorder with widely varying degrees of inflammation and fibrosis on lung biopsy. The relative proportions of inflammation and fibrosis correlate well with response to therapy and survival for the individual patient. Clinicians have struggled to find safe, cost-effective measures that correlate with histology and thus are predictive of response to therapy and prognosis. Variables studied include demographics (age, gender, and duration of disease), symptoms (degree of dyspnea), roentgenographic patterns (plain chest radiograph and high resolution CT scan), release of prostaglandin E2 from alveolar macrophages, bronchoalveolar lavage cell populations, clearance rates of 99mTc-DTPA, and PFTs.2-6

In this issue of CHEST (see page 51), Erbes and colleagues demonstrate that measurement of total lung capacity (TLC) alone or in combination with vital capacity (VC) held greater prognostic value than the less available and more expensive single breath diffusing capacity (Dsb, Dsb/VA [diffusing capacity corrected for alveolar volume]) and measures of gas exchange (PaO2 at rest, alveolar-arterial oxygen difference during exercise (P[A-a]O2), and ΔPaO2 with exercise). Their retrospective review of 99 patients with histologically proven IPF showed that the 50 patients with a TLC <78% of predicted at the time of diagnosis had a 51% reduction in survival at 5 years compared to those patients with a TLC >78%. A combined reduction in TLC and VC resulted in an estimated 46% reduction in survival at 5 years. Reduction in diffusion, reduction in PaO2 at rest, a >8 mm Hg decrease in PaO2 with exercise and a P[A-a]O2 >35 mm Hg during exercise were not associated with a decreased survival. The practical importance of the study by Erbes and colleagues is that the simple, cost-effective TLC and VC offer clinicians some assessment of prognosis for the individual patient. In our institution, eliminating the measures of a Dco, arterial blood gas at rest, and exercise gas exchange would result in a savings of $497 per patient.

We came to a similar conclusion about the value of simple PFTs in following patients with IPF in a recent study of the correlation between change in PFTs after one year of treatment and survival in 58 patients. Those patients with a significantly increased (>10%) or unchanged FVC and/or increased (>20%) or unchanged Dsb after one year of treatment showed a survival advantage over those with a similar decrease in FVC, Dsb, or both. As with Erbes and colleagues, we did not find a correlation between change in arterial blood gas measurement at rest and prognosis. However, our numbers were small and the matter requires further study.

Previous studies of baseline lung volumes in IPF have failed to demonstrate a correlation with survival. In a retrospective analysis of 220 cases, Turner-Warwick and colleagues found that younger age, female gender, greater cellular histology, less dyspnea, and minimal chest radiograph involvement related to a longer survival, but that VC and TLC had no influence. Also, Schwartz et al noted diminished survival to be associated with a lower percent predicted FVC, TLC, and Dco, but after controlling for age, only male gender and a higher FEV1/FVC remained as indicators of a worse prognosis. Erbes and colleagues also found that advanced age at the time of diagnosis portended a poor prognosis; it remains unclear from their analysis whether the pulmonary function results are age-dependent or not. The variability in results between these studies is difficult to explain, but may lie in differences in patient groups. Restricting IPF patients to those with a surgical lung biopsy usually results in a younger group and eliminates patients with the most severe disease, as they are not operative candidates. The patient group of Erbes et al is uncommonly young (mean age, 53 years) and minimally affected, with a mean TLC of 79% and mean VC of 89%. In contrast, the patients studied by Schwartz and colleagues had a mean age of 64 years and mean VC of 62% predicted, and the group reported by Turner-Warwick and colleagues a mean age of 59 years and