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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.1 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 DPaO2 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.7 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 colleagues3 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
mean VC of 64% predicted. Younger and less affected patients may have fewer intercurrent diseases affecting mortality. Unfortunately, Erbes and colleagues do not provide the cause of death in their patients.

In their discussion, Erbes and colleagues raise the question: what are the histologic correlates of PFT abnormalities in patients with IPF? The authors theorize that VC correlates with unresponsive fibrosis, while DCo and ΔPaO₂ cannot discriminate between fibrosis and infiltration of the lung by inflammatory cells, and thus may be more responsive to treatment. This is an oversimplification. Clinical data, as well as structure-function studies in animal models, suggest that both inflammation and fibrosis impair gas exchange and lung volumes. Recently, Chinet et al⁸ studied 21 patients with diffuse lung fibrosis confirmed by lung biopsy (14 with IPF and 7 with pneumoconiosis). They found a positive correlation between the intensity of cellular infiltration and that of fibrosis; lung volumes and DCo were correlated with both cellular infiltration and fibrosis. To date, there is no substantiation of the ability of PFTs to predict the relative degree of inflammation versus fibrosis in IPF.

The current study of Erbes et al and our own experience show that simple PFTs can provide significant information for patients with IPF at baseline as well as assess the response to therapy. Until further data is forthcoming, we will continue to measure TLC, VC, and Dsb at baseline and during follow-up of this patient group. We also measure arterial blood gas at rest, breathing room air at baseline, and then as required to define a need for supplemental O₂ in the failing patient. Measures of exercise gas exchange are not indicated as a routine measurement. A caveat about PFTs in IPF: patients with severely decreased lung volumes should not be presumed irreversible and no set of PFTs eliminates the individual patient from a therapeutic trial.

Steven H. Kirtland, MD
Richard H. Winterbauer, MD, FCCP
Seattle

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Vagotonia and Bronchial Asthma

The paper of Lodi and colleagues (see page 65) on “Autonomic Regulation in Asthmatics With Gastroesophageal Reflux” presents a set of important observations resulting in their conclusions that (1) asthmatics with gastroesophageal reflux (GER) have evidence of autonomic dysfunction and (2) the presence of a heightened vagal tone may be partially responsible for the increased airway responsiveness to esophageal acidification in asthmatics with reflux. Since these findings conjure up the turn-of-the-century ideas of Eppinger and Hess ¹ who formulated the concept of “vagotonia” as the constitutional basis of diseases of allergy (the “allergic diathesis”), it may well be appropriate to take this opportunity to reexamine this issue in the perspective of nearly a century of progress in our understanding of these disorders.

Even though antigen-antibody reactions undoubtedly serve as a means for eliciting manifestations associated with atopie disorders, they do not appear sufficient to account for all the peculiarities observable in atopie states. An example of this is the unusual predilection for certain effector tissues in atopy: the bronchial tree in asthma, the nasal mucosa in allergic rhinitis, and the skin in atopic dermatitis. Given an individual with any of these disorders, the symptomatology peculiar to that particular disorder can be reproduced by the exogenous administration of the chemical mediators of the allergic responses. For example, in patients with asthma, the injection of histamine induces wheezing primarily, whereas in individuals suffering from allergic rhinitis, it induces nasal symptoms. Furthermore, the amounts of chemical mediators needed to induce symptoms in atopie individuals is on the order of several hundred-