population. All patients were nonsmokers who were identified during a hospitalization. IPF has a marked association with smoking. In addition, choosing hospitalized patients may result in a spectrum bias toward acutely ill or deteriorating patients. There are several observations that make this likely: the incidence of acute exacerbation was extraordinary high (57% overall and 64% in the placebo group). Also, the median survival for the placebo arm was 399 days, a distinctly shorter period of time than previously reported.  

Second, several issues raise concerns regarding a potential misclassification bias. Only nine patients had surgical lung biopsy–confirmed IPF. Furthermore, the inclusion of radiographic ground-glass attenuation in the case definition of IPF differs from the recommended criteria. High-resolution CT is accurate in the diagnosis of IPF when specific criteria are met: bilateral basal predominant subpleural reticulation (with our without traction bronchiectasis), honeycombing, and the absence of atypical features such as significant ground-glass opacity.  

Commentary on the percentage of patients with significant ground-glass opacity on high-resolution CT would be informative.

Finally, the study was unblinded, and eight patients (26%) randomized to anticoagulation therapy withdrew after randomization. Such a high percentage of differential dropouts eliminate the benefit of randomization, as those who withdrew may somehow be different from those who did not (perhaps they were more ill). Consequently, the differences between groups could be due to confounding variables and not a true treatment effect. A better approach would have been to include those patients who withdrew as part of the “treatment group” in an intention to treat analysis. Less robust but still valid, the investigators could have analyzed the data using a Cox proportional hazards model including well-characterized covariates that may influence mortality in IPF patients such as age, smoking status, and baseline FVC. The results of this trial are dramatic but must be interpreted with caution and confirmed by future studies addressing the concerns outlined above before anticoagulation is adopted as a new standard of care in IPF.

The authors have no conflicts of interest to disclose.

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Use of Exhaled Breath Condensate in the Study of Airway Inflammation After Hypertonic Saline Solution Challenge

To the Editor:

The recent study by Carpagnano et al (November 2005) found that the inhalation of hypertonic saline solution increased exhaled breath condensate (EBC) concentrations of interleukin-6 and tumor necrosis factor-α in healthy subjects and patients with asthma or COPD. Hypertonic aerosols also reduced the pH of BAL fluid samples. No significant changes in these parameters were observed after the inhalation of isotonic saline solution. The authors have concluded that hypertonic aerosols can induce airway inflammation.

Although the conclusions of the authors appear to be plausible, an alternative explanation is possible for their observations regarding EBC cytokine concentrations. The inhalation of hypertonic saline solution may have stimulated the release of airway secretions and/or caused an osmotic shift of water into the airways. Increases in the volume of airway secretions could in turn augment the contribution of respiratory droplets to the EBC, most (approximately 99.99%) of which is condensed water vapor. Increased EBC concentrations of cytokines could reflect the production of more or larger respiratory droplets rather than an increase in cytokine concentrations in the airway fluid. This possibility could have been addressed by measuring the dilution of respiratory droplets by water vapor, which can be readily determined by measuring the conductivity of EBC samples after lyophilization. Such measurements could also indicate whether the concentrations of cytokines in EBC are consistent with those reported from sputum samples and BAL fluid samples. The interpretation of EBC studies will always be difficult if no effort is made to measure the dilution. The effect of hypertonic aerosols on the pH of EBC is also problematic since it may be related to the effect of these solutions on the pH of the saliva and the release of volatile acids and bases (eg, NH₃ and acetic acid) from the mouth rather than to any effect on airway pH.

The author has no conflicts of interest to disclose.

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