CPAP minus during CPAP withdrawal) in extracellular water and weight was observed ($R = 0.590$; $P = 0.004$).

Discussion

This study provides strong evidence that the weight gain associated with the treatment of OSA with CPAP is due to fluid accumulation. Extracellular fluid volume during CPAP was not statistically higher than during CPAP withdrawal. However, weight gain occurred after 1 week of CPAP and could not be explained by the level of physical activity, calorie intake, water intake, or BMR, all of which remained stable. The magnitude of weight change in this acute study was remarkably similar to a meta-analysis of previous longer-term studies (0.37 vs. 0.42 kg, respectively) (1). Positive energy balance and increase in fat (4) and lean body mass (3, 4) have been suggested as a mechanism of weight gain during CPAP. If positive energy balance were a prevailing explanation, one would expect progressive weight gain over time. However, the recent evidence of lack of weight gain after an average of 3.8 years of CPAP (9) suggests that weight gain during CPAP is not cumulative. Moreover, fluid accumulation may explain the previously reported increase in lean body mass (3), as the vast majority of lean body mass (70%) is composed of water (10). Similar to mechanical ventilation, the treatment of OSA with CPAP reduces preload and urinary volume and may lead to fluid accumulation (5). In line with other studies, we did not find reduction in B-type natriuretic peptide levels associated with CPAP, indicating that other mechanisms such as antidiuretic hormone release may be involved. Twenty-four–hour urinary volume and sodium excretion between CPAP and CPAP withdrawal groups were similar, suggesting that patients had already reached a steady state after 1 week. Future studies are necessary to understand fluid balance within the first week of CPAP. Finally, we found a positive correlation between changes in weight and extracellular fluid volume. In conclusion, extracellular fluid volume did not increase during CPAP use. However, weight gain occurred within the first week of CPAP use and could be explained by fluid accumulation caused by reversal of nocturia. Our findings provide evidence against a negative metabolic impact promoted by CPAP during OSA treatment. ■

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BAL Is Safe and Well Tolerated in Individuals with Idiopathic Pulmonary Fibrosis: An Analysis of the PROFILE Study

To the Editor:

Diagnosing interstitial lung disease (ILD) is frequently challenging. Improvements in the recognition of disease-specific radiological patterns have resulted in many cases of ILD being diagnosed noninvasively. Nonetheless, there remain many circumstances

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Table 1. Demographics

	No Bronchoscopy (*n* = 391)	Bronchoscopy (*n* = 223)	*P* Value
Age, yr, mean (SD)	71.8 (8.3)	67.8 (8.1)	<0.001
Sex, M, *n* (%)	302 (77.2)	170 (76.2)	0.776
Smoking history, ever/current, *n* (%)	276 (70.6)	141 (63.2)	0.06
FVC, %, mean (SD)	76.3 (18.1)	77.8 (18.2)	0.591
D_{LCO}, %, mean (SD)	48.5 (17.6)	47.6 (14.1)	0.79
FEV_1/FVC, mean (SD)	79.8 (7.8)	79.6 (7.4)	0.71

in which further investigations beyond imaging are required to establish a definitive ILD diagnosis. This is reflected in recent diagnostic guidelines for hypersensitivity pneumonitis that suggest bronchoscopy and cellular analysis of BAL in patients with newly identified ILD for whom the differential diagnosis includes fibrotic hypersensitivity pneumonitis (1). The current idiopathic pulmonary fibrosis (IPF) guidelines also provide a conditional recommendation to perform BAL in cases of newly detected ILD of apparently unknown cause, in which the computed tomographic pattern is not one of definite usual interstitial pneumonia (2). However, not all centers perform diagnostic bronchoscopy in patients with ILD; in part, this reflects concerns about safety. A small number of retrospective and anecdotal observations have been used to suggest that bronchoscopy in individuals with IPF could be associated with an increased risk of acute exacerbations or acute respiratory deterioration (3, 4). We therefore aimed to clarify the safety of BAL in patients with IPF using the PROFILE (Prospective Observation of Fibrosis in Lung Clinical Endpoints) study cohort (5).

Incident cases of multidisciplinary diagnosed IPF were recruited prospectively as part of the PROFILE study through the following two coordinating centers in the United Kingdom: Nottingham University Hospitals in Nottingham (NCT01134822) and Royal Brompton Hospital in London (NCT01110694). Patients were assessed at baseline, 1 month, 3 months, and 6 months, and annually for 3 years. Fiberoptic bronchoscopy with BAL was undertaken in a subset of the Brompton cohort at baseline. BAL was performed by instillation of 240 ml of warm saline (in four 60-ml aliquots) into a segment of the right middle lobe with gentle aspiration by hand (6). No other bronchoscopic procedures were performed. Immediate, 30-day, and 90-day adverse events as well as overall survival were evaluated and compared between subjects undergoing BAL and those who did not. Continuous variables are presented as means (SD), and categorical variables are presented as proportions. Differences between subject groups were evaluated with the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables. Time-to-event curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Associations between continuous explanatory variables and overall survival were explored with a Cox proportional hazards model.

Of 614 subjects who were prospectively recruited into the PROFILE study, 223 underwent bronchoscopy (36%). The 391 individuals with IPF who did not undergo BAL were older (71.8 vs. 67.8 yr; $P < 0.001$) than subjects in the bronchoscopy cohort but otherwise were well matched (Table 1). All subjects in the bronchoscopy cohort tolerated the procedure well, a cell differential

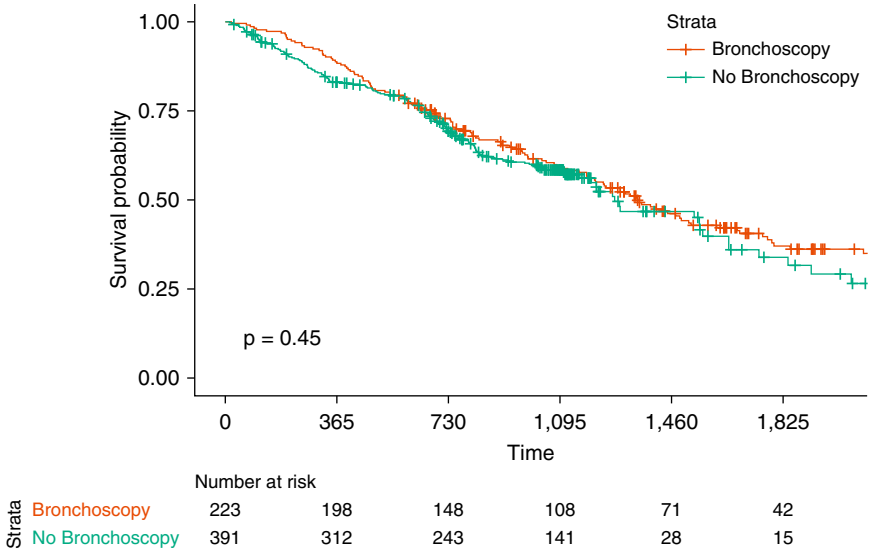

Figure 1. No significant difference in overall mortality in patients with idiopathic pulmonary fibrosis undergoing bronchoscopy. Shown are Kaplan-Meier curves comparing survival between individuals in the PROFILE (Prospective Observation of Fibrosis in Lung Clinical Endpoints) study undergoing bronchoscopy and those not undergoing bronchoscopy. Log-rank *P* test value is reported.

was available for all, and there were no immediate (<72 h) complications.

In the first 30 days after BAL, six patients (2.7%) reported complications. Two subjects described transient viral-type symptoms after the procedure, one subject described odynophagia (again transient), and three subjects were treated with antibiotics for presumed lower respiratory tract infection, with one case (0.4%) requiring an emergency room attendance but not admission. There was no difference in 30-, 60-, or 90-day all-cause mortality in those undergoing bronchoscopy compared with the no-bronchoscopy cohort. All-cause mortality at 90 days was 1.4% in the bronchoscopy cohort and 3.6% in the nonprocedure cohort.

There was no significant difference ($P = 0.45$) in overall mortality between patients who underwent bronchoscopy and those who did not (Figure 1). The median survival for patients undergoing bronchoscopy was 3.7 years. There remained no difference in survival after adjustment for age, sex, baseline % predicted FVC, baseline % predicted $D_{L_{CO}}$, smoking status, and recruitment site in a multivariable Cox proportional hazards model (hazard ratio, 0.84; 95% confidence interval, 0.59–1.22; $P = 0.364$).

There are a number of limitations to our work. First, subjects were not randomly assigned to either the procedure or no-procedure arm, as the bronchoscopy component of the study was optional. Second, some of the most severe cases of IPF were not included, as only subjects able to safely undergo bronchoscopy were enrolled; all-cause mortality was used as an endpoint rather than respiratory-related mortality because the necessary level of detail regarding cause of death was not available for the whole cohort. Finally, the no-bronchoscopy cohort was on average older than the intervention cohort, a known risk factor for mortality in IPF. However, there remained no difference in overall survival when incorporating this into a Cox model of survival, implying the age difference between groups had no meaningful impact. Although we demonstrate no negative safety signal, we do not address cost effectiveness; something which may impact local decisions to perform BAL in the diagnostic assessment of ILD.

In summary, this prospectively recruited longitudinal cohort study demonstrates that bronchoscopy is a safe and well-tolerated procedure in individuals with IPF. Although the assessment of BAL in the diagnosis of fibrotic lung disease may have recently been overshadowed by the emergence of cryobiopsy (7) and other novel molecular techniques (8), it remains important in distinguishing specific forms of ILD from IPF (something that is highlighted in recently published diagnostic guidelines for hypersensitivity pneumonitis). Furthermore, BAL has an important role in proof-of-concept clinical trials (9) and as a research tool for understanding disease pathogenesis and discovering novel biomarkers (10, 11). ■

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Is IL-6 the Right Target in COVID-19 Severe Pneumonia?

To the Editor:

We read with great interest the article by McElvaney and colleagues, "Characterization of the Inflammatory Response to Severe COVID-19 Illness," published in the *Journal* (1). Systemic inflammation that characterizes acute respiratory distress syndrome (ARDS) in coronavirus disease (COVID-19) is associated with a high mortality rate (2). The term "cytokine storm" has emerged to explain the immunopathogenesis of most severe forms of COVID-19, because the release of many inflammatory cytokines (e.g., IL-6) was correlated with the disease severity (3). However, immune pathogenesis is still unsettled and comparisons with community-acquired pneumonia (CAP) from other origins are scarce. Interestingly, McElvaney and colleagues showed that COVID-19 cytokinemia is distinct, with circulating levels of IL-6 significantly higher in patients with COVID-19 than in those with non–COVID-19 severe CAP (1).

These results are challenged by an editorial by Sinha and colleagues showing that plasma concentrations of IL-6 in patients with severe COVID-19 were lower than those observed in patients with ARDS from other origins (4). However, such comparisons are only possible if the respiratory severity is comparable between both groups.

We performed a prospective study that is part of the LYMPHONIE project (clinicaltrials.gov NCT03505281). We included non–immune-compromised patients with severe pneumonia (at least two criteria of the quick Sequential Organ Failure Assessment score and/or need for mechanical ventilation or vasopressors). Patients with COVID-19 all tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by RT-PCR. Plasma was collected within 48 hours of hospital admission and the concentration of IL-6 quantified using a Luminex assay (R&D Systems). Oral consent was obtained from the patient or their legal representatives. Approval was obtained from the ethics committee (Comité de Protection des Personnes Sud-MEDITERRANEE V) (2017-A03404-49).

Thirty-six patients without COVID-19 were enrolled between November 2018 and February 2020 (before the COVID-19 pandemic started in Burgundy, France) and 27 patients with COVID-19 in March and April 2020. Median age (interquartile range) was 67.5 (63–76.5) and 64 (57–71) in the non–COVID-19 and COVID-19 groups, respectively ($P = 0.0559$). ICU admission was needed for 32 (89%) and 27 (100%) patients of the non–COVID-19 and COVID-19 groups, respectively ($P = 0.07$). Pa_{O_2}:FI_{O_2} ratios were not different between groups (115.9 [74.6–157.9] vs. 145 [86–175.7] mm Hg, respectively; $P = 0.3073$). The IL-6 plasma concentrations were higher in the patients without COVID-19 than in those with COVID-19 (460.4 [138.2–4434.7] vs. 121 [75.7–236.6] pg/ml; $P = 0.0003$) (Figure 1).

Here, we showed that despite similar respiratory severity, plasma concentrations of IL-6 were dramatically lower in severe forms of COVID-19 than in CAP from other origins. Thus, although immune modulation is a promising therapeutic avenue that is likely to improve outcomes for COVID-19, the most relevant target and strategy remain to be found. ■

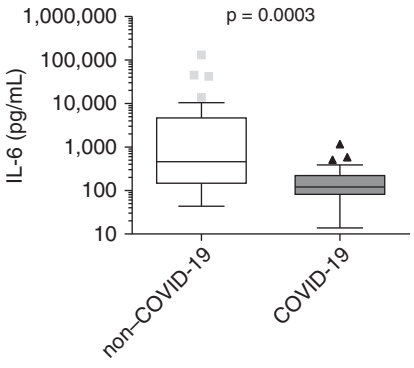

Figure 1. Box plot showing the plasma concentration of IL-6 within 48 hours of hospitalization in 36 patients with non–COVID-19 and 27 patients with COVID-19 severe pneumonia (LYMPHONIE study, 2018–2020). COVID-19 = coronavirus disease.

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