presentation, received lower flow rates, and had an overall lower frequency of severe ARDS oxygenation criteria. As criteria for transition to IMV were heterogeneous between the included cohorts, a more severe clinical picture at presentation may have biased the decision to intubate, thus exposing patients to complications and increased mortality associated with IMV (5).

The coronavirus disease (COVID-19) pandemic has encouraged the revision of the widely accepted Berlin criteria for ARDS. This manuscript brings to consideration the inclusion of patients with hypoxemia, and bilateral lung infiltrates using HFOT as fulfilling current ARDS criteria; on the basis of their results, the authors acknowledge this approach may select patients with lower mortality. As illustrated in the study, an updated definition should contemplate the disease severity adjusted by PEEP variability, with the requirement of higher values suggesting a more severe disease. To this end, the oxygenation index ($F_{I_{O_2}}$ · mean airway pressure · 100/Pa_{O_2}), which has been shown to be superior in predicting outcomes in patients with ARDS (6), may be a better option to assess the true degree of lung injury and severity. The monitoring of respiratory mechanics in patients who are not intubated, such as mean airway pressure in HFOT, should be an area for further research. ■

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Julián E. Barahona-Correa, M.D.
Pontificia Universidad Javeriana
Bogota, Colombia

Andres Laserna, M.D.
University of Rochester Medical Center
Rochester, New York

Cosmo Fowler, M.D.
Case Western Reserve University–MetroHealth
Cleveland, Ohio

Antonio Esquinas, M.D., Ph.D.*
Hospital Morales Meseguer
Murcia, Spain

ORCID ID: 0000-0003-0571-2050 (A.E.).

*Corresponding author (e-mail: antmesquinas@gmail.com).

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Reply to Barahona-Correa *et al.*

From the Authors:

We thank Barahona-Correa and coworkers for their interest in our study (1). In their letter, the authors raised a number of points about noninvasive ventilatory support: high-flow nasal oxygen (HFNO) does not allow routine assessment of respiratory mechanics, oxygenation index ([$F_{I_{O_2}}$ * mean airway pressure * 100]/Pa_{O_2}) may be better than $Pa_{O_2}/F_{I_{O_2}}$ in assessing the severity of acute respiratory distress syndrome, and better means of monitoring respiratory mechanics in nonintubated patients would be helpful. These are interesting points but not directly related to our study, and as such, we will not comment on them.

They also make the point that length–time bias may explain the reported low mortality rate of the patients on HFNO who did not transition to invasive mechanical ventilation. We think that length–time bias is not needed as an explanation: It's simply that the sicker patients ended up getting intubated. This is certainly not a surprise. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Tommaso Tonetti, M.D.
V. Marco Ranieri, M.D.
Department of Medical and Surgical Science (DIMEC),
Alma Mater Studiorum – University of Bologna,
Bologna, Italy

and

Anestesia e Terapia Intensiva Polivalente,
IRCCS Azienda Ospedaliero Universitaria di Bologna,
Bologna, Italy

Paolo Navalesi, M.D.
Department of Medicine (DIMED),
University of Padua,
Padua, Italy

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and
Institute of Anesthesia and Intensive Care,
Padua University Hospital,
Padua, Italy

Stefano Nava, M.D.
Department of Experimental, Diagnostic and Specialty Medicine (DIMES),
Alma Mater Studiorum – University of Bologna,
Bologna, Italy

and

Pneumologia e Terapia Intensiva Respiratoria,
IRCCS Azienda Ospedaliero Universitaria di Bologna,
Bologna, Italy

Arthur S. Slutsky, M.D.*
Keenan Research Centre for Biomedical Science, St Michael's Hospital,
University of Toronto,
Toronto, Ontario, Canada

On behalf of all the authors

ORCID ID: 0000-0001-9676-3595 (T.T.).

*Corresponding author (e-mail: arthur.slutsky@unityhealth.to).

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Small Airways in Pulmonary Fibrosis: Revisiting an Old Question with New Tools

To the Editor:

I read with much interest the article by Ikezoe and colleagues (1), in which the authors elegantly described the involvement of small airways in patients with idiopathic pulmonary fibrosis (IPF). Using ultra-high–resolution micro–computed tomography and three-dimensional imaging–based stereology in explant lungs, they demonstrated a reduction in the number of conducting terminal and respiratory transitional bronchioles in patients with IPF. In addition, they observed thickening of the airway walls of terminal bronchioles in regions of the lung that have no microscopic fibrosis and dilation and distortion of airway wall lumen of the remaining terminal bronchioles, which may be implicated in honeycomb cyst formation. These findings build on previous work by Verleden and colleagues (2) and Miller and colleagues (3), demonstrating wall thickening in small airways, reduction in the number of terminal bronchioles, and increased airspace size within fibrotic lungs, and support the hypothesis that traction bronchiectasis and honeycombing may represent diverse aspects of a continuous spectrum of lung remodeling (4). Involvement of small airways may be prominent in patients with smoking-induced lung fibrosis and particularly combined pulmonary fibrosis and emphysema, but it is also present in isolated IPF.

It is worth mentioning that the study of bronchiolar structural changes in IPF was pioneered by Fulmer and colleagues, who reported the first evidence of small airways morphologic abnormalities in lung biopsy specimens from patients with IPF (5), consisting predominantly of peribronchiolar fibrosis even in nonsmokers. Small airways were found narrowed in two-thirds of the patients and were dilated or normal in the remaining cases. Some degree of bronchiolectasis was present in approximately one-fourth of all airways evaluated. No distinction was made, however, between airways morphology in fibrotic versus nonfibrotic areas of the lung. These authors further described physiologic abnormalities compatible with small airways involvement (e.g., increased residual volume/TLC ratio) in the majority of patients with small airways histopathologic abnormalities, in line with a previous article by Ostrow and Cherniack published nearly 50 years ago (6).

The article by Ikezoe and colleagues (1) exemplifies how a long-standing hypothesis can be revisited through an innovative approach and taking advantage of novel technology. As is often the case, modern research successfully revisits old questions with new tools. Benchmarking the latest research (1) with older articles (5, 6) demonstrates how far morphologic research on diseased lungs has come in half a century. ■

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Vincent Cottin, M.D., Ph.D.*
Hospices Civils de Lyon
Lyon, France

and

Claude Bernard University Lyon 1
Lyon, France

ORCID ID: 0000-0002-5591-0955 (V.C.).

*Corresponding author (e-mail vincent.cottin@chu-lyon.fr).

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