re patterning of the adult human small airway epithelium. *Am J Respir Crit Care Med* [online ahead of print] 27 Mar 2017; DOI: 10.1164/rccm.201608-1672OC. Published in final form as *Am J Respir Crit Care Med* 2017;196:340–352 (this issue).

2. Mahmood MQ, Sohal SS, Shukla SD, Ward C, Hardikar A, Noor WD, Muller HK, Knight DA, Walters EH. Epithelial mesenchymal transition in smokers: large versus small airways and relation to airflow obstruction. *Int J Chron Obstruct Pulmon Dis* 2015;10:1515–1524.
3. Sohal SS, Reid D, Soltani A, Ward C, Weston S, Muller HK, Wood-Baker R, Walters EH. Reticular basement membrane fragmentation and potential epithelial mesenchymal transition is exaggerated in the airways of smokers with chronic obstructive pulmonary disease. *Respirology* 2010;15:930–938.
4. Soltani A, Walters EH, Reid DW, Shukla SD, Nowrin K, Ward C, Muller HK, Sohal SS. Inhaled corticosteroid normalizes some but not all airway vascular remodeling in COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:2359–2367.
5. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest* 2009;119:1420–1428.
6. Sohal SS, Soltani A, Reid D, Ward C, Wills KE, Muller HK, Walters EH. A randomized controlled trial of inhaled corticosteroids (ICS) on markers of epithelial-mesenchymal transition (EMT) in large airway samples in COPD: an exploratory proof of concept study. *Int J Chron Obstruct Pulmon Dis* 2014;9:533–542.

Copyright © 2017 by the American Thoracic Society

Reply

From the Authors:

We thank Dr. Sohal and colleagues for their interest in our recent study (1) [this issue, pp. 340–352], which identified a novel molecular phenotype in chronic obstructive pulmonary disease (COPD), characterized by smoking-dependent reprogramming of the small airway epithelium (SAE) from a typical “distal” toward the “proximal airway”-like transcriptome pattern. This “distal-to-proximal repatterning” was mediated, at least in part, by the epidermal growth factor receptor (EGFR) signaling in SAE-resident basal stem cells (BCs), a signaling pathway that drives all major smoking-related hyperplastic and metaplastic lesions in the airway epithelium (2, 3).

In their letter, Sohal and colleagues aim to link our findings to the epithelial-mesenchymal transition (EMT)-like phenotype, characterized by decreased expression of epithelial-specific E-cadherin, up-regulation of vimentin and other mesenchymal cell-associated markers, and airway basement membrane remodeling, observed in the airway epithelium of subjects with COPD (4–7). In previous studies, augmented EGF/EGFR signaling in airway BCs has been shown to shift the differentiation program of these cells toward the EMT-like remodeling phenotype accompanied by squamous metaplasia and decreased apical-basal polarity (2, 8), potentially relevant to impaired SAE barrier integrity observed in this disease (9–11).

Although our current study did not focus specifically on EMT-like remodeling, we found that expression of several genes implicated in this process, such as well-known EMT-related

transcription factors twist family basic helix-loop-helix transcription factor 1 (TWIST1) and snail family transcriptional repressor 2 (SNAI2, also known as SLUG), was enriched in the proximal airway epithelium compared with the SAE. This enrichment was paralleled by higher expression of EGFR and BC markers keratin 5 and tumor protein P63 in this region and, thus, might reflect higher frequency of BC, known to express EGFR (2) and SLUG (12), in the proximal airway epithelium compared with the SAE. However, no significant up-regulation of the EMT-related gene expression program was observed in the SAE of smokers with COPD in association with distal-to-proximal repatterning, except for TWIST1, which was slightly up-regulated in smokers with COPD compared with healthy nonsmokers, suggesting that distal-to-proximal repatterning of SAE in COPD likely occurs independent from EMT-like remodeling. Molecular features of distal-to-proximal repatterning were detected in the airway epithelium of subjects with COPD without overt histologic abnormalities, suggesting that this phenotype may develop early during the pathogenesis of airway remodeling in this disease, before derangement of the SAE architecture (1).

EMT has been one of the most “popular,” yet commonly misinterpreted, concepts in modern biology, particularly owing to different, sometimes relatively loose, criteria used by various investigators to define this process. Epithelial cells can acquire mesenchymal-like features (“partial EMT”), with loss of apical-basal polarity, disassembled cell-cell junctions, and up-regulation of vimentin, extracellular matrix proteins, and matrix metalloproteinases not only in pathologic conditions but also in response to injury, without becoming mesenchymal cells (13). Acquisition of EMT-like traits by the COPD airway epithelium could reflect an activated or aberrant repair process in response to chronic airway injury characteristic for this disease. Whether therapeutic targeting of this process in COPD can help restore airway epithelial homeostasis, as proposed by Sohal and colleagues (14), without compromising its ability to repair, remains an open, scientifically intriguing, and clinically relevant question. ■

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

Jing Yang, M.D.
West China Hospital of Sichuan University
Chengdu, China

Renat Shaykhiev, M.D., Ph.D.
Weill Cornell Medical College
New York, New York

References

1. Yang J, Zuo W-L, Fukui T, Chao I, Gomi K, Lee B, Staudt MR, Kaner RJ, Strulovici-Barel Y, Salit J, et al. Smoking-dependent distal-to-proximal repatterning of the adult human small airway epithelium. *Am J Respir Crit Care Med* [online ahead of print] 27 Mar 2017; DOI: 10.1164/rccm.201608-1672OC. Published in final form as *Am J Respir Crit Care Med* 2017;196:340–352 (this issue).
2. Shaykhiev R, Zuo W-L, Chao I, Fukui T, Witover B, Brekman A, Crystal RG. EGF shifts human airway basal cell fate toward a smoking-associated airway epithelial phenotype. *Proc Natl Acad Sci USA* 2013;110:12102–12107.
3. Zuo WL, Yang J, Gomi K, Chao I, Crystal RG, Shaykhiev R. EGF-amphiregulin interplay in airway stem/progenitor cells links the

Supported by National Institutes of Health grants R01HL123544 and R01HL127393 (R.S.).

Originally Published in Press as DOI: 10.1164/rccm.201705-0981LE on June 22, 2017

- pathogenesis of smoking-induced lesions in the human airway epithelium. *Stem Cells* 2017;35:824–837.
4. Sohal SS, Reid D, Soltani A, Ward C, Weston S, Muller HK, Wood-Baker R, Walters EH. Evaluation of epithelial mesenchymal transition in patients with chronic obstructive pulmonary disease. *Respir Res* 2011;12:130.
 5. Milara J, Peiró T, Serrano A, Cortijo J. Epithelial to mesenchymal transition is increased in patients with COPD and induced by cigarette smoke. *Thorax* 2013;68:410–420.
 6. Wang Q, Wang Y, Zhang Y, Zhang Y, Xiao W. The role of uPAR in epithelial-mesenchymal transition in small airway epithelium of patients with chronic obstructive pulmonary disease. *Respir Res* 2013;14:67.
 7. Gohy ST, Hupin C, Fregmilicka C, Detry BR, Bouzin C, Gaide Chevrone H, Lecocq M, Weynand B, Ladjemi MZ, Pierreux CE, et al. Imprinting of the COPD airway epithelium for dedifferentiation and mesenchymal transition. *Eur Respir J* 2015;45:1258–1272.
 8. Faris AN, Ganesan S, Chatteraj A, Chatteraj SS, Comstock AT, Unger BL, Hershenson MB, Sajjan US. Rhinovirus delays cell repolarization in a model of injured/regenerating human airway epithelium. *Am J Respir Cell Mol Biol* 2016;55:487–499.
 9. Heijink IH, Noordhoek JA, Timens W, van Oosterhout AJM, Postma DS. Abnormalities in airway epithelial junction formation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014;189:1439–1442.
 10. Shaykhiev R, Otaki F, Bonsu P, Dang DT, Teater M, Strulovici-Barel Y, Salit J, Harvey B-G, Crystal RG. Cigarette smoking reprograms apical junctional complex molecular architecture in the human airway epithelium in vivo. *Cell Mol Life Sci* 2011;68:877–892.
 11. Staudt MR, Buro-Auriemma LJ, Walters MS, Salit J, Vincent T, Shaykhiev R, Mezey JG, Tilley AE, Kaner RJ, Ho MW, et al. Airway Basal stem/progenitor cells have diminished capacity to regenerate airway epithelium in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014;190:955–958.
 12. Rock JR, Randell SH, Hogan BLM. Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodeling. *Dis Model Mech* 2010;3:545–556.
 13. Coraux C, Roux J, Jolly T, Birembaut P. Epithelial cell-extracellular matrix interactions and stem cells in airway epithelial regeneration. *Proc Am Thorac Soc* 2008;5:689–694.
 14. Sohal SS, Soltani A, Reid D, Ward C, Wills KE, Muller HK, Walters EH. A randomized controlled trial of inhaled corticosteroids (ICS) on markers of epithelial-mesenchymal transition (EMT) in large airway samples in COPD: an exploratory proof of concept study. *Int J Chron Obstruct Pulmon Dis* 2014;9:533–542.

Copyright © 2017 by the American Thoracic Society

Could Noninvasive Ventilation Failure Rates Be Underestimated in the LUNG SAFE Study?

To the Editor:

In a recent issue of the journal, Bellani and colleagues reported the characteristics and outcomes of patients with acute respiratory distress syndrome (ARDS) treated by noninvasive ventilation (NIV) (1). From the recent large international LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) survey (2), the authors analyzed the 349 patients with ARDS who were treated by NIV without treatment limitations. Among them, 28% had mild, 52% had moderate, and 19% had severe ARDS. The overall intubation rate was 38%, and it significantly increased according to the severity of hypoxemia, going from 22% in mild to 42% in moderate and 47% in severe ARDS (1).

However, these rates of intubation seem markedly lower than those reported to date (3–6). In a multicenter survey, Antonelli and colleagues

reported an overall intubation rate of 46%, which reached 59% in those with $\text{PaO}_2/\text{FiO}_2 \leq 175$ mm Hg (4). In another cohort, the rate of intubation was 61% all in all, and more than 80% in severe ARDS (6). The relatively low rate of intubation in the present study could be a result of, first, the low proportion of severe ARDS, and, second, the classification of patients who received NIV. Indeed, patients treated by NIV the first day and subsequently intubated the second day after NIV failure were excluded from the analysis and considered in the “invasive mechanical ventilation” group (1). Given that a high proportion of patients with ARDS need intubation within the first 24 hours after NIV initiation in case of failure (4–6), the intubation rate could have been markedly underestimated by excluding these patients.

To demonstrate this underestimation, we performed a secondary analysis by pooling all the patients with ARDS treated with NIV from two previous studies (5, 6). Among 223 patients with acute respiratory failure treated with NIV, 172 met the criteria for ARDS within the first 24 hours, including 93 patients from a cohort (6) and 79 patients from a randomized controlled trial (5). Patients included in these two studies were more likely to be immunocompromised (38% vs. 22%) and to have severe ARDS (33% vs. 19%) than in the LUNG SAFE study—two conditions associated with worse outcomes (6). Our pooled overall intubation rate reached 58% (100/172), and the median time to intubation was 26 hours (interquartile ranges, 6–54 hours), meaning that many patients were intubated on the first day of admission. By using the same method as in the present study (i.e., after excluding the patients who received only 1 day of NIV), our overall rate of intubation decreased from 58% to 42% (53/125), a rate very close to the 38% reported by Bellani and colleagues (Figure 1). Whereas hypercapnic patients were excluded from our studies, in the LUNG SAFE study the PaCO_2 level under NIV was relatively high (mean $\pm$ SD, 46 ± 17 mm Hg) and could be explained by a high proportion of patients with underlying chronic lung disease (31%) or heart failure (15%). Intubation rates consequently could have been relatively lower, as NIV is particularly effective in hypercapnic patients.

The LUNG SAFE study is of major interest to stratify the risk of intubation after NIV failure according to the severity of ARDS. However,

Figure 1. Intubation rates in patients with acute respiratory distress syndrome (ARDS) treated by noninvasive ventilation (overall rate and in each band of hypoxemia) in the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) survey (white bars) and in our two studies (5, 6), including the real rates (black bars) and the rates estimated according to the LUNG SAFE method (gray bars). These results indicate that the rates of intubation reported in the LUNG SAFE study are probably underestimated compared with real intubation rates.