4. Gray EL, McKenzie DK, Eckert DJ. Obstructive sleep apnea without obesity is common and difficult to treat: evidence for a distinct pathophysiological phenotype. *J Clin Sleep Med* 2017;13: 81–88.
5. Husebø GR, Bakke PS, Aanerud M, Hardie JA, Ueland T, Grønseth R, *et al.* Predictors of exacerbations in chronic obstructive pulmonary disease–results from the Bergen COPD cohort study. *PLoS One* 2014; 9:e109721.
6. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.

Reply to Khoury and Hakim

From the Authors:

We thank Khoury and Hakim for highlighting the clinical relevance and major impact of our study on the basis of the strengths of our real-world sample of patients with obstructive sleep apnea and chronic obstructive pulmonary disease (COPD), the overlap syndrome. The dataset comprises objectively measured positive airway pressure (PAP) therapy and administrative claims data (1). We agree with the authors that our study does have some limitations; however, we would like to comment on several issues they raised.

We expected to see differences in covariates between our comparison cohorts, and therefore, we used multiple statistical analysis methods to control for potential confounding. Although there was still some imbalance in the propensity score matching analysis, the sensitivity analysis we ran using inverse probability of treatment weighting (IPTW) achieved balance on the covariates mentioned by Khoury and Hakim. The balance between the cohorts was assessed using standardized mean differences (SMDs) of baseline covariates; the absolute value of SMDs of less than 0.1 generally indicates negligible difference (2). The IPTW analysis demonstrated the following results: psychotic disorders, 10.8% in the adherent and 11.6% in the nonadherent cohort (SMD = −0.03); morbid obesity, 40.7% in the adherent and 39.7% in the nonadherent cohort (SMD = 0.02); obesity not listed, 31.4% in the adherent and 32% in the nonadherent cohort (SMD = −0.01); and tobacco use, 47.4% in the adherent and 47.6% in the nonadherent cohort (SMD = 0.0).

As previously stated in our study, results from the IPTW sensitivity analysis were consistent with the propensity score analysis results, showing increased hospitalizations, emergency room visits, and costs for overlap patients not adherent to PAP. Therefore, we believe the covariates mentioned by Khoury and Hakim are unlikely to explain major differences observed in healthcare resource usage between adherent and nonadherent patients.

Khoury and Hakim incorrectly stated that we "[excluded] previous COPD exacerbations in patients with COPD as inclusion criteria". Although we did not specifically create a covariate for prior COPD exacerbations, the claims-based algorithm adapted from Mapel and colleagues used for the number of "2-year severe acute exacerbation model" includes the number of respiratory-related hospitalizations and COPD-related emergency room visits (3). On the basis of this criterion, most prior COPD exacerbations are captured in prior hospitalizations and emergency room visits. Thus, the inclusion of this specific variable would have caused multicollinearity issues and violated statistical modeling principles.

As discussed extensively in the limitations, we acknowledge that we lack laboratory data, and therefore, we were unable to characterize patients as hypercapnic or nonhypercapnic on the basis of concentrations of Pa_{CO_2} from an arterial blood gas draw. We speculate that our observed PAP benefits would be particularly pronounced in patients who are hypercapnic (4, 5). Of note, in our study, 85% of patients used automatic PAP or continuous PAP mode, and 15% used bilevel modes, predominantly spontaneous mode (i.e., without a backup rate). None of the patients in our analytic cohort used other modes of noninvasive ventilation. Future research should assess the impact of hypercapnia in overlap syndrome and the potential benefits of bilevel PAP over automatic/continuous PAP in these patients.

Although we are supportive of further randomized clinical trials, challenges regarding baseline differences in covariates and healthy user effect can still be an issue in this context. Moreover, multicentered randomized clinical trials are logistically challenging and are unlikely to be conducted in as large of sample sizes as our present analyses. Nonetheless, we hope our new data encourage further rigorous research in overlap syndrome. Until more definitive data are available, we believe our data may be clinically directive because they are consistent with the existing mechanistic and clinical literature (6). ■

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References

1. Sterling KL, Pépin JL, Linde-Zwirble W, Chen J, Benjafield AV, Cistulli PA, *et al.* Impact of positive airway pressure therapy adherence on outcomes in patients with obstructive sleep apnea and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2022;206: 197–205.
2. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
3. Mapel DW, Dutro MP, Marton JP, Woodruff K, Make B. Identifying and characterizing COPD patients in US managed care. A retrospective, cross-sectional analysis of administrative claims data. *BMC Health Serv Res* 2011;11:43.
4. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.
5. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, *et al.* Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017;317: 2177–2186.
6. Malhotra A, Schwartz AR, Schneider H, Owens RL, DeYoung P, Han MK, *et al.*; ATS Assembly on Sleep and Respiratory Neurobiology. Research priorities in pathophysiology for sleep-disordered breathing in patients with chronic obstructive pulmonary disease. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2018; 197:289–299.

Pneumothorax: Challenging the Paradigm of Persistent Air Leak, but Where Is the Leak?

To the Editor:

Walker and colleagues (1) suggest that chest tube drainage of pneumothoraces may increase air leaks and that chest tube drainage decreases pleural pressure, thereby increasing the pressure gradient between the site of the leak in the parenchyma and the pleural space. Their conclusion is on the basis of the premise that the air is leaking across the visceral pleura. Although they cite one paper that identified transpleural air leaks in eight patients who had multiple bullous lesions and large air leaks (2), and certainly direct transpleural air leaks can occur as a result of stab wounds or rib fractures, Lee and colleagues (3) note in the accompanying editorial that "most patients do not have an obvious site of leak … even when surgeons submerge the lung underwater intraoperatively."

In 1944, Macklin and Macklin proposed that pneumothoraces occur when the base of an overdistended alveolus ruptures, resulting in air escaping into the perivascular interstitium and subsequently dissecting along the interstitium toward the mediastinum, after which it can track into the pleural space (bilaterally on occasion) as well as into the soft tissue of the neck, face, arms, chest wall, pericardium, or into the abdominal cavity (4). If this were the mechanism by which air enters the pleural space (which Macklin and Macklin considered to be far more likely than transpleural leakage), the pressure gradient of interest would be from the alveolus to the interstitium and factors affecting interstitial pressure (e.g., lung volume, surface tension, lung elasticity, and airway and vascular diameters) would need to be included when considering the pathophysiology and treatment of pneumothoraces.

Macklin and Macklin (4) also noted that the pulmonary vessels dilated and elongated in response to lung inflation (predating the description of the effects of inflation on extra-alveolar vessels by Howell and colleagues in 1961 [5] and the concept of parenchymal interdependence described by Mead and colleagues in 1970 [6]). Accordingly, expanding the lung by evacuating pleural air would reduce interstitial pressure and augment the alveolar-to-interstitial gradient, similar to what Walker and colleagues propose for the alveolar–pleural gradient. Expanding the lung will also induce or increase alveolar overdistension (which occurs most commonly in response to local or regional atelectasis or inhomogeneities in airway resistance) that initially resulted in the septal rupture. ■

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References

1. Walker SP, Hallifax R, Rahman NM, Maskell NA. Challenging the paradigm of persistent air leak: are we prolonging the problem? *Am J Respir Crit Care Med* 2022;206:145–149.
2. Nakanishi K, Goto H, Ito T, Nagata Y, Hayashi S, Ishihara T. Novel imaging detailing the origins of a pneumothorax. *Thorax* 2018;73:85–87.
3. Lee YCG, Singh B. Pneumothorax: clearing the air on the pressure-dependent airleak hypothesis. *Am J Respir Crit Care Med* 2022;206: 143–144.
4. Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment. *Medicine (Baltimore)* 1944;4:281–358.
5. Howell JBL, Permutt S, Proctor DF, Riley RL. Effect of inflation of the lung on different parts of pulmonary vascular bed. *J Appl Physiol* 1961;16: 71–76.
6. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol* 1970;28:596–608.

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