intubation (2). Schematically, treatment should aim at minimizing the risk of muscular exhaustion leading to rapid shallow breathing and hypercarbia, while avoiding the risk of additional lung injury, self-inflicted by high transpulmonary pressure and V_T. Noninvasive respiratory support that grants lung- and diaphragm-protective ventilation should then be considered as ideal (3, 4).

The authors should be commended for providing a complete set of physiological data that could enhance our understanding of the effects of different noninvasive support in patients with AHRF. Overall, helmet NIV dramatically decreased the inspiratory effort compared with HFNC. Thus, helmet NIV could be highly efficient in decreasing the diaphragm workload to a desired physiological level, able to protect it from myotrauma and failure (3). On the lung protection side, the authors measured transpulmonary pressure swings (ΔP_L) as a surrogate of dynamic lung stress during both study phases, reporting nonsignificant differences between HFNC and helmet NIV (Figure 2 of Reference 1, right upper panel; $P = 0.11$) (1). The reduction in inspiratory effort during helmet NIV might have been due to two different mechanisms: the improvement in respiratory mechanics because of higher positive end-expiratory pressure effect and/or the muscles unloading owing to pressure support. For a given V_T, with the first mechanism, the decrease in inspiratory effort (ΔP_{ES}) would be associated with a decrease in ΔP_L (5); on the opposite side, pressure support could decrease ΔP_{ES} with unchanged (if mechanics remain stable) or even increased ΔP_L (in the presence of overdistension). Thus, identifying which mechanism is predominant in each patient might help individualize the type of support and NIV settings more than looking at average global values. As an example, it could be interesting to investigate whether the changes in ΔP_{ES} and ΔP_L between HFNC and helmet NIV were correlated with end-expiratory transpulmonary pressure during HFNC (6), with subjects with highly negative values experiencing unchanged or even decreased ΔP_L. If this correlation does exist, helmet NIV would be preferred to HFNC in patients with very low end-expiratory transpulmonary pressure. The finding that patients with lower ΔP_{ES} during HFNC increased ΔP_L more during helmet NIV could further corroborate this hypothesis: indeed, there was no correlation between ΔP_{ES} and oxygenation during HFNC, suggesting that the major determinant of respiratory effort is not altered gas exchange, but rather worse respiratory mechanics and inflammation (4).

The authors also describe that higher ΔP_L during helmet NIV was associated with the need for intubation and with mortality. The latter is undoubtedly an exploratory analysis, but it is interesting to note that seven out of eight patients who ultimately required intubation were clinically supported by helmet NIV for a certain number of hours. It would be interesting to explore whether this might have led to higher lung stress and additional lung injury. Additional explorative analyses could include comparing gas exchange during the study protocol and the last one measured before intubation to check whether lung edema worsened or if derangements of pH and Pa_{CO_2} were the main determinants of intubation.

Already, looking at the results, it seems that the ability to limit lung stress by helmet NIV might be lower than during HFNC. Helmet NIV could be considered as step-up support before intubation only in selected patients or if monitoring confirms lung-protective conditions. ■

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References

1. Grieco DL, Menga LS, Raggi V, Bongiovanni F, Anzellotti GM, Tanzarella ES, *et al*. Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2020;201:303–312.
2. Rochwerg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, *et al*. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. *Intensive Care Med* 2019;45:563–572.
3. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, *et al*. Mechanical ventilation–induced diaphragm atrophy strongly impacts clinical outcomes. *Am J Respir Crit Care Med* 2018;197:204–213.
4. Grieco DL, Menga LS, Eleuteri D, Antonelli M. Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. *Minerva Anestesiol* 2019;85: 1014–1023.
5. Bellani G, Grasselli G, Teggia-Droghi M, Mauri T, Coppadoro A, Brochard L, *et al*. Do spontaneous and mechanical breathing have similar effects on average transpulmonary and alveolar pressure? A clinical crossover study. *Crit Care* 2016;20:142.
6. Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, *et al*.; EPVent-2 Study Group. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2019;321:846–857.

Reply to Spinelli and Mauri

From the Authors:

We read with great interest the letter by Drs. Spinelli and Mauri discussing our recently published manuscript (1). We are grateful to the authors for their positive comments, useful suggestions for further analyses, and brilliant insights regarding interpretation of

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the results. We believe these remarks will foster an important debate about the role of noninvasive strategies in patients exhibiting intense inspiratory effort because of acute hypoxemic respiratory failure (2). Excessive inspiratory effort may be detrimental in hypoxemic patients because it leads to increased VT and lung stress; causes abnormal increases in transvascular pressure and worsening lung edema; generates overstretch in the dependent lung owing to a pendelluft phenomenon; and contributes to diaphragm injury (3–5).

In our study, we showed that, as compared with high-flow nasal cannula (HFNC), helmet noninvasive ventilation (NIV) is capable of reducing inspiratory effort. The decrease in inspiratory effort by helmet NIV is proportional to the degree of inspiratory effort during HFNC; accordingly, patients with low inspiratory effort while on HFNC may experience increases in transpulmonary pressure swings with helmet NIV. This suggests that monitoring of inspiratory effort would be crucial to tailor interventions and balance the benefits and harms of noninvasive strategies. Unfortunately, neither oxygenation nor respiratory rate was related to inspiratory effort in our cohort. Following the authors' suggestion, we performed additional analyses, which showed that inspiratory effort during HFNC was weakly but significantly related to end-expiratory esophageal pressure ($r = 0.64$; $P = 0.011$). Changes in inspiratory effort and in transpulmonary pressure swings with helmet NIV were associated with this parameter as well (Figure 1). Indeed, the end-expiratory esophageal pressure reflects the lung weight, which can be increased to a variable extent according to different degrees of edema, alveolar flooding, and disease severity (6).

In our cohort, eight patients (53%) required endotracheal intubation. Drs. Spinelli and Mauri question whether hypercapnia and pH derangements occurred after the end of the study and eventually led to the need for intubation. None of the intubated patients developed hypercapnia; unbearable dyspnea was the most common primary cause of endotracheal intubation (four patients), followed by worsening oxygenation (three patients) and altered consciousness with ineffective cough (one patient). Whether worsening oxygenation reflects increased lung edema cannot be established by our data. In our unit, we apply strict monitoring

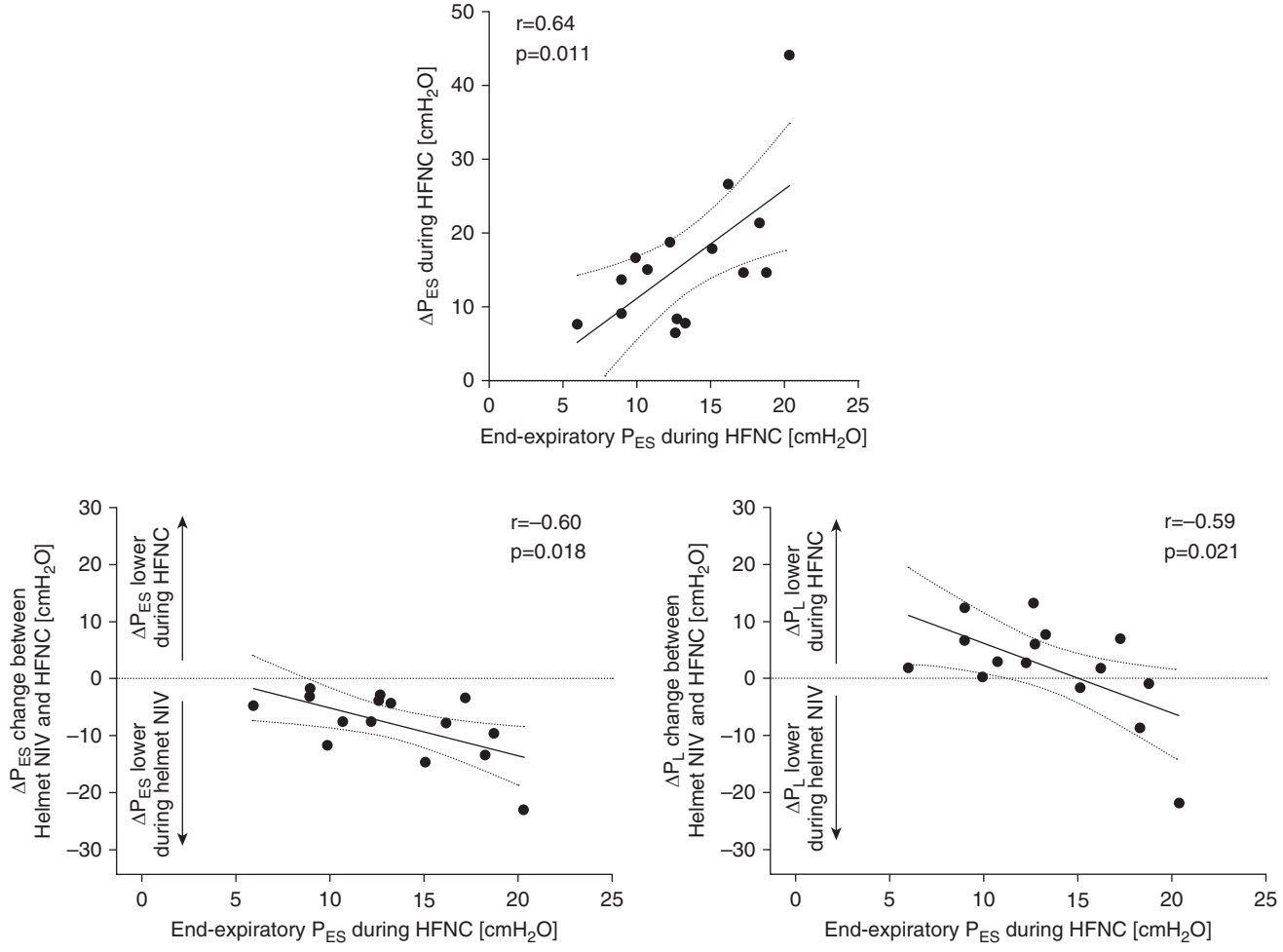

Figure 1. (Top) Correlation between end-expiratory esophageal pressure (P_{ES}) and inspiratory effort (ΔP_{ES}) during high-flow nasal cannula (HFNC). Patients with higher end-expiratory P_{ES} had more intense inspiratory effort. (Bottom) Correlation between end-expiratory P_{ES} and the change in ΔP_{ES} and transpulmonary pressure swings (ΔP_L) induced by helmet noninvasive ventilation (NIV). In all graphs, data from individual patients (1) and Pearson's correlation are reported.

of patients undergoing noninvasive respiratory support due to hypoxemic respiratory failure, to avoid any delay in endotracheal intubation. It is possible that prompt detection of treatment failure prevented muscle exhaustion–induced hypoventilation in failing patients.

Finally, because in some patients (i.e., those with lower inspiratory effort) helmet NIV increased transpulmonary pressure swings, the authors suggest that helmet NIV is less able to limit lung stress than HFNC and that this treatment should be reserved for selected patients as a step-up support. Unfortunately, we fear that it is not possible to draw conclusions regarding this specific aspect from our results. However, global lung stress (estimated by transpulmonary pressure swings) is only one determinant of self-inflicted lung injury, and inspiratory effort seems the most important parameter to be taken into account in this setting. Helmet NIV allows the application of high positive end-expiratory pressure, which reduces inspiratory effort and prevents pendelluft-induced overstretch in the dependent lung, as well as other ventilatory heterogeneities, making spontaneous effort less injurious (7). Importantly, during lung injury, limiting transpulmonary pressure swings cannot prevent injurious inflation patterns or diaphragm injury if inspiratory effort is not reduced as well (5, 8). ■

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References

1. Grieco DL, Menga LS, Raggi V, Bongiovanni F, Anzellotti GM, Tanzarella ES, *et al*. Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2020;201:303–312.
2. Grieco DL, Menga LS, Eleuteri D, Antonelli M. Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. *Minerva Anestesiol* 2019;85: 1014–1023.
3. Yoshida T, Fujino Y, Amato MBP, Kavanagh BP. Fifty years of research in ARDS: spontaneous breathing during mechanical ventilation. Risks, mechanisms, and management. *Am J Respir Crit Care Med* 2017;195: 985–992.
4. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017;195:438–442.
5. Goligher EC, Brochard LJ, Reid WD, Fan E, Saarela O, Slutsky AS, *et al*. Diaphragmatic myotrauma: a mediator of prolonged ventilation and poor patient outcomes in acute respiratory failure. *Lancet Respir Med* 2019;7:90–98.
6. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, *et al*. Esophageal manometry and regional transpulmonary pressure in lung injury. *Am J Respir Crit Care Med* 2018;197:1018–1026.
7. Morais CCA, Koyama Y, Yoshida T, Plens GM, Gomes S, Lima CAS, *et al*. High positive end-expiratory pressure renders spontaneous effort noninjurious. *Am J Respir Crit Care Med* 2018;197:1285–1296.
8. Yoshida T, Nakahashi S, Nakamura MAM, Koyama Y, Roldan R, Torsani V, *et al*. Volume-controlled ventilation does not prevent injurious inflation during spontaneous effort. *Am J Respir Crit Care Med* 2017; 196:590–601.

Loss of Alveolar Attachments as a Pathomechanistic Link between Small Airway Disease and Emphysema

To the Editor:

Vasilescu and colleagues are the first to provide confirmation that an imaging biomarker, parametric response mapping (PRM), has the ability to differentiate small airway disease (PRM^{SAD}) from emphysema (PRM^{Emph}) in patients with established chronic obstructive pulmonary disease (COPD) (1). This is of utmost importance given the urgent clinical and scientific need to noninvasively detect terminal bronchial pathology.

COPD is characterized by the presence of persistent airflow limitation and respiratory symptoms. Airways smaller than 2 mm in internal diameter are the dominant site of airflow obstruction in patients with COPD. This obstruction is caused by a mixture of pathogenic events (with)in and around the small airways, namely, loss of airways (2, 3), thickening of remaining airway walls (3), luminal obstruction by endobronchial mucus, and loss of bronchiolar–alveolar attachments leading to reduced radial traction.

Emphysema is a key pathological condition in COPD that is defined by an abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls and without obvious fibrosis. Whereas in an editorial addressing the landmark study of McDonough and colleagues (2), Mitzner (4) questioned whether emphysema formation starts in the small airways or lung parenchyma, accumulating evidence now strongly suggests that small airway disease precedes emphysema formation (2, 3, 5). It has been demonstrated that a significant proportion of terminal and transitional bronchioles are lost in lung samples from patients with COPD without signs of emphysema (2, 3), and that the

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