base by systematically testing the hypothesis generated by our initial clinical observation. At a minimum, their data provide reassurance that the risk of *P. jirovecii* coinfection in patients with COVID-19–related lymphocytopenia is likely not high. Further understanding of the clinical features of this novel disease requires a continued collaborative and systematic approach. ■

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

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Control of Respiratory Drive by Noninvasive Ventilation as an Early Predictor of Success

To the Editor:

Early prediction of failure of noninvasive ventilation (NIV) in patients with *de novo* acute hypoxemic respiratory failure is crucial to prevent patient self-inflicted lung injury and avoid delayed intubation. NIV should cope with the elevated respiratory drive to deliver effective yet still protective ventilation. However, drive increases for many different reasons: lung collapse and shunt lead to hypoxia, high dead space and elevated metabolic demand raise the concentrations of CO_2, lung inflammation and altered mechanics activate chemoreceptors and mechanoreceptors, and anxiety and subjective discomfort act on the neural respiratory drive, amplifying the response to chemical and mechanical stimuli (1). The clinical study by Tonelli and colleagues (2) testing the hypothesis that inspiratory effort estimated by esophageal balloon manometry might be an early predictor of NIV failure and worsening lung injury is a valuable addition to the field. Tonelli and colleagues report that lack of reduction in the swing of esophageal pressure (ΔPes) after 2 hours from start of NIV is an accurate predictor of NIV failure.

According to the study protocol, pressure support (PS) was initially set at 10 cm H_2O and then modified to maintain the expired V_T (V_{Te}) of <9.5 ml/kg predicted body weight (PBW) and the respiratory rate of <30 breaths/min. Of note, as a consequence of these per-protocol adjustments, PS level at 2 hours was significantly lower in the NIV failure group, whereas V_{Te} did not differ (3). As pointed out by Tuffet and colleagues (4), the amount of assistance during NIV influences the respiratory effort, and they

T.M. is supported by departmental funding.

Originally Published in Press as DOI: 10.1164/rccm.202007-2928LE on September 18, 2020

suggest a different interpretation of the study results according to which the amount of assistance, when properly modulated to decrease respiratory effort, may avoid intubation. Indeed, in the NIV success group, increasing PS allowed researchers to match the ventilation demand of the patient while maintaining protective ventilation, therefore controlling the respiratory drive. At the opposite end, the respiratory drive remained high despite NIV support in the failure group, halting the increase in PS level to maintain protective V_Te. Thus, we may speculate that if the PS level would have been left unchanged for the first 2 hours, we would have observed a persistently elevated V_Te (presumably higher than the targeted <9.5 ml/kg PBW) in the failure group versus lower protective V_Te in the other group. The results by Tonelli and colleagues are consistent with those previously published by Carteaux and colleagues (5), who reported that a V_Te higher than 9.5 ml/kg PBW is independently associated with NIV failure.

Improvement in lung mechanics and unloading of the respiratory muscles by NIV might have contributed to effective control of the respiratory drive in the success group. The correlation between ΔPes and V_Te/driving transpulmonary pressure (i.e., the dynamic lung compliance) at baseline confirms that effort is correlated with severity and that the "mechanical factors" related to the size of the baby lung act as strong determinants of the respiratory drive in this population. Nevertheless, other "nonmechanical" determinants of the respiratory drive must have been at play in the failure group. These factors could not be corrected by NIV and might require specific treatments, such as sedation to treat anxiety and discomfort, etiologic therapy to switch off inflammation, or extracorporeal CO_2 removal to decrease the ventilation demand (6). In this perspective, more precise understanding of the mechanisms of increased respiratory drive in each patient with *de novo* acute hypoxemic respiratory failure might allow an individualized "physiology-driven" treatment aimed at avoiding intubation. We believe that a multimodal approach for early identification and treatment of the contributing causes of elevated respiratory drive might be key to avoid patient self-inflicted lung injury and endotracheal intubation. ■

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

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Continued Vigorous Inspiratory Effort as a Predictor of Noninvasive Ventilation Failure

To the Editor:

This letter is in response to an article by Tonelli and colleagues published in a recent issue of the *Journal* (1). The authors' observation that a reduction in the magnitude of spontaneous respiratory effort after initiation of noninvasive ventilation (NIV) predicts the success of the NIV trial appears expected. Nevertheless, I do have a few interesting observations and explanations. $\dot{V}_E$ is influenced by respiratory drive, which in turn is guided by hypoxia, hypercarbia, systemic oxygen delivery, or cardiac output (2). A significant reduction in $\dot{V}_E$ (7.6 vs. 1.1 L/min) after 2 hours of NIV in the NIV success group with an almost similar expiratory V_T (V_Te) and respiratory rate (RR) change seems surprising. The $\dot{V}_E$ drive is always the primary determinant of the mechanical changes in the respiratory dynamics (3). An equal magnitude of mechanical pressure support and a similar V_Te in both the groups should have been supported by an almost similar reduction in tidal change in esophageal pressure (ΔPes) and tidal change in transpulmonary pressure (ΔP_L). As expected, the ΔP_L, V_Te, and $\dot{V}_E$ (slightly reduced because of a reduction in RR) remain unchanged before and after initiation of NIV in the failure group. A reduction in ΔPes was compensated by positive pressure to maintain the ΔP_L. A similar

Originally Published in Press as DOI: 10.1164/rccm.202008-3217LE on September 18, 2020