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. ■

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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

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V_{TE} in the NIV success group with a significantly lower ΔP_L indicated a higher lung compliance than the failure group. A differential change in ΔPes to ΔP_L (31.5→39.5 cm H_2O [Δ8 cm H_2O] vs. 11→30.5 cm H_2O [Δ19.5 cm H_2O]) with a similar level of pressure support and positive end-expiratory pressure (PEEP), 2 hours after the NIV trial in the failure and the success group, needs further clarification. Interestingly, $V_{TE}/\Delta P_L$ was lower in the NIV success group than the NIV failure group despite having a significantly lower ΔP_L. Even if a similar compliance is assumed for both groups, a persistent higher $\dot{V}_E$ indicates reduced cardiac output or systemic oxygen delivery in the NIV failure group. The success of mechanical ventilation and spontaneous breathing is inherently linked with cardiorespiratory interactions (4). A greater inspiratory drive in the NIV failure group resulted in lower intrapleural pressure, which could have further reduced the cardiac output and systemic oxygen delivery by increasing afterload and reducing the blood flow from the intrathoracic to the extrathoracic part of the aorta (5). In addition, an exaggerated venous return due to a higher negative intrapleural pressure coupled with increased afterload could have led to additional pulmonary congestion and deterioration in chest X-rays in the NIV failure group. Furthermore, a persistent higher inspiratory effort in the NIV failure group despite a nonsignificant difference in HACOR (Heart Rate, Acidosis, Consciousness, Oxygenation, Respiratory Rate) score suggests a different pathophysiology of hypoxemia. A continued higher $\dot{V}_E$ requirement did not allow ΔPes to reduce significantly in the NIV failure group. Therefore, a reduction in $\dot{V}_E$ could also have been a potential predictor of NIV success with reasonable accuracy. Furthermore, titration of pressure support and PEEP during the NIV trial may be guided by a reduction in $\dot{V}_E$ and work of breathing as the majority of the clinical parameters (RR, $P_{O_2}/F_{I_{O_2}}$, and $V_{TE}/\Delta P_L$) did not reach statistical significance to achieve the role of potential predictors. ■

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Reply to Spinelli *et al.* and to Jha

From the Authors:

We read with interest the letters by Dr. Spinelli and colleagues and by Dr. Jha commenting on our work on esophageal manometry and noninvasive ventilation (NIV) in acute *de novo* respiratory failure (ARF) (1). Both of them discussed the potential mechanisms behind the different behavior of lung mechanics in patients who failed NIV compared with those who succeeded.

Spinelli and colleagues pointed out that higher values of pressure support (PS) were allowed to fulfill the ventilation need (without increasing the expired V_T [V_{TE}]) in patients who succeeded the NIV trial, whereas significantly lower PS (at comparable ventilation) in the failure group suggested that higher assistance could have produced a harmful rise in V_{TE}.

In his letter, Jha also argued why in the failure group a persistently higher $\dot{V}_E$ with a higher inspiratory drive but lower intrapleural pressure could have driven an increased fluid afterload with a reduced $\dot{Q}$ and/or systemic oxygen delivery.

These points of discussion give us now the opportunity to further discuss the interplay between respiratory effort, lung mechanics (V_{TE} and dynamic transpulmonary pressure [ΔP_L]), respiratory drive, and the cardiopulmonary interactions.

V_{TE} at 2 hours was higher than the cutoff limit of 9.5 ml/kg of predicted body weight (2) in both groups of patients and started diverging significantly at 12 hours, with considerable reduction in the success group. This suggests that in patients with ARF, protective ventilation is difficult to achieve soon after NIV application and that V_{TE} alone might be an insufficient marker to identify those patients who may benefit from NIV. Moreover, in our patients, the magnitude of inspiratory effort as assessed by esophageal manometry at the time of NIV start correlated inversely with $V_{TE}/\Delta P_L$ (a surrogate measure of lung compliance) but not with the baseline V_{TE} (1). Therefore, V_{TE} did not reflect the intensity of the respiratory effort of our patients, introducing the concept of "baby lung assessment" during NIV that surely deserves further investigation. On the other hand, the values of ΔP_L increased similarly in both groups within the first 2 hours of NIV. However, this increase was due to the elevated values of esophageal pressure (ΔPes) (with low values of PS to avoid excessive V_{TE}) in patients who failed, whereas it was driven by a higher level of the PS set (associated with an unharmful V_{TE}) in those who succeeded. Overall, an average ΔP_L value $>$30 cm H_2O (as observed in our patients) could be harmful, although this is

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