The Respiratory Drive: An Overlooked Tile of COVID-19 Pathophysiology

Acute respiratory distress syndrome (ARDS) caused by coronavirus disease (COVID-19) (CARDS) has similarities and differences compared with ARDS from other etiologies (1). These traits stem from a distinctive pattern of lung injury in which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes alterations in the metabolism of angiotensin (2), vascular inflammation (3), immune thrombosis (4, 5), and neoangiogenesis (6). Of particular interest is the interaction between hypoxemia (which may be profound), the increased respiratory drive (primarily manifesting as increased V_T) (7), and dyspnea, which may even be absent in the early phase of the disease ("happy hypoxemia") (8). Measuring respiratory drive in patients with CARDS holds potential relevance in the selection of initial ventilatory support (9) and in the timing of liberation from mechanical ventilation. Indeed, vigorous breathing efforts can amplify the severity of lung injury, which in turn can influence the duration of mechanical ventilation and impact patient outcome.

The findings of a study reported in this issue of the *Journal* by Esnault and colleagues (pp. 1173–1178) illustrate the following two main things: first, the importance of measuring systematically the respiratory drive in ventilated patients who make spontaneous efforts and second, how high respiratory drive in CARDS portends subsequent worsening of respiratory function during attempts to liberate from mechanical ventilation (10). The study is the first to describe such an association in COVID-19. The authors report the threshold values of the following two measures of respiratory drive taken on the first day of spontaneous breathing: *1*) occlusion pressure in the first 100 ms of an occlusion ($P_{0.1}$) and *2*) the maximal deflection in airway pressure from positive end-expiratory pressure during an end-expiratory airway occlusion maneuver (ΔPocc). These simplified bedside measures of drive correlate well with relatively more precise methods for effort estimation (e.g., esophageal pressure and electrical activity of the diaphragm) (11, 12). Despite low Richmond Agitation Sedation Scale scores before measurement, 50% of the patient sample had $P_{0.1}$ >3.5 cm H_2O and 43% had ΔPocc <-15 cm H_2O. Patients who experienced a deterioration in respiratory function 24 hours after measurement had higher absolute values of $P_{0.1}$ (6.9 vs. 3 cm H_2O) and more negative ΔPocc (-18 vs. -15 cm H_2O). Both $P_{0.1}$ and ΔPocc displayed good prognostic performance in predicting respiratory deterioration at 24 hours, using cutoff values of $P_{0.1}$ ≥ 4 cm H_2O and ΔPocc <-10. None of the patients in the cohort experienced respiratory deterioration 24 hours after measurement if both measures were below the cutoff values, whereas deteriorations were recorded in 62.5% of the patient population if $P_{0.1}$ ≥ 4 cm H_2O and ΔPocc <-15 cm H_2O.

The relationship between high respiratory drive and worsening of respiratory status is complex, and therefore it is difficult to establish the direction of cause and effect. However, apart from reflex stimulation from the injured lungs, COVID-19 may affect angiotensin-mediated sensitivity of the carotid bodies (which express ACE2 receptors) and generate more complex brainstem-level alterations of the control of breathing, regardless of the degree of hypoxia or changes of lung mechanics. These relationships may become even more complicated over time as changing lung mechanics, ventilation needs, and neural sensitivity interact (13). At a relatively low level of pressure support, these patients exhibited a high corrected $\dot{V}_E$ of 12.8 L/min (14)—indicating a larger dead space—but a low rapid shallow breath index of 49 breaths $\cdot$ min^{-1} $\cdot$ L^{-1}. Yet, despite low rapid shallow breathing index, the respiratory drive was high in half of the studied population. This combination seems to differ from other forms of ARDS, in which the respiratory rate predictably increases with effort. Important information, which unfortunately is missing, relates to the respiratory mechanics either just before switching to spontaneous breathing or at the time of respiratory drive estimation. It would have been interesting to understand whether relatively high compliance (and lung volumes) could have explained this apparent paradox. In other words, under conditions of hypoxemia and unusually well-preserved compliance, higher respiratory drive would favor increasing V_T over respiratory rate (7). This possibility could explain the coexistence of the low shallow breath index, high respiratory drive, and high rate of complications in these patients. It can be speculated that the association between higher respiratory drive and respiratory complications may stem from the following two factors: *1*) worsening lung edema (from greater pulmonary blood flow and lung injury that follows larger swings in transpulmonary pressure) or *2*) an unfavorable relationship between oxygen delivery to $\dot{V}_{O_2}$ in response to greater inspiratory effort. The first hypothetical mechanism is the pathophysiological basis of self-inflicted lung injury (15), which may determine clinical and radiological deteriorations in proportion to respiratory effort (9). The study reports other interesting results. For example, most patients received invasive mechanical ventilation within the first day of ICU admission and experienced low 30-day mortality (4%). Given that ~60% of patients were still in the ICU at day 30, it would be of interest to see longer-term reports on the total duration of ventilation and mortality (e.g., 60 d or 90 d).

We may then wonder whether respiratory drive should be routinely assessed either by measuring $P_{0.1}$ and ΔPocc or by other methods (e.g., esophageal pressure swings or delta central venous pressures). It is likely that the assessment of the intensity of the inspiratory efforts—particularly in the early phase of the disease—is a first step toward clarifying the degree to which ventilation-induced lung injury plays a role in disease progression. Indeed, injury may

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be due either to the natural evolution of COVID-19—a consequence of the interaction between the viral load and the host response—or to the adverse effects of spontaneous breathing and/or inappropriate mechanical ventilation. The study by Esnault and colleagues is a first step in this direction. If further data confirm their findings, the ventilatory treatment should be modified accordingly to limit disease progression and duration. In this new disease, the "evidence" is not immediately available, but it is built by a number of contributions. The results of this paper suggest that excessive respiratory drive may be relevant in COVID-19. ■

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