Biomarkers to Guide Ventilation Management and Readiness for Extubation

Weaning from ventilatory support is a constant challenge for clinicians, especially in patients with acute hypoxemic respiratory failure (AHRF). Even in patients who succeed in a spontaneous breathing trial (SBT), failure of planned extubation occurs in up to 20% of the patients (1, 2). Importantly, failed extubation is associated with increased hospital mortality, prolonged ICU and hospital length of stay, and increased need for tracheostomy (3, 4). Despite the assessment of several respiratory and hemodynamic variables for predicting weaning success, few parameters present a substantial predictive power (1, 2). In addition, physiologic parameters may not reflect the degree of underlying lung injury, and new predictive tools are urgently needed.

Plasma biomarkers of lung injury are attractive tools for determining readiness for liberation from ventilator. Because common causes of AHRF are frequently associated with elements of lung inflammation and cardiac dysfunction (5, 6), circulating biomarkers of cardiovascular stress and inflammation can provide objective measures of time to resolution of AHRF and potentially predict liberation from the ventilator (6). Among several biomarkers, sST2 (suppression of tumorigenicity-2), which is a member of the IL-1 receptor family, has been implicated in signaling pathways of cardiac and vascular stress as well as inflammation (6, 7). In patients with acute respiratory distress syndrome (ARDS), higher sST2 concentrations were associated with worse outcomes during weaning of ventilation and increased need for reintubation (6). Measurement of sST2 level in AHRF could provide real-time prognostic information on the patient's clinical trajectory and readiness for extubation.

In this issue of the *Journal*, Alladina and colleagues (pp. 1257–1265) published the first prospective observational study to investigate a biomarker-direct approach to bedside ventilator management in patients with AHRF (8). In this study, 200 adult patients with AHRF (95.2% with ARDS) were included, and daily measurements of sST2 and IL-6 were assessed. Baseline sST2 concentrations were higher in nonsurvivors and in patients still receiving ventilation on Day 29. In addition, higher concentrations of sST2 over time were associated with a decreased chance of liberation from the ventilator. Furthermore, a higher sST2 at the day of extubation predicted failed extubation. Based on their findings, the authors concluded that using sST2 concentrations to guide ventilator management may more accurately reflect underlying lung injury and outperform traditional measures of readiness for ventilator liberation.

In recent years, several biomarkers were assessed in patients with AHRF and ARDS. A recent study has looked into biomarkers of epithelial and endothelial lung injury, coagulation, and inflammation and has shown that a combination of clinical predictors with biomarkers predicted mortality better than clinical or biomarker assessment alone (9). In another study, direct lung injury caused by pneumonia and aspiration was characterized by more severe lung epithelial and less severe endothelial injury, with higher plasma levels of sRAGE (soluble for advanced glycation end-products) and lower levels of Ang-2 (angiopoietin-2) when compared with indirect lung injury (10). Plasma levels of sRAGE reflect the extent and severity of lung epithelial injury, and higher levels were strongly associated with impaired alveolar fluid clearance (11). sST2 and IL-6, as assessed in the study by Alladina and colleagues, are biomarkers that are elevated in lung inflammation and may provide measures of ongoing lung injury. However, it is important to emphasize that the present study did not include biomarkers of epithelial lung damage as a potential comparator. There is a potential difference between the systemic reaction and the local alveolar reaction associated with AHRF and ARDS, emphasizing the importance of assessing biomarkers of the alveolar compartment in future research. Also, another important element that has been studied recently in the field of lung injury is volatile organic compounds from exhaled breath analysis, and this could be considered in future research (12).

The development and clinical utility of point-of-care or clinical-grade assays of biomarkers, including the potential of an "acute lung injury or extubation chip," must first be confirmed to improve patient outcomes in well-powered studies. sST2 is still not widely available in clinical practice, and this should be taken into account when interpreting the results of the present study. In addition, the study focuses more on lung injury as a cause for failed extubation. However, other reasons not directly related to lung injury may contribute to extubation failure, such as respiratory muscle weakness or heart failure. Indeed, the SBT is a cardiovascular stress test, and failure to wean from mechanical ventilation often reflects cardiovascular insufficiency to cope with an increased oxygen demand from increased work of breathing. The relationship between sST2 and extubation failure related to other factors than lung injury is still a matter of study.

During the study period, Alladina and colleagues enrolled patients from November 2015 to January 2017. Over this period, some changes in the weaning process have occurred, mainly focused on the prevention of failed extubation (13–15). The main changes are related to a shorter and less demanding ventilation strategy for SBT (13), the use of a 1-hour rest after a successful SBT and before extubation (14), and the use of high-flow nasal cannula or noninvasive ventilation after extubation in patients at low or high risk for extubation failure (15). The implementation of these recommendations was very low in the patients included in the present study.

There is an urgent need for future randomized clinical trials comparing the performance of pulmonary and blood biomarkers combined with precise physiological criteria to guide ventilator management and to determine readiness for extubation in patients with AHRF at high risk for extubation failure. The

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present study from Alladina and colleagues is another important piece in this field. ■

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Smoothing the Edges of Lung Protection

Two deceptively simple tools for improving the gas exchange and mechanics of patients with the acute respiratory distress syndrome (ARDS)—positive end-expiratory pressure (PEEP) and prone positioning—were brought to clinical attention nearly 50 years ago (1). Although the potential was soon recognized for PEEP to simultaneously influence global lung mechanics, gas exchange, and hemodynamics (2), our understanding of its regional actions in ARDS and its relationship to body position has been slow to evolve. The early and elegant physiologic investigation of Suter and colleagues demonstrated that the PEEP associated with best tidal compliance during volume-controlled ventilation (lowest driving pressure) held simultaneous benefits for gas exchange efficiency and oxygen delivery. At the time, lung protection against ventilator-induced lung injury was not a recognized priority, and by today's standards, a large V_T was in use. It is interesting to note that the compliance-defined optimal value of PEEP was first shown in that early era (3) to be a function of the V_T delivered, a relationship that has been more recently confirmed (4). In today's routine practice, the effects of PEEP on the lung

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