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Weaning from Veno-Venous ECMO: Lessons from 60 Years of Weaning from Mechanical Ventilation

The optimal method for weaning (or liberation) from venovenous extracorporeal membrane oxygenation (VV-ECMO) remains uncertain. In this issue of the *Journal*, Lazzari and colleagues (pp. 973–980) used a "physiological cohort" ($n = 26$) and a retrospective clinical validation cohort ($n = 638$) of patients with respiratory failure supported with VV-ECMO, to define physiological reasons for weaning failure, and to identify variables with strong weaning predictive ability (1). Patients in the physiological cohort were prospectively subjected to stepwise standardized liberation trials after fulfilling specified weaning criteria (pressure support ventilation, tidal esophageal pressure swings $\leq$15 cm H_2O, respiratory rate $\leq$30 breaths/min, pH $>$ 7.25, $Pa_{CO_2} \leq 60$ mm Hg, $Pa_{O_2} \geq 70$ mm Hg, $FiO_2 \leq 60\%$). Physiological variables and esophageal pressure swings were measured during the first liberation attempt. Weaning was considered successful if the patient maintained all physiologic values within weaning criteria at sweep gas flow of 0 L/min. Weaning was unsuccessful in 42% of trials, and 70% of weaning failures were due to excessive inspiratory effort and respiratory rate. Evaluating variables that could predict weaning outcome, baseline (before weaning sweep gas flow) $P_{ET_{CO_2}}/Pa_{CO_2}$ ratio was significantly associated with weaning success. In the univariate logistic regression, a best cutoff value of $P_{ET_{CO_2}}/Pa_{CO_2} \geq 0.84$ had a sensitivity 92%, specificity 80%, and positive likelihood ratio of 4.6. Using the clinical cohort for external validation, the ratio was again strongly associated with weaning outcome. However, only 58% of patients were correctly classified (compared with 86% in the physiologic cohort), and sensitivity and specificity were considerably lower (54% and 66%, respectively). The authors concluded that the $P_{ET_{CO_2}}/Pa_{CO_2}$ ratio was significantly associated with weaning failure in the physiological and validation cohort and could serve as a tool to assess readiness to wean in patients supported with VV-ECMO.

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The $P_{ET_{CO_2}}/Pa_{CO_2}$ ratio is a very robust physiological parameter. It is a measure of the alveolar dead space, or hyperventilated/hypoperfused regions of the lung. The negative prognostic value of high dead space is evident (2, 3), but has not been widely adopted by clinicians for unclear reasons. The presence of extensive perfusion defects on the pulmonary circulation and increased pulmonary artery pressure are typical traits of acute respiratory distress syndrome (ARDS) recognized since the early 1980s. A ratio close to 1 suggests good ventilation/perfusion ($\dot{V}/\dot{Q}$) match, independently of the level of ECMO support, remaining sensitive to intrapulmonary shunt, particularly when the shunt is higher than 30%. In the era of protective ventilation, paying attention to alveolar dead space and its mechanisms may decrease the risk of ventilation induced lung injury (VILI). High alveolar dead space implies increased ventilatory requirements, and hence increased risk of VILI (4). We should always keep in mind that ECMO does not only improve oxygenation but decreases the intensity of ventilation required to maintain Pa_{O_2} and Pa_{CO_2} within target range, inherently reducing the risk of VILI.

We congratulate the authors in their commitment to use a sound pathophysiological approach to shed some light into the understudied area of liberation from ECMO for respiratory failure. However, there are some important considerations for their approach. The predictive variables were not selected *a priori*, they were rather identified using univariate screening and/or stepwise selection. Approaches using outcome data to select variables are flawed, rendering models uninterpretable due considerable overestimation of effect estimates (5).

The prediction index itself poses some challenges and limitations as well. In spite of the sound physiological reasoning and attractiveness of a simple bedside index, it might seem unlikely that a single value of baseline $P_{ET_{CO_2}}/Pa_{CO_2}$ (while still on ECMO) would adequately represent impaired $\dot{V}/\dot{Q}$ matching in two patients with large variations in minute ventilation and extracorporeal blood flow. We consider quantifying alveolar dead space essential in understanding the mechanism of liberation failure, however, we worry that systematically using the ratio to decide which patients should undergo a liberation trial may result in delayed liberation testing, particularly when the predictive index performance has poor sensitivity and specificity.

Weaning from mechanical ventilation has shown us that clinicians underestimate patient's readiness to wean (6), and that the utility of single predictors to identify readiness or successful liberation is limited (7). Evidence holds the best approach to identify when patients are ready to be liberated form mechanical ventilation is subjecting them to daily liberation trials (8, 9). Eligibility for such liberation trials is dictated by a set of predetermined pragmatic clinical criteria. This systematic and standardized approach has led to significant reductions in duration of mechanical ventilation, improved patient outcomes, and reduced costs (10).

It seems logical that weaning and liberation from ECMO will follow a similar path. Recently, we and others demonstrated that a considerable proportion of patients on VV-ECMO for ARDS are ready to be liberated from higher levels of ECMO support than previously considered (11, 12). However, although standardized liberation trials may safely reduce the duration of ECMO, we do not know if this reduction will translate into improved patient outcomes. Liberation from ECMO to mechanical ventilation is not a patient-centered outcome. Unless the patient is extubated while on ECMO, we are transitioning from one form of mechanical support to another. The tradeoffs between liberating patients to mechanical ventilation versus prolonging their exposure to systemic anticoagulation or other ECMO related complications still need to be defined. The significance of elevated airway pressures or high inspiratory efforts this far out in the management of ARDS is unclear. Masi and colleagues recently reported reasonable outcomes in patients decannulated without meeting classic liberation criteria (failed liberation trial or liberation without meeting weaning criteria) (13). To make matters more challenging, there is no standardized definition of successful decannulation (14), and ECMO centers generally do not collect information on escalation of support soon after elective decannulation.

As with mechanical ventilation, we will eventually realize that it is unlikely that a single predictor will be the answer to promptly and safely liberating patients from ECMO. No predictive test for liberation has greater predictive ability than the liberation test itself. We should instead direct our efforts to adopt a standardized approach to liberation, and to define criteria for when to test, how to test, how to define successful liberation, and how to approach liberation failure. Only then will we understand the outcomes of liberation and can attempt to seek weaning predictors for specific clinical scenarios. ■

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Pulmonary Hypertension Caused by Interstitial Lung Disease
A New iNK(T)ling into Disease Pathobiology

Interstitial lung disease (ILD) encompasses a heterogeneous group of conditions characterized by restrictive lung physiology and impaired gas transfer caused by lung parenchymal destruction with varying degrees of inflammation and fibrosis. The development of pulmonary hypertension (PH) in the context of ILD (PH-ILD) has a substantial impact on morbidity and mortality (1–3). In fact, among PVDOMICS (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics) study subjects with Groups 1–5 PH according to the World Symposium on Pulmonary Hypertension classification, those with Group 3 PH (>50% with PH-ILD) had the lowest transplant-free survival (4). Therefore, a sense of cautious optimism has emerged since the results of the INCREASE study (5, 6) and U.S. Food and Drug Administration approval of inhaled treprostinil, the first and only U.S. Food and Drug Administration–approved treatment for PH-ILD. Nonetheless, the substantial impact of PH-ILD on quality of life, functional capacity, and survival underscores the urgent need for translational studies that elucidate additional treatment paradigms.

In this issue of the *Journal*, Jandl and colleagues (pp. 981–998) describe a novel link between natural killer T (NKT) cell deficiency and pulmonary vascular fibrosis (7). Perivascular type I collagen deposition was increased in lung tissue from patients with PH-ILD, a cohort composed mainly of patients with idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonitis, and unclassified ILD, compared to samples from ILD patients without PH and donor lung controls. Multicolor flow cytometric analysis of immune cell subsets from isolated pulmonary arteries revealed an overall increase in perivascular $CD3^+$ lymphocytes in patients with PH-ILD compared to samples from donor lungs but a significantly lower proportion of NKT cells ($CD3^+/CD56^+$). Lower concentrations of IL-15, responsible for NKT cell maturation and survival, in lung tissue and plasma from patients with PH-ILD compared to controls further substantiated the observed perivascular NKT cell deficiency. Notably, NKT cell activation with a synthetic analog of α-galactosidase (KRN7000) not only preserved NKT cell ($CD3^+/NK1.1^+/TCR\beta$) number but also reduced pulmonary vascular muscularization, right ventricular systolic pressure, and right ventricular hypertrophy in mice with bleomycin-induced pulmonary fibrosis. Previous studies have demonstrated that NKT cell deficiency worsens lung fibrosis and increases mortality in the bleomycin-induced pulmonary fibrosis murine model (8) and that NKT cell activation with KRN7000 in mice attenuates lung fibrosis induced by intratracheal bleomycin (9). However, the impact of NKT cell activation on the pulmonary vasculature in this model was previously unrecognized.

The authors then determined that STAT1 expression was significantly reduced in isolated pulmonary arteries from patients with PH-ILD compared to both donor controls and vessels from ILD patients without PH. Expression appeared specifically decreased in

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