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Breathing and Ventilation during Extracorporeal Membrane Oxygenation: How to Find the Balance between Rest and Load

In theory, the application of extracorporeal membrane oxygenation (ECMO) in severe respiratory failure allows lung treatments varying from a lung at rest (continuous positive airway pressure) to all different levels of ventilatory support or even pure, spontaneous breathing. Although ECMO is increasingly used worldwide, very little is known about the respiratory settings applied during the course of ECMO, and even less is known about the optimal "balance" of ventilatory and extracorporeal support to minimize ventilator- or ventilation-induced lung injury, and the optimal conditions for lung healing and repair. In this issue of the *Journal*, Schmidt and coauthors (pp. 1002–1012) present an international, multicenter, prospective cohort study (LIFEGARDS [Ventilation Management of Patients with Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome]) in which data from 350 patients with ECMO in 23 international ICUs were collected during a 1-year period (1). In addition to demographics, the authors carefully compiled data regarding the ventilator settings applied before and during ECMO, the use of adjunctive therapies, and ICU and 6-month outcomes. The authors and their participating centers should be congratulated for providing the community with such sound data from different countries and ICUs, as well as the preferential ventilator settings used before and during the application of ECMO. The primary outcome measured was 6-month mortality, but the study also provides data on the type and use of adjunctive therapies, as well as the changes in driving pressure and mechanical power before and during the ECMO run. Some of these observational data are in part confirmatory and quite striking (2, 3). This study included only ICUs with an annual ECMO volume of more than 15 cases, and all of the participating centers treated a median of 30 patients with ECMO in the year before the study. Therefore, they could be clearly classified as "experienced." In this context, it is more than striking that the prone position was not used in more than 26% of the patients, especially when a plateau pressure of 32 cm H_2O was applied. Instead, the fact that a reported 15% of patients were turned to prone even during the ECMO course gives reason to hope that proning will be more regularly applied also in patients without ECMO. In contrast, with a V_T of 6.4 ± 2.0 ml/kg, patients were ventilated close to the magic "protective" value. However, the ventilatory setup as a whole led to a plateau pressure of 32 ± 7 cm H_2O, a ventilatory rate of 26 ± 8, a driving pressure (ΔP) of 20 ± 7 cm H_2O, and a mechanical power of 26 ± 12.7 J/min. It is interesting to note that after the ECMO initiation, while the reduction in DELTAP was only 30%, the reduction in mechanical power was as great as 75%, reflecting the importance of the frequency for energy transmission. With an overall 6-month survival of 61%, the study presents impressive outcome findings. The changes in respiratory settings after ECMO initiation resulted in both ΔP and power values below the thresholds that have been considered "critical" in both experimental and clinical studies (4–7). It is thus not surprising that the ventilator settings applied during the first 2 days after ECMO onset had no impact on survival, whereas age, immunocompromised state, extrapulmonary sepsis, and lactate and fluid balance—all of which could be considered indicators for the general severity of disease—were positively correlated. Given the ΔP and power values observed before ECMO was initiated, it is not unexpected that each day of delaying intubation to ECMO was also positively correlated with a higher 6-month mortality. Moreover, higher spontaneous respiratory rates during the first 2 days of ECMO were associated with higher 6-month mortality.

The strength of this study, which used data from different ICUs in 10 different countries, lies in the amount and quality of the data and the homogeneity of the treatment, including the use or nonuse of adjunctive measures. At the same time, this is also a limitation, as these data certainly do not reflect the real world of patients with ECMO treated in non-university hospitals or in hospitals with lower ECMO volumes and less experience in treating patients with severe respiratory failure and/or acute respiratory distress syndrome. In addition, the study describes how the patients were ventilated after

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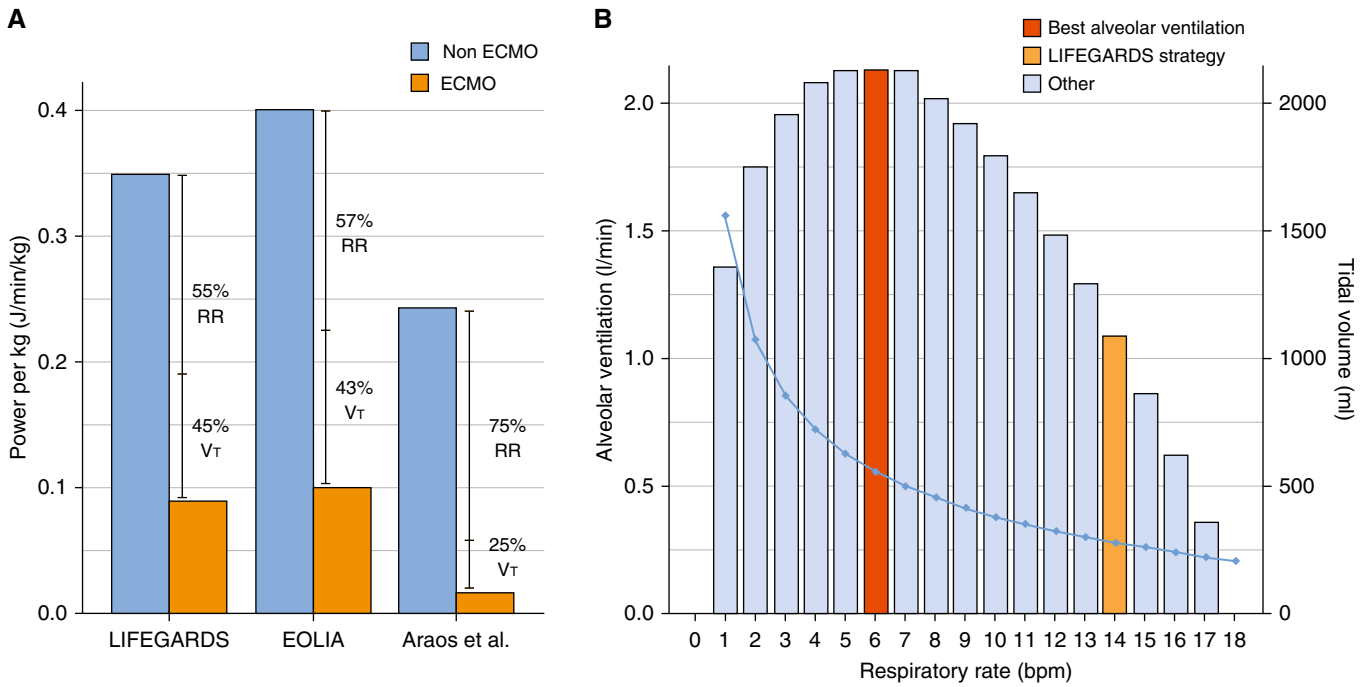

Figure 1. (*A*) Mechanical power (MP) normalized per kilogram of body weight delivered during mechanical ventilation before and after onset of extracorporeal membrane oxygenation (ECMO) in the LIFEGARDS (Ventilation Management of Patients with Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome) and EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) studies, as well as in the experimental study by Araos and colleagues (9), indicating a reduction (in percent) of MP attributed to the respiratory rate (RR) or the VT. (*B*) We built a model for an MP (here we use the one delivered during ECMO in the LIFEGARDS study, 6.6 J/min) and a given dead space (200 ml) to establish the best combination of VT and RR, with the aim of maximizing alveolar ventilation. Each column represents the alveolar ventilation at each different RR (left *y*-axis), and the light blue line represents the associated VT (right *y*-axis). Positive end-expiratory pressure was kept constant (11 cm H_2O) in this model, as were the airway resistances. bpm = breaths/min.

the onset of ECMO, but it does not provide the reasons for the chosen partitioning between gas exchange across the native lungs and the artificial lung, or the rationale behind each specific ventilatory pattern. It is also unclear why a VT of 3.7 ± 2.0 ml/kg ideal body weight and a respiratory rate of 14 ± 6, including 8 ± 11 spontaneous breaths at a positive end-expiratory pressure of 11 ± 3 cm H_2O, was chosen. This study clearly identifies crucial questions for further research: how much unloading of the lungs is most beneficial for healing and repair, and what is the best composition (i.e., ventilatory pattern) of the chosen load? It seems reasonable to choose a ventilator setting that enables the greatest alveolar ventilation (i.e., the highest amount of CO_2 removal) with the lowest price to pay (resulting power). A simplified mathematical approach makes it possible to determine for any given power the combination of VT and frequency that will result in the highest alveolar ventilation (*see* Figure 1A). The ECMO settings applied will determine how low the power could theoretically become to reach equivalent CO_2 removal. Figure 1B demonstrates the reduction in power achieved in LIFEGARDS, the EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) trial (8), and the animal experiment by Araos and colleagues (9), with the goal of near-apneic ventilation. Ultimately, the question remains as to what creates the best conditions for an organ accustomed to rhythmically expanding and relaxing: more rest or more movement?

Schmidt and coauthors did a great job of letting us know where—at least in experienced centers—we actually are on this issue. The LIFEGARDS study provides a more than solid basis for us to move forward. ■

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Call for Changes in Lung Allocation to Reduce Transplant Wait-List Mortality for Cystic Fibrosis

As lung transplantation is becoming increasingly common, the challenges involved in optimizing organ allocation and minimizing wait-list mortality are escalating. The demand for donor organs exceeds supply, making it imperative to allocate organs to individuals with the greatest need to maximize benefit from a scarce resource. The "common rule" mandate from the Department of Health and Human Services in 1999 requires that donor organs be allocated to the sickest patients first. To address this challenge, allocation based on wait-list time was replaced by the Lung Allocation Score (LAS) in 2005, which was used to distribute donor lungs based on parameters that predicted wait-list mortality, balanced twofold relative to factors that predicted 1-year survival (1). Since its implementation, the LAS has undergone revisions as additional data have provided clinical parameters predictive of wait-list mortality and/or 1-year post-transplant survival, and overall wait-list mortality has improved (2). Moreover, a lawsuit in 2017 led to the removal of some geographic constraints to organ allocation and prompted an evaluation of geographic sharing that has the potential to reduce wait-list mortality (3, 4). Despite these efforts, however, the LAS remains limited in its ability to identify patients who are most likely to benefit from transplantation. The wait-list mortality for patients with cystic fibrosis (CF) clearly illustrates this problem.

A major challenge for individuals with CF is that survival with advanced disease is heterogeneous. Although the median survival with $FEV_1 < 30\%$ predicted is 6.6 years, annual mortality is ~10% without transplantation (5). Although short-term survival may improve with the development of effective CFTR (CF transmembrane conductance regulator) modulators, the high risk of death in advanced CF lung disease prompted a strong recommendation for early transplant referral to provide a survival option for individuals who suffer a precipitous decline resulting in respiratory failure (6). Problematically, the wait-list mortality for individuals with CF has remained at >10% since implementation of the LAS (7). Experienced CF healthcare providers consider this wait-list mortality unacceptable because individuals with CF typically enjoy more dramatic quality-of-life improvements and a median post-transplant survival approaching 10 years, which is longer than that observed in individuals with other lung diseases (8, 9). Why is the wait-list mortality so high? One potential explanation is that the LAS does not consider many CF-specific patient characteristics associated with short-term mortality. Modification of the LAS by using CF-specific risk factors might improve the ability of the LAS to prioritize access to transplantation for patients with CF and the highest risk of wait-list mortality.

In a study presented in this issue of the *Journal*, Lehr and colleagues (pp. 1013–1021) addressed this problem by merging two datasets: the Scientific Registry of Transplant Recipients, which contains information on wait-list mortality and post-transplant survival, and the CF Foundation Patient Registry (CFFPR), which includes unique longitudinal data on more than 28,000 individuals with CF (10). The datasets were merged rigorously and provided a large sample. Using the combined dataset, the authors first updated the current LAS model (updated LAS revised [LAS-RU]) based on patients who were listed and/or underwent transplantation between 2011 and 2014. The authors then evaluated how variables from the CFFPR impacted the LAS-RU and derived a new LAS, termed LAS-RU-CF. Their analysis identified that for patients with CF, the trajectory of FEV_1 decline, colonization with any *Burkholderia* species, hospitalization days, and massive hemoptysis were associated with wait-list mortality, and pulmonary exacerbation time was associated with post-transplant mortality. Most importantly, inclusion of the variables from the CFFPR increased variability in the LAS score and LAS rank for patients with CF, and thus improved the predictive accuracy of the modified LAS (LAS-RU-CF). In aggregate, the modified LAS would potentially prioritize organ allocation to individuals with CF who would be most likely to benefit from transplantation. In addition, the combined database exemplifies the potential for detailed, longitudinal, disease-specific databases to facilitate mortality

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