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⊕ Rapid Changes in Arterial Carbon Dioxide Levels Caused by Extracorporeal Membrane Oxygenation: The Temptation of a Fascinating Technology

Since 2009, the publication year of the CESAR (Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial (1), the fascinating technique of extracorporeal support for the failing lung or for life-

threatening cardiac instability has celebrated a triumph that continues to this day (2). Without doubt, the application of new technologies, such as extracorporeal membrane oxygenation (ECMO), may save life in many cases. Yet, ECMO is a complex and risky measure, and it may be accompanied by severe adverse events, such as bleeding or neurologic injuries (3). The precise knowledge of ECMO management in critically ill patients is crucial for survival and for ensuring the health-related quality of life after transfer from the ICU. Interprofessional teamworking and a high level of expertise are required in terms of mechanical ventilation during ECMO (4), anticoagulation, positioning of the patients,

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and strategies of weaning. Incidentally, a position paper, among the quality aspects, on the use of such an attractive device was published in 2018 (5).

In accordance with the mostly accepted indications for ECMO (6), such a technique should be considered in severe hypoxemia or hypercapnia (venovenous ECMO), or in acute cardiac failure (venoarterial ECMO). Although most intensivists report a rapid (and perhaps lifesaving) increase in oxygenation after the initiation of ECMO, less attention was paid to changes in the carbon dioxide (CO₂) levels in the early phase of ECMO treatment. Most ECMO users are happy with a relatively high sweep gas flow resulting in a prompt oxygen increase in the blood, accompanied by a rapid decrease in PaCO₂ and an increase in the pH value. In a recent international multicenter prospective cohort study (7) on current practices in ECMO management, a sweep gas flow of around 5 L/min was preferred by most intensivists, resulting in a significant, and often rapidly occurring, reduction in arterial CO₂ levels because CO₂ removal is predominantly and very effectively regulated by the amount of the sweep gas flow. Remarkably, in an experimental animal study in 1995, Liem and colleagues (8) observed adverse effects of hypercapnia and hypocapnia in pigs on ECMO, and they recommended that “it is important to keep arterial CO₂ tension stable and in normal range during clinical ECMO.” Over and above this, some small retrospective observational studies found deleterious effects of a rapid reduction in CO₂ levels in patients using ECMO after cannulation (9, 10).

In this issue of the *Journal*, Cavayas and colleagues (pp. 1525–1535) report on the data of around 12,000 patients with ECMO derived from the registry of the Extracorporeal Life Support Organization (11). They retrospectively recorded the relative changes in arterial P_{CO₂} levels in the first 24 hours after initiation of ECMO, and they associated these findings with neurologic complications. The results of this investigation are impressive and deserve attention. Patients with an early relative decrease in P_{CO₂} of greater than 50% (19% of patients) had a higher incidence of neurologic adverse events (9.8%) compared with the group of patients with a smaller relative decrease in P_{CO₂} (6.4%; $P < 0.001$). Interestingly, a “U-shaped” association was observed: a marked rapid decrease in PaCO₂ and a significant relative CO₂ increase were associated with high numbers of neurologic complications, whereas patients on the ground of the “U” (lowest relative PaCO₂ changes) had a low incidence of neurologic complications. Furthermore, after adjustment for confounders and risk factors by multiple logistic regression analyses, a large relative decrease in PaCO₂ greater than 50% was still independently associated with adverse neurologic events (odds ratio, 1.7; 95% confidence interval, 1.3–2.3; $P < 0.001$).

Registry-based clinical research is an important retrospective observational tool in assessing healthcare interventions, whereas randomized trials assess efficacy for a carefully selected patient group (12). The interpretation of registry data should be handled with caution because the quality, completeness, and accuracy of the entered data might be critical. The large database in the present study by Cavayas and colleagues (11) combined with a convincing concept among the pathophysiologic essentials of adverse effects due to rapid alterations in the CO₂ homeostasis make the results conclusive. A marked and rapid shift in PaCO₂ was associated with seizure, cerebral hemorrhage, or brain death, but we do not know

the effect of the altered CO₂ homeostasis on the general cognitive function or on mental disorders in surviving patients. We may expect a similar impact on cognitive capability in daily life activities. Such an important aspect has not been investigated yet. In a multivariate adjusted dichotomized analysis of a recent German prospective multicenter observational study (DACAPO) on health-related quality of life in survivors of acute respiratory distress syndrome (13), low V_T ventilation (≤ 7 ml/kg) with hypercapnia was associated with a significantly more impaired 3-month mental quality-of-life score (SF-12) compared with the higher V_T group (> 7 ml/kg) representing normocapnia. Although “permissive,” pronounced hypercapnia may disturb the homeostasis of the CO₂ system as well as marked hypocapnia.

In light of the study by Cavayas and colleagues (11), the plea for a rapid (and sometimes rigorous) correction of hypercapnia in patients with acute lung failure after the insertion of ECMO must be reevaluated because a high price may be paid for the abrupt alteration in the CO₂ equilibrium. To facilitate a slow PaCO₂ removal, the authors suggest frequent monitoring by blood gases to avoid rapid PaCO₂ changes; furthermore, they postulate a moderate and “soft” level of sweep gas flow. The latter one is useful and important, whereas, unfortunately, frequent blood gas monitorings are time-consuming but have no alternative. Near-infrared spectroscopy for the assessment of cerebral vasoconstriction (14) and transcutaneous continuous CO₂ monitoring (15) are currently not suitable or precise enough to guide the management of CO₂ removal by sweep gas flow.

The fascinating technique of ECMO is lifesaving but has some serious and inherent shortcomings, requiring expertise to avoid them. The investigation of Cavayas and colleagues (11) yields very important insights on how to improve the quality of care. An ultima ratio strategy for critically ill patients needing the use of ECMO should be a medical and ethical dictate. Addressing the issues of physiological PaCO₂ and pH level in patients using ECMO may be beneficial; but, if so, be gentle and patient with your patient using ECMO! ■

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Calling Time on Spirometry: Unlocking the Silent Zone in Acute Rejection after Lung Transplantation

Lung transplantation is the only effective treatment for patients with end-stage lung disease, yet median survival is only 6 years and significantly shorter than that observed with other solid-organ transplants (1). Acute cellular rejection (ACR) causing graft failure is the major cause of death in the first year, and is also a risk factor for chronic lung allograft dysfunction (CLAD) (2). The International Society for Heart and Lung Transplantation reported that 28% of lung transplant recipients experience at least one episode of treated ACR within the first year (1). Graft rejection and transplant failure place an immense burden on both patients and healthcare systems, so the detection and treatment of ACR is paramount.

Transplant centers monitor patients routinely with spirometry indices, primarily FEV₁. Both ACR and CLAD begin in the small airways, yet FEV₁ only gives information relevant to large- and medium-sized airways and is rather insensitive and nonspecific to changes within the small airways (3). Progressive immunopathological disease in the “silent zone” may therefore

go unnoticed until it is significantly advanced before a change in FEV₁ occurs or the patient experiences symptoms (4). The role of routine surveillance bronchoscopy in screening asymptomatic patients for histopathological ACR remains controversial and varies among transplant centers (5). There is a real need to track changes in the small airways and lung parenchyma, preferably noninvasively, to identify disease early and thus allow a prompt diagnosis and timely intervention, but efforts have been limited by the lack of accurate techniques and accessible tools.

Recent years have seen the development and validation of physiological tests of small airway function, and commercially available machines that can monitor the lung periphery are being used in clinical practice (6). Indices of ventilation distribution reflecting small airway dysfunction have been studied in lung transplant recipients (7, 8) and shown to be abnormal 1 year before a 20% decrease in FEV₁ (9). Oscillometry has been available for over 50 years and can be used to detect small and large airway disease in patients with obstructive lung disease (10). Low-frequency signals (5 Hz) penetrate out to the lung periphery (all airways), whereas high-frequency signals (19 Hz) only reach the proximal airways, such that resistance at 5 Hz (R5) reflects the total airway resistance and the difference (R5–19 Hz) probes the distal smaller airways (Figure 1) (11). Studies of oscillometry in lung transplant recipients are limited.

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