Extracorporeal Carbon Dioxide Removal in Chronic Obstructive Pulmonary Disease: It Depends on the Objective!

Since the 1990s noninvasive ventilation (NIV) revolution in the treatment of chronic obstructive pulmonary disease (COPD) exacerbation and the subsequent reduction in intubation rate and mortality (1), we have been looking for new strategies to further improve these patients' outcomes. Because hypercapnia refractory to NIV stands as the primary cause of intubation in COPD exacerbation, and because persistent hypercapnia largely contributes to weaning difficulties, considering the use of extracorporeal carbon dioxide removal (ECCO2R) (2) is straightforward to try to optimize severe COPD exacerbation treatment. ECCO2R in COPD exacerbation has previously been evaluated in small studies. The device was used to prevent intubation in patients at high risk of NIV failure and to facilitate weaning from invasive mechanical ventilation. In a meta-analysis of 10 studies and 87 patients, ECCO2R proved effective in increasing pH, reducing Pa_{CO_2}, and lowering respiratory rate, without compromising oxygenation significantly (3). However, safety concerns arose, with frequent reports of bleeding and other adverse events (3). Regarding the outcome of preventing intubation, several small nonrandomized studies suggested potential reduction in intubation rates and ICU length of stay, whereas others were negative (4, 5). In 2022, Barrett and colleagues (6) published a first small randomized controlled trial, with 18 patients at risk for NIV failure randomized to receive ECCO2R and NIV (9 patients) or NIV only (9 patients). In this study, ECCO2R use resulted in lower Pa_{CO_2} after 4 hours, alleviated dyspnea, and reduced time to NIV discontinuation. However, ICU and hospital length of stay were longer in the ECCO2R group, and a trend toward increased mortality at 90 days was observed with ECCO2R (6). ECCO2R use to facilitate weaning in patients with COPD exacerbation has been reported in case reports and case series (7–9). A physiological study in 10 patients with a crossover design (ECCO2R in place with sweep gas flow switched on or off) showed reduced Pa_{CO_2}, increased pH, and decreased respiratory muscle CO_2 production with ECCO2R. The use of the technique, however, failed to reduce hyperinflation (10). Interestingly, work of breathing measured during the weaning process in 5 of the 10 patients tended to be lower with ECCO2R, clearly suggesting a potential interest of the technique to facilitate weaning. Overall, the use of ECCO2R in COPD exacerbation has a strong physiological rationale, but the lack of robust data does not allow providing any recommendation regarding its use in this context.

In this issue of the *Journal*, Duggal and colleagues (pp. 529–542) publish the results of a very interesting Prospective Multicenter trial (VENT-AVOID) (11). This study aimed to determine whether ECCO2R, compared with standard care alone, could increase the number of ventilator-free days within the first 5 days after randomization (VFD-5) in patients with COPD exacerbation at high risk of NIV failure or experiencing difficulties in being weaned from invasive ventilation. It thus assessed the interest of ECCO2R to both avoid intubation and facilitate extubation. Despite being prematurely stopped because of slow enrollment rate after the inclusion of 113 patients (instead of 180), the VENT-AVOID trial provides valuable insights regarding the potential use of ECCO2R for severe acute COPD exacerbation. This study is the largest to date addressing the question of preventing intubation with ECCO2R in COPD exacerbation, with 48 patients randomized to either ECCO2R plus NIV (26) or NIV alone (22). It is also the first randomized trial assessing the potential of ECCO2R in enhancing weaning. In this second study stratum, 32 patients were randomized to ECCO2R and 33 to standard care. Overall, in the VENT-AVOID trial, the use of ECCO2R did not lead to an increase in VFD-5. The study primary endpoint might appear unusual. However, compared with the more common VFD at Day 28, the VFD-5 endpoint allowed the capture of the direct effects of ECCO2R, given its short duration. In addition, by scoring early death as −1 (instead of 0) in VFD-5 calculation, the weighting of early death was substantial. Although the choice of the primary endpoint was very clever to capture the effects of ECCO2R, it is crucial to note that the study primary endpoint was modified during the study, as VFD at 60 days was initially considered. This adaptation in the trial protocol might be attributed to early recognition of the challenges in demonstrating a significant impact of ECCO2R.

The independent analysis of the two study strata reveals noteworthy findings. In patients at risk of NIV failure (first stratum), in line with previous studies, ECCO2R use lowered Pa_{CO_2} and alleviated dyspnea within 24 hours of the start of the therapy. However, a higher intubation rate was observed in the ECCO2R arm (13% vs. 4%), and ECCO2R significantly increased ICU length of stay and in-hospital and 60-day mortality, despite no increase in the total number of severe adverse events with ECCO2R. Severe bleeding complications nevertheless occurred in the intervention group. The poor outcomes observed with ECCO2R in the NIV stratum cannot be attributed to baseline differences between the groups. Importantly, the VENT-AVOID study results likely have good extrinsic validity, as baseline patient characteristics were typical of patients with COPD experiencing severe exacerbation. It is also crucial to mention that the study results are consistent with the trend toward increased mortality previously observed in the smaller study published in 2022 by Barrett and colleagues, which also addressed the interest of ECCO2R in avoiding intubation (6). Consequently, the results of the VENT-AVOID study NIV stratum clearly suggest refraining from the use of ECCO2R in attempting to avoid intubation in patients with COPD exacerbation at risk of NIV failure.

The results of the VENT-AVOID trial regarding ECCO2R use in facilitating weaning (second study stratum) are much more encouraging, showing a trend toward more VFD-5 with ECCO2R than with standard care. This was also true for VFD at 10 days. Interestingly, the potential benefit of ECCO2R to enhance weaning in patients with

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COPD experiencing difficulties in being separated from the ventilator was visible even if an increase in pH and decrease in $\dot{V}_E$ with ECCO2R were no longer observed after 24 hours of treatment. Importantly, no increases in ICU or hospital length of stay or in mortality were observed when ECCO2R was used in difficult-to-wean intubated patients with COPD. Although the VENT-AVOID trial has acknowledged limitations, it suggests that additional studies powered to assess mortality outcomes are warranted to explore the role of ECCO2R to facilitate weaning in patients with COPD exacerbation who had to be intubated and are difficult to wean. However, given the high prevalence of bleeding complications and other adverse events reported with the currently available ECCO2R devices, not only in patients with COPD but also in patients with acute respiratory distress syndrome (12, 13), it is advisable to address technical issues and enhance the safety of the technique before planning large-scale trials. ■

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References

1. Brochard L, Isabey D, Piquet J, Amaro P, Mancebo J, Messadi AA, *et al.* Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *N Engl J Med* 1990;323: 1523–1530.
2. Giraud R, Banfi C, Assouline B, De Charrière A, Cecconi M, Bendjelid K. The use of extracorporeal CO_2 removal in acute respiratory failure. *Ann Intensive Care* 2021;11:43.
3. Sklar MC, Beloncle F, Katsios CM, Brochard L, Friedrich JO. Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: a systematic review. *Intensive Care Med* 2015;41:1752–1762.
4. Del Sorbo L, Pisani L, Filippini C, Fanelli V, Fasano L, Terragni P, *et al.* Extracorporeal Co2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. *Crit Care Med* 2015;43:120–127.
5. Braune S, Sieweke A, Brettner F, Staudinger T, Joannidis M, Verbrugge S, *et al.* The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. *Intensive Care Med* 2016;42:1437–1444.
6. Barrett NA, Hart N, Daly KJR, Marotti M, Kostakou E, Carlin C, *et al.* A randomised controlled trial of non-invasive ventilation compared with extracorporeal carbon dioxide removal for acute hypercapnic exacerbations of chronic obstructive pulmonary disease. *Ann Intensive Care* 2022;12:36.
7. Abrams DC, Brenner K, Burkart KM, Agerstrand CL, Thomashow BM, Bacchetta M, *et al.* Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013;10:307–314.
8. Burki NK, Mani RK, Herth FJF, Schmidt W, Teschler H, Bonin F, *et al.* A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest* 2013;143: 678–686.
9. Roncon-Albuquerque R Jr, Carona G, Neves A, Miranda F, Castelo-Branco S, Oliveira T, *et al.* Venovenous extracorporeal CO2 removal for early extubation in COPD exacerbations requiring invasive mechanical ventilation. *Intensive Care Med* 2014;40:1969–1970.
10. Diehl JL, Piquilloud L, Vimpere D, Aissaoui N, Guerot E, Augy JL, *et al.* Physiological effects of adding $ECCO_2R$ to invasive mechanical ventilation for COPD exacerbations. *Ann Intensive Care* 2020;10:126.
11. Duggal A, Conrad SA, Barrett NA, Saad M, Cheema T, Pannu S, *et al.*; VENT-AVOID Investigators. Extracorporeal carbon dioxide removal to avoid invasive ventilation during exacerbations of chronic obstructive pulmonary disease: VENT-AVOID trial. *Am J Respir Crit Care Med* 2024;209:529–542.
12. McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, *et al.*; REST Investigators. Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. *JAMA* 2021;326: 1013–1023.
13. Combes A, Fanelli V, Pham T, Ranieri VM; European Society of Intensive Care Medicine Trials Group and the "Strategy of Ultra-Protective lung ventilation with Extracorporeal CO2 Removal for New-Onset moderate to severe ARDS" (SUPERNOVA) investigators. Feasibility and safety of extracorporeal CO_2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med* 2019;45:592–600.

Can We Predict Acute Respiratory Distress Syndrome in Hematopoietic Stem Cell Recipients?

Immunocompromised patients represent up to one-third of critically ill patients and one-fifth of those admitted to the ICU with acute respiratory distress syndrome (ARDS) (1). This group has distinct risk factors for lung injury and increased mortality compared with nonimmunocompromised patients with ARDS, demanding expertise for clinical management. Among critically ill immunocompromised patients, hematopoietic stem cell transplantation (HCT) recipients exhibit the highest mortality (2). Three significant differences set HCT recipients apart from other immunocompromised patients. First, factors like transplant type, conditioning regimen, and underlying malignancy contribute to clinical heterogeneity (3).

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