Optimizing Anticoagulation for Venovenous Extracorporeal Membrane Oxygenation

Finding the Right Balance

Recent guidelines advocate for venovenous extracorporeal membrane oxygenation (VV ECMO) use in selected patients with severe acute respiratory distress syndrome (ARDS) (1). This recommendation is based on the collective data from both randomized (2–4) and nonrandomized (5) landmark studies reporting survival benefits in patients with ARDS treated with VV ECMO compared with those receiving conservative care (6). Of note, these mortality benefits occurred despite significantly increasing bleeding events in VV ECMO–supported patients (3). Although bleeding events are associated with worse outcomes (7), it is likely that a reduction in their occurrence could further improve VV ECMO–supported patient outcomes. As such, studies examining, preventing, or mitigating complications represent an important unmet need.

To prevent or mitigate the consequences of bleeding events, a thorough understanding of their occurrence, risk factors, pathophysiology, and impact on clinical outcomes is needed. In this issue of the *Journal*, Martucci and colleagues (pp. 417–426) report the PROTECMO (Prospective Observational study on Transfusion in VV ECMO) study results of the evaluation of 652 VV ECMO–supported patients treated between 2018 and 2021 in 41 centers participating in the ECMONet consortium (8). The PROTECMO study examines a highly granular longitudinal cohort that includes details on bleeding events, type and doses of anticoagulants and antiplatelet therapies, and monitoring tests and clinical outcome results.

There are seven important findings in this report, as follows: *1*) A total of 342 (52.5%) of 652 patients developed bleeding events during 16.5% of ECMO support days; *2*) bleeding occurred most frequently at the cannulation site; *3*) the incidence of bleeding varied over time and gradually increased over the course of ECMO support; *4*) bleeding events significantly increased the risk for ICU-related mortality; *5*) the activated partial thromboplastin time (aPTT) levels were associated with bleeding risk, but heparin doses poorly correlated with aPTT values; *6*) heparin was most frequently used as an anticoagulant, aPTT was the major monitoring strategy, and average targets ranged between 40 and 60 seconds; and *7*) anticoagulation and monitoring regimens were frequently changed throughout the course of treatment.

The first four findings in VV ECMO–supported patients suggest that bleeding remains a significant clinical problem, even though target anticoagulation levels have been reduced over time; improvements in oxygenators, circuits, and tubing architecture have reduced hemostatic activation and consumptive coagulopathy; and increasing use, education efforts, and improved familiarity with ECMO deployment and use have facilitated safer cannulation and management practices (7). The persistently high incidence of bleeding in ECMO patients is also influenced by the underlying critical illness and associated multiorgan dysfunction that are common in critically ill patients. The clinical presentation, however, is frequently complicated by the fact that bleeding is accompanied by thrombotic events in approximately 21% of VV ECMO–supported patients (6). This frequent yin–yang coexistence of bleeding and thrombosis and their higher incidence in COVID-related ARDS seem to point to an important role of inflammation as a trigger and catalyst for coagulation disorders (8). Findings 5 and 6 listed above clearly describe clinical practice variation and, at the same time, question the validity of aPTT for monitoring the heparin effect in light of the poor correlation between heparin dosages and serum aPTT levels. The latter uncertainty was underscored by a meta-analysis of observational studies finding a higher bleeding risk and similar thrombotic risk in a time-guided versus anti-Xa–guided anticoagulation strategy, respectively (9). Observation number 7 demonstrates that bleeding risk is not constant over time, leading to frequent monitoring strategies and anticoagulant changes.

The mechanistic evidence in this study provides several leads for future developments that may help reduce bleeding risk and improve patient outcomes. First, because the cannulation site is most often involved in the bleeding site, improved cannula designs and interplay between cannula and vasculature could help reduce local complications. Further improvements in oxygenator biocompatibility could potentially reduce coagulopathy and could lower or omit the need for systemic anticoagulation. Additional therapeutic strategies to minimize the contributory role of thromboinflammation in the pathophysiology of bleeding and thrombosis could also further minimize and improve the diathesis risk in non–COVID-19-related ARDS. In light of the weak association between heparin doses and plasma aPTT levels, future studies should expand on identifying optimum monitoring biomarkers and their corresponding targets. We hope that a current randomized clinical trial investigating low-molecular-weight heparin and unfractionated heparin with different anticoagulation targets will provide further guidance regarding some of these important questions (10). For establishing specific anticoagulation monitoring targets, dedicated prediction tools could help assess the risk for bleeding and thrombosis and could further contribute to personalized care (11). Given the variability of bleeding risk across patients and within patients over time, such prediction tools would also need to be dynamic and able to update risk profiles over time by incorporating clinical (bleeding) events, degree of inflammation, and circuit changes. The future development of such dynamic models faces considerable challenges, including counterfactual prediction and their validation. Recent advances in epidemiological and biostatistical approaches may, however, be able to overcome these difficulties (12). Although allogeneic blood product

Originally Published in Press as DOI: 10.1164/rccm.202311-2061ED on December 6, 2023

administration is associated with worse outcomes in critically ill patients, much of this data is from retrospective observational studies; however, a critical appraisal and restriction of transfusion thresholds may also be important as an additional strategy for improving outcomes in ECMO patients who bleed.

Although this comprehensive study by Martucci and colleagues (8) provides insights into the impact of bleeding events during concurrent treatment variation in VV ECMO anticoagulation, the underlying disease state that necessitated VV ECMO continues to be an important influence on outcomes. This variable is difficult to quantitate but may also be responsible for the continued ongoing high and consistent mortality of patients requiring VV ECMO. Also, despite the important findings of this investigation, as a reminder, association does not always imply causality. With the increasing use of VV ECMO, additional guidance documents are also reported that may provide better anticoagulation management strategies (13). The present study results inspire future studies to further examine bleeding and the impact of target-specific anticoagulation and interventions. Future studies and randomized clinical trials may further improve the impact of VV ECMO on outcomes in patients with severe ARDS. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Christiaan L. Meuwese, M.D., Ph.D.
Department of Intensive Care Adults
Department of Cardiology
and
Thorax Center
Cardiovascular Institute
Erasmus Medical Center
Rotterdam, the Netherlands

Jerrold H. Levy, M.D.
Department of Anesthesiology
Department of Critical Care
and
Department of Surgery (Cardiothoracic)
Duke University School of Medicine
Durham, North Carolina

ORCID IDs: 0000-0002-1901-1653 (C.L.M.); 0000-0003-3766-4962 (J.H.L.).

References

1. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, *et al.*; European Society of Intensive Care Medicine Taskforce on ARDS. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med* 2023;49:727–759.
2. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, *et al.*; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374:1351–1363.
3. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, *et al.*; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018;378:1965–1975.
4. Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, *et al.* Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA* 2018;320: 2251–2259.
5. Urner M, Barnett AG, Bassi GL, Brodie D, Dalton HJ, Ferguson ND, *et al.*; COVID-19 Critical Care Consortium Investigators. Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study. *BMJ* 2022;377:e068723.
6. Combes A, Peek GJ, Hajage D, Hardy P, Abrams D, Schmidt M, *et al.* ECMO for severe ARDS: systematic review and individual patient data meta-analysis. *Intensive Care Med* 2020;46:2048–2057.
7. Nunez JI, Gosling AF, O'Gara B, Kennedy KF, Rycus P, Abrams D, *et al.* Bleeding and thrombotic events in adults supported with venovenous extracorporeal membrane oxygenation: an ELSO registry analysis. *Intensive Care Med* 2022;48:213–224.
8. Martucci G, Giani M, Schmidt M, Tanaka K, Tabatabai A, Tuzzolino F, *et al.*; International ECMO Network (ECMONet). Anticoagulation and bleeding during veno-venous extracorporeal membrane oxygenation: insights from the PROTECMO study. *Am J Respir Crit Care Med* 2024; 209:417–426.
9. Willems A, Roeleveld PP, Labarinas S, Cyrus JW, Muszynski JA, Nellis ME, *et al.* Anti-Xa versus time-guided anticoagulation strategies in extracorporeal membrane oxygenation: a systematic review and meta-analysis. *Perfusion* 2021;36:501–512.
10. van Minnen O, Oude Lansink-Hartgring A, van den Boogaard B, van den Brule J, Bulpa P, Bunge JJH, *et al.* Reduced anticoagulation targets in extracorporeal life support (RATE): study protocol for a randomized controlled trial. *Trials* 2022;23:405.
11. Pladet L, Luijken K, Fresiello L, Miranda DDR, Hermens JA, Smeden MV, *et al.* Clinical decision support for extracorporeal membrane oxygenation: will we fly by wire? *Perfusion* 2023;38:68–81.
12. van Geloven N, Swanson SA, Ramspek CL, Luijken K, van Diepen M, Morris TP, *et al.* Prediction meets causal inference: the role of treatment in clinical prediction models. *Eur J Epidemiol* 2020;35:619–630.
13. Helms J, Frere C, Thiele T, Tanaka KA, Neal MD, Steiner ME, *et al.* Anticoagulation in adult patients supported with extracorporeal membrane oxygenation: guidance from the Scientific and Standardization Committees on Perioperative and Critical Care Haemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost* 2023;21: 373–396.