However, the authors noted a reduction in CO at higher ECMO flow. Expectedly, all direct or derived hemodynamic variables—namely, pulmonary artery pressure, transpulmonary gradient, diastolic pressure gradient, PVR, and right ventricular workload—were lower in the higher ECMO blood group compared with lower ECMO blood flow group because of the reduction in CO. A reduction in the need for native CO at higher ECMO flow does not offer a convincing physiological explanation. As explained, thermodilution-based CO measurement may yield erroneous data because of recirculation in femorojugular circulation. Recirculation could be negligible and thus produce errors in CO measurement in femorofemoral cannulation. Therefore, the reduction in CO could be possible because of reduced venous return as a result of improved $S\dot{v}_{O_2}$-induced venodilatation and reduction in mean circulatory filling pressure, thereby causing a diminished gradient for venous return (4). At higher ECMO blood flow, the circuit reservoir expands at the cost of the systemic reservoir to maintain a constant total blood volume.

Second, improved oxygenation may lead to increased systemic vascular resistance and left ventricular afterload. Therefore, the authors should have also reported the changes in mean arterial pressure (MAP) and systemic vascular resistance at different ECMO flow rates. MAP drives venous return, and pulmonary artery pressure may decrease with a decrease in MAP. Poor oxygenation and hypercarbia at low ECMO flow could have increased sympathetic activity (5). The increased sympathetic activity may have chronotropic and inotropic effects. It was evident, as heart rate (95 ± 18 vs. 87 ± 19 beats per minute) and stroke volume (94 ± 25 vs. 87 ± 4 ml per beat) were higher at low ECMO flow (low $S\dot{v}_{O_2}$) compared with high ECMO flow (high $S\dot{v}_{O_2}$). An insignificant reduction in pulmonary artery occlusion pressure (13 mm Hg to 12 mm Hg), despite a greater reduction in CO (9.2 L/min to 7.9 L/min), may suggest an increase in left ventricular afterload or reduction in ventricular contractility. Therefore, an echocardiographic assessment of left ventricular systolic function could have further helped in physiological explanations.

In conclusion, ECMO flow may be optimized to improve $S\dot{v}_{O_2}$ and should sustain improvement in DO_2 and $DO_2/\dot{V}O_2$ ratio. This may be possible only when CO is maintained or increased, accompanied by the reduction in hypoxic pulmonary vasoconstriction and PVR. ■

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

Correspondence and requests for reprints should be addressed to Ajay Kumar Jha, M.D., D.M., Department of Anaesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India. Emails: drajaykjha@rediffmail.com or drajaykjha@jipmer.ac.in.

References

1. Spinelli E, Giani M, Slobod D, Pavlovsky B, di Pierro M, Crotti S, *et al.* Physiologic effects of extracorporeal membrane oxygenation in patients with severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2024;210:629–638.
2. Roberts JK, Disselkamp M, Yataco AC. Oxygen delivery in septic shock. *Ann Am Thorac Soc* 2015;12:952–955.
3. Pinsky MR. The right ventricle: interaction with the pulmonary circulation. *Crit Care* 2016;20:266.
4. Tomarchio E, Momigliano F, Giosa L, Collins PD, Barrett NA, Camporota L. The intricate physiology of veno-venous extracorporeal membrane oxygenation: an overview for clinicians. *Perfusion* 2024;39: 49S–65S.
5. Morgan BJ, Crabtree DC, Palta M, Skatrud JB. Combined hypoxia and hypercapnia evokes long-lasting sympathetic activation in humans. *J Appl Physiol (1985)* 1995;79:205–213.

Reply to Jha: Cardiopulmonary Effects of Increased Mixed Venous Saturation during Venovenous Extracorporeal Membrane Oxygenation

Marco Giani[1,2], Douglas Slobod[3], Elena Spinelli[4], and Tommaso Mauri[4,5]

[1]School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy; [2]Dipartimento di Emercenza e Terapia Intensiva, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [3]Department of Critical Care Medicine, McGill University, Montreal, Quebec, Canada; [4]Department of Anesthesia, Critical Care and Emergency, Maggiore Policlinico Hospital, Milan, Italy; and [5]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

ORCID ID: 0000-0002-7708-8034 (D.S.).

From the Authors:

We thank Ajay Kumar Jha for his thoughtful commentary on our study (1). His insights on the complex cardiopulmonary interactions during venovenous extracorporeal membrane oxygenation (ECMO) are appreciated and merit careful consideration.

Regarding the reduction in cardiac output observed at higher ECMO flow rates, as noted in our study, this is likely due to increased arterial oxygen content and the decreased demand from the native circulation. By augmenting the mixed venous oxygen saturation (SvO2), ECMO allows for a lower native cardiac output to maintain oxygen delivery and sufficient tissue oxygenation. On the other hand, as highlighted by Jha, the slightly lower Pa_{O_2}, although still physiologic, and increase in Pa_{CO_2} at lower ECMO flow could have increased sympathetic activity, with chronotropic and inotropic effects.

The precise mechanisms by which ECMO lowers native cardiac output are open to speculation. Chemoreceptors in the pulmonary circulation might modulate sympathetic tone in response to mixed venous oxygen content. Jha's suggestion that changes in venous capacitance and reduced venous return contribute to the reduction in cardiac output may be plausible. We respectfully disagree, instead,

Supported by Current Research from Italian Ministry of Health, Rome, Italy.

Author Contributions: Drafting the work or revising it critically for important intellectual content: all authors. Final approval of the version submitted for publication: all authors. Accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Originally Published in Press as DOI: 10.1164/rccm.202409-1866LE on October 29, 2024

with his point regarding pulmonary artery occlusion pressure. The small reduction from 13 mm Hg to 12 mm Hg passing from lower to higher flow actually suggests that neither an increase in left ventricular afterload nor a reduction in ventricular contractility occurred. On the contrary, this change likely reflects the reduction in sympathetic tone, which resulted in decreased cardiac workload and decreased volume centralization.

Jha's letter gives a sense of the intricate overlapping of several cardiocirculatory effects, which could result in unexpected changes in hemodynamic variables. Indeed, mean arterial pressure (MAP) was slightly but not significantly higher at lower blood flow rates and $S\dot{v}_{O_2}$ (MAP: 83 mm Hg [range = 79–96 mm Hg] vs. 85 mm Hg [range = 79–90 mm Hg] vs. 79 mm Hg [range = 74–86 mm Hg]; $P = 0.217$), whereas systemic vascular resistance was not different (689 dynes/s/cm^{-5} [range = 601–871 dynes/s/cm^{-5}] vs. 730 dynes/s/cm^{-5} [range = 625–914 dynes/s/cm^{-5}] vs. 684 dynes/s/cm^{-5} [range = 619–894 dynes/s/cm^{-5}]; $P = 0.717$). We disagree with the statement that "MAP drives venous return." Rather, venous return depends on venous resistance and the difference between right atrial pressure and the mean systemic filling pressure, the latter being determined by the distribution of vascular compliance and overall blood volume.

The suggestion to assess ventricular systolic function by means of echocardiography is well received. As pulmonary hemodynamics and right ventricular workload may be significantly affected by ECMO blood flow, a more comprehensive evaluation of biventricular function could enhance the physiological understanding of ECMO's effects, especially in patients with right ventricular dysfunction or failure.

We also disagree with Jha's comment regarding the ratio between oxygen delivery (DO_2) and $\dot{V}O_2$ falling below the critical threshold of 2. Across the different study steps, the DO_2 remained consistently above 1,000 ml/min, whereas the estimated $\dot{V}O_2$ likely ranged between 200 and 300 ml/min. As blood flow rates increased, the patient's $\dot{V}O_2$ decreased from approximately 200 ml/min to 100 ml/min, with an estimated ECMO $\dot{V}O_2$ contribution changing from 75 to 175 ml/min (approximately 50 ml/L of blood flow). Therefore, given the "clinically safe" steps of the study design, the $DO_2/\dot{V}O_2$ ratio was consistently above 3 (2), well above the critical threshold.

Far from believing that we have provided a definitive description of the complex interaction between ECMO and cardiocirculatory function, we stick to the study results, which did not show that the decrease in cardiac output at higher ECMO blood flow affected the adequacy of DO_2 in relation to total $\dot{V}O_2$.

Once again, we appreciate Dr. Jha's thoughtful feedback and believe that this exchange will contribute to further optimizing ECMO support in patients with severe acute respiratory distress syndrome. ■

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

Correspondence and requests for reprints should be addressed to Tommaso Mauri, M.D., Department of Pathophysiology and Transplantation, University of Milan, Via F. Sforza 35, 20122 Milan, Italy. Email: tommaso.mauri@unimi.it.

References

1. Spinelli E, Giani M, Slobod D, Pavlovsky B, di Pierro M, Crotti S, *et al.* Physiologic effects of extracorporeal membrane oxygenation in patients with severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2024;210:629–638.
2. Spinelli E, Bartlett RH. Relationship between hemoglobin concentration and extracorporeal blood flow as determinants of oxygen delivery during venovenous extracorporeal membrane oxygenation: a mathematical model. *ASAIO J* 2014;60:688–693.

Lung-Protective Mechanical Ventilation in Patients with Severe Acute Brain Injury

Guanyu Yang

Department of Anesthesiology and Perioperative Medicine, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou, China

ORCID ID: 0000-0002-6087-2180 (G.Y.).

To the Editor:

I have reviewed the recent trial by Mascia and colleagues (1) that explores the application of lung-protective ventilation strategies in patients with acute brain injury. The trial was terminated early, and the results indicated that the lung-protective ventilation strategy did not lead to improved outcomes for the patients. Although appreciation is extended to the authors for their contribution to the quest for optimal ventilation strategies for patients with acute brain injury, there are three points I would like to discuss with them.

First, the baseline characteristics of the patients did not include preoperative comorbidities. The premature termination of the trial compromised the randomization, resulting in a discrepancy of 17% in the number of participants enrolled in each group. Furthermore, the preoperative status of the patients, encompassing the types and severity of comorbidities, may have had an impact on the primary outcomes.

Second, lung-protective ventilation strategies encompass a range of measures, including low V_T, positive end-expiratory pressure (PEEP), low inspiratory oxygen concentration, low plateau pressure, and recruitment maneuvers (2). Notably, the conventional group also used PEEP, low inspiratory oxygen concentration, and low plateau pressure; however, their V_T was only 0.5 ml/kg higher than the upper limit of the low V_T (8 ml/kg). It is concerning that the minimal differences in the interventions between the groups may obscure the effects of the lung-protective ventilation strategy. Furthermore, recruitment maneuvers can reopen collapsed alveoli and reduce the incidence of atelectasis, suggesting that their inclusion in the lung-protective group may enhance the patients' pulmonary function.

Third, this study used a fixed PEEP in the lung-protection group, which does not align with current practices. Presently, it is recommended that PEEP be titrated individually through various methods, as this may be more beneficial in improving patient

Originally Published in Press as DOI: 10.1164/rccm.202409-1809LE on November 5, 2024