To the Editor:

We read with great interest the article by Cavayas and colleagues (1) in a recent issue of the Journal. This group demonstrated that early changes in partial PaCO2 are associated with neurological complications in patients with severe respiratory failure who have undergone extracorporeal membrane oxygenation (ECMO). This great insight could change the current management of ECMO. However, several factors potentially affecting the reported findings should be discussed.

First, there can be a discrepancy between the real maximum change in PaCO2 during the first 24 hours after initiation of ECMO and the relative change in CO2, which is calculated by a formula incorporating PaCO2 before and at 24 hours after initiation of ECMO. The greatest reduction in PaCO2 can occur immediately after introduction of ECMO. Furthermore, the PaCO2 immediately before initiating ECMO is not always equivalent to the pre-ECMO PaCO2 defined in this study because ECMO cannulation involves frequent changes in ventilator settings and body position. Our data on 25 patients who underwent ECMO include a mean of 9 (interquartile range, 6–11) separate arterial blood gas evaluations per patient during the first 24 hours after initiating ECMO, and the lowest PaCO2 values occurred a median of 6 (interquartile range, 2–13) hours after initiating ECMO (K. Kikutani and colleagues, unpublished results). Using Cavayas and colleagues’ (1) definition, the relative change in CO2 is −23% in our cohort. However, it is doubled to −46% if we use the following formula: (lowest PaCO2 during the first 24 hours after initiating ECMO − maximum PaCO2 in the 6 hours before ECMO introduction)/maximum PaCO2 in the 6 hours before ECMO introduction. Thus, Cavayas and colleagues (1) may have underestimated the real dynamics of PaCO2 that occur at earlier stages after initiating ECMO.

Second, we consider that there was insufficient consideration of the range of PaCO2 within which a cerebrovascular response to CO2 can be preserved. The cerebrovascular response to CO2 has a linear association with PaCO2 (2) between certain ranges of PaCO2. The lowest cerebral blood flow, corresponding to maximal vascular resistance, appears to occur in the PaCO2 range of 10–15 mm Hg. Conversely, cerebral blood flow increases by approximately 3–4% for each unit increase in PaCO2, reaching its highest degrees when PaCO2 is 10–20 mm Hg above normal resting values (3). Further changes in PaCO2 no longer induce vasoconstrictive and vasodilatory reactions, resulting in a sigmoidal correlation (4). Consequently, rapid changes in PaCO2 do not always induce rapid changes in cerebrovascular tone in patients with severe hypercapnia because cerebrovascular reactivity to PaCO2 can be absent (3). Subgroup analysis according to the baseline PaCO2 would be helpful for precise evaluation of the effect of PaCO2 dynamics.

Finally, common risk factors for neurological complications, including hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, and use of anticoagulants (5), were not included in the multivariate analysis in this study, despite the fact that these risk factors could be potential confounding factors.

References

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*Corresponding author (e-mail: mtobin2@lumc.edu).
Reply to Kikutani et al.

From the Authors:

We would like to thank Dr. Kikutani and colleagues for their thoughtful comments on our article on the association between early changes in PaCO2 and neurological complications in patients on extracorporeal life support (ECLS) (1). Here, we will try to address them. First, as stated in the discussion, we fully acknowledge that the availability of only two blood gases is the main limitation of the study. Indeed, this may result in an underestimation of the maximal change in PaCO2 in the first 24 hours, as illustrated by Dr. Kikutani’s data. It is unclear, however, if a transient drop in PaCO2, more likely to be missed by the Extracorporeal Life Support Organization (ELSO) data, is more harmful than a sustained decrease, which is more likely to be adequately captured. More granular data would be needed to better evaluate the impact of different types of changes in PaCO2 over time. The main challenge, however, is that neurological complications are relatively infrequent, and large sample sizes would be needed to provide adequate power to detect a relatively small effect size.

Second, we performed an analysis of the association between a PaCO2 drop >50% and neurological complications stratified by baseline PaCO2 subgroups as requested (Figure 1). Visual inspection of the forest plot suggests a more pronounced effect in patients with baseline hypocapnia or severe hypercapnia (U-shaped relationship), which goes against Dr. Kikutani’s hypothesis of reduced cerebrovascular consequences of changes in PaCO2 in patients with the most severe hypercapnia. In the stratified analysis, the Breslow-Day test did not suggest significant heterogeneity ($P = 0.718$), and the Mantel-Haenszel estimate of the common odds ratio was 1.45 (95% confidence interval,

![Figure 1. Unadjusted odds ratio of neurological complications associated with a relative PaCO2 drop >50% stratified by baseline PaCO2 subgroup. OR = odds ratio.](image-url)

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