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

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Early Pa_{CO_2} Changes after Initiating Extracorporeal Membrane Oxygenation: Considerations for Future Research

To the Editor:

We read with great interest the article by Cavayas and colleagues in a recent issue of the *Journal* (1). This group demonstrated that early changes in partial Pa_{CO_2} 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 Pa_{CO_2} during the first 24 hours after initiation of ECMO and the relative change in CO_2, which is calculated by a formula incorporating Pa_{CO_2} before and at 24 hours after initiation of ECMO. The greatest reduction in Pa_{CO_2} can occur immediately after introduction of ECMO. Furthermore, the Pa_{CO_2} immediately before initiating ECMO is not always equivalent to the pre-ECMO Pa_{CO_2} 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 Pa_{CO_2} values occurred a median of 6 (interquartile range, 2–13) hours after initiating ECMO (K. Kikutani and colleagues, unpublished results).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 CO_2 is −23% in our cohort. However, it is doubled to −46% if we use the following formula: (lowest Pa_{CO_2} during the first 24 h after initiating ECMO − maximum Pa_{CO_2} in the 6 h before ECMO introduction)/maximum Pa_{CO_2} in the 6 h before ECMO introduction. Thus, Cavayas and colleagues (1) may have underestimated the real dynamics of Pa_{CO_2} that occur at earlier stages after initiating ECMO.

Second, we consider that there was insufficient consideration of the range of Pa_{CO_2} within which a cerebrovascular response to CO_2 can be preserved. The cerebrovascular response to CO_2 has a linear association with Pa_{CO_2} (2) between certain ranges of Pa_{CO_2}. The lowest cerebral blood flow, corresponding to maximal vascular resistance, appears to occur in the Pa_{CO_2} range of 10–15 mm Hg. Conversely, cerebral blood flow increases by approximately 3–4% for each unit increase in Pa_{CO_2}, reaching its highest degrees when Pa_{CO_2} is 10–20 mm Hg above normal resting values (3). Further changes in Pa_{CO_2} no longer induce vasoconstrictive and vasodilatory reactions, resulting in a sigmoidal correlation (4). Consequently, rapid changes in Pa_{CO_2} do not always induce rapid changes in cerebrovascular tone in patients with severe hypercapnia because cerebrovascular reactivity to Pa_{CO_2} can be absent (3). Subgroup analysis according to the baseline Pa_{CO_2} would be helpful for precise evaluation of the effect of Pa_{CO_2} 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. ■

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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 Pa_{CO_2} 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 Pa_{CO_2} in the first 24 hours, as illustrated by Dr. Kikutani's data. It is unclear, however, if a transient drop in Pa_{CO_2}, 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 Pa_{CO_2} 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 Pa_{CO_2} drop >50% and neurological complications stratified by baseline Pa_{CO_2} 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 Pa_{CO_2} 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,

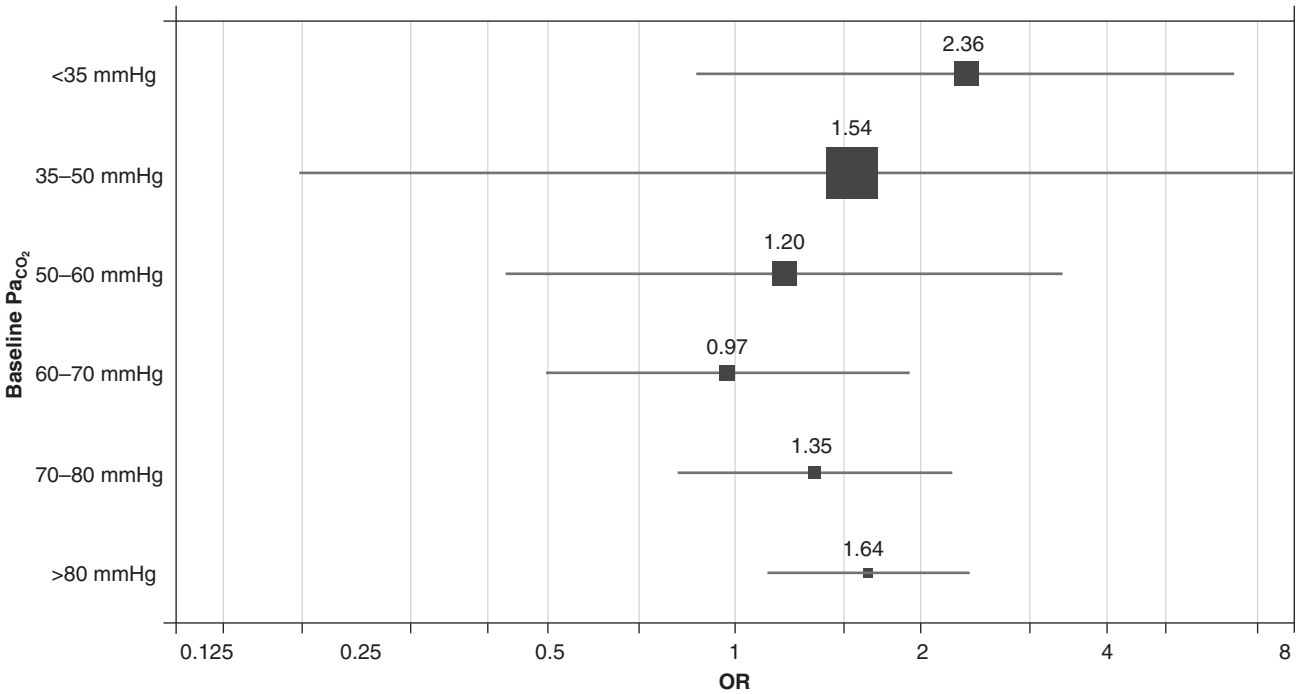

Figure 1. Unadjusted odds ratio of neurological complications associated with a relative Pa_{CO_2} drop >50% stratified by baseline Pa_{CO_2} subgroup. OR = odds ratio.

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