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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,

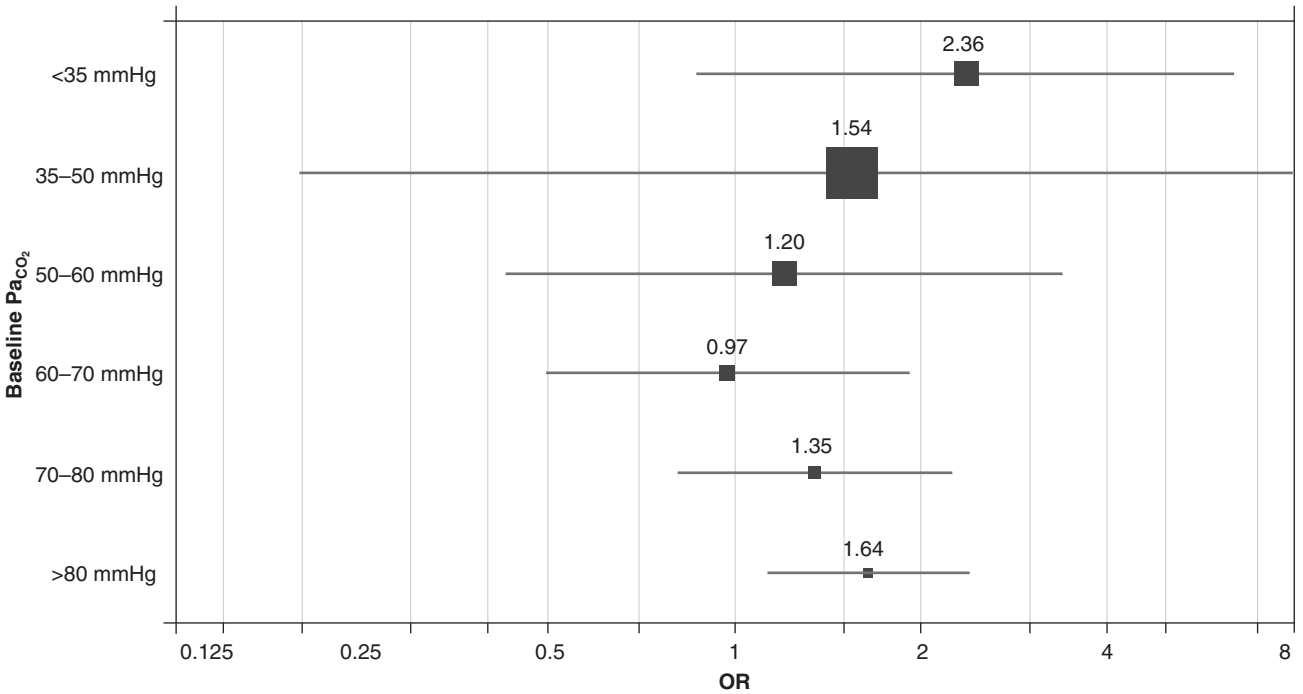

Figure 1. Unadjusted odds ratio of neurological complications associated with a relative Pa_{CO_2} drop >50% stratified by baseline Pa_{CO_2} subgroup. OR = odds ratio.

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1.13–1.89; $P = 0.005$), which is in line with other analyses. The observed effect of changes in Pa_{CO_2} in the extremes of baseline Pa_{CO_2} could be explained by a reset in the range of Pa_{CO_2} cerebrovascular response (2). Although chronic conditions such as chronic obstructive pulmonary disease have been associated with blunted cerebrovascular reactivity, the sensitivity of cerebral blood flow to acute changes in both O_2 and CO_2 is increased by sustained exposure (48 h) to hypoxemia (3).

Third, we agree that known risk factors for neurological complications, including hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, and chronic use of antithrombotic therapy, could have been included in the multivariate analysis if they had been available. However, that data is not reliably recorded in the ELSO registry. Moreover, to act as confounding factors, those variables should not only be associated with the outcome variable (neurological complications) but also the exposure variable relative change in Pa_{CO_2} ($Rel\Delta CO_2$). It is improbable that factors such as hyperlipidemia or atrial fibrillation are associated with $Rel\Delta CO_2$, making them unlikely to be true confounders. $Rel\Delta CO_2$ is mainly determined by baseline Pa_{CO_2} as well as ventilator and ECLS parameters selected by the clinical team. We thus think that the association found between $Rel\Delta CO_2$ and neurological complications is robust despite not controlling for certain known risk factors. Since the publication of our article, a similar association has now also been reported in patients on venoarterial extracorporeal membrane oxygenation by another group also using data from the ELSO registry (4).

What remains unclear, in our opinion, is the optimal rate of Pa_{CO_2} correction after initiation of ECLS to prevent neurological injury. It is possible that there is no one-size-fits-all target and that Pa_{CO_2} correction should be individualized to optimize cerebral blood flow by using neuromonitoring such as near-infrared spectroscopy or transcranial doppler. ■

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Mesenchymal Stem Cell–derived Exosomes: Are They Another Therapeutic Method for Extracorporeal Membrane Oxygenation–supported Acute Respiratory Distress Syndrome?

To the Editor:

We read the article by Millar and colleagues with great interest (1). They illustrated that even though induced pluripotent stem cell (iPSC)-derived mesenchymal stem cells (MSCs) reduced lung injury and inflammation, they impaired the membrane oxygenator and did not ameliorate oxygenation in a sheep model of acute respiratory distress syndrome (ARDS) and extracorporeal membrane oxygenation (ECMO). Based on the therapeutic promise of MSCs, it is important to explore the effect of MSCs in a preclinical model of ECMO-supported ARDS.

The result reported impaired membrane oxygenator and increased transmembrane pressure caused by iPSC-derived MSCs, coinciding with the results of their other *ex vivo* model of ARDS and ECMO. It reported that the intravascular delivery of MSCs also led to declined function of the membrane oxygenator and increased transmembrane pressure gradient at 4 hours (2). It is obvious that these results demonstrated that the delivery of MSCs by intratracheal or intravenous method was not beneficial for oxygenation and the membrane oxygenator. In addition, the results showed iPSC-derived MSCs led to pulmonary arterial thrombosis. This result might be associated with the instability of iPSC-MSCs and the changed cell function by altered microenvironment after cell adhesion to the oxygenator. It is worth discussing the solution for these results. Early clinical trials of MSCs excluded the patients with ARDS supported by ECMO. Could we have another method to apply MSCs in patients with ARDS with ECMO?

ARDS is caused by multiple reasons, such as severe infection (including the current epidemic coronavirus disease [COVID-19)], trauma, or shock. The mortality of severe ARDS was even over 40% (3). Although multiple studies have been conducted on mechanisms and therapy, the effective treatment for ARDS is still uncertain, especially for severely ill patients. The disorder is characterized by dyspnea, refractory hypoxemia, and diffused alveolar injury, and severely ill patients are also in a hyperinflammatory state. It is difficult to manage the complicated

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