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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state. Therefore, the application of MSCs in severe ARDS supported by ECMO is a chance to improve the survival rate.

The authors provided a profound discussion on the possible reasons. However, given the adhesion and cell size of MSCs and the little efficacy of MSCs on an ECMO-supported ARDS model as reported in existing studies, we think it may be not be proper to deliver the cells to ECMO-supported patients directly. The therapeutic effects of MSCs are largely attributed to their paracrine effects. Exosomes (exos) are considered to be the critical products of MSC efficacy. They are one kind of extracellular vesicles. MSCs have immunomodulatory and antiinfection effects that have possessed therapeutic prospects in various preclinical models. The exos from MSCs also have these effects. It has been reported that MSC-derived exos (MSC-exos) could restore oxygenation and alleviate cytokine storm in patients with moderate to severe ARDS caused by COVID-19 (4). Accumulating studies have found the potential role of MSC-exos in preclinical models of ARDS (5). As a result, compared with MSCs in ECMO, the advantages of MSC-exos are pretty significant. First, MSC-exos are secreted by MSCs actively *in vitro*, packaging effective biological molecules from MSCs such as KGF (keratinocyte growth factor) and Ang-1 (angiopoietin-1). Furthermore, exos are more stable and have lower immunogenicity than MSCs. Even if the microenvironment changed, the effect of MSC-exos will not be altered. Therefore, they may not have the same procoagulant effects as transplanted MSCs have in an ECMO circuit. Second, the diameter of MSC-exos is 30–100 nm, which is much smaller than the diameter of MSCs and pores in the membrane oxygenator. This may potentially avoid adhesion to the oxygenator to impair it. Thus, the application of MSC-exos may contribute to oxygenation. Third, MSCs are activated or primed by an abnormal microenvironment, which can be made *in vitro*. MSCs in the desired microenvironments will produce more ideal exos, such as stronger antiinflammatory MSC-exos (6).

It is expected that MSC-exos can be considered in the ECMO-supported ARDS model as a next step. ■

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Reply to Zhang and Hei

From the Authors:

We thank Zhang and Hei for their insightful comments on our study of mesenchymal stromal cells (MSCs) in a sheep model of extracorporeal membrane oxygenation and acute respiratory distress syndrome (ARDS) (1). Their principal thesis is that the adverse interaction that we observed, between MSCs and the membrane oxygenator, may be overcome by substituting MSCs with MSC-derived exosomes. This proposal has merit. The MSC secretome has been of interest as a therapeutic for some time, particularly MSC-derived extracellular vesicles (2), MSC-derived exosomes (3), and MSC-conditioned media (4). These each offer several theoretical advantages over conventional MSC therapy. First, contents of the secretome do not express major histocompatibility complex antigens, removing concerns about immunogenicity. Second, components of the secretome are, in general, easier to store and less susceptible to the adverse effects of storage on efficacy. Third, components of the MSC secretome are much smaller than the cells from which they are derived and thus less likely to be subject to "trapping" in the pulmonary circulation (5). Recently, an early phase trial of an MSC-derived exosome treatment for severe coronavirus disease (COVID-19) has been reported with no apparent safety issues (6). However, there are some unresolved issues that should be borne in mind.

Paracrine actions are the principle means by which MSCs exert benefit in ARDS, although several alternative mechanisms have been described, such as mitochondrial transfer from MSCs to damaged alveolar epithelial cells (7). The inability of secretome-based therapies to reproduce these actions may limit their efficacy (8, 9). The translation of MSC secretome–based therapies is also limited by challenges in scaling manufacturing for clinical purposes, an issue that is overcome by the use of induced pluripotent cell–derived MSCs, like those used in our study (1). With specific regard to our study, the observation that pulmonary emboli were more frequent in the induced pluripotent cell–derived MSC group may not be uniquely associated with the use of a cell-based therapy. A variety of preclinical studies have described the procoagulant activity of MSC-derived extracellular vesicles (10, 11).

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