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).

Despite these caveats, Zhang and Hei's point is well made and highlights the work that is still required to successfully advance cell therapy for ARDS, especially in the context of extracorporeal organ support. We hope that our study illustrates the usefulness of clinically relevant, high-fidelity animal models in advancing these efforts. ■

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Considerations for an Optimal Electrical Activity of the Diaphragm Threshold for Automated Detection of Ineffective Efforts

To the Editor:

We have read with great interest the research letter authored by Jonkman and colleagues (1), and we agreed with the notion that suboptimal filtering of the electrical activity of the diaphragm (EAdi) signal together with a low threshold (>1 μV), could lead to incorrect interpretation of patient–ventilator interactions when detected by automated software.

In our reported validation investigation of Better Care software (2), the algorithm performance was made against five different experts' opinions using 1,024 tracings of airway flow and airway pressure waveform from 16 different patients, with a reported sensitivity of 91.5% and specificity of 91.7%. Subsequently, as an additional confirmation, we used EAdi tracings with a threshold >1 μV in eight mechanically ventilated patients, obtaining a sensitivity of 65.2% and a specificity of 99.3%. This value was selected on an *a priori* basis, considering a midpoint between 0.1 μV and 2 μV and was intended to avoid inspiratory assistance during expiration in those cases when the EAdi peak is <1.5 μV and the cycling-off is at a 40% threshold from EAdi peak, instead of the usual 70% (3).

The drop in sensitivity of Better Care algorithm when EAdi was used could be due to, as the authors speculate, a mistaken overestimation of ineffective efforts by EAdi, leading to an increase in false-negative results in the Better Care algorithm. We have seriously considered this possibility in those tracings validated against EAdi, and we have reanalyzed tracings from that previously published cohort, searching for the best cutoff value of EAdi signal with the best performance. The new findings show that the best cutoff value of EAdi is 2.3 μV, with a sensitivity of 89.2%, a specificity of 96%, a positive predictive value of 72.5%, and a negative predictive value of 98.7%.