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%.

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Overall, it seems that increasing the threshold of EAdi would decrease the false-negative rate, improving the sensitivity of any given automated detection software and keeping a good specificity. We believe that, according to our reassessed results, an EAdi >2 μV could be suitable for this purpose. In addition, as Jonkman and colleagues mentioned, the removal of cardiac electrical activity is technically challenging, particularly when the signal:noise ratio of the crural diaphragm electromyography signal is low. In this scenario, we hypothesized that the automatic detection of true ineffective efforts from EAdi will be improved by using a personalized adaptive threshold for each patient considering the signal:noise ratio of the diaphragm electromyography signal. Interestingly, nonlinear methods less sensitive to ECG interference based on sample entropy algorithms (4) could be used to reduce the delay on the neural onset when an ECG peak matches at the beginning of the breath. ■

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Reply to Aquino-Esperanza *et al.*

From the Authors:

We greatly appreciate the interest of Aquino-Esperanza and colleagues in our research letter (1) regarding the influence of suboptimal filtering of the electrical activity of the diaphragm (EAdi) signal on the detection of patient–ventilator asynchronies. In that letter, we raised the concern that cardiac activity–related artifacts in the EAdi signal may be mistakenly detected as ineffective efforts when the EAdi threshold is too low. Based on this work, Aquino-Esperanza and colleagues have thoughtfully reanalyzed the performance of their Better Care algorithm (2) to find an appropriate EAdi threshold for the automatic detection of ineffective efforts. They conclude that increasing the EAdi threshold from 1 μV to 2.3 μV improved the sensitivity of their algorithm and maintained adequate specificity. We appreciate this careful reanalysis and agree with the authors that a threshold >2 μV is reasonable. It should be noted that in our work (1), EAdi artifacts were mostly <4 μV, but we agree that a threshold of 4 μV would be clinically disproportionate and increase the false-negative rate.

We also agree with the authors that a personalized adaptive EAdi threshold may improve the performance of automatic detection of true ineffective efforts. We considered testing this with our dataset; however, the incidence of true ineffective efforts was too low (1). In contrast, because the processing of these EAdi artifacts is a technical issue, it might be rather impossible to distinguish between artifacts and true ineffective efforts based on a certain EAdi threshold solely. As part of our earlier work, we aimed to quantify waveform characteristics of the cardiac activity–related artifacts (e.g., slope of the inspiratory EAdi increase, timing, and amplitude) and predict the occurrence of these artifacts based on patient characteristics. For instance, we hypothesized that cardiac activity–related peaks had steeper increases ("sharp waves", possibly consistent with fast cardiac depolarization); however, slopes of the artificial and true peaks were similar on average, and artificial peaks with both lower and higher slopes compared with true EAdi peaks were found within patients. Furthermore, factors such as the presence of ventricular hypertrophy were not related to the occurrence of these artifacts. We did not include these findings in our research letter, as this is clinically not very helpful at this time.

Importantly, the main challenge with developing a (personalized) EAdi threshold using signal characteristics is the

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