they used reference ranges to set Phigh. Furthermore, when the parameters needed to be adjusted, they also directly adjusted the parameters to a certain range. Additionally, the physiological characteristics of the respiratory system in children can be different for different ages. For example, the younger children are, the faster they breathe, and the smaller their V_T. Compared with 12-year-olds, 2-month-old children have higher airway resistance, higher chest wall compliance, less alveolar area, and more abdominal breathing. All of this means that children of different ages should be ventilated in different ways, and individual APRV settings are required. Thus, we believe that the initial parameters that were inconsistent with the pathophysiology of the patients may have caused the worse outcomes in the APRV group.

Third, the type of ventilator used is an important factor that is often overlooked in our daily research. In our previous study, we used a Puritan Bennett 840 ventilator (Medtronic) to deliver APRV, whereas Lalgudi Ganesan and colleagues used Hamilton Galileo (Hamilton Medical) or Servo I (MAQUET) ventilators. Different ventilators have different features—for instance, at the end of high pressure time and with the expiratory phase of a spontaneous breath, the Puritan Bennett 840 could synchronize the transition from Phigh to Plow (5). We suggest that using a single ventilator for all patients in a trial might minimize the bias caused by different types of ventilators.

Finally, we are delighted to participate in this "APRV debate." To ensure a more reasonable use of APRV in adult and pediatric patients with ARDS, more evidence is needed. ■

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Reply to Dong *et al.*

From the Authors:

We thank Dong and colleagues for their keen interest in our recent publication on airway pressure release ventilation (APRV) (1). The concerns raised by Dong and colleagues have been touched upon in our response to previous letters to editors (2) and in the recent review article on the utility of this mode in children by the first author (3). However, we are pleased to have the opportunity to elaborate on these aspects of APRV and participate in the "APRV debate."

Some baseline characteristics were not equally distributed between the two groups in our trial (1), as pointed out by Dong and colleagues. This can happen frequently in randomized controlled trials (RCTs) with a small sample size. However, despite adjustment for the higher severity of acute respiratory distress syndrome (ARDS) in the intervention arm, multivariate-adjusted relative risk of death was approximately 2 in the APRV arm. Testing for baseline differences, covariate adjustment, and subgroup analyses in randomized clinical trials continue to generate debate among experts (4, 5). Although we agree that it is unwise to generalize ARDS as a single phenotype, there are several problems with attempting to stratify patients according to ARDS physiology in a single-center trial with a sample size of 26 in each group (1).

As explained in our response to previous letters to editors (2), the empirical Phigh approach based on Pa_{O_2}:FI_{O_2} ratios proposed in our protocol was intended for use only in children with pleural pathology or other clinical circumstances where plateau pressure estimation may not be reliable. In our trial, we had to use this approach in only one child with disseminated staphylococcal sepsis and bilateral empyema (2). Furthermore, the suggestion that we directly adjusted the APRV parameters to predetermined empirical ranges without incorporating physiological data from the bedside is unfounded. We adjusted the ventilator settings to optimize lung inflation, respiratory mechanics, and expiratory flow termination, and we described our strategies elaborately in our paper to enhance clarity and reproducibility (1–3).

Maturational aspects of respiratory mechanics are challenging to measure and account for in research on APRV in pediatric ARDS (3). In addition to those listed by Dong and colleagues, the following factors (3) may also have contributed to the differences seen in outcomes between the adult (6) and pediatric (1) trials:

1. In noncooperative infants and younger children, ensuring regular, synchronized spontaneous breathing while keeping them safely intubated can be challenging.

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2. Younger children, especially infants receiving APRV, may demonstrate fatiguability with inconsistent and variable spontaneous breathing rates and efforts.
3. Given the higher airway resistance and compliant chest walls causing a lower driving force for recoil and exhalation, infants and young children are likely to experience higher and highly variable intrinsic positive end-expiratory pressures with APRV.
4. In young children, collateral channels of ventilation, such as pores of Kohn, may not be well developed. This may impede the recruitment and redistribution of alveolar volume (and pressure) throughout the lung.

One of the relatively underappreciated aspects of APRV is its dependence on the delivery system (3, 7–10). The mechanical profile of the APRV breath may vary significantly across ventilators from different manufacturers (7–10). We agree completely that the type of ventilator is a key factor in APRV research and should not be overlooked, but we do not know whether one ventilator is superior to another for providing this mode of ventilation.

We think that the APRV debate needs to focus on Plow and prevention of repetitive lung injury during release. Zhou and colleagues used a personalized-APRV approach with Plow of 5 cm H_2O (6), and the two RCTs by Varpula and Putensen used a fixed-APRV approach with a nonzero Plow (11, 12). The only adult RCT (13) that used a personalized-APRV approach with a Plow of zero similar to the one used in the recent pediatric trial (1) showed a trend toward worse secondary outcomes in the APRV arm with increased ventilator days, ICU length of stay, and ventilator-associated pneumonia. The worse outcomes seen with the personalized-APRV approach using a Plow of zero could be mediated through repeated alveolar collapse or right ventricular dysfunction secondary to abrupt deflation. Therefore, future clinical research should evaluate personalized-APRV with nonzero Plow or a fixed-APRV strategy in both adults and children with ARDS.

In summary, it is possible that applications of APRV truly differ between adults and children, as is true for several aspects of mechanical ventilation and critical care. Given the small number of studies to date, we do not have a clear understanding of APRV strategies that will work in either group. ■

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Selection of Biologics for Type 2–High Asthma

To the Editor:

We read with great interest the review article by McGregor and colleagues. The authors have reviewed the mechanism of action, indications, expected benefits, and adverse effects of each of the currently approved biologics for severe uncontrolled asthma (1). We would like to thank McGregor and colleagues for their contribution to literature with such a valuable review.

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