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Airway Pressure Release Ventilation: Is It Really Different in Adults and Children?

To the Editor:

In a recent issue of the *Journal*, we read the article by Lalgudi Ganesan and colleagues entitled "Airway Pressure Release Ventilation in Pediatric Acute Respiratory Distress Syndrome: A Randomized Controlled Trial" (1). We now have two small randomized controlled trials in patients with acute respiratory distress syndrome (ARDS) comparing airway pressure release ventilation (APRV) with low-V_T lung-protective ventilation (LTV). The APRV research we previously conducted in a population of adult subjects showed that APRV had a better effect than LTV in adult patients with ARDS. Subsequently, Lalgudi Ganesan and colleagues performed an APRV study in pediatric subjects and their trial was terminated early because of high mortality in the APRV group. Does APRV treatment for ARDS really differ between adults and children? We think there are some issues that are worth discussing.

First, some baseline characteristics were unbalanced between the groups in Lalgudi Ganesan and colleagues' study. We found that there was a difference in the percentage of males and females between their APRV and LTV groups (65.4% vs. 34.6%, $P = 0.027$), and the severity of ARDS at enrollment also differed between the two groups ($P = 0.056$). Patients with different severities of ARDS have different responses to various treatments (2, 3); hence, these differences must be considered in the baseline balance between two groups. Furthermore, not only the severity but also the type of ARDS will produce a difference in treatment effect. In our recent research, we performed a secondary analysis of our original study (4), and we found that APRV has different effects on pulmonary and extrapulmonary ARDS. Our study showed that patients with extrapulmonary ARDS had more ventilator-free days at 28 days than those with pulmonary ARDS (14 vs. 20 d, $P < 0.05$) when early APRV was administered to adults in the ICU (Table 1). Rather than generalizing ARDS as a single phenotype, we need to stratify patients according to their ARDS physiology, and this may be a major point that greatly affected the results of their study.

Second, we recommend setting initial parameters based on the pathophysiology of patients, despite the current lack of standard APRV settings. In our previous study (4), the initial parameters we set were based on the patients' measured plateau airway pressure (Pplat), compliance, and other respiratory mechanics indicators, and individualized adjustments were made according to the actual situation of the patients. In their study, Lalgudi Ganesan and colleagues set the high pressure time at 4 seconds, and if the Pplat could not be reliably determined,

Table 1. Outcome Variables of Patients Who Underwent Airway Pressure Release Ventilation in Our Recent Study

Outcome Variables	Pulmonary ARDS ($n = 26$)	Extrapulmonary ARDS ($n = 45$)	*P* Value
No. of ventilator-free days at 28 d	14.0 (0.0–20.5)	20.0 (15.0–22.5)	0.046
No. of days of ventilation	11.0 (5.0–18.0)	7.0 (5.0–10.0)	0.082
Length of ICU stay, d	17.0 (7.8–23.5)	12.0 (7.5–18.5)	0.162
Length of hospital stay, d	12.0 (7.5–18.5)	20.0 (11.0–32.5)	0.844

Definition of abbreviation: ARDS = acute respiratory distress syndrome. All data were analyzed by Mann-Whitney *U* tests, and a two-sided *P* value of <0.05 was considered statistically significant. Data are shown as median (interquartile range).

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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. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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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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