hospitalization and intensive care are mostly covered by the national insurance program. Further well-designed studies are warranted to clarify the causes of sex difference in outcomes following cardiac arrest.

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The authors have disclosed that they do not have any potential conflicts of interest.

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Airway Pressure Release Ventilation in COVID-19: There's More to This Than Meets the Eye

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To the Editor:

We read with great interest the article by Ibarra-Estrada et al (1). We congratulate the authors for their fascinating randomized controlled trial. However, we would like to highlight specific points regarding the study.

The authors have taken the high pressure (P-high) based on the plateau pressure (Pplat) in the previous volume-controlled ventilation mode. According to the authors, this derivation of P-high on airway pressure release ventilation (APRV) mode is based on a previously unpublished protocol. The APRV group had tidal volume (TV) of 7.4 ± 1.1, 8.1 ± 1.3, and 8.6 ± 1.0 on days 3, 5, and 7, respectively. Although the TV generated on APRV cannot be equated with the TV generated on low tidal volume (LTV) ventilation, it still places patients at risk of ventilator-induced lung injury due to the high TV generated (2). APRV encourages spontaneous breathing efforts. This may increase the final end-inspiratory transpulmonary pressure much higher than the set P-high of 30. We suggest using 2–5 cm H_2O above mean airway pressure (Pmean) to limit adverse events such as barotraumas. Our suggestion is based on the physiologic concept that under normal conditions, the Pmean correlates with the mean alveolar pressure, which is in turn a surrogate marker of the stresses on the lung parenchyma with ventilation (3).

A high frequency of severe hypercapnia in the APRV group (42%) was seen, which was also statistically significant (p = 0.009). Patients with severe obstructive lung disease are not ideal candidates for APRV. The high inspiratory time in APRV leads to hypercapnia. A few case reports have used APRV in resistant cases of chronic obstructive pulmonary disorder to reduce hypercapnia. However, in such cases, multiple adjustments in the ventilatory settings of APRV have been made to achieve control of the hypercapnia (4). No such adjustments were accommodated in the trial protocol for COPD patients. Another reason for the lower incidence of hypercapnia in LTV group could be allowing for the Pplat

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target limit to be exceeded in case of severe respiratory acidosis (pH < 7.15).

A significant advantage of APRV over LTV is that it allows for spontaneous ventilation with patient efforts. Ibarra-Estrada et al (1), in this study, were able to achieve deficient spontaneous minute ventilation (MVspont) in the APRV group (zero up to day 5, first time by day 7). This is in stark contrast to the study by Zhou et al (5) who have achieved it by day 3. Zhou et al (5) also targeted MVspont, approximately 30% total minute ventilation in their study protocol. The low MVspont could be a consequence of using neuromuscular blockade in a large proportion (93%) of patients of APRV group in this study, compared with study by Zhou et al (5) who used it in only 2.8% of patients in APRV group. A second reason could be the absence of any targets for achieving MVspont in the study protocol. Deficient MVspont in APRV group may be one of the reasons why no improvement in ventilator-free days was noted.

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Author Contribution:

Dr. Patnaik helped with concept, design, literature search, data acquisition, article preparation, editing, and article review. Dr. Mishra helped with concept, design, article editing, and article review. Dr. Samal helped with data acquisition and article editing.

The authors have disclosed that they do not have any potential conflicts of interest.

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The authors reply:

We thank Patnaik et al (1) for their comments regarding our study about airway pressure release ventilation (APRV) in patients with COVID-19 (2). However, we wish to clarify some points that could have been misinterpreted.

The initial setting of high pressure (P-high) according to previous plateau pressure was based on the original protocol published almost 2 decades ago (3) and is part of the most current protocol for time-controlled adaptive ventilation (4). To our knowledge, there are no published clinical studies to support a threshold for P-high based on mean airway pressure in order to limit barotrauma, as suggested by Patnaik et al (1). Importantly, the pathogenesis of ventilator-induced lung injury is multifactorial, and the propensity for alveolar air leak in patients with COVID-19 may be different to other acute respiratory distress syndrome patients, as it occurs even in the absence of positive pressure (5). The rate of barotrauma in our study was exactly the same in both groups, which suggests no increased risk attributable to ventilatory settings.

Patnaik et al (1) raises the question of specific adjustments for patients with chronic obstructive pulmonary disease (COPD) affecting our overall results. Our patients had restrictive physiology (as evidenced by the lung compliance), and none had a prior diagnosis of COPD. To our knowledge, there are no such "special" APRV settings for patients with COPD; in fact, most studies

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