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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have excluded these patients. The case report cited by Patnaik et al (1) does not offer insight into specific settings in patients with obstructive physiology; it was just based on an inspiratory-to-expiratory ratio of 1:4, neglecting the monitoring of lung mechanics through the analysis of expiratory flow waveform.

Contrary to the statement of Patnaik et al (1), we indeed had target ranges of spontaneous minute ventilation (MVspont) according to oxygenation (Pao_2/Fio_2) and ventilatory support (P-high) (2), as we are aware of the potential risk of spontaneous efforts during P-high. In fact, this protocolized limitation of spontaneous efforts while P-high still greater than 24 cm H_2O contributed to the lower MVspont during the first days compared with the control group. Unlike patients in previous studies, our patients with COVID-19 had higher respiratory drive, so the dosages of sedatives, opioids, and neuromuscular blockers were high but similar in both groups. In terms of hypercapnia, as shown in a recent systematic review and meta-analysis of APRV in patients with COVID-19 (6), Pco_2 was not higher along the whole study period. The study protocol addressed hypercapnia by modifying specific recommended settings to increase minute ventilation (decrease T-high and increase P-high) (4). It is important to understand that regardless of MVspont, total minute ventilation can still be manipulated in APRV. As we mentioned in the article, the main reason for "transient" increases in Pco_2 was the reluctance by bedside clinicians to decrease T-high to less than 3 seconds (2). Considering these issues, the lack of benefit of APRV cannot be attributed to the lower MVspont within the first 3 days only as Patnaik et al (1) suggest.

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Dr. Mireles-Cabodevila receives royalties for books and chapters and co-owns a patent for Mid Frequency Ventilation. He received funding from IngMar Medical, Elsevier Publishers, and the American College of Physicians; he disclosed that he is the co-owner of Patent Mid Frequency ventilation. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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