acutely gravely ill ICU patient who chooses aggressive measures. This decision might not be premature based on the patient characteristics or preferences.

As we continue to strive to individualize care for our critically ill patients and guide patients and their families through goals of care discussions, we would like to hope that our actions are not swayed by a unit culture that trends toward optimism versus pessimism. Yet, this study definitely gives us pause. Maharaj et al (5) attempt to objectively determine whether a decision to withdraw care might be untimely in certain patients and found that there are certain ICU characteristics that may contribute to this decision. Despite the limitations of this study, it is prudent that we continue to check our own biases as we continue to provide the best care and comfort to our patients.

1 *Critical Care Department, Mayo Clinic Arizona, Phoenix, AZ*

2 *National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD*

3 *Critical Care Medicine Department, National Institutes of Health, Bethesda, MD*

Drs. Athale and Grazioli received support for article research from the National Institutes of Health. Dr. Sun disclosed government work.

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A Ventilator Mode Cannot Set Itself, Nor Can It Be Solely Responsible for Outcomes*

KEY WORDS: acute respiratory distress syndrome; airway pressure release ventilation; coronavirus disease; time-controlled adaptive ventilation; ventilator-induced lung injury; volume control ventilation

Nader M. Habashi, MD, FACP, FCCP[1]

Penny Andrews, RN, BSN[1]

Michaela Kollisch-Singule, MD[2]

Gary F. Nieman, BS[3]

We read with great interest the article published in this issue of *Critical Care Medicine* by Ibarra-Estrada et al (1) comparing the outcome in coronavirus disease 2019 (COVID-19)-induced acute respiratory distress syndrome (CARDS) patients using two ventilation strategies. Treatment arms included: 1) Acute Respiratory Distress Syndrome Network (ARDSNet) low tidal volume (LVT) method of setting the volume control ventilation (VCV) mode and 2) the Ibarra-Estrada et al (1) method of setting the

***See also p. 586.**

DOI: 10.1097/CCM.0000000000005403

airway pressure release ventilation (APRV) mode. The aim of the study by Ibarra-Estrada et al (1) was to compare outcomes between APRV and LVT in patients with severe COVID-19.

As with any ventilator mode, VCV itself is neither lung protective nor injurious but rather it is the method by which the mode is set and adjusted with changes in lung pathophysiology that is critical to outcome. Prior to the 2000 ARDSNet ARMA trial (2), three LVT studies using various methods failed to show any benefit (3–5). Subsequently, the ARMA trial compared two methods of setting VT in VCV with the LVT method (6 mL/kg) showing a significant reduction in mortality as compared with the high VT (HVT) method (12 mL/kg) (2). The ARDSNet ARMA trial (2) did not conclude that the mode VCV itself caused ventilator-induced lung injury (VILI) rather using the LVT method was superior to the HVT method as a lung-protective strategy, affirming it is not the mode itself that is lung protective or injurious but the way the mode is set and adjusted. As a result, a protocolized method to set and adjust VCV was established known as the "LVT strategy" that if not followed precisely may result in worse outcomes. Would this not also be true for APRV? Because a mode cannot set itself, one method of setting and adjusting APRV may be superior to another as with VCV set with a VT of 6 versus 12 mL/kg.

Hallmarks of acute respiratory distress syndrome (ARDS) pathophysiology include regional alveolar instability, which evolves to tissue damage from repetitive alveolar collapse and expansion (RACE) (atelectrauma) (6) and stress multipliers causing overdistension of open alveoli adjacent to collapsed alveoli (volutrauma) (7). Combined, atelectrauma and volutrauma lead to a synergistic VILI complex. The suggested physiologic benefits of APRV include: 1) stabilizing alveoli and minimizing RACE with a brief time (T_{Low}) during low airway pressure (P_{Low}), known as the release phase and 2) gradually opening collapsed alveoli over time (hours or days) with an extended time (T_{High}) during high airway pressure (P_{High}), known as the continuous positive airway pressure (CPAP) phase. If both physiologic goals are met, the lung would remain stable eliminating the primary mechanisms of the VILI complex and mortality should be reduced.

Although APRV has been available on a commercial ventilator since 1987 (8), there is still no consensus on the optimal method to set and adjust this mode (9). Multiple methods of setting APRV are used and thus it is not surprising that outcomes from these studies vary greatly (1, 10–15). The key to APRV is understanding the time-dependent behavior of alveolar ventilation. Unlike inverse ratio pressure control ventilation, one unique aspect of APRV is the precise and independent control of time in milliseconds at both the release and CPAP phase. The efficacy of APRV is reliant on the ability to quickly stabilize alveoli with a very brief release phase (T_{Low}) and then gradually expand collapsed alveoli over an extended time with a progressive prolonged CPAP phase (T_{High}) (16). In contrast, current open lung approach (OLA) methods attempt to recruit the entire lung within seconds or minutes (17). This is problematic since much of this newly opened lung tissue will have dysfunctional surfactant and even with high PEEP will not prevent collapse at expiration. Therefore, "opening the lung" prior to stabilizing the airspaces only increases the number of airspaces subjected to lung tissue injury from the VILI complex (7, 18–20). We postulate the above mechanism partially explains the failed clinical trials using current OLA methods (17). A more physiologically sound strategy may be to reverse the approach by first stabilizing the lung and then gradually reopening it over an extended time (hours or days).

Next, it is important to understand the correlation between T_{Low} and respiratory system elastance (E_{RS}). With the time-controlled adaptive ventilation (TCAV) method of setting APRV, the slope of the expiratory flow-time curve ($SLOPE_{EF}$) is a breath-by-breath assessment of E_{RS} and is used to set the T_{Low}, which controls the recoil force of increasing or decreasing elastance. It has been shown that the expiratory flow termination/expiratory peak flow (E_{FT}/E_{PF}) ratio of 75% optimizes alveolar stability in acute restrictive lung disease (9, 10, 18–20). An increase in E_{RS} causes the $SLOPE_{EF}$ to become more acute with the E_{FT}/E_{PF} decreasing to less than 75%, requiring a T_{Low} reduction. The corresponding time reduction in T_{Low} to maintain E_{FT}/E_{FP} 75% results in a progressively lower VT paralleling the increase in E_{RS}. In patients with high E_{RS}, such as ARDS, the VT with TCAV is typically less than 6 mL/kg on transition to APRV and does not increase until there is a concomitant decrease in E_{RS}. Ultimately, this means the T_{Low} is adaptive to an evolving disease process and should not be set to a fixed duration or adjusted to target VT or manage $PaCO_2$. Rather, the primary role of the T_{Low} is to personalize and precisely

adapt to recoil forces of E_{RS}, thereby maintaining alveolar stability with evolving or resolving lung pathology (16). Using a very brief T_{Low}, set and adjusted by changes in lung physiology, rapidly stabilizes alveoli and permits the extension of time (T_{High}) during the CPAP Phase that gradually persuades collapsed airspaces to expand. Thus, the TCAV method uses a Stabilizing Lung Approach rather than the traditional OLA.

The Ibarra-Estrada et al (1) method for initial APRV settings were: P_{High} set at the plateau pressure measured during an inspiratory pause in VCV (maximum 30 cm H_2O); P_{Low} set to 0 cm H_2O; T_{High} 4–6 seconds; and T_{Low} 0.4–0.6 seconds. The methods to change these settings were to adjust T_{Low} to E_{FT}/E_{FP} = 75% or 50%, with 50% used to increase $PaCO_2$ removal and 75% to increase oxygenation and P_{High} adjusted to keep expiratory Vt as close to 6 mL/kg as possible. Three options were used to optimize gas exchange: 1) increase P_{High} by 1–2 cm H_2O increments, 2) increase T_{High} by 1–2 second increments, or 3) increase both P_{High} and T_{High}. These methods of setting and adjusting APRV did not significantly improve relevant outcomes as compared with the ARDSnet method of setting VCV.

Although there are many methods to set and adjust APRV (1, 12–15), the most studied is the TCAV method showing high efficacy in both clinical and basic science studies (10, 11, 21–23). While the Ibarra-Estrada et al (1) method used in the study by Ibarra-Estrada et al (1) is similar to the TCAV method, two key differences may explain the lack of improved outcome.

First, the Ibarra-Estrada et al (1) method adjusted T_{Low} from E_{FT}/E_{FP} 75% to 50% to increase Vt in an attempt to negate a rise in $PaCO_2$ resulting from the low respiratory rate in the APRV group. Because T_{Low} balances ventilation with alveolar stability, using a T_{Low} of E_{FT}/E_{FP} 75% defines the longest duration that optimizes alveolar stability. Increasing E_{FT}/E_{FP} from 75% to 50% generally fails to increase $PaCO_2$ clearance and sacrifices alveolar stability resulting in RACE-induced VILI complex (7, 18–20). Consequently, to compensate for the increase in Vt from the T_{Low} of E_{FT}/E_{FP} 50%, the P_{High} was reduced, which further compounds regional alveolar instability and stress multipliers aggravating RACE-induced VILI complex (7, 18, 19, 24–28). As a result, the APRV mode itself was implicated for the higher Vt and hypercarbia rather than the method of applying the APRV mode.

Second, in the study by Ibarra-Estrada et al (1) of established CARDS patients, the APRV group was managed with a T_{High} 4–6 seconds, which resulted in a significantly lower respiratory rate as compared with LVt group ($p < 0.001$). The resultant hypercarbia from the lower minute ventilation (MVe) is therefore not unexpected, particularly in CARDS known for a high degree of deadspace. The T_{High} duration differs with the degree of lung dysfunction (i.e., mild vs severe ARDS) to allow adequate convective frequency as with a set rate in any other mode. When APRV TCAV is used for established ARDS, the initial T_{High} is typically set at 1–2 seconds (24–35 breaths/min) to provide for adequate ventilation. Therefore, the lower respiratory rates from a T_{High} set 4–6 seconds as in the APRV group would be more appropriate for stable mechanically ventilated patients, recovering ARDS patients or patients placed on APRV TCAV for ARDS prevention (29, 30).

When initiating the TCAV method with T_{Low} 75% on patients with established ARDS, the resultant Vt is generally reduced to less than 6 mL/kg because there is only a small functional lung available to accept volume. Such patients require a temporary decrease in T_{High}, which would result in an increased rate and subsequent MVe to compensate for the Vt reduction and achieve adequate convective elimination of $PaCO_2$. However, in the study by Ibarra-Estrada et al (1), rather than decreasing the T_{High} to adjust for hypercarbia the T_{Low} was increased, which further lowered the respiratory rate. As a result, the Ibarra-Estrada et al (1) method had a significantly reduced MVe as compared with the LVt group ($p = 0.001$). To compensate for the low respiratory rate, the T_{Low} was increased beyond 75% to increase Vt, simultaneously exacerbating alveolar derecruitment, decreasing ventilation efficiency and increasing hypercarbia. More concerning is the potential to further lung injury by increasing alveolar instability, microstrain, and stress multipliers throughout the lung (7, 18, 19) producing the VILI complex.

Similar to T_{Low}, the role of T_{High} is often confused in APRV studies and clinical practice. Once the T_{Low} is set appropriately to E_{FT}/E_{PF} 75% in acute restrictive lung disease or E_{FT}/E_{PF} 25% for diseases of expiratory flow limitation (i.e., chronic obstructive pulmonary disease) and the T_{Low} personalized for the individual patient's lung mechanics, the T_{High} becomes

the primary respiratory rate controller. Although the T_{High} has a role in progressively increasing the number of open airspaces, it must be tempered with the need to provide adequate ventilation. As surface area for gas diffusion improves, reliance solely on convection of gases diminishes. Over time, improving alveolar stability increases ventilation efficiency and permits a gradual and progressive increase in T_{High} adaptive to $PaCO_2$ goals (31–41). Conversely, attempts to correct hypercarbia in ARDS with T_{Low} to less than E_{FT}/E_{PF} 75% would only produce larger Vt and kill alveolar stability.

Although the optimal method of limiting the VILI complex remains undefined, methods should be based on physiologically validated settings and goals that have biologic and mechanistic plausibility rather than arbitrary protocols. Currently, the TCAV method of setting APRV has added the largest body of scientific data that has calibrated alveolar behavior through in-vivo microscopy with a real-time bedside method of monitoring evolving distal airspace behavior and respiratory mechanics. Therefore, when developing methods of mechanical ventilation designed to limit the VILI complex, one must consider the physiology of the distal airspaces and work backward to establish appropriate ventilator settings. The precise application of the release and CPAP phases with TCAV has been shown to stabilize and then gradually recruit the lung, even in the setting of a heterogeneous lung with multiple alveolar opening and collapse time constants (22, 23). Until a consensus of the optimal method of setting and goals of APRV is agreed upon in clinically applicable animal models or clinical trials, we have no way of knowing if a poor outcome in a study using APRV was because of an ineffective method to set and adjust this mode. Misunderstanding the key role of time controllers in APRV can lead to a sequential undoing of the TCAV goals. Similar to blaming a pen for misspelling, a ventilator mode should not be blamed solely for poor outcomes.

1 *Department of Trauma Critical Care Medicine, R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, MD*

2 *Department of Pediatric Surgery, SUNY Upstate Medical University, Syracuse, NY*

3 *Department of Surgery, SUNY Upstate Medical University, Syracuse, NY*

Drs. Habashi and Andrews received compensation for travel to sponsored conferences. Drs. Kollisch-Singule's and Nieman's institutions received funding from Draeger Medical. Dr. Neiman received support for article research from the National Institutes of Health and the Department of Defense.

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