Airway Pressure Release Ventilation: A Review of the Evidence, Theoretical Benefits, and Alternative Titration Strategies

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ABSTRACT

OBJECTIVE: To review the theoretical benefits of airway pressure release ventilation (APRV), summarize the evidence for its use in clinical practice, and discuss different titration strategies.

DATA SOURCE: Published randomized controlled trials in humans, observational human studies, animal studies, review articles, ventilator textbooks, and editorials.

DATA SUMMARY: Airway pressure release ventilation optimizes alveolar recruitment, reduces airway pressures, allows for spontaneous breathing, and offers many hemodynamic benefits. Despite these physiologic advantages, there are inconsistent data to support the use of APRV over other modes of ventilation. There is considerable heterogeneity in the application of APRV among providers and a shortage of information describing initiation and titration strategies. To date, no direct comparison studies of APRV strategies have been performed. This review describes 2 common management approaches that bedside providers can use to optimally tailor APRV to their patients.

CONCLUSION: Airway pressure release ventilation remains a form of mechanical ventilation primarily used for refractory hypoxemia. It offers unique physiological advantages over other ventilatory modes, and providers must be familiar with different titration methods. Given its inconsistent outcome data and heterogeneous use in practice, future trials should directly compare APRV strategies to determine the optimal management approach.

KEYWORDS: Hypoxia, respiratory failure, respiratory disease, ventilation, lung diffusion

Background and General Principles

Airway pressure release ventilation (APRV) is a novel form of ventilation first described by Stock et al in 1987.¹ Although this initial account introduced the term “APRV,” the genesis of this ventilatory mode began years earlier. Previous studies had investigated the effects of increased inspiratory time, termed “inverse ratio ventilation,” on oxygenation in the setting of acute respiratory distress syndrome (ARDS).²–⁴ Often used as salvage therapy in refractory cases of ARDS, this mode simply inverted the traditional inspiratory to expiratory (I:E) ratio of 1:2 to 2:1 or even 4:1 in some case reports. The idea behind the inversion was to provide a shortened expiratory phase to permit an adequate tidal volume to escape without allowing alveoli to fall below their closing volume.²

While inverse ratio ventilation is technically different from the mode which is now known as APRV, the notion of using the ventilator to open the lung and keep it inflated was expanded upon by Papadakos and Lachmann as the “open lung concept” of mechanical ventilation.⁵,⁶ Using maneuvers such as the early application of alveolar recruitment and positive end-expiratory pressure (PEEP), the basic goals of the open lung concept are the following:

Open the whole lung with the required pressure;

Keep the lung open with PEEP levels above the closing pressure;

Maintain optimal gas exchange at the smallest possible pressure amplitude to optimize carbon dioxide removal.

Overall, APRV used these techniques in an attempt to minimize alveolar overdistension and simultaneously prevent alveolar collapse. Before describing the specific mechanics of APRV, it is helpful to consider the open lung concept in the context of a pressure-volume curve as shown in Figure 1.

The lower inflection point (LIP) of the pressure-volume curve represents the initial point at which alveoli are most readily recruited and below which alveoli will tend to collapse.
The upper inflection point (UIP) represents the point at which alveoli become overdistended and thus most susceptible to volutrauma. In theory, ventilation strategies that only operate in the area above the LIP and below the UIP would maximize alveolar recruitment and prevent alveolar distention.7

Although the above model provides a means to conceptualize the theory underlying APRV, it should be noted that the LIP is not the actual point of derecruitment in the human lung. Although the above pressure-volume curve shows the LIP and UIP during inspiration, it does not consider the expiratory portion of the respiratory cycle. Tomographic studies evaluating lung volumes along these various inflection points on both the inflation and deflation limbs show that a point called the PMC, or point of most curvature, is a better marker of derecruitment than the LIP in the deflation limb of the curve. This point is higher on the curve than the LIP and is similar to the UIP in terms of aeration and recruitment of alveoli in the inflation limb.8

Fundamentally, APRV is a form of continuous pressure support ventilation in which 2 pressures are set: pressure high (P high) and pressure low (P low). Instead of delivering tidal volumes based on predetermined inspiratory pressures or volumes at a set respiratory rate, APRV delivers mandatory breaths through brief transitions from P high to P low and then resumption of P high to avoid alveolar collapse. P low is traditionally set at 0 cm H2O due to the presence of auto-PEEP that develops with APRV. This auto-PEEP maintains the airway pressure above the LIP on the pressure-volume curve.9 The P high is set below the UIP. By keeping the P high and P low between the 2 inflection points, the patient receives tidal volumes on the most compliant portion of the curve.7 The amount of time spent at the higher pressure (T high) is generally 80% to 95% of the cycle, and the amount of time spent at the lower pressure (T low) is often 0.6 to 0.8 seconds.9

The patient is allowed to breathe spontaneously throughout the respiratory cycle, facilitating CO2 removal. Other variables that affect alveolar ventilation include the pressure gradient (difference between P high and P low), the airway pressure release time (T low), and the airway pressure release frequency (frequency = 60/cycle time = 60/[T high + T low]). Most commonly, frequency rather than pressure gradient is manipulated to improve ventilation. One way to achieve an increased frequency is to shorten T high, as less time spent at inflation results in a higher frequency of release and thus greater minute ventilation. A basic APRV waveform showing the inflation and release phases is shown in Figure 2.10

Because of the potential for improved alveolar recruitment without overdistention offered by APRV, this mode of ventilation has been extensively studied as an alternative to other ventilation strategies. Despite a large number of trials evaluating its effectiveness, there remains a dearth of information describing APRV initiation and titration recommendations. While some described settings are based on clinical trials, others are based on expert opinion alone. Furthermore, no direct comparison studies of APRV strategies have been performed, and thus a single “best” titration strategy cannot be recommended. In light of this current knowledge gap, the purpose of this article is to discuss the theoretical benefits of APRV, summarize the evidence for its use in clinical practice, and review different initiation and titration strategies.

**Theoretical Benefits of APRV**

As described above, APRV is a type of inverse ratio ventilation that combines time-triggered, time-cycled, pressure-limited mandatory breaths with spontaneous breaths at any point in the ventilatory cycle.11,12 Within this broad conceptual framework, there is no clear definition for the settings that should be termed “APRV.” This ambiguity has resulted in considerable variation in practice, often complicating direct efficacy and outcome assessments.13 Inconsistency in application may also explain why many of the theoretical benefits of APRV have not been consistently demonstrated in humans. Despite the lack of a standard definition, the fundamental principles underlying APRV are the provision of near continuous positive airway pressure (CPAP) with the allowance of unrestricted spontaneous ventilation. These 2 characteristics account for many of the proposed advantages over conventional ventilation strategies.
**Optimizes ventilation-perfusion matching and improves alveolar recruitment**

Airway pressure release ventilation prevents alveolar overdistension by optimally matching lung volume with the volume of delivered gas. In a rat model of pulmonary ARDS, compared with the use of volume-controlled ventilation, the use of APRV resulted in less expression of amphiregulin, a gene expressed during times of alveolar stretch.\(^{14}\) Because patients are able to breathe spontaneously (especially at P high), they can adjust the delivered gas volume by taking larger or smaller breaths whenever needed.\(^{15}\) This improves ventilation-perfusion matching and minimizes lung injury caused by pendelluft.\(^{16}\)

The long T high and constant airway pressure supplied at P high ensure that a large number of alveolar units are recruited, even those with slow time constants.\(^{11,15}\) This feature may offer considerable benefit in patients with ARDS as heterogeneous alveolar collapse is a pathophysiological hallmark of the disease.\(^{17}\) Given that the P high is set by the operator, the potential for ventilator-induced lung injury (VILI) from alveolar overdistension is further minimized.\(^{11}\) As another mechanism to reduce alveolar distension, the prolonged duration of P high promotes ventilation through collateral channels (eg, pores of Kohn). Ventilation through these auxiliary pathways may recruit additional alveolar units and facilitate the redistribution of alveolar gas volume throughout the lung.\(^{11,16}\) Although there is a reduction in airway pressure during the release phase, these periods are short and thus minimize both alveolar derecruitment and atelectrauma from repetitive alveolar collapse and expansion.\(^{17}\)

**Reduces peak and plateau pressures while increasing mean airway pressure**

In addition to spontaneous ventilatory efforts, the intermittent release periods to P low promote alveolar ventilation and removal of CO\(_2\).\(^{11}\) In this manner, APRV can generate lower peak and plateau pressures (P plat) for a given tidal volume than conventional modes.\(^{11,16}\) This feature may decrease the likelihood of inducing VILI from the generation of dangerously high airway pressures to maintain adequate ventilation. Because of the prolonged time spent in inspiration as a function of the inverted I:E ratio, APRV generates higher mean airway pressures than conventional ventilation modes.\(^{16}\)

Within a certain physiologic range, higher mean airway pressures result in both greater mean lung volumes and higher Pao\(_2\) values.\(^{12}\)

**Permits spontaneous breathing**

*Allows for less sedation and paralysis.* As APRV mandates spontaneous ventilation, pharmacologic paralysis should be avoided to maximize the mode’s benefits. Although the use of neuromuscular blocking agents in patients with ARDS has been associated with improvements in mortality and other clinical outcomes, the means by which they achieve these effects remain unknown.\(^{18,19}\) One widely postulated theory for their value is the minimization of alveolar overdistension and collapse from patient-ventilator asynchrony. Given that APRV allows patients to breathe spontaneously and reduces alveolar overdistension, these mechanisms may be less applicable to patients ventilated with APRV. In addition, the use of neuromuscular blocking agents in critically ill patients has been associated with the development of critical illness polyneuromyopathy.\(^{20}\) The allowance of spontaneous breathing reduces the need for deep sedation to achieve patient-ventilator synchrony.\(^{16,21}\) Reduced doses of opioids and benzodiazepines in critically ill patients may subsequently decrease the incidence of their negative side effects (eg, constipation, delirium, development of tolerance). Finally, patients who are awake and breathing comfortably can participate in physical therapy and mobilization efforts, whereas deeply sedated and paralyzed patients cannot.

**Preserves diaphragm activity.** Spontaneous ventilation preferentially exercises the dorsal and lateral aspects of the diaphragm. In the supine patient, this feature allows for regional ventilation redistribution to the dependent and well-perfused areas of the diaphragm and a reduction in hyperinflation of the nondependent regions.\(^{22,23}\) The net effect is a decrease in intrapulmonary shunt and optimization of ventilation-perfusion matching. Furthermore, spontaneous breathing promotes the expansion of the lungs and chest wall at functional residual capacity and may prevent diaphragm muscle atrophy associated with prolonged mechanical ventilation.\(^{22,23}\)

**Improves hemodynamic profiles.** Positive pressure ventilation creates an increase in intrathoracic pressure during inspiration, manifesting as decreased venous return, right ventricular output, and pulmonary blood flow.\(^{24}\) Spontaneous breathing during APRV mimics normal negative pressure ventilation. Intrathoracic pressure decreases during inspiration, augmenting systemic venous return to the heart from the abdominal organs and alleviating pressure on the pulmonary capillaries.\(^{24-26}\) These hemodynamic changes can improve cardiac performance and oxygen delivery at the tissue level. Compared with conventional ventilation modes that do not permit spontaneous respirations, the use of APRV has been associated with the following:\(^{15,16,21,27}\)

- Improvements in urine output, heart rate, and blood pressure;
- Reductions in vasopressor and inotrope administration;
- Improvements in cardiac index and lactate clearance;
- Increases in arterial oxygenation, saturation of central venous blood (S\(_o\)\(_2\)), and saturation of mixed venous blood (S\(_v\)\(_2\)).
Outcomes in Human Studies

When compared with other modes of ventilation, human studies evaluating the use of APRV have not demonstrated consistent benefits. This may be due to the lack of a standardized definition of APRV as well as considerable variability in the settings and parameters implemented in different trials. Furthermore, when analyzing studies using APRV, it is paramount to evaluate whether or not the specific protocol used within the ventilation mode is protective or injurious. For example, in 2000, the ARDS Network investigators published a landmark multicenter randomized controlled trial comparing one mode of ventilation (assist control-volume control) in 2 separate protocol groups: low tidal volumes and low plateau pressures versus higher “conventional” tidal volumes and higher plateau pressures. There was a significant increase in mortality in the higher tidal volume group. The conclusion of this study was not that the assist control-volume control ventilation mode itself is injurious but that low tidal volume ventilation is superior to higher tidal volume ventilation in this patient population. This notion should serve as an important reminder that the specific protocol used within a given mode is the key to determining whether a ventilation strategy is protective or injurious. With this background understanding, the following section highlights a number of APRV studies in humans.

In the 1990s, multiple crossover studies found that APRV, when compared with conventional positive pressure ventilation, maintained similar oxygenation with significantly decreased peak inspiratory pressures. In the largest of these early studies, Räsänen et al explored conventional ventilation and a subsequent transition to APRV in 50 patients with acute lung injury. The authors demonstrated that APRV, while preserving adequate arterial oxygenation and circulatory support, allowed a substantial (>50%) reduction in peak airway pressures. This study did not evaluate morbidity or mortality, and 3 of the patients failed APRV presumably due to a preceding or developing respiratory acidosis, suggesting ventilatory difficulties. In another crossover study of 15 ARDS patients published in 1993, Davis et al observed decreased peak airway pressures and increased mean airway pressures with APRV compared with intermittent mandatory ventilation. The authors found no hemodynamic advantages associated with the use of APRV, although they did not comment on long-term outcomes.

In addition to studying the immediate hemodynamic and respiratory consequences of APRV, later trials began to examine the long-term effects. A 2001 randomized prospective study by Putensen et al compared APRV with pressure control ventilation in trauma patients. The authors found that patients in the APRV group had fewer ventilator days and a decreased intensive care unit (ICU) length of stay. Of note, only 20% of patients in the APRV group had ARDS compared with 74% of patients in the pressure control group. In 2003, a randomized prospective intervention study by Varpula et al compared the response to proning (6 hours, 1 or 2 times daily) during APRV to pressure-controlled synchronized intermittent mechanical ventilation (SIMV). The authors found a significantly increased improvement in oxygenation in the APRV group, particularly after the second pronation. This study included only 33 patients, potentially limiting the conclusions that can be drawn from its results. The same group of investigators conducted an additional study in 2004 comparing APRV with pressure-controlled SIMV in 58 patients with acute lung injury. They found similar mortality and ventilator-free days between the 2 groups.

In 2009 and 2010, 2 retrospective studies comparing APRV with conventional ventilation modes showed a significant improvement in oxygenation with APRV but failed to show mortality benefit. In 2010, a randomized prospective trial by Maxwell et al compared APRV with low tidal volume ventilation in 63 trauma patients. The results showed no significant difference in mortality, ventilator days, ICU length of stay, or other major complications. Interestingly, the authors found a trend toward increased ventilator days and ICU length of stay in the APRV group; however, this finding did not reach statistical significance and may have been related to a significantly higher Acute Physiology and Chronic Health Evaluation (APACHE) II score in the APRV group. Although the design and intervention of the 2 studies evaluating APRV in trauma patients were not identical, the results of Maxwell et al’s 2010 study directly conflict with those of Putensen et al’s 2001 study.

In 2016, a small randomized trial by Li et al compared APRV with SIMV in 52 patients with moderate to severe ARDS and found that the APRV group had significantly improved oxygenation (as measured with \( \text{S}_\text{O}_2 \)), respiratory mechanics, and cardiac index values. Although the APRV group had a decrease in ventilator days, days requiring sedation, and ICU length of stay, no difference in mortality or organ failure was found compared with the conventional ventilation group.

The largest and most recent trial to date was published by Zhou et al in 2017 and compared APRV with lung-protective ventilation modes guided by the ARDS Network trial. The study randomized patients to receive APRV or low tidal volume lung-protective ventilation early in the course of their disease. They found that patients randomized to the APRV group had a shorter duration of mechanical ventilation, improvement in oxygenation, improvement in respiratory compliance, required less sedation, and had a shorter ICU length of stay. Much like other studies, the authors were unable to show any mortality benefit. Despite the results, the findings generated skepticism among APRV experts. As described in a published commentary, the small study size raises concerns about poorly matched groups, with the control group having more patients with comorbidities, a higher incidence of vasopressor support, and pneumonia as the cause of their ARDS. Furthermore, the single-center characteristic of the trial potentially reduces...
external validity. Finally, sedation management was different between the 2 groups, making it difficult to draw comparisons regarding sedation requirements.

Overall, although data on the use of APRV for ARDS appear promising, there is a lack of large randomized controlled trials showing consistent benefits. This deficiency has likely discouraged many providers from using APRV in standard practice. Furthermore, there is no consensus on the optimal APRV strategy, and one potential reason for the inconsistency of outcomes is variability in the approach to initiating and titrating encountered in the literature. The remaining sections will review 2 of the most commonly described and evidence-based approaches, those proposed by Habashi and Zhou. These 2 specific protocols were selected for this review as they have their foundations backed by nearly 50 years of basic science research. A brief summary of the literature supporting these approaches is shown in Table 1.

**Initiation and Titration Strategies**

As above, there are several ways to initiate and titrate APRV therapy, and the modality has different variables that affect oxygenation and ventilation. The clinician must set P high, P low, T high, and T low. P high is essentially the CPAP used to recruit alveoli. T high and T low determine the frequency of breath releases. The patient can spontaneously breathe throughout the respiratory cycle, and both the spontaneous breaths and set releases accomplish ventilation. P high, which determines mean airway pressure and the pressure gradient of the releases, and FiO₂ are titrated for oxygenation. All of these settings must be adjusted in the context of the patient’s lung compliance.11,58 Studies evaluating the benefit of APRV have used widely different titration protocols. In reviewing the literature, APRV titration strategies are generally categorized as Fixed APRV (F-APRV) or Personalized APRV (P-APRV). Many of the older APRV studies have implemented the F-APRV strategy. With F-APRV, P high is typically less than 80% of the respiratory cycle, and T low is not titrated based on physiologic lung parameters. In contrast, P-APRV is characterized by 90% of the cycle spent at P high with subsequent titration of T low parameters. In reviewing the literature, the protocol achieving T high.58 Observational, retrospective data in trauma patients demonstrated a significant improvement in mortality and ARDS incidence using this titration strategy.63

When addressing hypercarbia, this protocol again advocates for optimizing release lung volumes or increasing alveolar ventilation by increasing P high alone or P high and T high simultaneously. The operator must be cautious when increasing the minute ventilation by decreasing T high due to the resultant reduction in mean airway pressure and derecruitment that can be accompanied by this maneuver. However, this process can be counteracted by simultaneously increasing P high when dropping T high.58

**The Habashi protocol**

In his 2005 landmark paper, Habashi58 first describes a technique to personalize APRV. Specific initiation and titration goals are set based on the etiology of the patient’s respiratory failure. The setup advocates for a P high set to a desired P plat (e.g., 20–35 cm H₂O), P low of 0 cm H₂O, T high of 80% to 95% of the cycle time (or about 4–6 seconds in adults), T low of 0.2 to 0.8 seconds in restrictive lung disease, and T low of 0.8 to 1.5 seconds in obstructive lung disease. If transitioning from volume control ventilation or pressure control ventilation, then the P high is set to the P plat or the peak airway pressure respectively. Higher P high may be needed based on patient-specific factors such as decreased abdominal compliance, decreased thoracic compliance, or obesity. A P low of 0 is selected to allow a larger pressure gradient and to maximize peak expiratory flow rate (PEFR) during the release. In addition, P low is not set > 0 because the inherent airway resistance will create auto-PEEP.58

When considering T low, it is important to understand the basis for such a short release time. The rationale for this has been updated since publication of the original 2005 review article. It has been demonstrated in a laboratory setting that adjustment of the T low to terminate at 75% of the PEFR (a point on the flow/time curve called T-PEFR) resulted in only 10% variation of alveolar volume between end-inspiration and the release phase.59 Conversely, when the T low was adjusted to a percentage less than 75% of PEFR, the alveolar volume change between end-inspiration and the release phase increased, causing alveolar instability and collapse as seen using alveolar microscopy. As a result, 0.35 to 0.6 seconds may represent a more appropriate initial T low setting in adults.60

To treat hypoxemia, the protocol aims to optimize release lung volumes by titrating P low to between 50% and 75% of the PEFR. In patients with severe ARDS, it has been argued that operators should maintain an EEFR:PEFR of 0.75.61 Figure 3 shows this method on the SERVO-i ventilator by Maquet. To find the PEFR using this ventilator, the operator must first save the image, then select “Menu,” then select “Review,” and then select “Recorded Waveforms.” From here, the operator can measure the PEFR and adjust T low based on the value to achieve an EEFR:PEFR ratio of 0.5 to 0.75. Compared with low tidal volume ventilation, the use of this titration strategy reduced the development of lung edema in a porcine model of ARDS.62 Further attempts to improve oxygenation include maneuvers that increase the mean airway pressure. The protocol achieves this by increasing P high first, or P high and T high concomitantly.

When addressing hypercarbia, this protocol again advocates for optimizing release lung volumes or increasing alveolar ventilation by increasing P high alone or P high and T high simultaneously. The operator must be cautious when increasing the minute ventilation by decreasing T high due to the resultant reduction in mean airway pressure and derecruitment that can be accompanied by this maneuver. However, this process can be counteracted by simultaneously increasing P high when dropping T high.58

**The Zhou protocol**

As described above, the most successful human randomized controlled trial to date using APRV was published by Zhou et al
in 2017.\textsuperscript{16} Because of this study’s results, it is important to understand the titration strategy used by the authors. In the study, patients were initially ventilated using assist control-volume control ventilation with a Puritan Bennett 840 ventilator. Prior to transitioning the patient to APRV, the providers reduced the respiratory rate to 4 to 6 breaths per minute, and then decreased...
the flow rates to 30 L/min while increasing sedation as needed to allow the ventilator to calculate desired parameters. P high was set to the previous P plat, whereas P low was set to 5 cm H₂O. The initial T low was set using 1.0 to 1.5 multiplied by the calculated time constant. The time constant is calculated by multiplying resistance (cm H₂O/liter/second) and compliance (liter/cm H₂O). Of note, not all ventilators will calculate airway resistance, and this may need to be manually calculated by the practitioner using the following formula: \( \frac{(P_{aw} - P_{plat})}{peak inspiratory flow rate} \). This is shown using the SERVO-i in Figures 4 and 5.

The use of the time constant to initially set T low is considerably different than the method proposed by Habashi. The notion of using time constants stems from the concept that pressure, flow, and volume all decay at the same rate. For each time constant, the pressure (P high setting in APRV) will decay to 63.2% of its previous value. In APRV, this resultant value is the PEEPi of the respiratory system. For example, if P high is set to 30 cm H₂O, then at one time constant during the release phase, this value is calculated to be approximately 19 cm H₂O which is the PEEPi. However, this calculation of PEEPi may be inaccurate, often underestimating the PEEPi as seen in a previous lung simulator model. Thus, following this initial setting of T low based on the time constant, the operator following the Zhou protocol would further titrate T low to maintain an EEFR:PEFR ratio of 0.5 as previously discussed. Further titrations of T low could be accomplished by viewing the flow-time curve on the ventilator to achieve an angle of expiratory deceleration of 45°.

In the protocol used by Zhou et al., release frequencies were typically set between 10 and 14 releases per minute. Spontaneous breathing goals were 10% to 60% of the respiratory cycle depending on the severity of ARDS. With worsening hypoxia, P high was first increased by 1 to 2 cm H₂O to a maximum of 30 cm H₂O. If this did not resolve the hypoxia, T low was decreased by 0.05 to 0.1 seconds. Further therapy to alleviate refractory hypoxia required P low to be increased by 1 to 2 cm H₂O, and then release frequencies were decreased by 1 to 2. If the previously described efforts did not resolve the hypoxia, the authors attempted recruitment maneuvers, prone positioning, increasing the minute ventilation, increasing the inspired oxygen, or transitioning the patient to other therapies. Hypercapnia was treated by decreasing sedation to promote additional spontaneous ventilation followed by methods to increase the release volumes or increase the release frequencies. When implementing this titration strategy, the authors found that patients had significantly fewer ventilator days, improved oxygenation and respiratory compliance, decreased plateau pressures, and decreased sedation requirements compared with low tidal volume ventilation.

**Conclusion**

For over 3 decades, APRV has remained a mode of ventilation often reserved for cases of refractory hypoxemia. Despite its physiologic advantages over other ventilatory modes, its benefits have not been consistently demonstrated in patient populations. Heterogeneity in its application in clinical trials has
likely contributed to this disparity. As detailed in this review, there are several approaches to the initiation and titration of APRV, and the practical features discussed will allow providers to best tailor this therapy for their patients. Given the current lack of empirical evidence to support one specific strategy, a new research direction should be undertaken. Instead of comparing a single APRV protocol with conventional ventilation, future studies should directly compare the outcomes of different APRV initiation and titration approaches (such as those proposed by Zhou and Habashi) to determine the optimal protocol.

Author Contributions
All authors participated in the drafting, editing, and approval of the manuscript.

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