

# APRV for ARDS: the complexities of a mode and how it affects even the best trials

Eduardo Mireles-Cabodevila<sup>1,2</sup>, Siddharth Dugar<sup>1,2</sup>, Robert L. Chatburn<sup>1,2</sup>

<sup>1</sup>Respiratory Institute, Cleveland Clinic, Ohio, USA; <sup>2</sup>Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Ohio, USA  
Correspondence to: Eduardo Mireles-Cabodevila. 9500 Euclid Avenue, G62, Cleveland, OH 44120, USA. Email: mirelee@ccf.org.

*Provenance:* This is an invited Editorial commissioned by Section Editor Dr. Xue-Zhong Xing [National Cancer Center (NCC)/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China].

*Comment on:* Zhou Y, Jin X, Lv Y, *et al.* Early application of airway pressure release ventilation may reduce the duration of mechanical ventilation in acute respiratory distress syndrome. *Intensive Care Med* 2017;43:1648-59.

Submitted Feb 01, 2018. Accepted for publication Mar 21, 2018.

doi: 10.21037/jtd.2018.03.156

View this article at: <http://dx.doi.org/10.21037/jtd.2018.03.156>

APRV is a mode of mechanical ventilation that has generated enough controversy to fuel a war. A major challenge has been the lack of randomized control studies on the application of APRV in patients with ARDS. All preexisting data did not address the question for which APRV was being promoted, that is, that APRV should be used as initial mode of mechanical ventilation for patients with ARDS. Multiple reports and studies in animals and humans have not helped answer this question. Not only is there paucity in the number of high quality trials in humans, but there is a lack of consistency on how APRV is applied (1,2).

Recently, Zhou and colleagues (3) published, perhaps the best (and first) evidence, on use of APRV on patients with ARDS. They studied 138 patients with a diagnosis of ARDS, and randomized them within 48 hours to conventional low tidal volume (LTV) ventilation with a low positive end-expiratory pressure (PEEP) strategy *vs.* APRV with a clearly defined implementation protocol. The study methods are transparent and clearly reported. Their primary outcome, ventilator free days was median 19 days (IQR 8–22 days) in APRV group *vs.* 2 days (IQR 0–15 days) in LTV group. This, along with several relevant secondary outcomes (better respiratory system compliance, improved gas exchange, less days in ICU) would make it sound as a straight hit: some will call it a home run.

We commend Dr. Zhou and colleagues (3) on their work, as this is the type of research that helps us move the field ahead. Clinicians often interpret a positive study as an affirmation of a treatment's efficacy and effectiveness.

However, the role of this editorial is to dissect this study in the context of current available literature, physiological concerns and technology issues. This is important, as we need to use the best available evidence, taken in the proper context, to make our clinical decisions.

## External validity

The study by Zhou *et al.* (3) is an efficacy trial conducted at a single center, where the team was trained on use of APRV and followed a detailed protocol. The study was well powered to reach the primary outcome. The results demonstrate an impressive difference in the median days free of mechanical ventilation. The LTV group days on the ventilator (15 days) and ventilator free days (2 days) were worse than those reported in several large ARDS studies (*Table 1*). Why would this be the case? There are three important factors that may have affected the length of mechanical ventilation:

- (I) The population studied had a higher proportion (58–69%) of ARDS from extra-pulmonary causes (sepsis, pancreatitis, trauma, and surgery) compared to other recent trials on ARDS (8,9). Although pulmonary *vs.* extra-pulmonary causes of ARDS have not shown to affect mortality (4,10), the response to positive pressure and ventilation strategies can be quite different depending on the cause, and this issue remains to be prospectively studied (11). This is important because of the

**Table 1** Comparison of outcomes

Outcome	Zhou <i>et al.</i> (3)		ARMA 2000 LTV arm (4)	ALVEOLI 2004 low PEEP arm (5)	LOVS 2008 LTV control arm (6)	OSCILLATE 2013 LTV control arm (7)	Lung Safe 2016 (8)
	APRV arm	LTV arm					
Length of mechanical ventilation (days)	8 [5–14]	15 [7–22]	8–10	NR	10[6–16]	10 [6–18]	8 [4–15]
No. of ventilator-free days	19 [8–22]	2 [0–15]	12±11	14.5±10.4	NR	NR	10 [0–22]
Pneumothorax (%)	4.2	10.4	10	10	9.1	13	NR
Length of ICU stay (days)	15 [8–21]	20 [10–32]	NR	12.2±10.4*	13 [9–23]	14 [9–26]	10 [5–20]
Length of hospital stay (days)	21 [14–30]	27 [18–41]	NR	NR	29 [16–51]	25 [15–41]	17 [8–33]
ICU mortality (%)	19.7	34.3	NR	NR	35	31	35.3
Hospital mortality (%)	23.9	37.3	31	24.9	40.4	35	40

\*, notice some report median and others mean. APRV, airway pressure release ventilation; LTV, low tidal volume; PEEP, positive end-expiratory pressure.

relatively small number of patients in this study. Even with randomization, the groups were imbalanced in some baseline variables that could have affected the primary and secondary outcomes. For example, the LTV group had a higher incidence of pneumonia as a cause for ARDS along with more co-morbidities (COPD, renal dysfunction and malignancy), and a higher percentage of these patients were on vasopressors (68.7% *vs.* 56.3%). The presence of pre-existing conditions, shock and differing etiologies can obviously affect the outcomes of any mechanical ventilation strategy.

- (II) The successful extubation rate in the LTV group was low, 38.8% (i.e., >60% of patients got re-intubated!). Failed extubation was not defined in the manuscript. Assuming the classic definition of extubation failure (need for re-intubation within 48–72 hours of extubation), a 60% extubation failure seems very high compared to the average reported in other studies (15 %). Failed extubation is associated with increased mortality, ventilator days and, ICU/Hospital length of stay (12). The incidence of tracheostomy in the LTV group (29.9%) was higher than the 13% reported in Lung Safe study (8) which number was comparable to the 12.7% for the APRV group. Interestingly, the criteria used by the study team to perform a tracheostomy were related to airway patency, mental status, or physician expectations for prolonged MV. Failure to wean or prolonged mechanical ventilation, the most common cause for

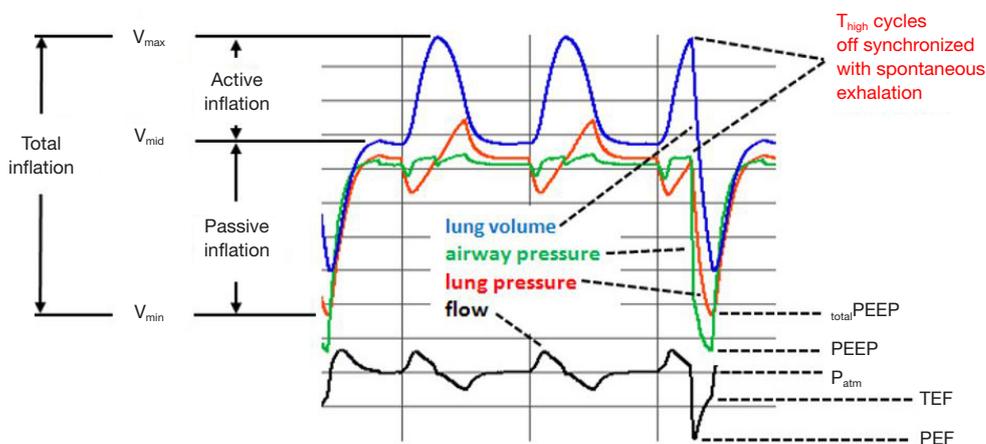
tracheostomy in ARDS, is not listed.

- (III) The sedation on the LTV group was not titrated by the respiratory therapists as it was for the APRV group, thus potentially creating a treatment bias. The LTV group had a significantly higher need for sedation compared to APRV group, contrary to a previous study showing a trend towards increased sedation requirement for patient treated with APRV (13). Sedation, of course, is another important variable associated with prolonged mechanical ventilation. The depth of sedation and sedation protocols are associated with mechanical ventilation outcomes. How much, is yet to be determined, but different sedation practices can introduce unrecognized bias (14–16). More importantly, at least in the US, respiratory therapists do not titrate analgesics and sedatives. We commend Zhou *et al.* (3) on their respiratory therapists' advanced training and privileging.

Thus, the results of this study should be taken with caution before generalizing to our patient population and clinical practice. It is a single center, efficacy study, with a small study population and a very strict research protocol. From the scientific standpoint, this study needs replication in larger populations and more centers before APRV can be considered as a standard of care.

### Ventilator performance

In terms of ventilator performance, this is a major area of caution for the APRV enthusiast. Zhou *et al.* (3) used a PB



**Figure 1** Spontaneous breaths superimposed on a mandatory breath during BiLevel mode with a PB 840 ventilator. When  $T_{high}$  cycles off in synchrony with a spontaneous exhalation, actual  $T_{low}$  becomes longer than set  $T_{low}$  resulting in lower end expiratory lung volume and pressure.  $P_{atm}$ , atmospheric pressure; TEF, terminal expiratory flow; PEF, peak expiratory flow.

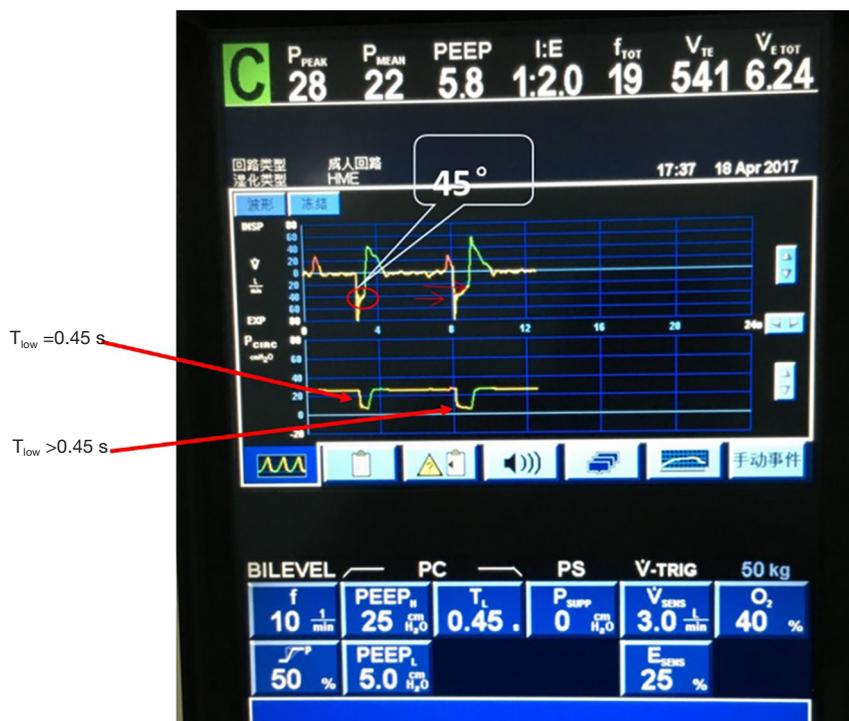
840 to deliver Medtronic's version of APRV. This ventilator has some particular issues that we need to consider. The authors carefully and appropriately measured the static compliance and resistance, and used this to calculate the time constant. They initially set the  $T_{low}$  to 1–1.5 times the time constant. Then, they adjusted the  $T_{low}$  to achieve a termination peak expiratory flow rate of  $\geq 50\%$ . The technical issues are: (I) the PB 840 does not measure the peak end expiratory flow rate or end (terminal) expiratory flow rate while on BiLevel ventilation, thus, calculations have to be made by trying to read on the ventilator screen the peak and terminal expiratory flow, which is difficult and can easily lead to errors. (II) The PB840 has a synchronization feature, which synchronizes the transition from  $P_{high}$  to  $P_{low}$  with the expiratory phase of a spontaneous breath (if present) that occurs at the end of  $T_{high}$ . This leads to a variable  $T_{low}$  despite the fact that  $T_{low}$  is preset (i.e., the synchronization feature overrides the setting). This phenomenon was described in a study of the BiLevel mode on the PB 84 ventilator (17). The study noted that the PB 840 ventilator is designed to cycle mandatory breaths (i.e.,  $P_{high}$ ,  $T_{high}$ ) early if a spontaneous exhalation is detected in a synchronization window at the end of  $T_{high}$ . As a result, the actual  $T_{low}$  values (during simulated ventilation of an ARDS patient with spontaneous efforts) were not the ones set on the ventilator settings. The implication is that use of very short values for  $T_{low}$  made the generation of total PEEP unpredictable. Tidal volumes were excessive (average 12.4 mL/kg) and total PEEP was not controllable using  $T_{low}$  in this

model (Figure 1). These results were actually confirmed in the supplemental material of the Zhou *et al.* study (Figure 2) demonstrate the variable  $T_{low}$ .

### Physiological premises

Finally, the issue with physiology; a major point in this study is the rapid improvement in gas exchange and respiratory system characteristics with APRV. We commend the authors for the precise methods they used to record these outcomes. We would like to make some points here. The first is related to the concept of “release” *vs.* “inflation” pressures, implying these are somehow unrelated. This notion is a misconception. It obscures the fact that APRV is identical to other modes in that the “releases” are nothing other than the last half of mandatory pressure controlled breaths. With every “re-pressurization”, the lung starts the first half of the mandatory breath, exposing the alveoli to volume increase and the risk of strain damage. Emphasizing only the exhalation portion of such a breath that APRV is less likely to injure the lung, and that tidal volume and pressure swings are of no consequence. On the contrary, the risk of injury is associated with that portion of the pressure-volume curve of the lungs on which the tidal volume occurs, which depends not only on the ventilator settings in APRV but on the patient's inspiratory effort, and hence on the total change in transpulmonary pressure (18).

The second is to highlight the concern about the presence of spontaneous breaths during a  $T_{high}$ . The



**Figure 2** The supplemental material of the paper by Zhou *et al.* shows exactly this result as well (screen shot from supplemental material labeled as Figure S1 Case One). This screen shot of the PB 840 in BiLevel mode with ARPV settings shows the first breath has a  $T_{low}$  set at 0.41 s, as indicated in the figure legend. However, the flow waveform for the second breath shows that due to synchrony of mandatory breath cycling with a spontaneous breath exhalation, the  $T_{low}$  is considerably longer.

presence of respiratory muscle pressure during  $T_{high}$  exposes the lung to higher transpulmonary pressures. In the setting of heterogeneous lung injury, the potential for very high local transpulmonary pressures, raises the potential for more lung injury (19). Perhaps these swings can be ameliorated with some ventilator strategies (20,21), but the method has yet to be determined. Another important issue is the intensity and amount of minute ventilation supported by spontaneous breathes. Zhou *et al.* presented a novel strategy, in which the RTs controlled the level of sedation to maintain a specific level of respiratory effort. This strategy may minimize those transpulmonary pressure swings. Evidently, more studies are needed here.

The study by Zhou *et al.* provides images, respiratory characteristics, and gas exchange consistent with lung recruitment. This is likely due to the fact that the mean airway pressure was higher in the patients with ARPV, as expected. The LVT group received the low PEEP ARDSnet table, and this plus lower I:E ratios led to lower mean airway pressures and worse markers of recruitment. Now, this begs two questions: if the LTV group had the same

mean airway pressures, would the results be similar? And, does this matter? Literature on use of higher PEEP and thus, higher mean airway pressures, has shown improved gas exchange, and perhaps a decrease in rescue therapies, but no difference in ICU or hospital mortality (5,6,22). More importantly, not all patients respond similarly to PEEP, and we still work on trying to define what is the optimal level. With this in mind, we would caution readers on concluding overall success in the face of just improving gas exchange.

Finally, we must address the concept setting  $T_{low}$ . As stated in the study by Zhou *et al.*, “brief release phase ( $T_{low}$ ) could permit only partial lung volume loss at the release phase, avoid cyclic alveoli collapse, and provide dynamic homogeneity”. This statement has continued to permeate the literature. In recent years, very detailed studies (23,24) examining the effects of setting  $T_{low}$  on ARPV demonstrated that de-recruitment occurs very rapidly in animal lung models of ARDS. Actually, to maintain recruitment of the injured alveoli population requires a very short  $T_{low}$ , less than 0.2 sec [which, by the way, not many ventilators can achieve (25)]. Thus, ARPV remains a mode with a potential

to expose the lung to high transpulmonary pressures, cyclic de-recruitment and potentially high tidal volumes, along with the possibility of overconfidence in the face of improved oxygenation (26).

So overall, the article by Zhou and colleagues adds to the literature several items. First, it is the best described APRV protocol applied to patients with ARDS to date. Second, it describes a protocol where the respiratory therapists adjusted the level of sedation to achieve clearly delineated ventilation goals. Finally, it raises the potential for a strategy with APRV to be studied in a larger group. On the same breath we will highlight major concerns with APRV and ARDS that will have to be taken into account in any future trial. That the ventilator performance is not homogenous across platforms and software, that each ventilator has a different implementation of APRV and that we lack clear data on how to optimize ventilator settings for both the APRV and the control group. Furthermore, we emphasize that improvement in gas exchange is not equal to improved morbidity and mortality, that future studies should match sedation practices between experimental and control groups, and that we need to learn more about APRV and lung injury in spontaneous breathing.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* Eduardo Mireles-Cabodevila and Siddharth Dugar have no conflicts of interest to declare. Robert L. Chatburn is a consultant for IngMar Medical and Drive Medical.

### References

- Jain SV, Kollisch-Singule M, Sadowitz B, et al. The 30-year evolution of airway pressure release ventilation (APRV). *Intensive Care Med* 2016;4:11.
- Rose L, Hawkins M. Airway pressure release ventilation and biphasic positive airway pressure: a systematic review of definitional criteria. *Intensive Care Med* 2008;34:1766-73.
- Zhou Y, Jin X, Lv Y, et al. Early application of airway pressure release ventilation may reduce the duration of mechanical ventilation in acute respiratory distress syndrome. *Intensive Care Med* 2017;43:1648-59.
- Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
- Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327-36.
- Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:646-55.
- Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;368:795-805.
- Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315:788-800.
- Cavalcanti AB, Suzumura EA, Laranjeira LN, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA* 2017;318:1335-45.
- Agarwal R, Srinivas R, Nath A, et al. Jindal SK. Is the mortality higher in the pulmonary vs the extrapulmonary ARDS? A meta analysis. *Chest* 2008;133:1463-73.
- Pelosi P, D'Onofrio D, Chiumello D, et al. Pulmonary and extrapulmonary acute respiratory distress syndrome are different. *Eur Respir J Suppl* 2003;42:48s-56s.
- Krinsley JS, Reddy PK, Iqbal A. What is the optimal rate of failed extubation? *Crit Care* 2012;16:111.
- Maxwell RA, Green JM, Waldrop J, et al. A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma* 2010;69:501-10; discussion 511.
- Ouellette DR, Patel S, Girard TD, et al. Liberation From Mechanical Ventilation in Critically Ill Adults: An Official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline: Inspiratory Pressure Augmentation During Spontaneous Breathing Trials, Protocols Minimizing Sedation, and Noninvasive Ventilation Immediately After Extubation. *Chest* 2017;151:166-80.
- Aitken LM, Bucknall T, Kent B, et al. Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients. *Cochrane Database Syst*

- Rev 2015;1:CD009771.
16. Kallet RH, Zhuo H, Yip V, et al. Spontaneous Breathing Trials and Conservative Sedation Practices Reduce Mechanical Ventilation Duration in Subjects With ARDS. *Respir Care* 2018;63:1-10.
  17. Haug K, Chatburn RL. Interactions among tidal volume, expiratory time, and total-PEEP in APRV. *Respir Care* 2014;59:OF12.
  18. Sasidhar M, Chatburn RL. Tidal volume variability during airway pressure release ventilation: case summary and theoretical analysis. *Respir Care* 2012;57:1325-33.
  19. Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:1420-7.
  20. Morais CCA, Koyama Y, Yoshida T, et al. High Positive End-Expiratory Pressure Renders Spontaneous Effort Non-Injurious. *Am J Respir Crit Care Med* 2018. [Epub ahead of print].
  21. Yoshida T, Roldan R, Beraldo MA, et al. Spontaneous Effort During Mechanical Ventilation: Maximal Injury With Less Positive End-Expiratory Pressure. *Crit Care Med* 2016;44:e678-88.
  22. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865-73.
  23. Kollisch-Singule M, Jain S, Andrews P, et al. Effect of Airway Pressure Release Ventilation on Dynamic Alveolar Heterogeneity. *JAMA Surg* 2016;151:64-72.
  24. Kollisch-Singule M, Emr B, Smith B, et al. Airway pressure release ventilation reduces conducting airway micro-strain in lung injury. *J Am Coll Surg* 2014;219:968-76.
  25. Daoud EG, Chatburn RL. Comparing surrogates of oxygenation and ventilation between airway pressure release ventilation and biphasic airway pressure in a mechanical model of adult respiratory distress syndrome. *Respir Investig* 2014;52:236-41.
  26. Chatburn RL, Kallet RH, Sasidhar M. Airway Pressure Release Ventilation May Result in Occult Atelectrauma in Severe ARDS. *Respir Care* 2016;61:1278-80.

**Cite this article as:** Mireles-Cabodevila E, Dugar S, Chatburn RL. APRV for ARDS: the complexities of a mode and how it affects even the best trials. *J Thorac Dis* 2018;10(Suppl 9):S1058-S1063. doi: 10.21037/jtd.2018.03.156