Editorial

Airway pressure release ventilation (APRV): do good things come to those who can wait?

Thomas Bein[1], Hermann Wrigge[2]

[1]Department of Anesthesiology, University Hospital, Regensburg, Germany; [2]Department of Anesthesiology and Intensive Care, University of Leipzig, Leipzig, Germany

Correspondence to: Prof. Dr. Thomas Bein, M.A. Department of Anesthesiology, University Hospital, D-93042 Regensburg, Germany. Email: thomas.bein@ukr.de.

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 Dec 27, 2017. Accepted for publication Jan 04, 2018.
doi: 10.21037/jtd.2018.01.107
View this article at: http://dx.doi.org/10.21037/jtd.2018.01.107

The landmark moment for mechanical ventilation (MV) came with the polio epidemic in the 1950s, leading to the widespread use of MV around the world (1). While controlled MV was favoured over the next three decades, the 1980s witnessed a shift from controlled to augmented spontaneous MV. Such a paradigm change was driven by technical improvements in ventilators in terms of fast-reacting valves, microprocessors, better flow delivery, and better triggering. In the following period, an exciting competition began among new modes of spontaneous ventilation aimed at the improvement of patient-ventilator interaction and the patient's comfort, and the preservation of respiratory pump capacity. Following the emergence of synchronized intermittent mandatory ventilation (SIMV), pressure support ventilation (PSV), proportional assist ventilation (PAV), automatic tube compensation (ATC), and a few other such modes, a special mode was first introduced in 1987 (2). It was characterized as the combination of continuous positive airway pressure (CPAP) with a brief release to ambient pressure short enough to generate auto-positive end-expiratory pressure (PEEP) while the patient was allowed to breathe spontaneously throughout the circle. This was called airway pressure release ventilation (APRV).

The physiological hypothesis was that APRV would ideally combine recruitment of the lung by prolonged CPAP and thus high mean airway pressure, including a short release period (preventing alveolar collapse and allowing partly controlled ventilation) with low tidal ('lung protective') spontaneous breathing, thus preventing diaphragm and muscle pump dystrophy (3). In the 'traditional' modes of MV, intensivists and respiratory therapists were accustomed to setting parameters like respiratory frequency, PEEP, level of pressure support, and tidal volume. In APRV, however, they had to set two pressure levels—'low' (P_{low} corresponds to PEEP) and 'high' (P_{high} corresponds to inspiratory pressure)—and two times—'low' (T_{low} corresponds to inspiratory time) and 'high' (T_{high} corresponds to release time)—accompanied by 'superimposed' spontaneous ventilation. The resulting pattern of such a setting is a combination of total PEEP (P_{low} plus auto-PEEP) with controlled ventilation characterized by frequency (60 s divided by the sum of T_{low} plus T_{high}) and inspiratory pressure (P_{high}). Sounds complicated? Yes, it is—especially for those who feel safe living with 'fixed' minute ventilation by setting a fixed frequency and a fixed tidal volume.

The history and overview of prospective randomized studies on the use of APRV in humans was only partly encouraging: While the physiological concept is attractive and in animals models some improvement in the pulmonary gas exchange (4), systemic blood flow, and organ perfusion was found (5), in none of the 23 reviewed human studies [summarized in (6)] was a worse outcome found using APRV compared to controlled positive pressure ventilation (CPPV). On the other hand, many studies observed significant cardiopulmonary stabilization in the APRV

patients compared to patients using 'traditional' controlled ventilation. However, in a large retrospective case series (7) involving 362 patients ventilated by APRV or CPPV, increased time on the ventilator was observed in the APRV group. All these results were sobering, but from a critical point of view, it was probably not the APRV method *per se* to blame; rather, some under-recognized inherent problems might be responsible for the 'negative' studies. For example, a major problem seemed to be that there was no strict definition of APRV allowing a broad variation in the settings (high and low times and pressures using auto-PEEP or not). In a recent systematic review (6), it was not possible to assess the efficacy of APRV since nearly all the study designs differed in defining a certain pattern of breathing as APRV. For example, Putensen *et al.* (8) chose an 'individualized' APRV setting in 24 patients presenting with acute respiratory distress syndrome (ARDS), while the times (goal: normocapnia) and pressures (goal: low pressure 2 cmH_2O above the inflection pressure on a static pressure/volume curve) were set according to each individual patient's lung mechanics. In contrast, in the study by Maxwell *et al.* (9) involving 63 trauma patients with acute respiratory failure, APRV was set in a predetermined way and remained unchanged throughout the study.

A prospective randomized study from China by Zhou *et al.* (10) brought new insights to the uncertainty regarding 'pros' and 'cons' in the APRV debate. This study focused on 138 patients presenting with ARDS who received MV less than 48 h. The setting for patients in the APRV group included high airway pressure according to the last plateau airway pressure, but did not exceed 30 cmH_2O, while the low airway pressure was set at 5 cmH_2O. The release time (T_{low}) was adjusted to terminate the peak expiratory flow rate to ≥50% resulting in some auto-PEEP, and a frequency of 10–14 cycles/min was targeted. Patients in the control group (low tidal volume [LTV]) were placed in a volume-assisted/controlled mode with a tidal volume of 6 mL/kg predicted body weight (not exceeding 30 cmH_2O) and PEEP guided by the ARDS-Network PEEP/FiO_2 chart. The main results were as follows: The APRV patients had a higher median number of ventilator-free days [median: 19 (range, 8–22) days] compared to the LTV-ventilated patients [median 2 (range, 0–15), P<0.001]. Furthermore, patients in the APRV group had a shorter stay in the ICU (P=0.003), and the ICU mortality rate tended to be lower in the APRV group (19.7%) compared to the LTV group (34.3%, P=0.053). Regarding the respiratory variables 3 days after begin of the study a significant higher PEEP, and higher pressures of the respiratory system (peak, plateau) were noticed in the LTV group, but the driving pressures were not significantly different between the groups. As expected due to higher mean airway pressures, patients in the APRV group demonstrated significantly better PaO_2/FiO_2 ratios three days after enrolment compared to LTV patients (P=0.001), along with improved hemodynamic variables (mean arterial and diastolic pressures). The rate of ventilation-associated complications (pneumothorax, barotrauma) did not differ between the groups.

Is the study by Zhou *et al.* the beginning of a renaissance for APRV as the 'best' ventilation mode in (early) acute lung injury/ARDS, combining lung protection with assisted spontaneous breathing? No, it is too early to rejoice about having found the philosopher's stone. First, the study by Zhou *et al.* (10) has some limitations: It is not blinded, which is an inherent limitation for nearly all intervention studies in critical care. Furthermore, patients in the LTV group had a significantly higher rate of comorbidities (P=0.029) compared to the APRV group. Additionally, it is accepted that the outcome parameter 'length of ICU stay' is no longer a good parameter, since the transfer of a patient from the ICU to a normal ward or rehabilitation is guided by many variables which are not associated with the patient's condition. Second, we have learnt from many other studies that the application of just one strategy in a heterogeneous patient group characterized by a syndrome like ARDS (which is not a clearly defined disease!) often does not lead to significant results automatically. Meanwhile, the call for individual and personalized medicine has reached the area of care for the critically ill (11).

Third, an important issue was not touched upon in this study, but is of high relevance: the importance of patient-ventilator interaction and the level of dys-synchrony in such a mixed mode of controlled and spontaneous ventilation (12). In past years, the influence of augmented spontaneous ventilation modes on synchrony and the work of breathing (WOB) was examined (13). Although augmented spontaneous ventilation modes like bi-phasic positive airway pressure or APRV should be theoretically advantageous in terms of a patient's WOB or patient–ventilator synchrony, such a benefit was not demonstrated in patients with acute lung injury (12). Furthermore, in the present era of lung protective ventilation, we lack sufficient data on whether spontaneous breathing in the early phase of acute lung failure may counteract lung protection by increased dys-synchrony and high spontaneous tidal volumes (14). In the study by Zhou *et al.* (10), such a physiological conflict

was 'circumnavigated' by relatively deep sedation of the patients (mean Richmond Agitation-Sedation Scale score on Day 3: –2.9). In other words, based on the present study by Zhou *et al.*, we cannot conclude that APRV prevent patient-ventilator dys-synchrony and/or negative effects on lung protection induced by spontaneous ventilation *per se* in patients who are relatively awake. To answer such a complex question, further studies are needed that include the parameters of (dys-)synchrony (assessments of esophageal pressure) and lung protection (markers of inflammation).

In summary, the merit of the work by Zhou *et al.* (10) is that it contributes to a more optimistic re-evaluation of APRV. The combination of controlled ventilation with patient-guided spontaneous ventilation should form the focus of further investigations, since the physiological advantages of APRV (adequate mechanical support to offload the respiratory muscles) are still attractive. On the other hand, whether such a mode fulfils all the criteria for lung protective ventilation has to be determined in future. At present, we cannot claim that the early application of airway pressure release ventilation in ARDS is a 'therapy for all!' (15,16).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Bein T, Wrigge H. Airway pressure release ventilation (APRV): do good things come to those who can wait? J Thorac Dis 2018;10(2):667-669. doi: 10.21037/jtd.2018.01.107

Editorial

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

Eduardo Mireles-Cabodevila[1,2], Siddharth Dugar[1,2], Robert L. Chatburn[1,2]

[1]Respiratory Institute, Cleveland Clinic, Ohio, USA; [2]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 *et al.* (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

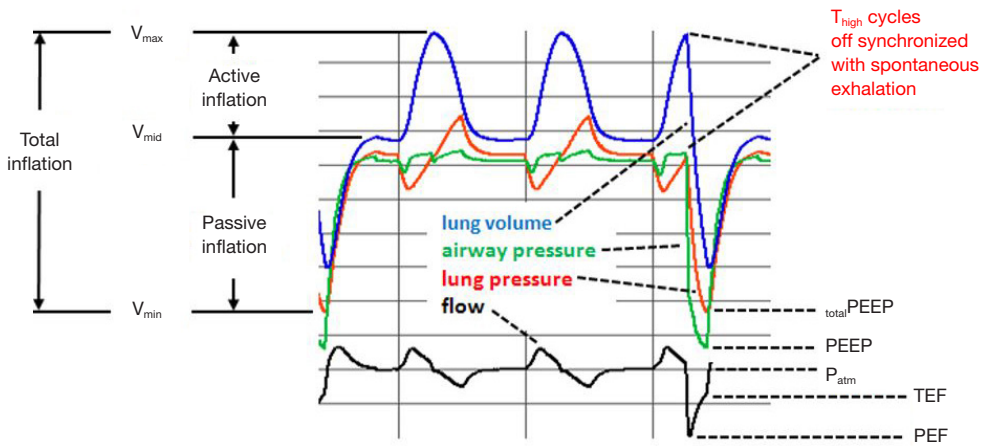

Figure 1 Spontaneous breaths superimposed on a mandatory breath during BiLevel mode with a PB 840 ventilator. When T_{high} cycles off in synchrony with a spontaneous exhalation, actual T_{low} becomes longer than set T_{low} resulting in lower end expiratory lung volume and pressure. P_{atm}, atmospheric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

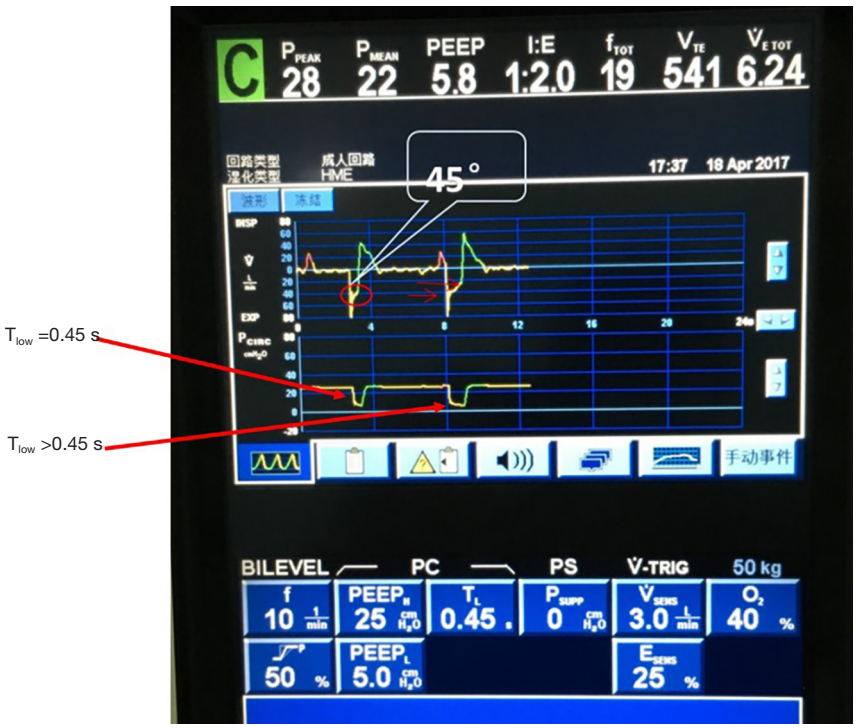

Figure 2 The supplemental material of the paper by Zhou *et al.* shows exactly this result as well (screen shot from supplemental material labeled as Figure S1 Case One). This screen shot of the PB 840 in BiLevel mode with ARPV settings shows the first breath has a T_{low} set at 0.41 s, as indicated 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 APRV, 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 APRV 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, APRV 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.

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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

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COMMENTARY

Protocolized APRV Versus Assist Control for ARDS

Aaron B. Holley, MD

November 27, 2017

Settling the APRV in ARDS Debate

The 2017 American Thoracic Society/European Respiratory Society guidelines on mechanical ventilation for acute respiratory distress syndrome (ARDS)[1] failed to address airway-pressure release ventilation (APRV). Although many consider APRV to be a "rescue mode" for refractory hypoxemia,[2] others argue that it minimizes ventilator-induced lung injury[3-5] and maintain that APRV should be the primary mode of ventilation for patients with ARDS.

A recently published, randomized trial[6] compared APRV versus the current standard of care, low-tidal-volume ventilation (LTV). The study enrolled 138 patients who met the Berlin definition for ARDS[7] and had a $PaO_2/FiO_2 \leq$ 250 mm Hg. Respiratory therapists were charged with ventilator management in both groups. The therapists followed the ARDSNet protocol in the LTV group: a tidal volume of 4-8 cc/kg ideal body weight with positive end-expiratory pressure (PEEP) adjusted using a PEEP-FiO_2 table.[8] The ventilator protocol for the APRV group roughly mirrored the strategy outlined by Habashi in 2005.[3] Of importance, patients were weaned using a specific algorithm of "drop and stretch" with spontaneous breathing trials when appropriate.

The primary outcome was ventilator-free days by day 28. There was a large difference between groups in favor of APRV: 19 (interquartile range [IQR], 8-22) versus 2 (IQR, 0-15) days ($P < .001$). The APRV group had a high rate of successful extubation and shorter intensive care stays. Between-group differences in intensive care unit mortality ($P = .053$) and duration of hospitalization ($P = .055$) weren't significant, but a trend was seen. Sedation was lighter in the APRV group, and physiologic measures (oxygenation, compliance, plateau pressures) were superior to LTV. Driving pressures were equivalent.

Viewpoint

In my opinion, these results were spectacular. Of course, the APRV for ARDS debate isn't over. This was a small, single-center, unblinded study. It's hard to believe the dramatic increase in ventilator-free days is due only to ventilator mode. Still, APRV proponents will argue that the physiologic improvements and lighter sedation levels prove biologic plausibility. They'll also gloat. They've been asking for a study with a protocolized, consistent, and individualized APRV titration strategy to prove efficacy.[5] Now they have it, and the results are as positive as predicted.

As for me, I'm starting to come back around. High airway pressures still give me pause, but we know that LTV doesn't entirely prevent lung injury either.[9,10] The *American Journal of Respiratory and Critical Care Medicine* just published a series of reviews celebrating 50 years of ARDS research. One paper in the series[11] lauded the physiologic benefits of using a nonsynchronized mode that optimizes recruitment; in other words, APRV. The same review noted a lack of clinical data to support its use. Perhaps now we have it.

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Intensive Care Med
DOI 10.1007/s00134-017-4912-z

ORIGINAL

Early application of airway pressure release ventilation may reduce the duration of mechanical ventilation in acute respiratory distress syndrome

Yongfang Zhou, Xiaodong Jin, Yinxia Lv, Peng Wang, Yunqing Yang, Guopeng Liang, Bo Wang and Yan Kang*

Abstract

Purpose: Experimental animal models of acute respiratory distress syndrome (ARDS) have shown that the updated airway pressure release ventilation (APRV) methodologies may significantly improve oxygenation, maximize lung recruitment, and attenuate lung injury, without circulatory depression. This led us to hypothesize that early application of APRV in patients with ARDS would allow pulmonary function to recover faster and would reduce the duration of mechanical ventilation as compared with low tidal volume lung protective ventilation (LTV).

Methods: A total of 138 patients with ARDS who received mechanical ventilation for <48 h between May 2015 to October 2016 while in the critical care medicine unit (ICU) of the West China Hospital of Sichuan University were enrolled in the study. Patients were randomly assigned to receive APRV ($n = 71$) or LTV ($n = 67$). The settings for APRV were: high airway pressure (P_{high}) set at the last plateau airway pressure (P_{plat}), not to exceed 30 cmH_2O) and low airway pressure (P_{low}) set at 5 cmH_2O; the release phase (T_{low}) setting adjusted to terminate the peak expiratory flow rate to ≥ 50%; release frequency of 10–14 cycles/min. The settings for LTV were: target tidal volume of 6 mL/kg of predicted body weight; P_{plat} not exceeding 30 cmH_2O; positive end-expiratory pressure (PEEP) guided by the PEEP–FiO_2 table according to the ARDSnet protocol. The primary outcome was the number of days without mechanical ventilation from enrollment to day 28. The secondary endpoints included oxygenation, P_{plat}, respiratory system compliance, and patient outcomes.

Results: Compared with the LTV group, patients in the APRV group had a higher median number of ventilator-free days {19 [interquartile range (IQR) 8–22] vs. 2 (IQR 0–15); $P < 0.001$}. This finding was independent of the coexisting differences in chronic disease. The APRV group had a shorter stay in the ICU ($P = 0.003$). The ICU mortality rate was 19.7% in the APRV group versus 34.3% in the LTV group ($P = 0.053$) and was associated with better oxygenation and respiratory system compliance, lower P_{plat}, and less sedation requirement during the first week following enrollment ($P < 0.05$, repeated-measures analysis of variance).

Conclusions: Compared with LTV, early application of APRV in patients with ARDS improved oxygenation and respiratory system compliance, decreased P_{plat} and reduced the duration of both mechanical ventilation and ICU stay.

*Correspondence: Kangyan_5626@hotmail.com
Department of Critical Care Medicine, West China Hospital of Sichuan University, Chengdu 610041, China

Yongfang Zhou and Xiaodong Jin contributed equally to this work.

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Keywords: Acute respiratory distress syndrome, Airway pressure release ventilation, Low tidal volume, Spontaneous breathing

Introduction

Although mechanical ventilation is an essential life support for patients with acute respiratory distress syndrome (ARDS), it can cause lung injury due to regional alveolar overstretch and/or repetitive alveolar collapse with shearing (atelectrauma) [1]. Ideally, mechanical ventilation should maintain lung units open throughout the ventilator cycle, which minimizes lung injury due to repetitive alveolar collapse and/or over distention. However, the lung injury may be heterogeneous, with the different lesion areas possibly needing markedly different levels of positive end-expiratory pressure (PEEP) [2, 3]. In the conventional lung protective ventilation strategy, which combines low tidal volume with sufficient PEEP, the selection of the "optimum" PEEP level to balance the recruitment and over-distension for an individual patient is still an unresolved problem in clinical practice [3–5], and mortality still remains high among those receiving mechanical ventilation [6].

Unlike conventional ventilation which generates tidal volume by raising the airway pressure above the PEEP, airway pressure release ventilation (APRV) delivers a continuous positive airway pressure with a brief intermittent release phase, allowing the release of only partial lung volume and spontaneous breathing throughout the high level [7]. Recent experiments have suggested that compared with the low tidal volume ventilation (LTV), the use of more physiology-driven APRV protocols in animals with ARDS improved alveolar recruitment and gas exchange, increased homogeneity, and reduced lung injury [8–10]. Nonetheless, data on ARDS are limited and usually sourced from small clinical trials in which variable outdated APRV settings have been used to study the use of APRV; consequently, the findings of these studies are controversial [11–15]. As such ARPV remains an unproven therapy for patients with ARDS. We hypothesized that in patients with ARDS, early application of the updated APRV methodology would better improve oxygenation and respiratory system compliance and reduce the duration of mechanical ventilation compared to conventional LTV [4].

Materials and methods

Patients

We performed this trial in the critical care medicine department of West China Hospital of Sichuan University, Sichuan province, China. This study was approved by the ethics committee of West China Hospital of Sichuan University in accordance with the Helsinki Declaration. Written informed consent was obtained from the patients' authorized surrogates. The clinical trial registration number was NCT02639364.

Patients who met the inclusion criteria were enrolled in the study from May 2015 to October 2016: fulfilled the diagnostic criteria of ARDS, according to the Berlin definition [16]; had a ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2: FiO_2) of ≤250 during invasive mechanical ventilation [17]; had received endotracheal intubation and mechanical ventilation for <48h prior to inclusion [17]. The exclusion criteria of the study were as follows: pregnancy; anticipated duration of invasive mechanical ventilation for <48 h; intracranial hypertension (suspected or confirmed); neuromuscular disorders that are known to prolong the need for mechanical ventilation; severe chronic obstructive pulmonary disease; preexisting conditions with an expected 6-month mortality exceeding 50%; presence of documented barotrauma; treatment with extracorporeal support (ECMO) at enrollment; refractory shock; lack of commitment to life support; age of <18 years or >85 years. Eligible patients were randomly assigned to the APRV group or to the LTV group by random selection of opaque sealed envelopes for consecutive patients from a box of 138 envelopes. Each envelope contained a number by a random allocation process using a computer-generated random block design.

Ventilator setting

Respiratory therapists performed ventilator management. All patients were initially ventilated with volume assisted-control ventilation (VCV) using a Puritan Bennett™ 840 Ventilator (Covidien, Medtronic Inc. Minneapolis, MN) prior to randomization to the APRV study arm or LTV study arm. In both groups, the mechanical ventilation goals were to maintain plateau airway pressure (P_{plat}) at no more than 30 cmH_2O, PaO_2 at between 55 and 100 mm Hg (or pulse oximeter between 88 and 98%), and arterial pH at ≥7.30. [4, 18].

LTV group

In the LTV group, tidal volume target (V_T) was 6 mL/kg predicted body weight (PBW), with allowances for 4–8 mL/kg PBW to minimize asynchrony between the patient and ventilator; PEEP levels were adjusted, guided by the PEEP-FiO_2 table, and then V_T and the respiratory rate were regulated to achieve the above target pH

Table 1 Baseline characteristics of the patients

Patient characteristic	APRV group ($n = 71$)	LTV group ($n = 67$)
Male sex	50 (70.4%)	41 (61.2%)
Age (years)	51.5 ± 15.0	52.0 ± 15.1
Predicted body weight (kg)	61.7 ± 8.2	60.5 ± 7.3
APACHE II score at admission	22.0 ± 7.9	20.2 ± 7.6
Duration of mechanical ventilation (h)	24.6 ± 12.6	22.1 ± 13.5
Duration of ICU stay before inclusion (h)	25.6 ± 12.6	23 ± 13.3
Chronic disease		
Chronic obstructive pulmonary disease	2 (2.8%)	5 (7.5%)
Chronic cardiac dysfunction	2 (2.8%)	3 (4.5%)
Chronic renal dysfunction	0%	3 (4.5%)
Hematological disease	2 (2.8%)	3 (4.5%)
Hepatic disease	3 (4.2%)	5 (7.5%)
Cancer	7 (9.9%)	12 (17.9%)
Immunodeficiency	4 (5.6%)	4 (6.0%)
Diabetes	3 (4.2%)	2 (3.0%)
Coexisting one or more of the above diseases	23 (32.4%)	34 (50.7%)
Reason for ARDS		
Pneumonia	18 (25.4%)	26 (38.8%)
Extrapulmonary sepsis	13 (18.3%)	10 (14.9%)
Severe acute pancreatitis	19 (26.8%)	13 (19.4%)
Severe trauma	9 (12.7%)	7 (10.4%)
Major surgical procedures	8 (11.3%)	9 (13.4%)
Other	4 (5.6%)	2 (3.0%)
Arterial blood gases at baseline		
pH	7.37 ± 0.09	7.38 ± 0.10
$PaCO_2$ (mmHg)	40.1 ± 7.4	41.7 ± 10.5
FiO_2	0.66 ± 0.19	0.62 ± 0.19
PaO_2 (mm Hg)	72.5 ± 13.1	76.8 ± 20.5
PaO_2:FiO_2 at baseline	121.7 ± 46.8	138.3 ± 56.1
PaO_2:$FiO_2 \leq 150$	47(66.2%)	41(61.2%)
Co-interventions		
Vasopressor	40 (56.3%)	46 (68.7%)

Data are presented as the mean ± standard deviation (SD), or as a number with the percentage in parenthesis, as appropriate (%)

APRV Airway pressure release ventilation, *LTV* low tidal volume lung protective ventilation (ARDSnet protocol), *APACHEII* Acute Physiology and Chronic Health Evaluation II, *ICU* intensive care unit, *ARDS* acute respiratory distress syndrome, *$PaCO_2$* partial pressure of arterial carbon dioxide, *PaO_2* partial pressure of arterial oxygen, *FiO_2* fraction of inspired oxygen,

and P_{plat} values according to the ARDSnet protocol [4, 19]. In the setting of hypotension (mean arterial pressure of <60 mm Hg) or pneumothorax occurrence, PEEP levels were allowed to be further modified, according to the individual patient's needs; if the PaO_2:FiO_2 ratio was <150 with FiO_2 > 0.6, PEEP levels could be further titrated by the ways of optimum respiratory compliance or oxygenation, at the clinician's discretion. If the patient presented severe respiratory acidosis (pH < 7.15), the respiratory rate was increased to 35 breaths per minute, with titrations made in V_T (P_{plat} target of 30 cmH_20 may be exceeded), according to the ARDSnet protocol [4]. If severe respiratory acidosis persisted (pH < 7.15), $NaHCO_3$ could be given [Appendix in Electronic Supplementary Material (ESM)].

APRV group

Patients were transitioned from their previous volume assist-controlled ventilation to APRV with the following initial settings: high airway pressure (P_{high}) was set at the P_{plat} measured at the previous VCV settings, not to exceed 30 cmH_2O; low airway pressure (P_{low}) was set at 5 cmH_2O (minimal pressure level was used to prevent atelectasis per standard practice); duration of release

phase (T_{low}) was initially set at one- to 1.5-fold the expiratory time constant, and then adjusted to achieve a termination of peak expiratory flow rate (PEFR) of ≥50% of PEFR; release frequency was 10–14 frequency/min; duration of P_{high} (T_{high}) was indirectly calculated based on the T_{low} and release frequency [9, 20]; initially spontaneous respiratory level was targeted as spontaneous minute ventilation (MV_{spont}), approximately 30% total minute ventilation (MV_{total}) (for details on the APRV settings for titration, see ESM Appendix Tables 3–5).

Analgesia and sedation

In the both groups, analgesia and sedation were managed to achieve the desired level of analgesia and sedation. The analgesia target level was a Critical-Care Pain Observational Tool (CPOT) score of 0–2, and the sedation goal was a Richmond Agitation Sedation Scale (RASS) score of − 2 to 0. If patients exhibited anxiety, agitation, and/orrespiratory distress, or they fought the ventilator, they would receive deeper sedation at less than a RASS score of − 2. According to our local sedation procedure, RASS and CPOT scores were assessed and recorded every 4 h (or more frequently when indicated) by the nursing staff, who adjusted the dosages of analgesic and sedative drugs to maintain the analgesia and sedation target level. In the APRV group, respiratory therapists would further titrate APRV settings and dosages of analgesics and sedatives to achieve the target level of spontaneous breathing level [21] (for details, see ESM Appendix Tables 3–5).

Procedures in both groups

For patients with severe hypoxemia (with no response to the assigned protocol and a PaO_2:FiO_2 ratio of <100 during invasive mechanical ventilation for at least 12 h), clinicians could apply other supportive therapies for hypoxemia (e.g., recruitment maneuvers, prone positioning, neuromuscular blockade, or inhalation nitric oxide) in both groups (see ESM Appendix for details). Patients could receive rescue measures (including high frequency oscillatory ventilation or ECMO) at the clinician's discretion, in case of any one of the following life-threatening events: refractory hypoxemia (PaO_2 < 55 mm Hg with an FiO_2 of 1.0), refractory barotrauma (chest tube with active air leak, persistent pneumothorax, and/or subcutaneous emphysema despite pleural space drainage), refractory respiratory acidosis (pH of ≤7.15), or refractory shock (even if sufficient fluid resuscitation and usage of vasoactive drugs).

Additionally, physicians applied usual care interventions for the general management of critically ill patients, according to the current guideline standards. Starting the first day following enrollment, in the LTV group if patients received deeper sedation (RASS score of <−2), the physicians would once daily interrupt the sedation, and the respiratory therapists would manage patients with the Spontaneous Breathing Trials (SBT) safety screen every morning. Those patients who passed the SBT safety screen underwent a 30-min SBT with a pressure support ventilation of 5–7 cmH_2O, PEEP of 5 cmH_2O, and FiO_2 of ≤40% [21]. In the APRV group, in the first stage, as published previously [15, 20], P_{high} was gradually reduced by 2 cmH_2O, simultaneously with a reduction in release rate by two frequencies/min, twice daily unless the patient's cardiopulmonary function deteriorated. In the second stage, when patients achieved the criteria with a P_{high} of 20 cmH_2O on 40% FiO_2, the respiratory therapist immediately started to perform the same weaningprotocol with SBT trial as in the LTV group [17]. When the SBT was successful, physicians and respiratory therapists decided to extubate the patients (for details see ESM Appendix).

The primary endpoint was the number of ventilator-free days at day 28 (if patients died during the 28-day period after enrollment, the number of ventilator-free days was zero). The secondary endpoints included oxygenation and respiratory mechanics, such as P_{plat}, mean airway pressure, respiratory system compliance at baseline and on days 1, 2, 3, and 7, as well as clinical outcomes [the length of stay in the intensive care unit (ICU) and hospital, ICU mortality and hospital mortality, and the occurrence of adverse events]. (P_{plat} and respiratory system compliance measurements during the APRV are detailed in ESM Appendix. Fig. S1).

Statistical analysis

The primary outcome was the number of ventilator-free days at day 28. The mean (± standard deviation) number of ventilator-free days from day 1 to day 28 is 14.5 ± 10.4 days in the low tidal volume and lower PEEP group according to Brower and colleagues, the ARDS network [22]. Putensen reported that APRV could shorted the duration of ventilator support by 6 days in patients at risk of ARDS compared with those pressure-controlled ventilation [11]. We conservatively estimated that a sample size of 110 patients would be required to detect an increment of 5 days in the number ventilator-free days at day 28 in the APRV group with 80% power and a two-sided significance level of 0.05. In total, 138 patients were enrolled in the study in order to manage the drop-outs.

Data are expressed as the mean ± standard deviation, and as the median and interquartile ranges (IQR), or percentages. Continuous variables with a normal distribution were analyzed with the Student's *t* test, Continuous variables with non-normal distribution were compared with the use of the Kruskal–Wallis analysis of variance.

Dichotomous or nominal categorical variables were analyzed by either the Pearson Chi-square or Fisher's exact test. The trend was assessed over time in oxygenation and respiratory mechanics repeated measurements by comparing the LTV group and APRV group at baseline and on days 1, 2, 3, and 7, with the use of the repeated-measures analysis. A two-sided P value of <0.05 was considered to indicate statistical significance.

Results

From May 2015, through to October 2016, a total of 138 patients with ARDS were enrolled in this intention-to-treat analysis: 71 patients in the APRV group and 67 patients in the LTV group (Fig. 1). The proportion of patients with an arterial oxygenation index (PaO_2/FiO_2) of <150 mmHg was similar between the APRV and LTV groups (66.2 vs. 61.2%, respectively; $P = 0.541$). Most of the patients in the two groups were severely ill, with a mean APACHE II (Acute Physiology and Chronic Health Evaluation II) score of 22.0 ± 7.9 in the APRV group and 20.2 ± 7.6 in the LTV group ($P = 0.178$) (Table 1).

Respiratory and hemodynamic parameters and analgesia and sedation variables at baseline and on days 1, 2, 3, and 7 after enrollment

Respiratory parameters and arterial blood gas measurements at baseline in the APRV group were similar to those in the LTV group, with the exception of respiratory rate which was higher in the APRV group ($P = 0.039$) (Table 2). On the third therapeutic day (Table 2), respiratory system compliance and the PaO_2:FiO_2 ratio were significantly improved in the APRV group compared to the LTV group ($P < 0.001$, respectively). The ventilation setting frequency was lower in the APRV group ($P = 0.002$), but the monitoring of respiratory rates was similar in both groups. The values of P_{peak}, PEEP, and P_{plat} were significantly lower in the APRV group ($P < 0.01$), the mean airway pressure was 5.8 cmH_2O higher in the APRV group than in the LTV group ($P < 0.001$), but the driving pressure was similar in both groups. The mean spontaneous minute ventilation was 1.78 ± 1.37 L/min in the APRV group. The total minute ventilation was lower in the APRV group than in the LTV group ($P = 0.001$); however, the values of $PaCO_2$ and pH were similar in both groups. Heart rate and arterial blood pressure were slightly improved ($P < 0.05$, respectively).

On days 1, 2, 3, and 7, compared to the LTV group, the mean airway pressure was higher in the APRV group ($P < 0.001$, by repeated-measures analysis of variance) (Fig. 2b) and respiratory system compliance and PaO_2:FiO_2 were significantly better in the APRV group ($P = 0.003$ by repeated-measures analysis of variance) (Fig. 2c, d). On day 1, the PaO_2:FiO_2 value was 66.3 mmHg higher in the APRV group than in the LTV group ($P < 0.001$). Heart rates were lower and mean arterial pressures were a little higher in the APRV group than in the LTV group on days 2, 3, and 7 ($P < 0.05$ by repeated-measures analysis of variance) (Fig. 2e, f). The average doses of norepinephrine were similar ($P = 0.612$) (Fig. 2g). Compared with the LTV group, the sedation depth in the APRV group was lighter ($P < 0.001$) (Fig. 2h), and the average doses of fentanyl and midazolam were significantly lower ($P < 0.01$) (Fig. 2i, j), and the average doses of propofol were similar ($P = 0.112$) (Fig. 2k).

Study Outcomes

Study outcomes are presented in Table 3. The APRV protocol was associated with an increased number of ventilator-free days on day 28 than the LTV protocol [median 19 days (IQR 8–22) vs. 2 days (IQR 0–15), respectively; $P < 0.001$] (Table 3 and Fig. 3); this result was supported by the per-protocol analysis results which also showed a similar difference [median 19 days (IQR 11–22) vs. 8 days (IQR 0–16), respectively; $P < 0.001$] (ESM Appendix Table S5). Although there were more patients with coexisting chronic diseases and lower sedation depth in the APRV group than in the LTV group ($P < 0.05$), only lighter sedation increased ventilator-free days at day 28, and APRV still significantly increased ventilator-free days at day 28 ($P < 0.001$) according to the multiple linear regression analysis for correction of the coexisting chronic diseases and sedation depth differences (ESM Appendix Table S4). There was a higher rate of successful extubation in the APRV group than in the LTV group (66.2 vs. 38.8%; $P = 0.001$), and fewer patients underwent tracheostomy in the APRV group ($P = 0.013$). The APRV protocol significantly decreased the length of ICU stay ($P = 0.015$). The ICU and hospital mortality rates and length of hospital stay were similar for both groups. During the course of the study, more patients in the LTV group received neuromuscular blockers, recruitment maneuvers, and prone ventilation than in the APRV group ($P < 0.05$).

Discussion

The main findings of this study were that compared with the LTV group, there was a shorter duration of mechanical ventilation in the APRV group, and early use of APRV in patients with ARDS could significantly improve oxygenation and respiratory system compliance, decrease plateau airway pressure, and reduce sedation requirement. Patients in the APRV group also had shorter length of stay in the ICU, higher rate of successful extubation, and lower tracheostomy rate than did patients in the LTV group. However, there was no

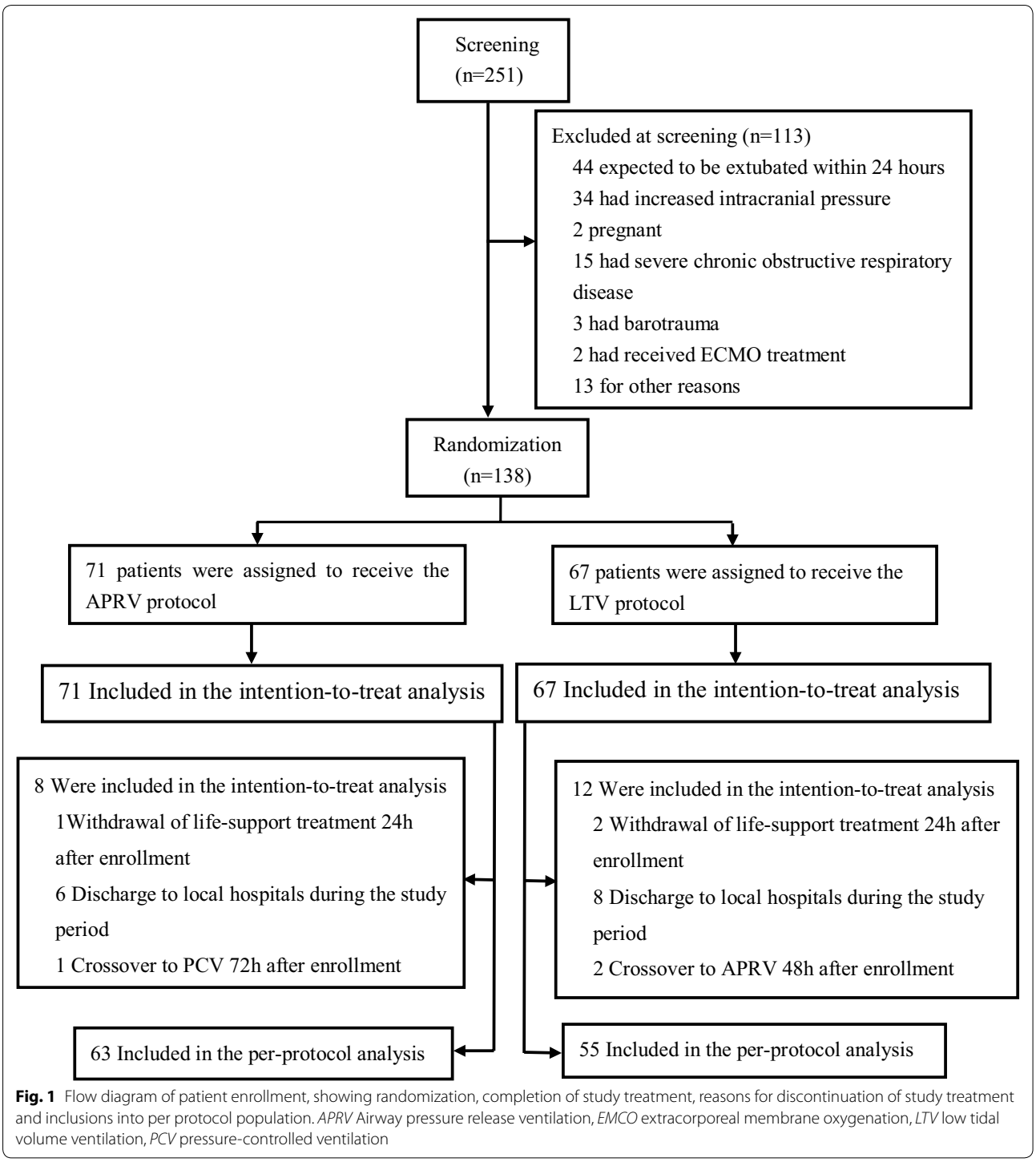

Fig. 1 Flow diagram of patient enrollment, showing randomization, completion of study treatment, reasons for discontinuation of study treatment and inclusions into per protocol population. *APRV* Airway pressure release ventilation, *EMCO* extracorporeal membrane oxygenation, *LTV* low tidal volume ventilation, *PCV* pressure-controlled ventilation

difference in hospital length of stay, ICU mortality, hospital mortality, or incidence of pneumothorax between the two groups.

Respiratory mechanics and gas exchange

The data of the present study are in agreement with previously reported clinical and experimental findings

Table 2 Respiratory and hemodynamic variables at baseline and on day 3

Variable	Baseline			Day 3 after enrollment [c,d]		
	APRV	LTV	*P* value	APRV	LTV	*P* value
No. of patients	71	67		62	56	
Respiratory variables						
Ventilator setting (tidal volume in mL)	437.8 ± 40.6	429.6 ± 47.5	0.277	_	423.8 ± 51.8	
Ventilator setting (tidal volume in mL/kg of predicted body weight)	7.2 ± 0.7	7.1 ± 0.7	0.534	_	7.0 ± 1	
Ventilator monitoring (tidal volume in mL)	466.6 ± 54.9	461.2 ± 59.7	0.578	476.9 ± 111.3	461.8 ± 64.1	0.364
Ventilator monitoring (tidal volume in mL/kg of predicted body weight)	7.6 ± 1.1	7.7 ± 1.3	0.619	7.8 ± 1.9	7.7 ± 1.1	0.575
Ventilator setting frequency (cycles/min)	15.1 ± 4.3	15.1 ± 3.8	0.977	12.7 ± 1.8	14.9 ± 4.8	0.002
P_{high}	_	_		24.1 ± 3.6	_	
PEEP (cmH_2O)	11.4 ± 3.0	10.4 ± 2.6	0.063	6.9 ± 1.8	10.4 ± 2.8	<0.001
FIO_2	0.66 ± 0.19	0.62 ± 0.19	0.198	0.43 ± 0.09	0.53 ± 0.19	0.001
Respiratory rate (cycles/min)	21.5 ± 6.6	19.5 ± 4.6	0.039	19.0 ± 6.0	20.3 ± 5.1	0.225
Peak inspiratory pressure (cmH_2O)	31.7 ± 4.5	30.4 ± 4.0	0.061	26.2 ± 3.6	28.5 ± 4.8	0.005
Mean airway pressure (cmH_2O)	18.3 ± 3.9	17.4 ± 3.5	0.140	21.8 ± 3.5	16.0 ± 3.3	<0.001
Plateau pressure (cmH_2O)	26.5 ± 4.0	25.3 ± 3.6	0.081	19.3 ± 3.9	23.3 ± 4.6	<0.001
Driving pressure (cmH_2O)[a]	15.2 ± 3.6	14.8 ± 3.4	0.550	12.6 ± 3.5	12.8 ± 4.1	0.822
Respiratory system compliance (mL/cmH_2O)	30.1 ± 7.6	32.6 ± 7.7	0.058	43.7 ± 11.3	34.1 ± 8.9	<0.001
Total minute ventilation (L/min)[b]	8.37 ± 2.36	8.42 ± 1.98	0.905	6.86 ± 2.06	8.22 ± 2.30	0.001
Spontaneous minute ventilation (L/min)	-	-		1.78 ± 1.37	-	
pH	7.37 ± 0.09	7.38 ± 0.10	0.427	7.42 ± 0.05	7.42 ± 0.07	0.648
$PaCO_2$ (mmHg)	40.1 ± 7.4	41.7 ± 10.5	0.307	40.8 ± 7.3	42.3 ± 8.6	0.291
PaO_2 (mmHg)	72.5 ± 13.1	76.8 ± 20.5	0.149	116.2 ± 28.5	84.8 ± 20.1	<0.001
PaO_2:FiO_2	121.7 ± 46.8	138.3 ± 56.1	0.060	280.3 ± 83.9	180.5 ± 68.6	<0.001
Hemodynamic variables						
Heart rate (beats/min)	105.4 ± 22.5	110.2 ± 24.6	0.238	92.7 ± 16.6	103.6 ± 19.3	0.001
Systolic blood pressure (mmHg)	122.2 ± 17.9	116.2 ± 22.5	0.088	126.6 ± 18.0	125.0 ± 20.3	0.646
Diastolic blood pressure (mmHg)	72.8 ± 13.2	68.6 ± 12.1	0.053	76.1 ± 14.5	69.3 ± 13.3	0.009
Mean arterial pressure (mmHg)	87.4 ± 14.7	84.2 ± 13.4	0.194	92.8 ± 14.9	87.1 ± 13.6	0.032

Data are presented as the mean ± SD of the values recorded from 7 am to 12 am on days 1, 2, 3, and 7 after enrollment in each treatment group

P_{high} High airway pressure

[a] Driving pressure was calculated as the plateau pressure (P_{plat}) minus positive end expiratory pressure (PEEP)

[b] Total minute ventilation = release minute ventilation + spontaneous minute ventilation

[c] Four patients were extubated at day 3, six patients died, three patients withdrew life-support treatment 24 h after enrollment, seven patients were discharged to their local hospitals; thus, the respiratory and hemodynamic values are given for the 62 ventilated patients in the APRV group and 56 patients in the LTV group

[d] Respiratory system compliance and plateau pressure were monitored by the ventilator (In the APRV group, APRV was temporarily changed to the volume-controlled ventilation, PEEP was set at the previous monitoring PEEP, tidal volume was set at the previous release volume)

[8–11, 21, 23], namely, that the early use of this APRV protocol in patients with ARDS significantly decreased plateau airway pressure, elevated mean airway pressure, and improved oxygenation and respiratory system compliance, in comparison with LTV ventilation. Furthermore, there was no difference in $PaCO_2$ and pH between the groups, despite APRV with lower minute ventilation, which indirectly indicated APRV decreasing dead space ventilation.

However, at present, data are only available from a limited number of small randomized prospective human studies with different APRV settings, with some studies showing benefits of APRV on pulmonary function and others showing similarities, as compared with CPPV or LTV [8, 11, 12, 15]. For example, one small randomized prospective trial [15] showed that adult trauma patients with acute respiratory failure on APRV or LTV had similar physiological parameters. However, the APRV methodology used in that study was outdated: the upper limit of P_{high} was 40 cmH_2O, while current evidence suggests that inspiratory-end pressure should be limited to 30 cmH_2O [4]; the T_{low} was set at 25–75% of the PEFR, while T_{low} of <50% of PEFR could result in dynamic heterogeneity between inspiration and expiration [10].

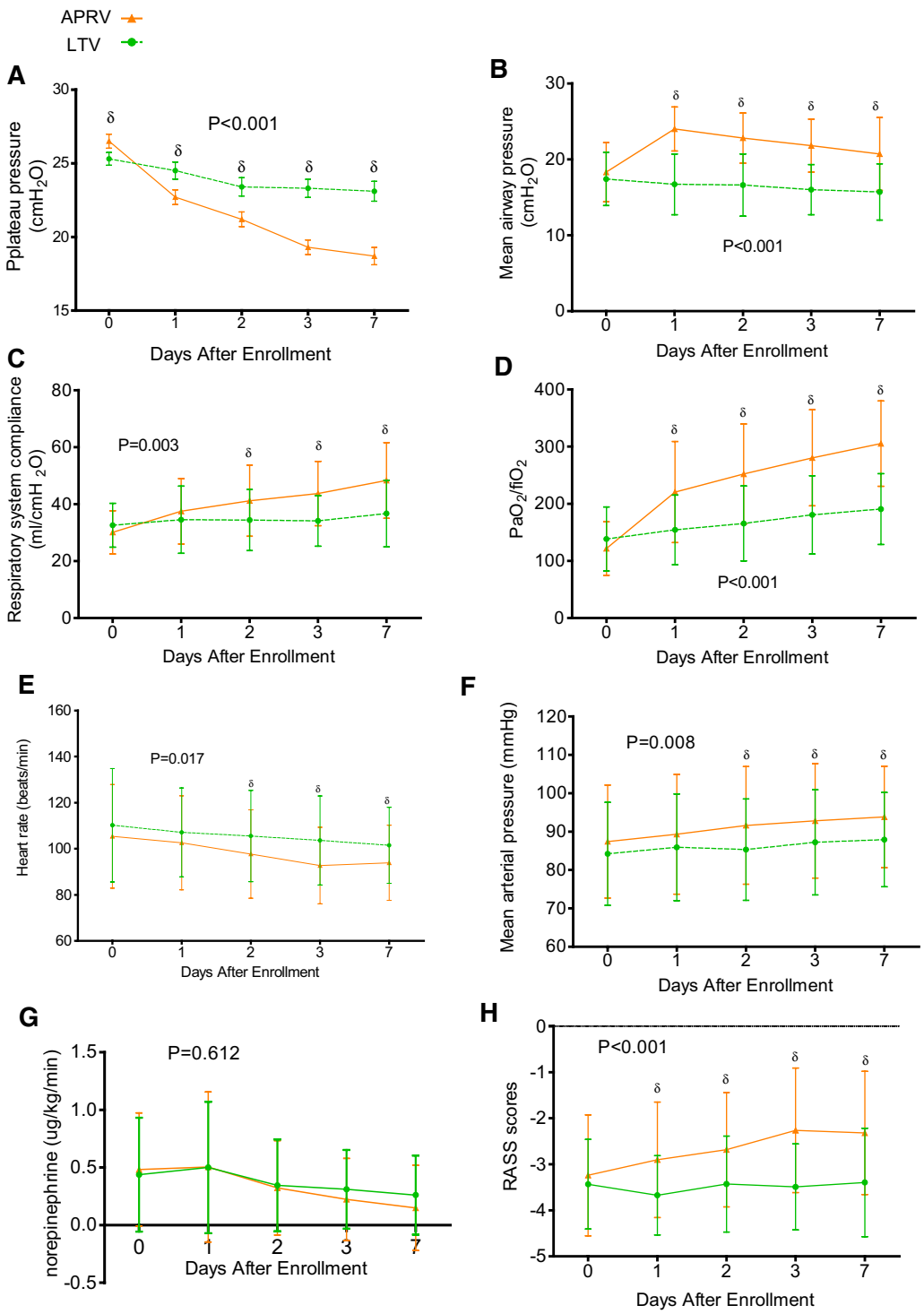

Fig. 2 Respiratory and hemodynamic parameters, and analgesia and sedation variables at baseline and on days 1, 2, 3, and 7 after enrollment. Data are presented as the mean (filled symbols) and standard errors (whiskers). *P* values were calculated by repeated-measures analysis of variance. **a** Plateau pressure, **b** mean airway pressure, **c** respiratory system compliance, **d** ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2), **e** heart rate, **f** mean arterial pressure, **g** average doses of norepinephrine, **h** Richmond Agitation Sedation Scale (RASS) scores, **i** average doses of fentanyl, **j** average doses of midazolam, **k** average doses of propofol. All parameters and variables were compared between the two groups at baseline and on days 1, 2, 3, and 7 after enrollment with the Student's *t* test. *Delta* denotes that the two-sided *P* value was <0.05

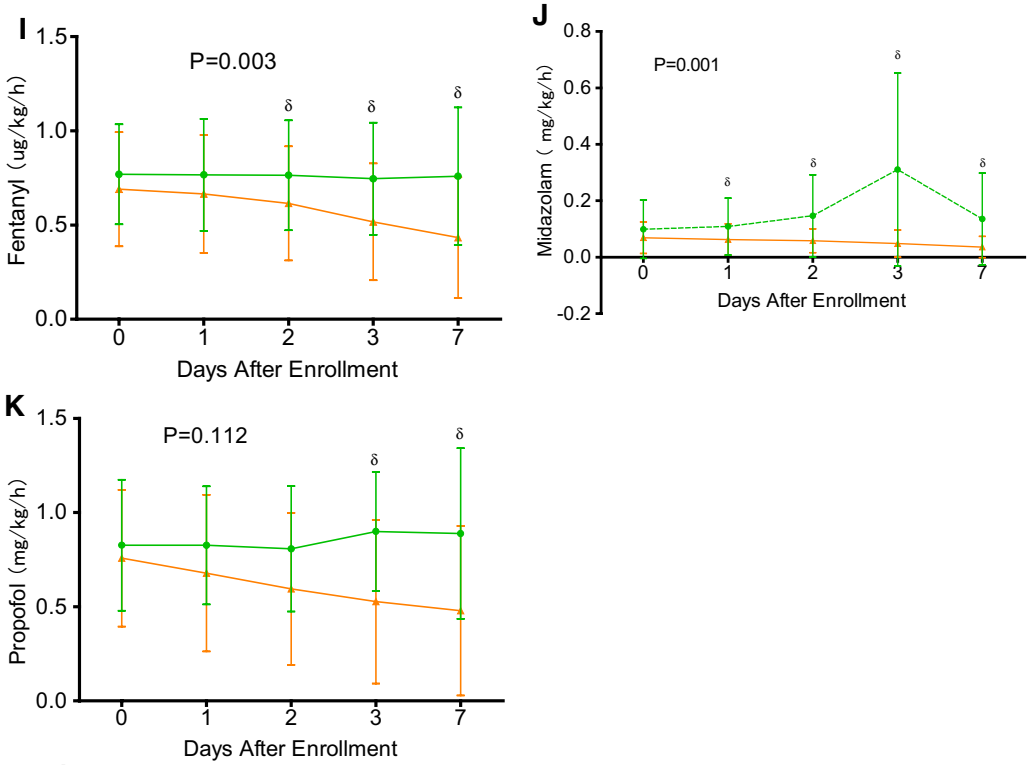

Fig. 2 continued

According to recent experimental findings, we set the P_{high} not to exceed 30 cmH_2O and the T_{low} to be at ≥50% of PEFR; these settings were combined with APRV settings and sedation titration to achieve the spontaneous breath target level.

There are collateral channels of ventilation, such as pores of Kohn, which might be additional pathways to facilitate recruitment and redistribute alveolar volume (pressure) throughout the lung over time [24]. The results of previous studies indicate that the process of recruitment and decruitment of lung units should be determined not only by pressure but also by time [25]. For heterogeneous lung injury, during APRV ventilation, the proper elevated baseline airway pressure (P_{high}) and prolonged duration of P_{high} would optimize the recruitment of alveoli gradually over time, while prevention of overinflation, and brief release phase (T_{low}) could permit only partial lung volume loss at the release phase, avoid cyclic alveoli collapse, and provide dynamic homogeneity [10]. Recent animal experiments [8–10, 21, 23] have also documented that the updated APRV methodologies attenuate lung injury, preserve surfactant protein and lung architecture, and improve oxygenation, resulting in dynamic alveolar homogeneity without any increase in lung stress and strain.

Additionally, during APRV, allowing moderate spontaneous breath level at the P_{high} phase (providing sufficient PEEP) favored lung recruitment and improved ventilation/perfusion matching and lung homogeneous aeration, while minimizing pendelluft and its associated injury [20, 26–28].

Hemodynamics

The hemodynamic performance and sedation requirement of the patients on APRV in this study are in accordance with previous study findings [11, 29, 30]. APRV favored hemodynamic improvement and reduced sedative and paralysis use, despite the higher mean airway pressure. Ventilation with APRV permitting spontaneous breaths decreased the intrathoracic pressure, thus improving systematic venous return and cardiovascular performance and reducing sedation requirement and the need for paralysis, which may decrease the cardiovascular depression caused by elevated airway pressures [10, 20, 30].

Study outcomes

This study showed that the APRV group was associated with more days without mechanical ventilation at day 28 and a shorter ICU stay than the LTV group. This finding

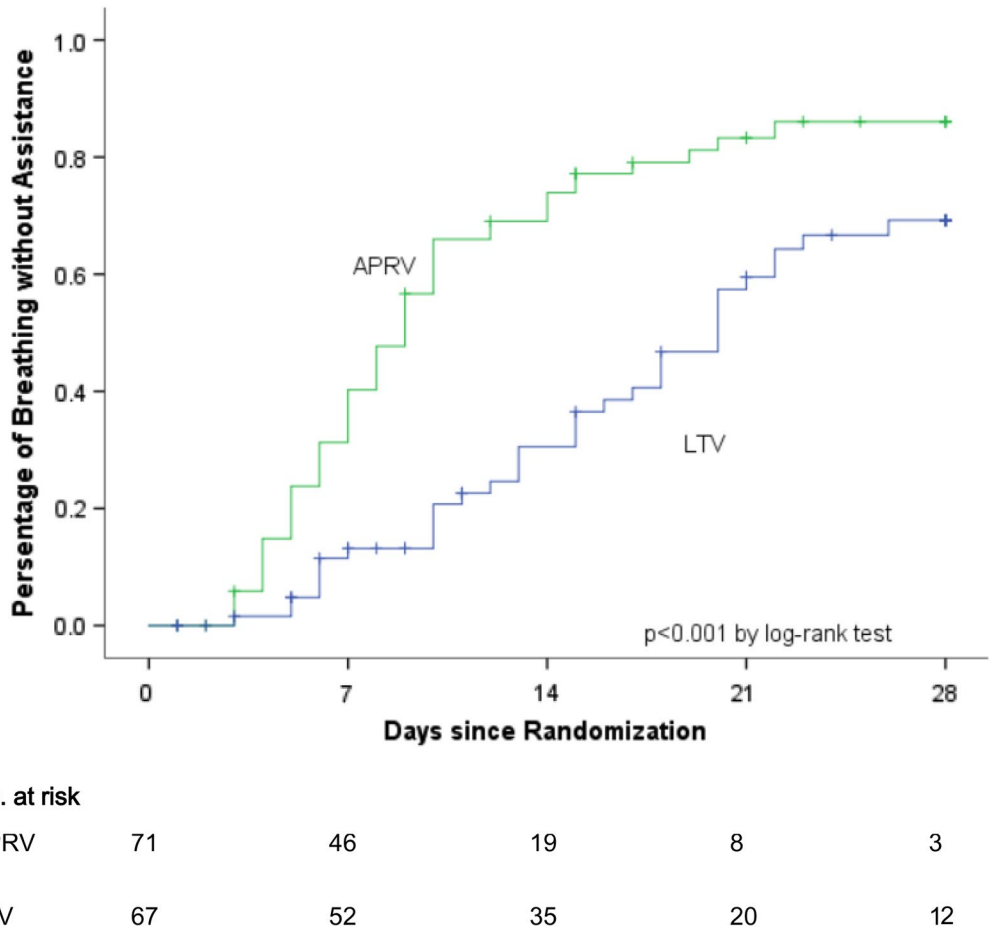

Fig. 3 Percentage of breathing without assistance from enrollment to day 28 in the APRV and LTV groups

is consistent with previously published results [11], and possible explanations for this finding are as follows. Firstly, early use of APRV improved pulmonary function, such as gas exchange and respiratory compliance. Recent experiments have also documented that early preventative use of APRV can more effectively block ARDS development than LTV [9, 21]. Putensen et al. reported that the use of APRV in patients with ARDS after 72 h on pressure-control ventilation improved but did not restore gas exchange and lung mechanics, and prolonged the mechanical ventilation and ICU stay [11]. Secondly, APRV allows moderate spontaneous breathing, reduces sedation and paralysis requirements, and decreases the duration of mechanical ventilation [11, 20, 30, 31]. In the present study, respiratory therapists titrated the APRV settings and dosages of analgesics and sedatives to achieve a moderate spontaneous breath level at the P_{high} phase. Our results also show that APRV was associated with lighter sedation, which could increase the number of ventilator-free days at day 28. Thirdly, in our study there was respiratory therapist-guided weaning protocol with the SBT trial in the LTV group. In the APRV group, in the first stage, to avoid aggressive weaning, the weaning process consisted of simultaneously decreasing both P_{high} by 2 cmH_2O and the release rate by two frequencies/min, twice daily unless the patient's cardiopulmonary function deteriorated. In the second stage, when patients achieved the criteria with a P_{high} of 20 cmH_2O on 40% FiO_2, respiratory therapists also performed the weaning protocol with the SBT trial as in the LTV group. Two trauma population studies have shown that APRV may increase the number of ventilator days; however, the APRV settings were outdated, and no formal weaning protocol was used [13, 15]. The current primary APRV weaning process is based on gradual withdrawal, using an alternate decrease in P_{high} by 2 cmH_2O, followed by an increase in T_{high} of 0.5–1.0 s [15], and extubation is assessed until the criteria of a P_{high} of 12 cmH_2O on 40% FiO_2 is achieved [10, 13, 15, 20]. However, evidence suggests that daily SBT can expedite weaning and reduce the duration of mechanical

Table 3 Main outcome variables

Main outcome variables	APRV ($n = 71$) [b]	LTV ($n = 67$) [b]	*P* value
No. of days of ventilation	8 [5–14]	15 [7–22]	0.001
No. of ventilator-free days at 28 days	19 [8–22]	2 [0–15]	<0.001
Successful extubation	47 (66.2%)	26 (38.8%)	0.001
Tracheostomy	9 (12.7%)	20 (29.9%)	0.013
Length of ICU stay (days)	15 [8–21]	20 [10–32]	0.015
Pneumothorax between day 1 and day 28[a]	3 (4.2%)	7 (10.4%)	0.199
Death during the ICU stay	14 (19.7%)	23 (34.3%)	0.053
Length of hospital stay (days)	21 [14–30]	27 [18–41]	0.055
Death during the hospital stay	17 (23.9%)	25 (37.3%)	0.088
Other supportive therapies			
Neuromuscular blocker	2 (2.8%)	9 (13.4%)	0.021
Recruitment maneuvers	4 (5.6%)	11 (16.4%)	0.042
Prone position	2 (2.8%)	10 (14.9%)	0.012
Inhaled nitric oxide	1 (1.4%)	1 (1.5%)	1.000
High-frequency oscillatory ventilation	1 (1.4%)	3 (4.5%)	0.355

Data are expressed as the median with the interquartile range in square brackets for non-normally distributed data or as a number with the percentage in parenthesis for nominal data. The Kruskal–Wallis analysis of variance was used for non-normally distributed data comparisons. Nominal data comparisons were based on either the Chi-squared test or Fisher's exact test

[a] Two cases of pneumothorax resulted from clinical puncture in the LTV group

[b] Fourteen patients were discharged to local hospitals and followed up by phone calls. Of these, six patients in the APRV group were discharged to local hospitals, of whom three died, and eight patients in the LTV group were discharged to local hospitals, of whom three died

ventilation as compared with gradually reducing ventilator support [32].

Limitations

There are several limitations to our study. First, the study was not blinded, as the ventilator settings were obviously different. Secondly, the sample size was small. APRV has evolved into a highly sophisticated, physiology-driven, dynamic mechanical breath profile with precise settings [13], thus a possibility of knowledge bias by the staff was another limitation. However, prior to conducting our study, we first conducted a single-center randomized controlled study and found that all of the respiratory therapists were well trained and skillfully used this study protocol. Thirdly, there were more patients with coexisting chronic diseases in the LTV group than in the APRV group ($P = 0.029$). Using a multivariable analysis for the correction of the coexisting chronic diseases difference, APRV was independent of increasing ventilator-free days at day 28. Finally, in accordance with our APRV protocol, in addition to nursing staff, respiratory therapists were able to further titrate APRV settings and dosages of analgesics and sedatives to achieve the target level of spontaneous breathing. The results of our study show that APRV was associated with lighter sedation, which could increase the number of ventilator-free days at day 28. However, APRV still significantly increased ventilator-free days at day 28 after correcting the sedation difference. Additionally, this study did not measure the patient–ventilator interaction. The questions of whether APRV permitting spontaneous breathing could promote the patient–ventilator synchrony and how the patient–ventilator dyssynchrony could affect the outcome require further study.

Conclusions

Compared with conventional LTV, the early application of APRV in patients with ARDS was associated with better oxygenation and respiratory system compliance, lower plateau airway pressure, less sedation requirement, more ventilator-free days at day 28, and a shorter duration of ICU stay.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-017-4912-z) contains supplementary material, which is available to authorized users.

Acknowledgements
The authors acknowledge all the physicians and respiratory therapists in the Department of Critical Care Medicine at West China Hospital of Sichuan University for their participation and assistance in the study.

Author contribution statement
YFZ, YK and XDJ conceived the trial. YFZ, XDJ, BW, YXL, PW, and YK participated in study design. YFZ, BW, PW, GPL, and YXL recruited patients and collected data, and YFZ, BW, XDJ, GPL, and YK analyzed the data. All authors participated in interpretation of results. YFZ drafted the manuscript, and all authors have reviewed and revised the manuscript. All authors have seen and approved the final version of the manuscript.

Compliance with ethical standards

Ethics approval and consent to participate
This study was approved by the ethics committee of West China Hospital of Sichuan University in accordance with the Helsinki Declaration. Written informed consent was obtained from the patients' authorized surrogates. The clinical trial registration number was NCT02639364.

Conflicts of interest
All authors declare that they do not have any conflict of interest relevant to this study.

Received: 22 February 2017 Accepted: 12 August 2017
Published online: 22 September 2017

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