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Review

Does airway pressure release ventilation offer new hope for treating acute respiratory distress syndrome? ☆

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ABSTRACT

Mechanical ventilation (MV) is an essential life support method for patients with acute respiratory distress syndrome (ARDS), which is one of the most common critical illnesses with high mortality in the intensive care unit (ICU). A lung-protective ventilation strategy based on low tidal volume (LTV) has been recommended since a few years; however, as this did not result in a significant decrease of ARDS-related mortality, a more optimal ventilation mode was required. Airway pressure release ventilation (APRV) is an old method defined as a continuous positive airway pressure (CPAP) with a brief intermittent release phase based on the open lung concept; it also perfectly fits the ARDS treatment principle. Despite this, APRV has not been widely used in the past, rather only as a rescue measure for ARDS patients who are difficult to oxygenate. Over recent years, with an increased understanding of the pathophysiology of ARDS, APRV has been reproposed to improve patient prognosis. Nevertheless, this mode is still not routinely used in ARDS patients given its vague definition and complexity. Consequently, in this paper, we summarize the studies that used APRV in ARDS, including adults, children, and animals, to illustrate the settings of parameters, effectiveness in the population, safety (especially in children), incidence, and mechanism of ventilator-induced lung injury (VILI) and effects on extrapulmonary organs. Finally, we found that APRV is likely associated with improvement in ARDS outcomes, and does not increase injury to the lungs and other organs, thereby indicating that personalized APRV settings may be the new hope for ARDS treatment.

Introduction

Mechanical ventilation (MV) is an essential life support approach used for patients with acute respiratory distress syndrome (ARDS).[1] However, it may potentiate lung damage due to regional alveolar overstretch and/or repetitive alveolar collapse with shearing (atelectrauma).[2] The low tidal volume (LTV) ventilation strategy was developed 20 years ago; since then, many MV strategies have aimed to reduce ventilator-induced lung injury (VILI) and assumed that alveoli behave elastically, up to an elastic load limit, based on the elastin/collagen interaction.[3,4] However, alveoli actually behave as a viscoelastic system, where alveolar recruitment and collapse depend not only on the amount of pressure applied to the lung but also on the time during which the pressure is applied, especially during lung injury.[5,6]

Based on the above knowledge, airway pressure release ventilation (APRV), first described in 1987 by Stock et al.,[7] is defined as a continuous positive airway pressure (CPAP) with a brief intermittent release phase, allowing the release of only partial lung volume and spontaneous breathing (SB) throughout the high level of pressure,[7,8] where the user can independently control inspiratory and expiratory time, and is based on the open lung concept.[9,10] Despite its theoretically attractive advantages over other conventional MV modes, APRV is not routinely used in daily clinical practice but rather only used in patients with acute lung injury (ALI)/ARDS as rescue therapy.[11] Because the methodologies of APRV vary greatly and the conclusions from

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related studies are still controversial, we tried to explain the rationale of APRV, and update the application of APRV in ARDS and summarize its effects on other organs.

Definition and Rationale of APRV

The original definition of APRV includes simple CPAP with a brief release to low-level positive end-expiratory pressure (PEEP).[7] It is characterized by the application of an inverse inspiratory–expiratory (I:E) ratio.[12] Based on the definition, APRV has four basic parameters, namely: high-level pressure (the pressure of CPAP, P_{high}); low-level pressure (PEEP or P_{low}); high-pressure time (T_{high}); and low-pressure time (T_{low}), where T_{high} and T_{low} form a respiratory cycle. As such, both mandatory breath and spontaneous breath are allowed, and SB can occur at P_{high} and P_{low} [Figure 1]. Oxygenation is mainly determined by P_{high}, $T_{high,}$ and the fraction of inspired oxygen (FiO_2). Ventilation is determined by the frequency with which P_{high} releases to P_{low}, the gap between P_{high} and P_{low}, and the proportion of SB.[8,13]

In some studies, APRV is called biphasic positive airway pressure ventilation (BIPAP); however, these two are distinct. APRV and BIPAP are time-triggered, pressure-limited, and time-cycled and allow unrestricted SB both during and between mandatory breaths, thus benefiting from active inhalation and exhalation servo valves. The biggest difference between these two modes is the I:E ratio.[13,14] APRV typically uses various time ratios for T_{high} and T_{low} ranging from 1:1 to 9:1, with the most common being inverse I:E ratios, while this is not the case for BIPAP.[14] Furthermore, T_{low} is usually controlled within 1.5 s, even <0.65 s in APRV mode, but there is no limit in BIPAP.[14,15]

Application of APRV in ARDS

ARDS is a serious clinical condition with a high incidence and mortality, characterized by an increased permeability of the alveolar-capillary barrier.[16] The current understanding of the lung-protective ventilation strategy to minimize VILI is to “open the lung and keep it open”.[17,18] Usually, the open lung concept consists of recruitment maneuvers (RMs) for re-inflating the collapsed lung tissue, and a high PEEP for keeping the lung open and avoiding cyclic opening and closing of alveoli to prevent injury.[19–21] Existing evidence has indicated that RMs combined with PEEP can improve oxygenation on the third day in ARDS patients and reduce the length of hospital stay. However, it has no beneficial effect on mortality.[22,23] As previously mentioned, APRV is an open lung approach based on the principles of open lung strategy (OLS).

A prolonged inspiratory time of high pressure in APRV and nearly continuous RM provides an alternative open lung approach. Maintaining open lung pressure (P_{high}) for a prolonged period promotes recruitment of slowly opening alveoli and gives unstable lung units enough time to fill and balance the volume due to the collateral ventilation.[24] In addition, T_{low} is also an important reason for preventing alveolar collapse in some studies, where T_{low} was even reduced to as little as 0.2 s.[25] The short release terminates expiratory flow early, permitting only partial discharge of lung capacity, thus causing auto-PEEP and preventing instability.[24] Consequently, APRV is considered an alternative, life-saving approach in patients with ARDS.

APRV in adults with ALI/ARDS

During the first few years of its use, APRV was not usually employed as a primary ventilation mode, but was considered an alternative approach for patients with ALI/ARDS refractory to conventional MV.[11] We reviewed the studies (case reports were not included) comparing APRV and conventional MV in adults with ALI/ARDS [Table 1]. Most were crossover studies (*i.e.*, switching from assist/control ventilation [A/CV] or synchronized intermittent mandatory ventilation [SIMV] to APRV) and randomized controlled trials (RCTs) with a small sample size (from n = 22 to n = 138).[8,26–28] However, the different studies used different settings, which indicate the inconsis-

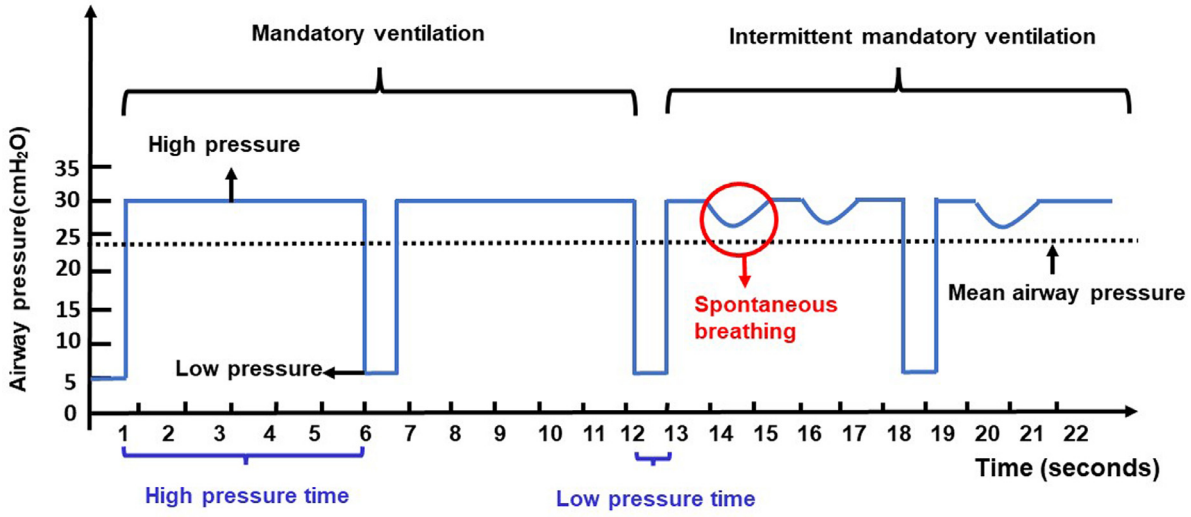

Figure 1. Pressure (longitudinal axis) and time (horizontal axis) curve in APRV. Two mandatory breaths (without SB, switched by time) and two intermittent mandatory breaths (with SB, triggered by flow or pressure, switched by both time and SB) are shown. Black arrows represent high pressure (P_{high}), low pressure (P_{low}), and mean airway pressure (P_{mean}). Red arrow represents SB. Blue fontin the horizontal axis represents high pressure time (T_{high}) and low-pressure time (T_{low}). APRV: Airway pressure release ventilation; SB: Spontaneous breathing.

Table 1
Application of ARPV in adults with ALI/ARDS.

Authors	Year	Country	Study design	Comparison	Sample size	APRV settings				Main findings and outcomes				
						P_{high}	T_{high}	P_{low}	T_{low}	Oxygenation	Respiratory mechanics	Hemodynamics	VILI	Outcomes
Varpula et al.[43]	2003	Finland	RCT	APRV *vs.* SIMV-PC/PS	45	<35 cm H_2O or UIP	Produce 12 pressure shifts per minute	Titrated according to PV-curve	Allow expiratory flow to decay to zero	Increased	Reduced P_{plat}	NA	NA	NA
Varpula et al.[78]	2004	Finland	RCT	APRV *vs.* SIMV-PC/PS	58	<35 cm H_2O or UIP	4.0 s	Titrated according to PV-curve	1.0 s	Similar	Reduced inspiratory pressure	Similar	NA	Similar mortality andventilator free days
Li et al.[29]	2016	China	RCT	APRV *vs.* SIMV	52	30 cm H_2O	4.0–8.0 s	0 cm H_2O	0.4–0.8 s	Increased	Reduced PIP	Improved	Similar	Decreased the duration of MV and ICU stay, survival rate, and days without organ failure were similar
Song et al.[28]	2016	China	RCT	APRV *vs.* SIMV + PEEP	22	UIP	4.0 s	LIP	1.0 s	Increased	Increased P_{mean}	Similar	Might exacerbate VILI	NA
Zhou et al.[8]	2017	China	RCT	APRV *vs.* LTV	138	P_{plat}	RR:10–14/min	5 cm H_2O	≥50% PEF	Increased	Reduced P_{plat}, improved respiratory compliance	Improved	Similar	Reduced the duration of MV and ICU stay
Liu et al.[32]	2009	Japan	Retrospective study	APRV *vs.* SIMV	58	30–35 cm H_2O	2.5–3.5 s	0 cm H_2O	RR:12–15/min	Increased	NA	NA	Similar	A trend toward lower mortality in ICU
Yoshida et al.[79]	2009	Japan	Retrospective study	APRV *vs.* LTV	18	<30 cm H_2O	4 s	0 cm H_2O	50–75% PEF	Increased	Similar	Improved	Decrease atelectasis	NA
Lim et al.[26]	2016	Australia	Retrospective study	APRV *vs.* CV	50	NA	NA	NA	NA	Increased	NA	NA	Decreased barotrauma	Reduced incidence of ECMO
Räsänen et al.[27]	1991	America	Crossover	APRV *vs.* CV	50	NA	NA	NA	1.5 s	Similar	Reduced PIP	NA	NA	NA
Sydow et al.[80]	1994	Germany	Crossover	APRV*vs.* VC-IRV	18	15–30 cm H_2O	2–4 s	5 cm H_2O	0.5–0.7 s	Similar	Reduced PIP	NA	NA	NA
Kaplan et al.[30]	2001	America	Crossover	APRV *vs.* IRV-PCV	12	75% PIP	4.5 s	NA	0.8	Similar	Reduced PIP and P_{mean}	Improved	NA	NA
Dart et al.[81]	2005	America	Crossover	APRV *vs.* CV	46	Slight increase in the mean airway pressure	3–4 s	0 cm H_2O	40–50% PEF	Increased	Reduced PIP	NA	NA	NA
Rozé et al.[45]	2017	France	Case series	APRV + ECMO	8	≤28 cm H_2O	1.0 s	≥10 cm H_2O	RR:12/min	NA	NA	NA	NA	May reduce the time under MV after ECMO
Lee et al.[44]	2020	Singapore	Case series	APRV + PP	5	NA	NA	NA	NA	Increased	NA	NA	NA	NA

ALI: Acute lung injury; APRV: Airway pressure release ventilation; ARDS: Acute respiratory distress syndrome; CV: Conventional ventilation; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; LIP: Lower inflection point; LTV: Low tidal volumeventilation; MV: Mechanical ventilation; MV: Mechanicalventilation; NA: Not available; PEEP: Positive end expiratory pressure; PEF: Peak expiratory flow; PEFR: Peak expiratory flow rate; P_{high}: High pressure; PIP: Inspiratory peak pressure; P_{low}: Low pressure; P_{mean}: Mean airway pressure; PP: Prone position; P_{plat}: Platpressure; PV-curve: Pressure-volume curve; RCT: Randomized controlled study; RR: Releaserate; SIMV: Synchronized intermittent mandatory ventilation; SIMV-PC/PS: Synchronized intermittent mandatory ventilation-pressure control/pressure support; T_{high}: High pressure time; T_{low}: Low pressure time; UIP: Upper inflection point; VC-IRV: Volume control- inverse ratio ventilation; VILI: Ventilator induced lunginjury.

tency and complexity of ARPV. Most of the studies reported that APRV could improve oxygenation compared to other modes and showed that APRV could improve hemodynamics and respiratory system compliance, reduce peak inspiratory pressure (PIP), airway pressure, plateau pressure (P_{plat}), and the need for paralysis and sedation.[8,29–31] No studies proved that APRV could improve the mortality of patients with ARDS; nevertheless, it was associated with a reduction of the duration of intensive care unit (ICU) stays and incidence of progression to extracorporeal membrane oxygenation (ECMO).[26,31–33]

Whether coronavirus disease 2019 (COVID-19) infection is a typical manifestation of ARDS is still controversial,[34–36] but the main pathology of COVID-19 including cytokine storm and excessive inflammation is similar to traditional ARDS.[37–39] Recently, Mahmoud et al.[40] found that APRV may improve oxygenation, alveolar ventilation, and CO_2 clearance in patients with COVID-19 and refractory hypoxemia. Moreover, Zorbas et al.[41] urged caution with the use of APRV in patients with COVID-19.

APRV combined prone position (PP)/ECMO in adults with ALI/ARDS

Research on combined APRV and PP has been limited to two case reports and one prospective RCT.[42–44] These studies reported that combining the two modalities resulted in a greater improvement in oxygenation. Varpula et al.[42] first discovered that APRV combined with the PP was feasible in the most severe ARDS, and a prospective RCT conducted 2 years later confirmed these results,[43] Lee et al.[44] reported five ARDS cases where APRV and PP were used and found that APRV could be safely used in the PP in a subtype of ARDS patients with improving oxygenation.

ECMO treatment for severe ARDS patients is also a current research focus, and there are few related studies on APRV MV mode under ECMO. Rozé et al.[45] reported eight cases of ARDS under ECMO, demonstrating that moderate SB with APRV was feasible while maintaining the tidal volume in an ultra-protective range without complications after ECMO.

APRV in children with ALI/ARDS

It is known that the philological characteristics of the respiratory system of adults and children are distinct.[46] Apart from considering the disease itself, the setting of the ventilator is always based on age, especially for children. Therefore, it is necessary to differentiate the use of APRV in children with ARDS. Although theoretically, APRV has many potential therapeutic benefits for pediatric ARDS patients, the safety concerns should be explored. Until 2020, the evidence for the application of APRV in children was insufficient; apart from a few retrospective studies and case reports, only one RCT compared LTV lung protective ventilation and APRV in children with ARDS [Table 2]. In 2001, Schultz et al.[47] compared APRV and SIMV for the treatment of pediatric ARDS and found that APRV provided similar ventilation, oxygenation, mean airway pressure, hemodynamics, and patient comfort as SIMV. Similarly, a recent RCT found that APRV was associated with a trend toward higher mortality than the conventional LTV.[48] However, because this study had

Table 2
Application of ARPV in children with ALI/ARDS.

Authors	Year	Country	Study design	Comparison	Sample size	APRV settings				Main findings and outcomes				
						P_{high}	T_{high}	P_{low}	T_{low}	Oxygenation	Respiratory mechanics	Hemodynamics	VILI	Outcome
Lalgudi et al.[48]	2018	India	RCT	APRV vs. LTV	52	1–2 cm H_2O above the P_{plat} (not to exceed 30 cm H_2O)	4 s	0 cm H_2O	Around 75% PEF	Increased	Increased P_{mean}	Similar	Similar	A trend toward higher mortality
Ning et al.[50]	2020	China	Retrospective study	APRV vs. HFOV	47	P_{mean}	NA	0 cm H_2O	1/2–3/4 of PEF	NA	NA	NA	NA	Similar of survival
Schultz et al.[47]	2001	America	Crossover	APRV vs. SIMV	15	NA	NA	NA	NA	Similar	Reduced PIP and P_{plat}, Similar P_{mean}	Similar	NA	NA
Kamath et al.[82]	2010	America	Crossover	APRV vs. CV	12	P_{plat} or PIP	Higher than T_{low}	PEEP	Higher than T_{low}	Increased	Increased Pmean	Similar	NA	NA
Yehya et al.[51]	2013	America	Crossover	APRV vs. HFOV	104	P_{mean}	NA	0 cm H_2O	50–75% PEF	NA	NA	NA	NA	Similar of survival
Yener and Udurgucu[83]	2020	Turkey	Crossover	APRV vs. CV	30	NA	NA	0 cm H_2O	Prevents end-expiratory pressure from reaching zero	Increased	Reduced PIP, increased P_{mean}	NA	NA	NA
Kawaguchi et al.[84]	2015	Japan	Case series	APRV	13	P_{plat}	3.0–5.0 s	0 cm H_2O	0.2–0.6 s	Similar	Increased P_{mean}	Similar	NA	NA

ALI: Acute lung injury; APRV: Airway Pressure Release Ventilation; ARDS: Acute respiratory distress syndrome; CV: Conventional ventilation; HFOV: High frequency oscillatory ventilation; LTV: Low tidal volume; NA: Not available; PEEP: Positive end expiratory pressure; PEF: Peak expiratory flow; PEFR: Peak expiratory flow rate; P_{high}: High pressure; PIP: Inspiratory peak pressure; P_{low}: Low pressure; P_{mean}: Mean airway pressure; P_{plat}: Platpressure; RCT: Randomized controlled study; SIMV: Synchronized intermittent mandatory ventilation; T_{high}: High pressure time; T_{low}: Low pressure time; VILI: Ventilator induced lung injury.

unbalanced baseline characteristics and non-personalized initial parameter settings, its results are worthy of further verification.

High-frequency oscillatory ventilation (HFOV), which was first developed to treat respiratory distress syndrome in neonates, is considered a very effective treatment in children with ARDS.[49] Ning et al.[50] retrospectively compared HFOV and APRV in the treatment of patients with moderate-to-severe ARDS and found that oxygenation at 48 h was improved with HFOV and APRV application, but no significant difference in the survival rates was noted in either group; this finding was consistent with that of Yehya et al.[51]'s study. Hence, more studies are needed to illustrate the therapeutic effect and safety for pediatric patients.

APRV in animal models with ALI/ARDS

Since 2000, 32 animal studies on APRV reported parameter setting and lung injury comparison with conventional ventilation (CV) modes, including 20 swine models, 5 rat models, 3 dog models, and 1 rabbit model [Supplementary Table 1]. There are three common methods for ARDS model establishment: (1) oleic acid injection, (2) saline lung lavage, and (3) ischemia-reperfusion and peritoneal sepsis. Most studies indicated that SB during APRV can improve oxygenation, decreases respiratory work, and redistribute ventilation to the dependent lung area, thereby reducing VILI.[52–58] Most studies compared CV modes and APRV in the animal ALI model and found that APRV had lower lung injury histological scores and could reduce cytokine mRNA expressions in lung tissue and reduce tumor necrosis factor (TNF)-a, interleukin (IL)−8, and IL-6 in the bronchoalveolar lavage fluid (BALF).[56,58–60] Moreover, APRV was reported to preserve surfactant concentrations of proteins A and B, which were associated with a lower incidence of basilar collapse.[61,62]

APRV and VILI

Although various lung-protective ventilation strategies such as LTV and high PEEP or respiratory physiological guiding titration of PEEP (also known as optimal PEEP) or combining lung recruitment maneuver have been developed in recent years, it is still difficult to prevent VILI.[63] Moreover, because alveolar volume change is viscoelastic in nature, there is a time lag between the time point of the airway pressure applied or removed and the time point at which alveoli open or collapse.[64] These data indicated that to minimize VILI, the MV strategies must open and stabilize the lung by appropriately applying the pressure/time profile. A few experiments with the expiratory time titrated to target end-expiration at 75% of the peak expiratory flow (PEF) in APRV demonstrated high effectiveness by recruiting/stabilizing alveoli and preventing VILI.[54,61,62,65]

Only a few studies have focused on VILI in humans; the majority of them have been conducted on animals. Roy et al.[61] found that early preventative MV with APRV blocked ARDS development, preserved surfactant proteins, and reduced pulmonary inflammation. They proposed that the injury prevention mechanism is related to preserving alveolar epithelial and endothelial integrity. Their conclusion was inconsistent with the results of Emr et al.[62] In this research, APRV blocked early drivers of lung injury, preventing ARDS, but improved endothelial permeability and maintained the concentrations of surfactant proteins A and B. *In vivo* microscopy demonstrated that compared with the A/CV, APRV significantly improved alveolar patency and stability. Another study also found that decreased T_{low} to achieve a termination of peak expiratory flow rate (PEFR) equal to 75% of the PEFR could reduce alveolar microstrain and improve alveolar recruitment.[56,57] These results were consistent with the study of Kollisch-Singule, who found that decreased T_{low} was associated with large alveoli and greater alveolar air space occupancy, resulting in the least conducting airway μ-strain.[66]

Effects of APRV on Extrapulmonary Organs

Patients with ARDS rarely die of hypoxia and/or hypercapnia but often have multiple organ system dysfunction syndromes, which increase mortality.[67] This suggests that in the treatment of ARDS, attention should also be given to extrapulmonary organs. APRV-related studies focusing on extrapulmonary organs mainly include the heart, brain, and kidney.

Heart

Preclinical and clinical studies have shown that increasing SB in APRV can improve hemodynamic function and lower the demand for vasopressor support.[29–31,68] Lewis's study demonstrated that during SB of APRV, the peak and average airway pressures decreased on the original high basis, resulting in decreased intrathoracic transmission pressure and decreased central venous pressure in patients with ALI/ARDS.[30] Reduced intrathoracic pressure enhances the venous reflux, thereby enhancing cardiac function, while reducing the need for a vasopressor to support mean arterial pressure and oxygen delivery (DO_2).[29] Finally, use of APRV is associated with improvement of cardiopulmonary function including increased cardiac index (CI) and DO_2 and decreased venous admixture (Q_{VA}/Q_T).[31]

Brain

In 2012, Marik et al.[69]. showed that APRV can be safely and effectively applied to patients with severe neurological diseases and can increase cerebral blood flow without increasing intracranial pressure (ICP), which was confirmed in a similar study by Fletcher et al.[70] in 2018. Similarly, Edgerton et al.[71] retrospectively studied the effects of APRV in 15 patients with traumatic brain injury. In this study, ICP did not significantly change after the transition to APRV. These data clearly show that the ventilation strategy of increasing mean airway pressure has little effect on ICP. However, Fletche et al.[70] verified the effect of APRV on the brain in a pig model and found that APRV was associated with increased cerebral ischemia and the risk increased over time.

Kidney

The analysis of risk factors for acute kidney injury (AKI) in patients with ARDS showed that ARDS did not significantly affect the occurrence of AKI.[72,73] Specifically, no correlation was found between MV parameters and AKI changes. In their prospective study, Hering et al.[74] evaluated the effects of APRV on renal perfusion and renal function in patients with

ALI/ARDS. They found that SB with APRV was related to the improvement of renal hemodynamics and function. However, renal perfusion and function did not improve once there was no SB during APRV ventilation.

Other organs

There are limited studies to explore the effect of APRV on other organs. Hering et al.[75] found that APRV with SB could increase intestinal blood flow in a pig model of ARDS. One case study reported that APRV could be a useful rescue therapy in pediatric hepatopulmonary syndrome.[76] However, APRV was not significantly associated with an improvement in hepatic arterial blood flow in the pig model.[77] Therefore, further studies are needed to provide more evidence of the effect of APRV on other organs.

Conclusions

Based on clinical and experimental data, APRV has been indicated to have many physiological benefits for patients with ARDS and those at risk of developing ARDS because it can improve oxygenation and hemodynamic function, perform alveolar recruitment, preserve SB, and decrease VILI, while not increasing the side effects on the function of extrapulmonary organs, which is highly consistent with the concept of ARDS treatment. However, evidence regarding the efficacy and safety of APRV is still insufficient for patients with ARDS, especially for children. Moreover, given the complicated and non-specific parameters, APRV has still not found widespread clinical application. Furthermore, because ARDS has many phenotypes, each associated with different pathophysiological changes, future well-organized, large-scale, multicenter RCTs are needed to validate the effect of APRV in patients with ARDS based on the pathophysiology, to clarify which specific subgroups of patients could benefit from APRV.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2022.02.003.

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