Review Article

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Airway pressure release ventilation: translating clinical research to the bedside in acute respiratory distress syndrome

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Abstract

Since its birth in the mid eighties of the last century, airway pressure release ventilation (APRV) has been a victim of much debate about its clinical use, benefits, and possible harms. With growing body of literature and evidence, APRV is gaining more acceptance and enthusiasm. Interesting research has been conducted in regards to its benefits in prevention of acute respiratory distress syndrome (ARDS), reduction of extra vascular lung water (EVLW), reduction in ventilator-induced lung injury (VILI), reduction of dead space, weaning off mechanical ventilation, improvement of hemodynamics, improvement in oxygenation, impact on mortality, its use as a non-invasive mode of ventilation, and its role in improving lung procurement for transplantation. The research and clinical application has expanded beyond the adult patients to include critically ill pediatric patients and critically ill animals. This article will review some of the plethora of research done in an attempt to promote its implementation to the bedside.

Key words: Acute respiratory distress syndrome, airway pressure release ventilation, extra vascular lung water, dead space, oxygenation, hemodynamics, ventilator-induced lung injury.

Introduction

ARDS is a syndrome of acute diffuse inflammatory lung injury, leading to increase pulmonary vascular permeability, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia, bilateral radiographic opacities, associated with increased venous admixture, increased dead space and decreased lung compliance. The histo-pathological hallmark is that of diffuse alveolar damage (DAD). (1) There has been no gold standard for diagnosis, and treatment is basically supportive with mechanical ventilation. Despite decades of research, mortality rate remains high, ranging from 30% to 60%. (1,2) The low tidal volume ventilatory strategy has shown a modest improvement in mortality. (3) Unfortunately despite this landmark study and the era of protective ventilation, mortality remains unacceptably high at more than 40%. (4) APRV is an inverse ratio, pressure controlled, intermittent mandatory ventilation with unrestricted spontaneous breathing, thus it is considered a partial ventilatory support mode. It is based on the principle of open lung approach. It has many purported advantages over conventional ventilation, including alveolar recruitment, improved oxygenation, preservation of spontaneous breathing, improved hemodynamics, and potential lung-protective effects. (5) Despite all those benefits, APRV has remained confined to a rescue mode for the difficult to oxygenate patients. (6) This article will review the recent and important exponential advances that APRV has made in the field of lung injury and ARDS in a hope to translate and implement the research to the bedside. **Table 1** summarizes some of the discussed research.

ARDS prevention

Once ARDS is established, there are no means of altering its patho-physiology and treatment remains supportive. Multiple ventilator modalities as well as pharmacological therapies have been studied. Unfortunately despite some success in oxygenation, few have translated to improved outcomes in the clinical realm. (7,8) Thus, prevention of ARDS rather than treating it seems prudent. Recent research has shown that early preemptive application of APRV can prevent ARDS development in animal model of sepsis and traumatic hemorrhagic shock. (9-11) Those studies suggest

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that early application of APRV in high risk subjects of developing ARDS can blunt the inflammatory response, attenuates lung permeability, alveolar edema and surfactant degradation. Though very promising and interesting concept, it has to be recognized that those were small sample animal model studies of sepsis and trauma. There are inherent difficulties of animal studies in re-producing the same results in human studies, as animal models do not always accurately represent the human condition they are trying to mimic. (12) An observational human study (13) conducted by the same group has shown that early application of APRV has reduced the incidence and mortality from ARDS in high-risk trauma patients compared to conventional mechanical ventilation. Success of this concept in animal models and in trauma subjects should foster pursuing the same concept in other human trials. Changing our current practice to a more proactive rather than reactive one at the bedside in high-risk patients of developing ARDS is imperative.

EVLW reduction

Extra vascular lung water plays an important role in the patho-physiology of acute lung injury and acute respiratory distress syndrome, and correlates with oxygenation and survival. (14) A small human pilot study conducted by our group has shown impressive results of reducing EVLW, and improved oxygenation by merely switching to APRV from conventional mechanical ventilation in ARDS patients. (15) Speculated theories of such improvements include the increased surface area of recruited alveoli may facilitate the EVLW reabsorption. The increased cardiac output may reduce the hydrostatic vascular pressure and transmural pressures with decreased fluid leakage from lung capillaries. Other possible mechanism is that the spontaneous breathing can cause pleural pressure swings, which may facilitate fluid movements along in the peri-bronchial lymphatics. Given the ease of the technology, (16) and the proven safety of APRV, measuring and targeting EVLW should be a priority in the routine management of ARDS especially in the setting of sepsis. Further research is required to expand using APRV not only in ARDS but also in patients with cardiogenic pulmonary edema who similarly have elevated EVLW. (16)

VILI prevention

VILI can affect up to 25% of patients with normal lungs who need mechanical ventilation. (17) There are multiple mechanisms by which mechanical ventilation can cause this injury, namely volutrauma, barotrauma, biotrauma, and atelectato-trauma. (18) APRV has many appealing features that conceptually may minimize the risk of such injury. Those include using lower inflating pressures, lower volumes, spontaneous breathing, and preventing the repetitive alveolar opening and collapsing and thus de-recruitment. (5,19) This was illustrated in a recent animal study, (20) which showed that compared to conventional mechanical ventilation, APRV reduced the histo-pathological changes, bronchoalveolar lavage protein, and preserved surfactant A and B concentration. Similarly, another animal trial (21) showed that APRV decreases bronchoalveolar lavage fluid high-mobility group box-1 levels (HMGB-1), and lung water compared to low tidal volume ventilation, signifying a decreased risk for VILI. Several studies are under way to further investigate this topic using biomarkers of inflammation during APRV compared to conventional mechanical ventilation. Translating this important research to the bedside should become a reality to avoid a costly common complication of a very common intervention (mechanical ventilation).

Dead space reduction

Pulmonary dead space is the component of ventilation that is wasted because it does not participate in gas exchange, and an increase in dead space represents an impaired ability to excrete carbon dioxide. Increased dead-space fraction is a feature of ARDS. Elevated values are associated with an increased risk of death. (22) Small human trial (23) has tested this concept and found significant reduction in the dead space. This reduction is multifactorial, including the effects of spontaneous breathing, lung recruitment, improved cardiac output, and effects of cardiogenic gas mixing. (5,24) This important benefit should be translated to the bedside, and dead space ventilation should be targeted as a goal in ARDS. Another patient population who might benefit from that reduction is the chronic obstructive lung disease (COPD) patients where dead space ventilation is a major issue. Further research would help clarify if there is a benefit of APRV in COPD.

Weaning off mechanical ventilation

Weaning off mechanical ventilation is usually a two-step process of assessing readiness of liberation using a "spontaneous breathing trial" (SBT) followed by the removal of the artificial airway if that SBT is deemed successful and other criteria of extubation are met. (25) Controlled mechanical

ventilation can cause diaphragmatic atrophy and weakness, that can cause delayed weaning and prolonged mechanical ventilation. (26) APRV as a partial ventilator support mode of ventilation incorporates unrestricted spontaneous breaths at any time of the respiratory cycle. (5) This feature theoretically reduces the incidence of diaphragmatic weakness and should facilitate weaning and liberation off mechanical ventilation. Additionally the reduced sedation and neuromuscular blockers using APRV helps reducing the time spent on mechanical ventilation. (5) A study by Rathgeber and colleagues (27) reported a small yet significant reduction in time on mechanical ventilation using APRV compared to two other modes of ventilation in postoperative cardiac patients. Similarly, Putensen and colleagues (28) have shown decreased duration of mechanical ventilation and ICU length of stay using APRV. A recent observational study (29) has failed to show a reduction in ventilator days using APRV. Better-designed studies comparing duration on mechanical ventilation and ventilator-free days between APRV and routine weaning using a standard protocol are required. Translating this research in the ICU is sensible given the cost burdens, and adverse events caused by mechanical ventilation. (30)

Hemodynamics improvement

ARDS is usually linked to sepsis and septic shock. (31) The shock state is defined by decreased oxygen delivery, tissue perfusion, hypotension, and organ dysfunction. (32) Treating the shock state requires volume resuscitation, vasopressor therapy, and steroids, all of which have their various adverse consequences. (32) Studies in medical, cardiac, surgical and trauma patients comparing APRV to conventional ventilation have shown improved cardiac index, hemodynamics, organ perfusion and oxygen delivery in patients on APRV. (5,33,34) Those findings make APRV an ideal mode of ventilation for ARDS especially in patients suffering a shock state.

Oxygenation improvement

Several studies (5,13,15,23,27-29,34,35) have compared APRV to conventional mechanical ventilation in humans with lung injury and ARDS. Consistently, most of them have shown improvement in oxygenation, and hemodynamics in the APRV group. This has led the medical community to utilize APRV mainly as a rescue therapy when conventional mechanical ventilation fails and in the difficult to oxygenate patients. (7,19) Unfortunately that delay of APRV application till the late course of the disease has hindered its ability to show significant mortality difference. It is well known that the lung is more recruitable in the early phase (<96 hours) of ARDS. (36) Clinical application of APRV may prove more beneficial if used appropriately early in the disease stage. (37)

Mortality benefits

For a decade, only the protective ventilatory strategy with low tidal volume stood alone as the only modality that has shown mortality benefits in ARDS. (3) Recently the prone positioning has shown improved mortality in severe ARDS. (38) Few studies have shown mortality benefits of APRV in ARDS. (13,39,40) On the other hand, other studies did not reproduce the same mortality benefits, (28,29,35) but no studies have shown worsening mortality or inferiority using APRV. There are ongoing studies registered in the National Institutes of Health (clinicaltrials.gov), mostly comparing APRV to low tidal volume ventilation as a lung-protective strategy. Hopefully the results of that research will help us take advantage of this mode and translate it to the bedside.

Non-invasive APRV

Non-invasive ventilation (NIV) refers to the provision of ventilatory support through the patient's upper airway using a mask. Continuous positive airway pressure (CPAP) is a common mode used non-invasively in patients with COPD, heart failure, obstructive sleep apnea and in weaning off mechanical ventilation. (41) APRV was described initially as two levels of alternating CPAP. (42) Only one case report has utilized APRV successfully using a non-invasive mask post extubation. (43) We have used APRV through a non-invasive mask in our practice in few patients with ARDS who did not wish to be intubated. It is logical to use this mode non-invasively in selected subgroups of patients.

Improved lung procurement

Lung transplantation has become a viable treatment option for patients with a variety of end-stage lung diseases. Donor's lung shortage has been a major limiting factor for such curative therapy, secondary to the lung's vulnerability and complications like pulmonary edema, hypoxia, aspiration, and VILI. (44) Important recent research has found significant improvement in lung procurement using APRV. (45,46) Those studies demonstrated that by switching the mode of ventilation from conventional ones to APRV can increase the pool of lungs available for transplants, and raise the hope for

increased number of salvageable lungs for such critical therapy.

Pediatric patients

Till recently, the use of APRV in the pediatric literature has been limited to case reports and small case series. (47) The clinical experience and its use have been emerging in the pediatric hypoxic respiratory failure patients even in the low birth weight infants. (48)

Veterinarian medicine

Mortality rates of ARDS in the veterinarian patients are very high. (49) To our knowledge, there is only one case report (49) of using APRV as a rescue therapy for a dog with refractory hypoxemia secondary to aspiration pneumonia with good results. The authors conclude that APRV was feasible in canine patients with ARDS. This case may open the door to utilize APRV in other cases or encourage research in this field of medicine.

Future research and ideas

Most of the APRV research was done with small animal or human series. We are in immense need for large randomized trials on most of the topics discussed above to answer some of the unknown questions and shed lighter on our current knowledge.

Furthermore new and innovative methods of setting and adjusting APRV parameters are future target for research. Examples are using esophageal balloon monitoring to assess the work of breathing and minimize lung injury, or measuring the functional residual capacity and lung volumes during APRV to maximize lung recruitment and minimize lung injury.

Conclusion

Translating research into clinical practice is a challenging process, and adoption of newer technologies or strategies are sometimes slow and met with resistance. The evidence presented above, along with the high morbidity, mortality, and the cost burdens of ARDS begs the question of why are we not adopting APRV more frequently in our practice? There are lots of foreseen obstacles: the mode is relatively new (30 years), the mode exists under different names in different commercially available ventilators, the technology is not exactly standardized between those ventilators, lack of training of clinicians on the newer non conventional modes of ventilation, lack of consensus and guidelines, and the lack of large non disputable research and evidence showing mortality benefits. Surely as more research and evidence are available, our understanding of both ARDS and APRV will be enhanced, and will ensue better outcomes for our patients with ARDS.

Acknowledgment

The author declares that he has no competing interests.

Table 1. Summary of some studies showing benefits of APRV

Study	Year	Population	Important finding
ARDS prevention			
Roy S, et al (9)	2012	Animal model of sepsis	Compared to conventional ventilation, APRV reduced lung injury and prevented ARDS
Roy S, et al (10)	2013	Animal model of sepsis	Compared to conventional ventilation, APRV reduced lung injury, inflammatory markers and prevented ARDS
Roy SK, et al (11)	2013	Animal model of trauma and hemorrhagic shock	Compared to conventional ventilation, APRV reduced lung injury, inflammatory markers and prevented ARDS
Andrews PL, et al (13)	2013	Observational human study in trauma patients	Compared to conventional mechanical ventilation, APRV reduced the incidence and mortality from ARDS in high risk trauma patients
EVLW reduction			
Daoud E, et al (15)	2013	Pilot human study in ARDS patients	APRV reduced EVLW, improved oxygenation. Oxygenation correlated with EVLW
VILI prevention			
Emr B, et al (20)	2013	Animal model of surgery	Compared to conventional ventilation, APRV reduced ventilator-induced lung injury, inflammatory markers and prevented ARDS
Matsuzawa Y, et al (21)	2010	Animal model of lung injury	Compared to conventional ventilation, APRV reduced bronchoalveolar lavage fluid HMGB1 levels and lung water and preserved oxygenation and systemic blood pressure
Dead space reduction			
Delgado M, et al (23)	2008	Observational human study in medical critically ill patients with ARDS	Compared to conventional ventilation, APRV improved oxygenation and decreased dead space ventilation in patients with refractory ARDS
Andrews P, et al (24)	2013	Case illustration	Compared to SIMV, APRV reduced dead space ventilation
Weaning off mechanical ventilation			
Rathgeber J, et al (27)	1997	Human study in post operative cardiac patients	Compared to CMV and SIMV, APRV reduced time spent on mechanical ventilation
Putensen C, et al (28)	2001	Human study in trauma patients	Compared to PCV, APRV improved oxygenation, hemodynamics, and reduced time on mechanical ventilation and ICU stay

Study	Year	Population	Important finding
Hemodynamics improvement			
Daoud E, et al (5)	2012	Review of the studies showing improvements in hemodynamics	Compared to conventional ventilation, APRV showed improvement in hemodynamics (blood pressure, cardiac index, oxygen delivery), reduced vasopressor and inotrope use, and improved organ perfusion (urine output, mesen-teric circulation)
Daoud EG (33)	2007	Review of the studies showing improvements in hemodynamics	
Oxygenation improvement			
McMullen SM, et al (34)	2012	Meta analysis of partial ventilatory support	Improved oxygenation, hemodynamics and respiratory mechanics using APRV
Marik PE, et al (37)	2009	Human study in critically ill medical patients	APRV with PS improved oxygenation, reduced dead space ventilation and reduced amount of sedation and vasopressors
Mortality benefits			
Liu L, et al (39)	2009	Retrospective human study in ARDS patients	Compared to SIMV, APRV improved oxygenation, reduced vasopressor usage and improved mortality
Dolinay T, et al (40)	2011	Prospective human study in medical ARDS patients	Compared to low tidal volume ventilation, APRV reduced ICU, and hospital LOS, and trend towards improved mortality
Non-invasive APRV			
Jousela IT, et al (44)	1988	Case report	APRV used non invasively prevented reintubation
Improved lung procurement			
Hanna K, et al (46)	2011	Retrospective case series of organ donors	The use of APRV prior to procurement increased the rate of successful lung donation
Koch RL, et al (47)	2009	Observational study in organ donors	APRV and open lung strategy improved oxygenation and may improve post transplant outcomes
Pediatric patients			
Krishnan J (48)	2007	One center experience of seven pediatric patients	Improved oxygenation
Gupta S, et al (49)	2013	Retrospective case series of five infants	All infants tolerated APRV with no complications and survived
Veterinarian medicine			
Sabino CV, et al	2013	Case report of one dog	Improved oxygenation, dog survived

Legend: APRV=Airway pressure release ventilation; ARDS=Acute respiratory distress syndrome; CMV=Controlled mandatory ventilation; EVLW=Extra vascular lung water; HMGB1=High-mobility group protein B1; ICU=Intensive care unit; LOS=Length of stay; PCV=Pressure controlled ventilation; PS=Pressure support ventilation; SIMV=Synchronized intermittent mandatory ventilation

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