Airway Pressure Release Ventilation Combined With Prone Positioning in Acute Respiratory Distress Syndrome: Old Tricks New Synergy: A Case Series

Si Jia Lee, MBBS, MMed (Anesthesiology), EDIC, EDRA,
Yilin Lee, MBBS, MMed (Anesthesiology), MRCP, EDIC, Andrew Kong, MBBS, FRCA, FFICM, EDIC,
and Shin Yi Ng, MBBS, MMed (Anesthesiology), EDIC, PGDip, FCCP, FCCM, FAMS

Airway pressure release ventilation (APRV) shares several overlapping mechanisms with prone positioning in improving ventilation-perfusion mismatch in patients with acute respiratory distress syndrome (ARDS). However, the combination of APRV and prone positioning is seldom performed because assist/controlled ventilation remains the mainstay ventilatory mode. We describe 5 cases of severe ARDS where APRV and prone positioning were applied. All patients' partial pressure of arterial oxygen (P_{aO_2}):inspired oxygen concentration (F_{iO_2}) ratios improved after treatment, and 3 patients were extubated within 72 hours of turning supine. In our experience, APRV can be safely used in the prone position in a select subgroup of ARDS patients with resulting significant oxygenation improvement. (A&A Practice. 2020;14:e01231.)

GLOSSARY

ACPC = assist control, pressure control mode; **ADL** = activities of daily living; **APACHE II** = Acute physiology, age, chronic health evaluation II; **APRV** = airway pressure release ventilation; **ARDS** = acute respiratory distress syndrome; **BMI** = body mass index; **CPAP** = continuous positive airway pressure; **CT** = computed tomography; **F** = female; **F_{iO_2}** = inspired oxygen concentration; **HAP** = hospital-acquired pneumonia; **ICU** = intensive care unit; **IRB** = Institutional Review Board; **LOS** = length of stay; **M** = male; **MAP** = mean arterial pressure; **MV** = mechanical ventilation; **NSTEMI** = non-ST-segment-elevation myocardial infarction; **NYHA** = New York Heart Association; **P/F** = P_{aO_2} : F_{iO_2} ; **P_{insp}** = peak inspired pressure; **P_{peak}** = peak airway pressures; **P_{aO_2}** = partial pressure of arterial oxygen; **PCV** = pressure control ventilation; **PE** = pulmonary embolism; **PEEP** = positive end-expiratory pressure; **POD** = postoperative day; **RASS** = Richmond Agitation Sedation Score; **RCT** = randomized clinical trial; **RR** = respiratory rate; **SBP** = systolic blood pressure; **T1RF** = type 1 respiratory failure; **TM** = tracheostomy mask; **VILI** = ventilator-induced lung injury

Following several landmark trials, patients with severe acute respiratory distress syndrome (ARDS) are now ventilated using low tidal volume of 6 mL/kg predicted body weight coupled with neuromuscular blockade and prone positioning.^{1,2} However, muscle paralysis in critically ill patients has been associated with longer mechanical ventilation and length of intensive care unit (ICU) stay.³ Meanwhile, spontaneous breathing during mechanical ventilation in the prone position is rarely practiced due to the perils of unregulated transpulmonary pressures, thought to be detrimental to the heterogeneous lung.⁴

Airway pressure release ventilation (APRV) is an alternative mode of ventilation, sometimes used in severe ARDS patients with refractory hypoxemia. First described in 1987, APRV is a time-cycled, pressure-limited inverse ratio ventilation mode characterized by high airway pressure and

intermittent pressure release breaths.⁵ Both the maintenance of high mean airway pressure in APRV and the physiological effects of gravity in prone position recruits consolidated alveolar units, allowing for equalization of stress and strain across the lung parenchyma and improves oxygenation.^{6,7}

Based on our understanding of the overlapping physiological mechanisms behind how prone positioning and APRV improves ventilation-perfusion mismatch, we postulate that combining the 2 can have potential synergistic effects. To date, research on combined APRV and prone positioning is limited to 1 case report and 1 randomized clinical trial (RCT).^{8,9} They discovered that combining the 2 modalities resulted in augmented improvement in oxygenation.

We aimed to describe our early experience in this technique and evaluate the feasibility and outcomes of its use in ARDS patients.

Between the period of January 2013 and October 2017, we manually searched through the registry of ICU admissions in Singapore General Hospital and Sengkang General Hospital, Singapore. All patients with ARDS fulfilling the Berlin criteria,¹⁰ who received both prone and APRV interventions, were included. This study was approved by the Institutional Review Board (IRB; Singhealth ref no: 2018/2024) and patient consent waived by the IRB due to its retrospective and observational nature. All patient

From Department of Surgical Intensive Care, SingHealth, Singapore.

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Address correspondence to Si Jia Lee, MBBS, MMed (Anesthesiology), EDIC, EDRA, Department of Anaesthesia, Block 5 Level 2, Singapore General Hospital Outram Rd, Singapore 169608. Address e-mail to lee.sjia@singhealth.com.sg.

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information reported in this study has been deidentified. A total of 5 patients met the inclusion criteria.

CASE DESCRIPTION

Case 1

A 77-year-old man with a background of bronchial asthma presented with gastric outlet obstruction secondary to pancreatic tumor, for which he underwent a gastric bypass. On day 4 of hospitalization, he developed severe ARDS, partial pressure of arterial oxygen (Pao₂):inspired oxygen concentration (Fio₂) (P/F) ratio 88 due to nosocomial pneumonia, requiring mechanical ventilation. He received a total of 25 hours of prone-APRV therapy, followed by 72 hours of mechanical ventilation in supine position, after which he was successfully extubated and discharged from ICU the following day. However, he was readmitted to ICU 1 week later for septic shock and eventually died of pneumonia 9 weeks later.

Case 2

A 21-year-old woman was admitted for aspiration pneumonitis. This was on a background of tracheal perforation after an elective hemithyroidectomy, subsequent surgical exploration, tracheal repair, and tracheostomy on postoperative day (POD) 4. She developed severe ARDS (P/F ratio 95) secondary to diffuse alveolar hemorrhage and aspiration pneumonitis, and was ventilated on APRV, before initiating prone-APRV therapy on day 9 of mechanical ventilation. She received in total 62 hours of prone-APRV therapy and was weaned off mechanical ventilation 2 days after completion of prone-APRV. Her trachea was

decannulated before her discharge from ICU and she was sent home 6 days later.

Case 3

A 53-year-old man had a prolonged 10-month stay in the hospital, with 2 ICU admissions. His initial and brief ICU admission followed a traumatic extradural hematoma requiring craniotomy for evacuation of hematoma. He was readmitted to the ICU 8 weeks later for nosocomial pneumonia and ARDS (P/F ratio 53). On day 12 of this admission, controlled ventilation was switched to prone-APRV therapy and continued for 48 hours. Subsequently, he received a tracheostomy and was weaned from ventilation 13 days later. The patient stayed in the general ward for another 6 months but eventually died.

Case 4

A 41-year-old man developed severe ARDS (P/F ratio 85) following influenza pneumonia. He was admitted from emergency department to ICU directly and underwent prone-APRV therapy on day 6 of ICU. He received a total of 28 hours of prone-APRV therapy. His initial P/F ratio of 56 mm Hg improved to 105 mm Hg by the end of the second session of prone-APRV therapy. Because the patient was deemed a poor responder, prone-APRV therapy was discontinued and patient died 11 days later of refractory hypoxemia.

Case 5

A 71-year-old man developed severe ARDS (P/F ratio 39) secondary to cholangitis sepsis. He received prone-APRV

Table 1. Baseline Characteristics of Patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Background					
Age (y)	77	21	53	41	71
Gender	M	F	M	M	M
Weight (kg)/height (cm)/BMI (kg/m ²)	157/55/22	148/42/19	163/50/19	155/53/22	162/69/26
Cardiopulmonary diseases	Bronchial asthma, ex-smoker	Nil	Nil	Nil	Hypertension, ischemic heart disease (NYHA class 1)
ADL status	Independent	Independent	Independent	Independent	Independent
APACHE II	24	22	28	21	20
LOS ICU (d)	9	14	46	20	5
LOS hospital (d)	107	22	303	20	12
Reason for ICU admission	HAP	Aspiration pneumonitis	HAP	Influenza A pneumonia	T1RF due to cholangitis
Other active issues	Hepatobiliary sepsis	Diffuse alveolar hemorrhage	Infective endocarditis	Infective endocarditis	NSTEMI, subsegmental PE
Details of ARDS					
Etiology	HAP	Aspiration pneumonitis	HAP	Pneumonia influenza A/pneumococcal	Sepsis (cholangitis)
P/F ratio on ICU admission (mm Hg)	88	95	222 (first admission) 53 (second admission)	85	39
P/F ratio before initiation of prone-APRV (mm Hg)	156	91	53	56	38
CT thorax confirmed ARDS	Not performed	Yes	Yes	Yes	Yes
Additional findings			Subsegmental pulmonary embolism		Subsegmental pulmonary embolism

Abbreviations: ADL, activities of daily living; APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; APRV, airway pressure release ventilation; ARDS, acute respiratory distress syndrome; BMI, body mass index; CT, computed tomography; F, female; Fio₂, inspired oxygen concentration; HAP, hospital-acquired pneumonia; ICU, intensive care unit; LOS, length of stay; M, male; NSTEMI, non-ST-segment-elevation myocardial infarction; NYHA, New York Heart Association; P/F, Pao₂/Fio₂ ratio; Pao₂, partial pressure of arterial oxygen; PE, pulmonary embolism; T1RF, type 1 respiratory failure.

therapy on day 1 of admission to ICU and completed 16 hours in total. This patient made a rapid improvement in P/F ratio (222 mm Hg) after 16 hours and was extubated 2 days later. He was eventually discharged home 2 weeks later.

A summary of these cases can be found in Tables 1–3.

DISCUSSION

In our experience of the patients with severe ARDS who received prone-APRV therapy, all 5 experienced a significant improvement in P/F ratio ranging from 49 to 222 mm Hg. While 4 survived beyond 30 days following prone-APRV therapy, 1 died of refractory hypoxemia, relatively early.

Table 2. Details of APRV-Prone Treatment

	Case 1	Case 2	Case 3	Case 4	Case 5
Treatment received					
Ventilator and settings					
Ventilator model	Drager V300	Drager V300	Drager Evita XL	Drager V300	Drager V300
Before prone	ACPC	APRV	APRV	ACPC	APRV
	PCV P_{insp} 30	P_{high} 25 P_{low} 0	P_{high} 25 P_{low} 0 T_{high} 4 T_{low}	P_{insp} 17 PEEP 15	P_{high} 24 P_{low} 0
	PEEP 12 FiO_2 0.75	T_{high} 5 T_{low} 0.9 FiO_2 0.75	0.45 FiO_2 0.85	RR 26 FiO_2 1.0	T_{high} 6 T_{low} 0.6 FiO_2 1.0
During prone	APRV	APRV	APRV	APRV	APRV
	P_{high} 25 P_{low} 0	P_{high} 25 P_{low} 0	P_{high} 30 P_{low} 0	P_{high} 22 P_{low} 0	P_{high} 26 P_{low} 0
	T_{high} 14 T_{low} 0.7	T_{high} 8.1 T_{low} 0.9	T_{high} 6 T_{low} 0.6	T_{high} 9 T_{low} 0.5	T_{high} 6 T_{low} 0.6
	FiO_2 0.55	FiO_2 0.6	FiO_2 0.8	FiO_2 0.8	FiO_2 0.65–1.0
After completion of prone-APRV regime	APRV 1 d CPAP 2 d	APRV 1 d CPAP 1 d	PCV 12 h APRV 5 d CPAP 3 d	APRV 2 d ACPC 10 d	APRV 1 d CPAP 1 d
Prone details					
Total duration of prone (h)	25	62	48	28	16
Prone regime	25 h (single session)	(7 h + 16 h + 39 h)	48 h (single session)	(12 h + 16 h)	16 h (single session)
Adjunctive treatment ^b	APRV Methylprednisolone (6 d) Antibiotics	APRV Methylprednisolone (5 d) Antibiotics, permissive hypercapnia	APRV Methylprednisolone (15 d) Antibiotics	APRV Neuromuscular blockade Antibiotics	APRV Antibiotics
Sedation					
Drugs (infusion)	Propofol, remifentanyl	Propofol, remifentanyl, ketamine, midazolam	Propofol, fentanyl	Propofol, fentanyl	Propofol, fentanyl
RASS score	–2 to –1	–3 to –5	–2 to –1	–2 to –1	–2 to –1

Abbreviations: ACPC, assist control, pressure control mode; APRV, airway pressure release ventilation; CPAP, continuous positive airway pressure; FiO_2 , inspiratory oxygen concentration; P_{insp} , peak inspiratory pressure; PCV, pressure control ventilation; PEEP, positive end-expiratory pressure; RASS, Richmond Agitation Sedation Scale; RR, respiratory rate.

^a16 h consists of semiprone position.

^bAdjunctive treatments include modalities implemented before and/or during prone-APRV therapy: APRV, methylprednisolone, antibiotics, fluid restriction, neuromuscular blockade, permissive hypercapnia, recruitment maneuvers.

Table 3. Results of Prone-APRV

	Case 1	Case 2	Case 3	Case 4	Case 5
Results					
P/F ratio pre/post prone session 1	156/252	91/190	53/146	56/101	38/260
P/F ratio pre/post prone session 2	-	172/127	-	80/105	-
P/F ratio pre/post prone session 3	-	152/212	-	-	-
Overall improvement in P/F ratio ^a	96	121	93	49	222
P_{peak} range (cm H ₂ O)	23–30	25–33	24–33	25–31	24–32
Criteria used to stop prone-APRV therapy	Improvement in P/F ratio	Improvement in P/F ratio	Improvement in P/F ratio	Minimal improvement in PaO_2	Improvement in P/F ratio
Total duration of MV (d)	5	13	27	20	4
Days to extubation (after turning supine)	3	2 (weaned to TM)	13 (weaned to TM)	Not extubated	2
Complications related to prone-APRV therapy ^b	Nil	Nil	Nil	Hypotension requiring noradrenaline	Hypotension requiring dopamine
Outcomes					
30 d reintubation	Yes	No	No	Not applicable (died)	No
30 d mortality	No	No	No	Yes	No

Abbreviations: APRV, airway pressure release ventilation; FiO_2 , inspiratory oxygen concentration; MAP, mean arterial pressure; MV, mechanical ventilation; P/F, $\text{PaO}_2/\text{FiO}_2$ ratio; P_{peak} , peak airway pressures; PaO_2 , partial pressure of arterial oxygen; SBP, systolic blood pressure; TM, tracheostomy mask.

^aOverall improvement in P/F ratio refers to P/F ratio at the end of final session of prone-APRV therapy minus the PF ratio before implementation of prone-APRV therapy.

^bComplications are defined as hypotension (MAP <65 or SBP <90), arrhythmias, lines dislodgement, pressure ulcers, airway obstruction, corneal abrasion/ulceration.

We propose APRV as an alternative to conventional ventilatory modes in ARDS patients undergoing prone therapy. Its benefits are manifold: first, it improves oxygenation in a synergistic way when combined with prone positioning; second, it has the potential to minimize ventilator-induced lung injury (VILI) by reducing patient-ventilator dyssynchrony; finally, it avoids the use and complications of neuromuscular blockade.

In the prone position, consolidated dorsal alveolar units are recruited, allowing for better aeration and lesser degree of hyperinflation in the normal lung units. This results in homogenization of transpulmonary pressures, lung ventilation, and decreased total shunt fraction.⁶ Similarly, in APRV, sustaining P_{high} achieves a higher mean airway pressure and facilitates open-lung ventilation.⁷ This minimizes lung derecruitment, equalizes strain and stress across the lung parenchyma, and complements the homogenizing effect of prone positioning. The overall effect is enhanced ventilation-perfusion matching and attenuated VILI.

APRV itself possesses properties that offset some of the physiological drawbacks of prone position. For instance, spontaneous breathing in APRV preserves diaphragm function, thereby counteracting the upward shift of lungs caused by compressed abdominal contents in the prone position. Consequently, basal atelectasis and airway pressures are reduced. Problems of hypotension and high sedation requirements sometimes seen in a paralyzed and prone subject can also be mitigated since spontaneous breathing in APRV improves overall hemodynamic and reduces sedation requirements.^{7,11}

Case 2, our first patient in whom prone-APRV was performed, was kept heavily sedated, partly due to unfamiliarity with the technique. Subsequent patients had their sedation lightened to achieve a higher Richmond Agitation Sedation Scale (Table 2), consistent with previous observations that APRV requires lesser sedation.⁷ Hypotension was not a significant issue because only 2 patients required low-dose vasoactive agents transiently during the period of prone-APRV therapy. One limitation of our study, however, is the lack of standardization in the timing of initiation and duration of prone-APRV sessions.

We have identified several potential clinical scenarios where the application of prone-APRV therapy may be of value:

1. In patients ventilated on APRV in the early stage of their ARDS, who subsequently progress to severe ARDS and fulfill criteria for prone positioning—APRV can be continued in the prone position.
2. As a rescue therapy in patients with refractory hypoxemia despite prone positioning, neuromuscular blockade and optimum positive end-expiratory pressure, and/or where extracorporeal membrane oxygenation is not a viable option.

Despite its theoretical physiological benefits, the prone-APRV technique failed to take off after Varpula's studies nearly 2 decades ago.^{8,9} An important explanation to this may be the significant interpatient variability in ventilator synchrony typically observed in APRV, sometimes requiring continual bedside evaluation and titration of

ventilation settings. Additional barriers include the perennial concern over the lack of control over tidal volumes and transpulmonary pressures in APRV mode and the logistical challenges of turning and maintaining prone position in a spontaneously breathing patient. Furthermore, research on APRV is scarce, mainly comprising small randomized studies with heterogeneous methodologies, making it difficult for meta-analyses to draw any reliable conclusions.^{12–14} Evidence on prone-APRV therapy is even scarcer.^{8,9} Notably, the potential to augment gas exchange in prone-APRV may not necessarily translate to morbidity and mortality benefit.¹²

Nonetheless, some encouraging evidence surrounding APRV has emerged. This is seen in the form of shorter days of mechanical ventilation, reduced duration and depth of sedation, shorter length of ICU stay, more mechanical ventilation-free days, and even mortality benefit.^{13–15} While these results need to be interpreted with caution, they begin to justify the use of APRV in ARDS and its complementary role in prone position.

We have shown that APRV can be feasibly applied in the prone position in patients with ARDS. The enhanced improvement in oxygenation seen in our subjects after prone-APRV is likely explained by their synergistic mechanisms of action, which serve an integral role in a select subgroup of ARDS patients. Future studies comparing APRV versus assist control modes in the prone patient may shed light on the optimal timing and duration and safety of prone-APRV therapy, its effect on lung strain and stress, and ultimately on patients' outcome. ■■

DISCLOSURES

Name: Si Jia Lee, MBBS, MMed (Anesthesiology), EDIC, EDRA.

Contribution: This author applied for the IRB, collected the relevant data from patient case notes and hospital computer systems, collated the information into a table, performed literature review on the topic, and wrote up the manuscript.

Name: Yilin Lee, MBBS, MMed (Anesthesiology), MRCP, EDIC.

Contribution: This author assisted in the IRB application, performed part of the literature search, and edited the manuscript.

Name: Andrew Kong, MBBS, FRCA, FFCM, EDIC.

Contribution: This author was directly involved in the care of several of the patients included in the case series, conceived the idea that underpinned our case report, and assisted in the editing of the manuscript.

Name: Shin Yi Ng, MBBS, MMed (Anesthesiology), EDIC, PGDip, FCCP, FCCM, FAMS.

Contribution: This author assisted in the application for IRB, provided guidance on the angle of the writing, and edited the manuscript.

This manuscript was handled by: Markus M. Luedi, MD, MBA.

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