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Practical Use of Airway Pressure Release Ventilation for Severe ARDS – a preliminary report in comparison with a conventional ventilatory support

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ABSTRACT

Airway pressure release ventilation (APRV) is a ventilatory mode that allows unsupported spontaneous breathing at any phase of the ventilatory cycle with high mean airway pressures. We hypothesized that use of APRV might produce potential beneficial effects on oxygenation, reducing mortality in patients with severe acute respiratory distress syndrome (ARDS) in comparison with synchronized intermittent mandatory ventilation (SIMV) as a conventional mode of ventilation. We retrospectively reviewed data of 58 patients with severe ARDS (the ratios of partial arterial oxygen tension to fraction of inspired oxygen, PaO_2/F_IO_2 ratio <150). The patients' data were divided into two groups: SIMV-group and APRV-group. Patients' backgrounds, oxygenation on day 0, 1, 3, 5 and 7 following initiation of each mode, vasopressor dependence, duration of ventilation, duration of ICU stay, and mortality in ICU were analyzed. PaO_2/F_IO_2 ratios were statistically higher in the APRV-group (APRV vs. SIMV on day 1, 3, 5, 7: 201.6 ± 76 vs.150 ± 59.1, 256.7 ± 71.5 vs.182.1 ± 65.4, 268.8 ± 73.3 vs. 204.6 ± 72.8, and 263 ± 74.5 vs.204.1 ± 67.1, respectively, $p<0.05$). Vasopressors were less used ($p=0.018$), and mortality in ICU tended to be lower in the APRV group (31%) than in the SIMV group (59%) ($p=0.050$). Use of APRV in patients with severe ARDS appears to be associated with improvements in oxygenation, and a trend toward lower mortality in ICU. No significant adverse effects were observed. Prospective controlled studies are required to confirm the benefits of this ventilatory mode in comparison with conventional methods for severe ARDS.

Key words: *Acute respiratory distress syndrome, Airway pressure release ventilation, Mechanical ventilation*

Ventilatory support for patients with severe acute respiratory distress syndrome (ARDS) remains challenging. Partial ventilatory support preserves spontaneous breathing activity while providing the desired degree of ventilatory assistance, and is increasingly used as a primary ventilatory mode for acute respiratory failure[6]. Compared with full mechanical ventilation, the physiological benefits of partial ventilatory support include better gas exchange, improved hemodynamics, improved organ perfusion, and shorter duration of ventilatory support and stay in the intensive care unit (ICU) among patients at risk of ARDS[9-11].

Airway pressure release ventilation (APRV) is a ventilation mode in which unsupported, spontaneous breathing is maintained throughout the entire ventilatory cycle with high mean airway pressures[13]. With APRV, spontaneous breathing is allowed at any phase of the ventilatory cycle, and mechanical support of ventilation is provided by time-cycled switching of two airway pressures. Although APRV has been shown to improve oxygenation in comparison with totally mechanical ventilation in crossover studies[14] and one randomized prospective study[10], few recent studies have been performed to support previous findings and indicate improved morbidity and mortality among patients with severe ARDS. We hypothesized that in severe ARDS, the use of APRV might demonstrate beneficial effects on gas exchange, and reduced morbidity and mortality in the ICU.

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To test this hypothesis, we designed a retrospective study comparing APRV with synchronized intermittent mandatory ventilation (SIMV) as a conventional ventilatory support for severe ARDS.

METHODS

This study was approved by the institutional review board at Hiroshima University Hospital. We retrospectively reviewed data from patients with ARDS admitted to the ICU at Hiroshima University Hospital from January 2003 to October 2009. Before the end of 2006, SIMV was used as the primary method of ventilatory support for ARDS patients. Since 2007 we have used APRV for severe ARDS when the ratio of partial arterial oxygen tension to fraction of inspired oxygen (PaO_2/F_IO_2 ratio) ≥ 150 mmHg could not be maintained despite initial conventional ventilatory support with SIMV.

ARDS was defined on the basis of the guidelines of the American-European consensus conference on ARDS[1], and we defined severe ARDS based on PaO_2/F_IO_2 ratio < 150. The etiology of ARDS was determined on the basis of medical history and physical examination, radiology, and the results of biochemical and microbiological investigations. Direct and indirect insults were defined according to the tabulated distinction made in the published consensus guidelines for the diagnosis of ARDS[1]. Patients with chronic pulmonary disorder or respiratory failure with a neurological etiology were also excluded. Clinical data including age, gender, causes of ARDS, acute physiology and chronic health evaluation (APACHE) II score, lung injury score (LIS) on admission, PaO_2/F_IO_2 ratio, and alveolar-to-arterial difference in oxygen tension ($A\text{-}aDO_2$) on days 0, 1, 3, 5 and 7 were analyzed retrospectively. Day 0 (baseline) was defined when PaO_2/F_IO_2 ratio ≥ 150 could not be maintained with SIMV ventilation. Duration of ventilatory support and ICU stay in addition to mortality in the ICU were also reviewed.The use of vasopressors and other complications such as pneumothorax were compared to see the adverse effects of high mean airway pressures between the groups.

Patients were divided into those admitted before 2007 who received SIMV only (SIMV group), and those admitted after 2007 who received APRV (APRV group) when PaO_2/F_IO_2 ratio ≥ 150 could not be maintained with SIMV ventilation. In both groups, ventilatory support was started on SIMV with initial settings of F_IO_2, 0.5; tidal volume, 6-8 ml/kg; respiratory rate, 12-15 breaths/min; PEEP, 10-15 cmH_2O. These settings were adjusted as required. An Evita-4 ventilator (Drager, Germany) was used for the APRV. In the APRV, the ventilator was set to a mode in which unsupported, spontaneous breathing was possible throughout the entire ventilatory cycle at two airway pressure levels. The high level of inspiratory pressure (P-high) was set at 30-35 cmH_2O, whereas the low level of inspiratory pressure (P-low) was set at 0 cmH_2O. Duration of P-high (T-high) was adjusted between 2.5-3.5 s, depending on the time cycle (12-15/min), and duration of P-low (T-low) was passively determined, i.e. time for one respiratory cycle minus T-high.

Table 1. Clinical characteristics of the patients in the study

	APRV-group	SIMV-group	p-value
Number of patients	19	39	
Gender (M/F)	13/6	28/11	0.791
Age (years old)	70 ± 14	63 ± 16	0.088
Primary ARDS/secondary ARDS	16/3	30/9	0.520
APACHE II	17.9 ± 5.9	20.1 ± 8.5	0.324
Lung injury score	3.3 ± 0.58	3.21 ± 0.51	0.543
Baseline PaO_2/F_IO_2 ratio	105.2 ± 29.1	97.7 ± 26	0.329
Baseline $A\text{-}aDO_2$	412.6 ± 138.4	466.4 ± 128.4	0.150

M/F: male/female; APRV: airway pressure release ventilation; SIMV: synchronized intermittent mandatory ventilation; ARDS: acute respiratory distress syndrome; primary ARDS: direct insult to lung by pneumonia, pulmonary contusion or aspiration; secondary ARDS: indirect insult to lung by, e.g. sepsis, pancreatitis; APACHE II: acute physiology and chronic health; PaO_2/F_IO_2 ratio: the ratio of partial arterial oxygen tension to fraction of inspired oxygen; $A\text{-}aDO_2$: alveolar-to-arterial difference in oxygen tension.
Baseline was defined when PaO_2/F_IO_2 ratio ≥ 150 could not be maintained with SIMV ventilation.
Values are mean ± SEM.

Supportive care included use of sedatives and narcotics, hemodynamic management, nutritional support, control of blood glucose levels, evaluation and treatment of nosocomial pneumonia, and prophylaxis against deep venous thrombosis and gastrointestinal bleeding.

Demographic variables are reported as the median and interquartile ranges. Physiological variables are presented as mean ± standard error of the mean. Fisher's exact test and the Mann-Whitney test were used for statistical analyses, as appropriate, using SPSS 11.5 software (SPSS, Chicago, IL). Values of $p<0.05$ were considered indicative of statistical significance.

RESULTS

During the study period, 88 patients were diagnosed with ARDS, including 58 patients with severe ARDS who were enrolled in this study. Patient characteristics are summarized in Table 1. No significant differences were found regarding age, gender, baseline PaO_2/F_IO_2 ratio (day 0), baseline A-aDO_2 (day 0), APACHE II score, LIS, or type of lung injury.

Changes in oxygenation following commencement of each ventilatory support are presented in Fig. 1 and Fig. 2. PaO_2/F_IO_2 ratios were significantly higher in the APRV group than in the SIMV group from day 1 to day 7 (APRV vs. SIMV on day 1, 3, 5, 7: 201.6 ± 76 vs. 150 ± 59.1, 256.7 ± 71.5 vs. 182.1 ± 65.4, 268.8 ± 73.3 vs. 204.6 ± 72.8, and 263 ± 74.5 vs. 204.1 ± 67.1, respectively). Likewise, A-aDO_2 was significantly lower in the APRV group than in the SIMV group from day 1 to day 5 (APRV vs. SIMV on day 1, 3, 5: 214.4 ± 105.1 vs. 394.3 ± 142.2, 150.6 ± 65.9 vs. 286.7 ± 127.9, and 133.9 ± 57.6 vs. 233.6 ± 110.4, respectively). No significant differences in pH, $PaCO_2$, HCO_3^- were observed during the study period between groups (Table 2).

There was a greater trend toward lower ICU mortality in the APRV group than in the SIMV group (Table 3). Vasopressors were less used in the APRV-group than in the SIMV-group with a significant difference found between the two groups ($p=0.018$). One case of pneumothorax was observed in each group.

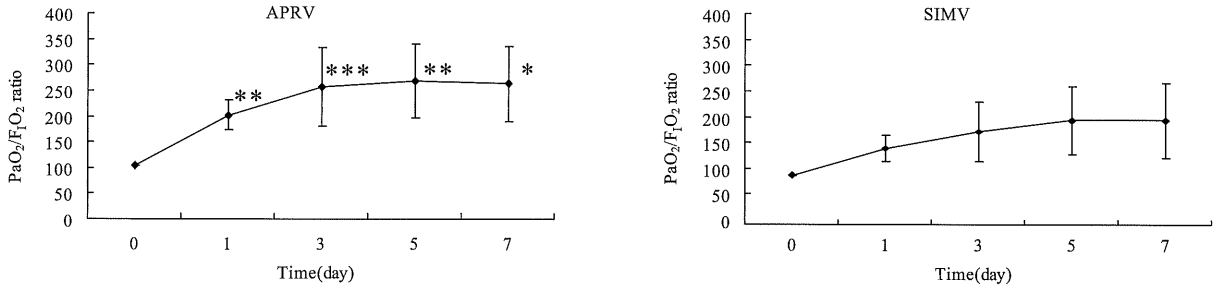

Fig. 1. PaO_2/F_IO_2 ratio at baseline and during 7 days in patients ventilated with airway pressure release ventilation (APRV) or with synchronized intermittent ventilation (SIMV).
PaO_2/F_IO_2 ratio: the ratio of partial arterial oxygen tension to fraction of inspired oxygen.
Day 0 (baseline) was defined when PaO_2/F_IO_2 ratio ≥ 150 could not be maintained with SIMV ventilation.
Values are mean ± SEM.
*$p<0.05$, **$p<0.01$, ***$p<0.001$, vs. SIMV, respectively

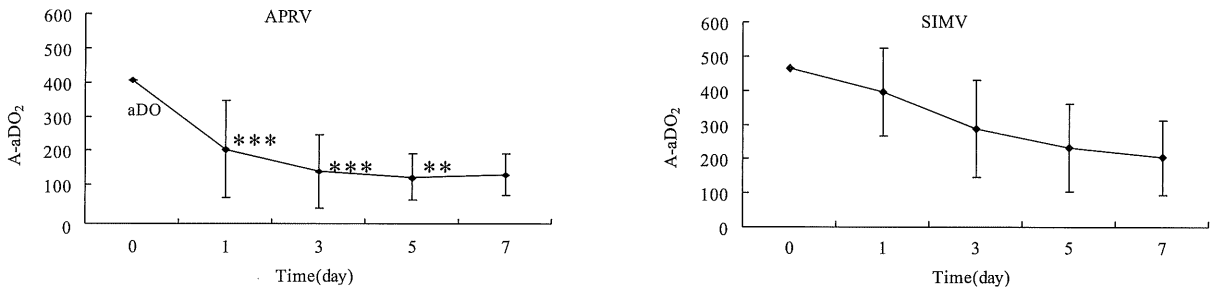

Fig. 2. A-aDO_2 at baseline and during 7 days in patients ventilated with airway pressure release ventilation (APRV) or with synchronized intermittent ventilation (SIMV).
A-aDO_2: alveolar-to-arterial difference in oxygen tension.
Day 0 (baseline) was defined when PaO_2/F_IO_2 ratio ≥ 150 could not be maintained with SIMV ventilation.
Values are mean ± SEM.
$p<0.01$,*$p<0.001$, vs. SIMV, respectively

DISCUSSION

The present retrospective analysis compared two different ventilatory strategies for patients with severe ARDS. The goal of this investigation was to assess the potential benefits and disadvantages of a ventilator strategy employing unsupported spontaneous breathing superimposed on mechanical ventilation for severe ARDS patients for whom a standardized initial management including tracheal intubation, mechanical ventilation using SIMV mode, hemodynamical support by intravascular volume control and use of vasopressors had failed. We found that APRV offered better oxygenation than SIMV during the first 7 days of mechanical ventilation. Also, our study indicated a trend toward improvements in mortality in the APRV group compared with a conventional ventilatory support.

Our hypothesis on the potential benefits of APRV was based on several experimental and clinical studies. Computed tomography (CT) of patients with ARDS has been used to identify radiographic densities corresponding to alveolar collapse localized primarily in dependent regions of the lung, correlating with intrapulmonary shunting[3]. Persistent spontaneous breathing has been considered to improve the distribution of ventilation to dependent areas of the lung and thereby ventilation/perfusion (VA/Q) matching, presumably by diaphragmatic contraction opposing alveolar compression[2,8]. This concept is supported by CT scan observations in anesthetized patients demonstrating that contractions in the diaphragm induced by phrenic nerve stimulation favor distribution of ventilation to dependent, well-perfused areas of the lung and decrease atelectasis formation[5]. Spontaneous breathing with APRV in experimentally induced lung injury has been associated with less atelectasis formation in end-expiratory spiral CT of the whole lungs and in scans above the diaphragm[17]. In patients at risk for developing ARDS, maintaining spontaneous breathing with APRV resulted in lower venous admixture and better arterial blood oxygenation over an observation period of longer than 10 days as compared with controlled mechanical ventilation with subsequent weaning[10]. These findings indicate that, even in patients requiring ventilatory support, maintenance of spontaneous breathing with high mean airway pressure could counteract progressive deterioration in pulmonary gas exchange. Conversely, when SIMV with pressure support is applied, every breathing effort is mechanically augmented to ensure stable alveolar ventilation. This might be explained in part by the finding that pressure support ventilation,

Table 2. Arterial blood gases at baseline and at days 1, 3, 5, and 7

	APRV				SIMV			
	pH	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	HCO_3-(mmol/L)	pH	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	HCO_3-(mmol/L)
Day 0	7.362 ± 0.131	42.8 ± 12.2	78 ±23.6	23.5 ±6.4	7.310 ±0.126	45.4 ± 11.2	80.2 ± 22.9	21.9 ± 5.2
Day 1	7.378 ± 0.122	42.8 ± 11.6	96.1 ±23.4	24.6 ±4.6	7.376 ±0.097	44.3 ± 10.7	107.9 ± 27.3	25.1 ± 4.3
Day 3	7.426 ± 0.053	42.3 ± 8.9	109.1 ±22.9	26.6 ±3.1	7.375 ±0.110	47.2 ± 13.9	112.9 ± 44.2	26.4 ± 4.8
Day 5	7.415 ± 0.065	44.7 ± 7.8	109.7 ±25.7	27.2 ±4.6	7.377 ±0.093	49.4 ± 11.0	108.1 ± 39.1	28.1 ± 4.4
Day 7	7.380 ± 0.123	50.1 ± 16.4	108.0 ±26.8	28.1 ±5.1	7.398 ±0.084	46.9 ± 10.8	95.7 ± 21.5	28.3 ± 5.9

APRV: airway pressure release ventilation; SIMV: synchronized intermittent mandatory ventilation.
Day 0 (baseline) was defined when PaO_2/F_IO_2 ratio ≥ 150 could not be maintained with SIMV ventilation.
Values are mean ± SEM

Table 3. Comparison of outcome of the patients ventilated with APRV or SIMV

Parameter	APRV-group	SIMV-group	p-value
Vasopressor dependence (%)	68	93	0.018
Duration of Ventilation	27 ± 39	23±20	0.581
Duration of ICU stay	35 ± 49	31±38	0.749
Mortality in ICU (%)	31	59	0.05

APRV: airway pressure release ventilation; SIMV: synchronized intermittent mandatory ventilation; ICU: intensive care unit
Values are mean ± SEM or percentage as indicated.

even as a patient-trigged mode of ventilation, did not differ from the totally controlled mode of ventilation in terms of effects on VA/Q matching or oxygen delivery[12].

Wrigge et al used X-ray computer-assisted tomography in a pig model demonstrating that the end-expiratory lung volume increased after 4 hr of spontaneous breathing as compared with ventilation at equal airway pressure without spontaneous breathing. This recruitment was seen as a larger amount of normally aerated lung in dependent regions of the lung[17]. In a prospective, crossover study, spontaneous breathing during APRV did not necessarily lead to instant improvements in gas exchange among patients with ARDS, but rather to continuous improvements in oxygenation over 24 hr after the start of spontaneous breathing[14]. The present results support other findings that oxygenation is significantly improved with APRV after day 1.

The ultimate challenge for proponents of any new technique is to show improved outcomes. Although physiological improvements appeal to clinicians, it must always be remembered that sometimes the ultimate outcome of physiological improvements may be unacceptable. A classic example is from the low-V_T study by the ARDS Network, which found that the high-V_T strategy produced better oxygenation and mechanical functioning over the first 2 days, but ultimately produced more volume-induced lung injury and higher mortality[15]. APRV has been used at the R Adams Cowley Shock Trauma Center in Baltimore since 1994 and has become a standard of care. The mortality rate after implementation of APRV in patients meeting criteria for ARDS was 21.4% overall, and lower than the 31% reported in the ARDS Net trial[7]. A long-term study focusing on APRV in patients at risk of ARDS (meaning "less severe" ARDS) showed that APRV with spontaneous breathing was associated with better cardiopulmonary function, and decreased durations of both ventilatory support and stay in the ICU[10]. However, another recent trial by Varpula et al demonstrated no difference in clinical outcomes (ventilator-free status at day 28 and all physiological variables) when patients were randomized to APRV versus SIMV after meeting ALI (Acute Lung Injury) criteria[16]. Differences in the results of the present study and those of Varpula et al may be due to differences in the severity of ARDS in the patients enrolled.

Potential disadvantages of APRV include barotrauma of the lung (i.e. pneumothorax) and negative hemodynamical effects such as hypotension caused by high mean airway pressures or potentially high tidal volumes produced at the pressure release phase of the APRV. Shearing of terminal lung units and vascular endothelium may occur during rapid deflation below some lower inflection point (LIP) of the pressure-volume curve. However, we experienced only one case of pneumothorax in the APRV group, and less use of vasopressors was observed in the APRV group. Habashi argues that the resistive load of the artificial airway sufficiently delays expiration to prevent derecruitment even if Plow is set at 0 cm H_20[4]. Small lung compliance due to severe ARDS may explain our favorable results in part.

The present study does have significant limitations. Firstly, this was an uncontrolled retrospective study that compared the effects of APRV with those of SIMV as a historic control. Second, the number of the subjects was relatively small particularly in the APRV group, and therefore the findings may be susceptible to statistical errors. Finally, although we observed a trend toward improvement in mortality in the APRV group, time-related changes in medical strategies occurred including new developments in general patient care over the 6-year study period. We recognize and stress that clinical decisions should derive from robust samples of patients with appropriate statistical controls. Prospective controlled studies are thus required to elucidate the exact benefits of this ventilatory mode in comparison with conventional methods for severe ARDS.

In summary, use of APRV in patients with severe ARDS appears to be associated with improvements in oxygenation and a trend toward a lower mortality in ICU. No significant adverse effects were observed.

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