*Acta Anaesthesiol Scand 2004; **48**: 722–731*
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2004.00411.x

Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome

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Background: Airway pressure release ventilation (APRV) is a ventilatory mode, which allows unsupported spontaneous breathing at any phase of the ventilatory cycle. Airway pressure release ventilation as compared with pressure support (PS), another partial ventilatory mode, has been shown to improve gas exchange and cardiac output. We hypothesized whether the use of APRV with maintained unsupported spontaneous breathing as an initial mode of ventilatory support promotes faster recovery from respiratory failure in patients with acute respiratory distress syndrome (ARDS) than PS combined with synchronized intermittent ventilation (SIMV-group).
Methods: In a randomized trial 58 patients were randomized to receive either APRV or SIMV after a predefined stabilization period. Both groups shared common physiological targets, and uniform principles of general care were followed.
Results: Inspiratory pressure was significantly lower in the APRV-group (25.9 ± 0.6 vs. 28.6 ± 0.7 cmH_2O) within the first week of the study ($P = 0.007$). PEEP-levels and physiological variables (PaO_2/FiO_2-ratio, $PaCO_2$, pH, minute ventilation, mean arterial pressure, cardiac output) were comparable between the groups. At day 28, the number of ventilator-free days was similar (13.4 ± 1.7 in the APRV-group and 12.2 ± 1.5 in the SIMV-group), as was the mortality (17% and 18%, respectively).
Conclusion: We conclude that when used as a primary ventilatory mode in patients with ARDS, APRV did not differ from SIMV with PS in clinically relevant outcome.

Accepted for publication 23 February 2004

Key words: Acute respiratory distress syndrome; airway pressure release ventilation; mechanical ventilation.

WELL-KNOWN physiological and clinical disadvantages of full ventilatory support have an increased tendency of dependent atelectasis, worsening of ventilation-perfusion matching, decreased oxygen delivery and organ perfusion, increased need of sedation, and muscle atrophy (1–4). Therefore, partial ventilatory support, which preserves the patient's own breathing activity but provides a desired degree of ventilatory assistance, is increasingly used as a primary ventilatory mode in acute respiratory failure (5). When 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 ICU stay with patients at risk of acute respiratory distress syndrome (ARDS) (6–8).

Supported by institutional funding from the Helsinki University Hospital Institute, Jorvi Hospital and Instrumentarium Scientific Foundation.

Interaction between spontaneous breathing and mechanical ventilation is a critical issue in the use of partial ventilatory support, when the physiological effects of spontaneous breathing on gas exchange and hemodynamics are considered. Spontaneous breathing can be either uncoupled from the mechanical part of ventilation or the ventilator can provide inspiratory assistance for each inspiratory effort. A representative of the former type of partial ventilatory mode is airway pressure release ventilation (APRV) (9). 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. Pressure support ventilation (PS) is one of the latter types of partial ventilatory mode (10). When studied in an animal model or in a clinical trial among patients with ARDS, gas exchange and cardiac output were similar during totally controlled ventilation and when each inspiratory effort was assisted by PS (11, 12). However, uncoupling of spontaneous breaths and mechanical

cycles of ventilator with APRV led to improved gas exchange and increased cardiac output (11, 12).

Pressure support is commonly combined to synchronized intermittent ventilation (SIMV) in order to provide the desired amount of mechanical support of ventilation (13). In an international survey, PS with or without SIMV was used in 47% of mechanically ventilated patients (14). In Nordic countries SIMV combined with PS was recently the most commonly used ventilatory mode for respiratory failure (15).

Airway pressure release ventilation may improve the clinical outcome measures when compared with partial ventilatory support with PS due to the potential beneficial effects on gas exchange and on hemodynamics between these two ventilatory modes. Therefore, we hypothesized that patients with a partial ventilatory strategy allowing unsupported spontaneous breathing as a primary mode of ventilation will demonstrate faster recovery from respiratory failure and hence an increased number of days alive without mechanical ventilation when compared with patients with ventilatory support assisting each breath. To test this hypothesis we designed a randomized, controlled trial comparing APRV with SIMV combined with PS in adult patients with early ARDS.

Methods

Patients and study design

The study protocol was approved by the Ethics Committee of Helsinki University Hospital. Surrogate informed consent was obtained for all patients. Patients were recruited from December 1997 through December 2001 in a single, closed, university hospital ICU.

We screened all adult, mechanically ventilated patients in the department. Those patients who at admission fulfilled the consensus criteria for ALI (16) were submitted to a stabilization phase during which they were ventilated with time-cycled, pressure-controlled, assist/control mode. Externally applied PEEP was set based on pressure-volume curves, as described later. During this stabilization phase, the monitoring was instituted and inclusion and exclusion criteria were confirmed. Routine monitoring included an arterial catheter and a thermistor-tipped and fiberoptic pulmonary artery catheter for mixed venous saturation measurement. At the end of this stabilization period, patients were included if they met the following criteria: PaO_2/FiO_2-fraction <27 kPa(200 mmHg), bilateral radiographic pulmonary infiltrates and pulmonary artery occlusion pressure of 18 mmHg or less. Patients were excluded if they had had greater than 72 h of mechanical ventilation, chronic pulmonary disorder, neurological cause of respiratory failure, contraindication to permissive hypercapnia, condition where full life-support was not indicated, or if the patient had participated in interventional trials of septic shock within 30 days. Stabilization period lasted from 2 to 24 h.

The patients were randomized using a concealed allocation approach with sealed envelopes provided by an independent statistician. Patients were randomized to one of the two protocol groups: the APRV or SIMV-PC/PS group consisting of two different ventilatory strategies with identical general ventilatory measures and general care. Randomized ventilatory strategy was started immediately after the inclusion and it was rigorously maintained until the weaning criteria were met or the patient deceased.

Demographical and prognostic data were collected during the first 24 h after admission to the ICU. Severity of illness was assessed by using APACHE II (17) and SOFA scores (18). Severity of lung injury was assessed by the Lung Injury Score (19). Median values of physiological variables during the stabilization period represent the baseline.

Ventilatory strategies

The physiological targets and basis for main ventilatory settings were similar during the stabilization period and thereafter in both groups. Oxygenation goal was PaO_2 8 kPa or greater. The target for $PaCO_2$ was between 5 and 8 kPa, but higher $PaCO_2$ was also allowed if pH at the same time remained greater than 7.20.

All patients were ventilated with a Servo 300 SV (Siemens-Elema, Gothenburg, Sweden) ventilator using pressure-controlled ventilatory modes. In order to set inspiratory pressure and PEEP, the following protocol was followed: the pressure-volume (PV) curve of the patient's respiratory system was constructed during the stabilization phase and thereafter according to judgements of attending clinicians until the weaning phase. Pressure-volume curves were reconstructed during the transient neuromuscular blockade. For the first 12 patients, the PV-curve was gained by applying variable tidal volumes and measuring static airway pressures, and for the rest of the patients by using the slow-flow inflation method (20). External PEEP was titrated above the lower inflection point (LIP) of the PV-curve. If the LIP was not detectable, PEEP was set to 10 cm H_2O. Inspiratory pressure (Pinsp) was set to accomplish a tidal volume between

8 and 10 ml kg^{-1}. However, the upper inflection point (UIP), if detected from the PV-curve, was never exceeded. Inspiratory pressure was always kept less than 35 cmH_2O.

Prone positioning was part of the protocol for both groups. Assessment for the prone position was performed twice a day and the patient was turned prone if the PaO_2/FiO_2-ratio decreased to less than 27 kPa. Prone positioning was accomplished without any special equipment and used in 6-h periods. We have previously reported the data of gas-exchange during the first two prone position periods (21).

A summary of the ventilator strategies followed after randomization is presented in Table 1. Attending physicians took care of ventilator management according to a written protocol. Briefly, in the APRV-group, the ventilatory mode was accomplished with a special module (Bivent, Siemens-Elema, Gothenburg, Sweden) attached to the Servo 300 SV ventilator. With this module, the ventilator can be set to a mode at which unsupported, spontaneous breathing is possible throughout the entire ventilatory cycle at two airway pressure levels. The time periods for the pressure levels can be set independently. The duration of the lower pressure level was adjusted to allow expiratory flow to decay to zero. The duration of the higher pressure level was adjusted to produce 12 pressure shifts per minute. The target for the patient's spontaneous breathing frequency was from 6 to 18 times per minute. Tidal volumes of spontaneous breathing greater than 10% the level of mechanical tidal volumes were considered sufficient. The presence of spontaneous breathing was continuously verified from the flow and pressure tracings of the ventilator's display. If spontaneous breathing was not achieved, the level of sedation was decreased. If sedation was adequate, the frequency of pressure shifts was decreased. If spontaneous breathing frequency increased greater than 20 per minute, sedation was increased and if needed the mechanical frequency increased.

In the SIMV-group patients were ventilated with the pressure-controlled SIMV-mode with pressure support. Rate of mandatory time-cycled, pressure-controlled breaths, was set initially to 12 per minute. Pressure support of 10 cmH_2O was used for triggered breaths. In pressure-supported breaths, inspiratory pressure was maintained until inspiratory gas flow decreased to 25% of its peak value. In the SIMV group triggered breaths were not required. If frequency of triggered breaths increased greater than 10 per minute, sedation was increased and, if needed, the rate of mandatory breaths increased.

Table 1

Summary of ventilatory strategies.

	APRV-group	SIMV-group
Response to patients effort	Unsupported, spontaneous breathing Required 6 to 18 per min	Pressure support of 10 cmH_2O Not required
Initial settings		
PEEP	Titrated according PV-curve	Titrated according PV-curve
Pplat allowed	$<$35 cmH_2O or UIP	$<$ 35 cmH_2O or UIP
Tidal volume	Driving pressure titrated to form 8 to 10 ml kg^{-1} tidal volume	Driving pressure titrated to form 8 to 10 ml kg^{-1} tidal volume
Set respiratory rate	12 pressure releases min^{-1}	12 SIMV-cycles min^{-1}
Length of inspiratory phase	4 s	35% of the SIMV-cycle
Length of expiratory phase	1 s	65% of the SIMV-cycle
Measures to achieve oxygenation target ($PaO_2 > 8$ kPa)		
FiO_2	Increase up to 1.0	Increase up to 1.0
IRV	Not used	IRV ad 2:1
Measures to achieve ventilation target ($PaCO_2 < 8$ kPa)		
Spontaneous breathing	Decrease of sedation	Not used
Mandatory ventilation	Shortening of inspiratory time	Increase of the set mandatory rate
Weaning		
Inspiratory pressure	to 20 cmH_20	to 20 cmH_20
FiO_2	to 0.35 T-piece trials applied with CPAP	to 0.35 T-piece trials applied with CPAP

PEEP = positive end expiratory pressure; Pplat = inspiratory plateu pressure; PV-curve = pressure-volume-curve; UIP = upper inflection point of the PV-curve; FiO_2 = fraction of inspired oxygen; IRV = inverse ratio ventilation; CPAP = continuous positive airway pressure.

General patient care

Excluding the prone position periods, patients were nursed in a 30% semirecumbent position. Infusion of fentanyl was given for analgesia based on a clinical subjective assessment of pain. Excessive ventilatory drive was also an indication for increasing the fentanyl dose in both groups. In the APRV-group the fentanyl dose was decreased if spontaneous breaths were suppressed. Infusion of propofol was given for sedation according to the underlying disease as clinically needed. Muscle relaxants were given only for the measurement of lung mechanics or occasionally for other procedures, such as bronchoscopy and tracheostomy. Besides the prone position, no other non-ventilatory cointerventions (inhaled nitric oxide, almitrine or extracorporeal membrane oxygenation) for ARDS were in use during the study. High dose methylprednisolone treatment for late stage fibroproliferative ARDS was considered if after 1 week of treatment the patient's X-ray showed signs of fibroproliferation and if at the same time oxygenation and lung compliance showed no trend for improvement (22). Before initiating steroids, CT scanning of the lung was performed in order to rule out lung empyema and to confirm fibrotic changes in lung parenchyma.

Other principles of treatment including nutrition, hemodynamic management, renal replacement therapy or airway management were administered according to the written protocols of the unit.

Collection of physiological variables and outcome measures

Hemodynamic measurements were performed by using the information obtained from arterial cannulae and pulmonary artery catheters. A side-stream spirometry (MCOVX, Datex-Ohmeda, Helsinki, Finland) integrated in a patient's monitor (CS/3, Datex-Ohmeda, Finland, Helsinki) was used for monitoring of ventilatory variables (minute ventilation (MV), tidal volume (TV), fraction of inspired oxygen (FiO_2), and end-tidal CO_2 ($ETCO_{2)}$, PEEP and Pinsp). Arterial blood gases were determined by using standard blood gas electrodes. Measurements were made under stable conditions. Sampling frequency of continuous variables was every second hour during the first 3 days and every 4 h during days 3–7. Median values of physiological parameters represent the values of each time period.

Endpoints and statistical analysis

The primary endpoint of the study was the number of ventilator-free days, defined as the number of days the patient is breathing without assistance from randomization to day 28. Sample-size calculations according to routine methods (a power of 80% and a *P*-value less than 0.05) revealed that approximately 40 patients per group is sufficient to detect a 15% difference in ventilator-free days between the study groups. Thus, the sample size of 80 patients was set.

Secondary endpoints were the effects of ventilation mode on ventilatory and hemodynamic variables and on the consumption of sedatives during 7 days after ICU admission. The duration of ICU stay, ICU-free days during the first 28 days and all causes of mortality in the hospital both within 90 days and within 1 year were also recorded.

Demographical variables are reported as the median and interquartile ranges. Outcome measures and continuous physiological variables are presented as mean and standard error of mean. For comparisons, the Fisher exact test and Mann–Whitney test were used when appropriate. Multiple logistic regression analysis was used to test the independency of APRV, age and APACHE II-score as a determinant of outcome. All analysis was performed by SPSS 11.5 software (SPSS Inc., Chicago, IL). A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Patient demographics

A total of 1584 patients were treated in the unit during the study period. After stabilization, 58 patients fulfilled the inclusion criteria, met none of the exclusion criteria and were thus enrolled and randomized. Demographical data at inclusion are presented in Table 2. There were no differences in any demographical or prognostic parameters between the groups. The majority of the patients in both study groups had primary lung injury (77%). Median length of mechanical ventilation prior to the start of the randomized ventilatory strategy was 39.1 (±2.3) h in the whole study population and there was no difference between the groups. Delays were caused by referral of the patient from other hospitals, and obtaining the consent and diagnostical procedures during the stabilization phase

Ventilatory variables and gas exchange

Ventilatory variables during stabilization and the first 7 days after randomization are presented in Fig. 1 and Table 3. During the stabilization phase the PaO_2/FiO_2-ratio was slightly higher in the SIMV-group (21.9 ± 1.4 kPa) than in the APRV-group (20.0 ± 1.4 kPa), but the difference was not significant

Table 2

Characteristics of patients at inclusion in the study.

	APRV-group	SIMV-group	*P*-value
No. of patients	30	28	
Gender (M/F)	21/9	18/10	
Age (years)	50.0 (38.5–60.5)	44.0 (35.5–53.0)	0.14
Primary ALI/ secondary ALI	23/7	22/6	0.23
APACHE II	15 (12.5–18.0)	14 (11.25–17.0)	0.61
SOFA	9.0 (7.0–10.5)	8.5 (8.0–9.8)	0.61
Lung injury score	3.0 (2.6–3.5)	3.1 (2.7–3.3)	0.82

APACHE II = Acute Physiology and Chronic Health Evaluation Score; M/F = male/female; SOFA = sequential organ failure assessment. Values are given as median and interquantile range.
Variables analyzed by Mann-Whitney rank sum test

($P = 0.213$). Changes in PaO_2/FiO_2-ratio after the randomization were similar in both groups (Fig. 2). Tidal volume per body weight during the first week was 9.38 (± 0.16) ml kg^{-1} in the whole population and there were no differences between the groups or with time. In both study groups moderate hypercapnia developed during the first study day and $PaCO_2$ was returned towards normal after 4 days. In both groups pH remained within normal range during the study. Inspiratory pressure was significantly lower in the APRV-group (25.9 ± 0.6 vs. 28.6 ± 0.7 cmH_2O) during the first week ($P = 0.007$). Externally applied PEEP did not differ during the first week: 11.2 ± 0.3 cmH_2O in the APRV-group and 11.9 ± 0.3 cmH_2O in the SIMV-group ($P = 0.08$).

Hemodynamic variables

Hemodynamic data is summarized in Table 4. Pulmonary catheter was dwelling in all patients during the first 3 days. Pulmonary artery wedge pressures and cardiac indexes were comparable in the groups during the first week. The number of patients receiving cathecholamines was also comparable between the groups. At study entry 96% of the patients in the APRV-group and 93% of patients in the SIMV-group received cathecholamines. At day 7, nine patients out of 24 patients alive in the APRV-group and 12/24 in the SIMV-group were given vasoactive medication.

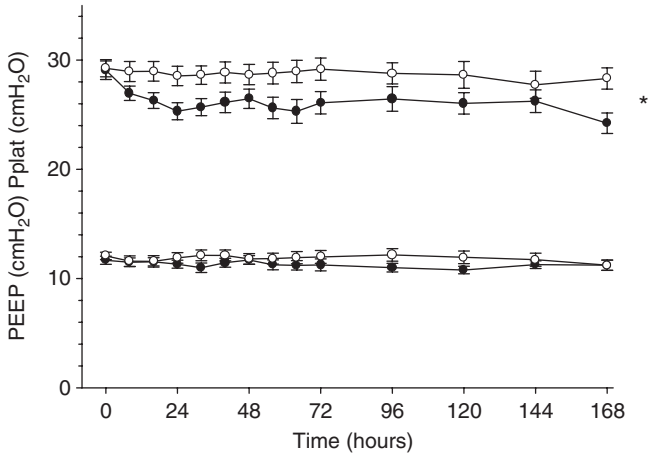

*Fig. 1. Inspiratory pressure (Pplat) and PEEP at baseline and during 7 days in patients ventilated with airway pressure release ventilation (APRV; ●) or with synchronized intermittent ventilation (SIMV) + pressure support (PS) (○). Values are mean ± SEM. *P=0.007.*

Sedation and adjunctive therapies

The use of sedatives (propofol) and analgesics (fentanyl) is presented in Fig. 3. The dosages of analgosedatives were comparable between the groups. Prone positioning was a part of the protocol as an adjunctive treatment. It was applied in a similar fashion in both groups. During the first week patients in the APRV-group spent 30.5 (±5.1) h in the prone position and those in the SIMV-group 30.3 (±4.5) h. The difference was not significant ($P = 0.11$). High-dose methylprednisolone for fibroproliferative ARDS was started for 62.1% (18/30) of patients in the APRV-group and 53.6% (15/28) in the SIMV-group. Protocol for supraphysiological doses of hydrocortisone (100 mg at 8-h intervals) for septic hypotension was added after June 2001. One patient in the APRV-group received this regimen and six patients in the SIMV-group. Renal replacement therapy (RRT) was given for eight patients in the APRV-group and for nine patients in the SIMV-group.

Outcomes

The primary outcome measure was the number of ventilator-free days after randomization. An interim analysis was carried out following two-thirds of the estimated 80 patients and it revealed that the APRV strategy would not achieve a significant difference within the planned frame of study. Therefore, the study was terminated for futility.

Table 3

Main ventilatory variables at inclusion and at days 1, 3, 5, and 7.

	Variable	n	APRV-group	n	SIMV-group	*P*-value
Tidal volume, ml kg^{-1}	Inclusion	30	8.8 (0.3)	28	9.3 (0.3)	0.22
	Day 1	26	9.2 (0.3)	28	9.0 (0.2)	0.69
	Day 3	22	9.3 (0.3)	26	9.2 (0.3)	0.54
	Day 5	21	9.3 (0.4)	22	10.0 (0.5)	0.26
	Day 7	18	9.3 (0.5)	21	9.7 (0.4)	0.71
Minute ventilation, l min^{-1}						
	Inclusion	30	9.6 (0.4)	28	9.6 (0.3)	0.93
	Day 1	26	8.5 (0.4)	28	9.1 (0.4)	0.41
	Day 3	22	9.9 (0.5)	26	10.6 (0.5)	0.51
	Day 5	21	10.1 (0.5)	22	11.2 (0.5)	0.19
	Day 7	18	10.1 (0.6)	21	10.9 (0.6)	0.41
$PaCO_2$, kPa	Inclusion	30	5.8 (0.3)	28	5.6 (0.2)	0.76
	Day1	30	6.8 (0.3)	28	6.5 (0.2)	0.50
	Day 3	28	6.7 (0.3)	27	6.7 (0.3)	0.91
	Day 5	25	6.3 (0.2)	26	6.4 (0.3)	0.39
	Day 7	24	6.3 (0.2)	24	6.2 (0.3)	0.76
pH	Inclusion	30	7.36 (0.01)	28	7.36 (0.01)	0.83
	Day1	30	7.31 (0.02)	28	7.33 (0.01)	0.22
	Day 3	28	7.36 (0.01)	26	7.38 (0.02)	0.09
	Day 5	25	7.40 (0.01)	26	7.39 (0.01)	0.40
	Day 7	24	7.40 (0.01)	24	7.40 (0.01)	0.86

Values are mean and SEM.
Variables analyzed by Mann-Whitney rank sum test.

The number of ventilator-free days was comparable in the APRV-group 13.4 (±1.7) and the SIMV-group 12.2 (±1.5) ($P = 0.83$). The number of ICU-free days out of 28 days was also similar: 11.9 (±1.7) in the APRV-group and 10.7 (±1.4) in the SIMV-group. The difference of means in respirator-free days was 1.2 days with 95% confidence intervals between −3.4 and 5.7 days.

Mortality at day 28 was 5/30 (17%) in the APRV-group and 5/28 (18%) in the SIMV-group ($P = 0.91$).

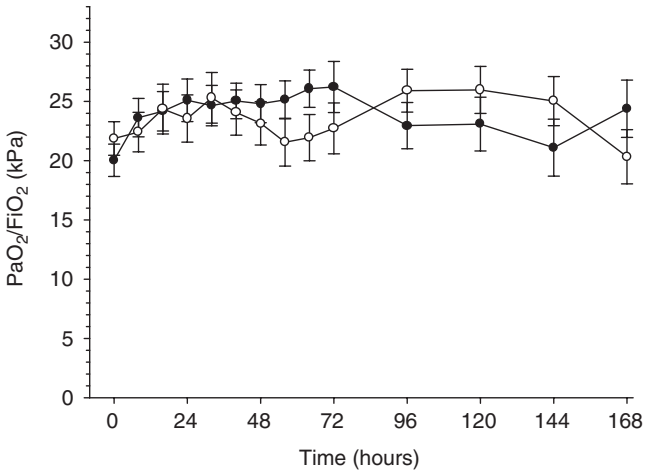

Fig. 2. PaO_2/FiO_2-ratio at baseline and during 7 days in patients ventilated with airway pressure release ventilation (APRV; ●) or with synchronized intermittent ventilation (SIMV) + pressure support (PS) (○). Values are mean ± SEM.

Mortality at 1 year was 21% in all patients: 17% (5/30) in the APRV-group and 25% (7/28) in the SIMV-group ($P = 0.43$). Survival curves and proportion of patients breathing without a ventilator are presented in Fig. 4. Development of organ failure was assessed by counting the change in SOFA-score between randomization and day 7. The SOFA-score decreased by 2.8 (±0.8) in the APRV-group and by 1.7 (±0.2) in the SIMV-group. The LIS-score decreased during the first 7 days by 0.8 (±0.1) points in the APRV-group and by 0.6 (±0.2) points in the SIMV-group.

Discussion

The present study is the first randomized and controlled trial comparing two different partial ventilatory modes in patients fulfilling the criteria of ARDS. Our goal in this investigation was to assess the potential benefits of a ventilator strategy, which employs unsupported spontaneous breathing superimposed on mechanical ventilation in ARDS patients. However, we found no significant differences in the clinically important outcome variables between this strategy and SIMV with pressure support. Our study was not powered to evaluate mortality between the groups.

Our hypothesis for the potential benefits of APRV was based on several experimental and clinical studies. In these studies APRV was associated with

Table 4

Main hemodynamic variables at inclusion and at days 1, 3, 5, and 7.

	Variable	n	APRV-group	n	SIMV-group	*P*-value
Mean arterial pressure, mmHg						
	Inclusion	30	75 (1.65)	28	74 (2.59)	0.75
	Day1	30	76 (1.79)	28	75 (1.62)	0.99
	Day 3	28	83 (2.53)	27	79 (1.87)	0.44
	Day 5	25	85 (3.10)	26	83 (2.28)	0.69
	Day 7	24	86 (2.65)	24	84 (2.71)	0.52
Pulmonary occlusion pressure, mmHg						
	Inclusion	30	14.8 (0.34)	28	15.1 (0.46)	0.64
	Day1	30	14.3 (0.36)	28	14.6 (0.44)	0.43
	Day 3	27	14.2 (0.55)	26	14.3 (0.39)	0.41
	Day 5	23	13.8 (0.50)	26	14.1 (0.55)	0.39
	Day 7	21	13.1 (0.61)	21	12.9 (0.49)	0.83
Cardiac index, $l\,min^{-1}\,m^{-2}$						
	Inclusion	30	4.3 (0.19)	28	4.3 (0.15)	0.88
	Day1	30	4.6 (0.20)	28	4.3 (0.16)	0.29
	day 3	27	4.5 (0.20)	26	4.5 (0.18)	0.90
	Day 5	23	4.3 (0.15)	26	4.5 (0.18)	0.24
	Day 7	21	4.4 (0.20)	21	4.5 (0.18)	0.98

Values are mean and SEM.
Variables analyzed by Mann-Whitney rank sum test.

improved ventilation-perfusion matching, decreased shunt and hence, better arterial oxygenation (23, 24). With maintained, diaphragmatic contraction ventilation is distributed more evenly and better to dependent and poorly aerated, but well perfused, lung regions when compared with controlled mechanical ventilation (25). Due to cyclic reduction of intrathoracic pressure resulting from spontaneous breathing, venous return is enhanced and filling of the heart is increased. This has been shown to contribute to enhanced cardiac output, which together with improved oxygenation results in increased oxygen delivery (26). These beneficial changes have been reported to occur even with a very small fraction of spontaneous minute ventilation of the total minute ventilation and with small unsupported tidal volumes (27). With this type of moderate amount of spontaneous breathing the oxygen consumption due to activity of respiratory muscles is not changed (12). In addition, spontaneous breathing has been associated with better organ perfusion when compared with total mechanical control of ventilation (28).

Most of the studies cited above have compared APRV with a strategy in which ventilator either

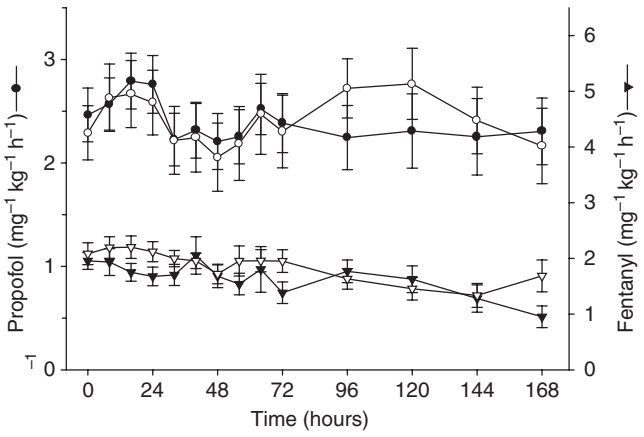

Fig. 3. Daily dose-rate of intravenously administered propofol (circles) and fentanyl (triangles) at baseline and for 7 days in patients ventilated with airway pressure release ventilation (APRV; closed symbols) or synchronized intermittent ventilation (SIMV) + pressure support (PS) (open symbols). Values are mean ± SEM.

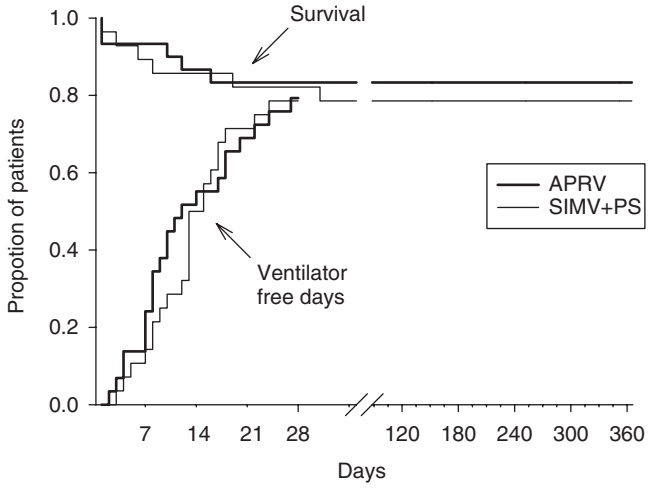

Fig. 4. Survival and being alive and breathing without assistance during the first year after randomization in patients ventilated with airway pressure release ventilation (APRV) (thick line) and synchronized intermittent ventilation (SIMV) + pressure support (PS) (thin line).

passively ventilates the subject and does the majority of the work of breathing even if the patient initiates some or even most of the breaths. In contrast to our prospective long-term study, Putensen and coworkers in a crossover setting compared APRV with spontaneous breathing to PS and to controlled ventilation (12). When equal pressure limits or minute ventilation were used they found that PS ventilation did not differ from controlled ventilation in its effects on gas exchange, hemodynamics, oxygen delivery or oxygen consumption, whereas beneficial effects in these variables were seen only with APRV and maintained unsupported spontaneous breathing (12).

In the present study the level of pressure support in the SIMV group was much lower (10 cmH20) than inspiratory pressure for controlled insufflations. Thus, spontaneous breathing with a low level of pressure support might have been associated with the same physiological benefits as with the unsupported spontaneous breathing with APRV. In other words, both our groups had the benefits of maintained spontaneous breathing. The difference between the groups might have been so small that possible benefits of particularly unsupported breaths could not be demonstrated.

In some studies, APRV has been demonstrated to improve oxygenation during early phases of ALI (8, 27). In a prospective and crossover study APRV has been shown to improve gas exchange and decrease venous admixture in ARDS-patients when compared with inverse ratio volume-controlled ventilation. This effect was observed after 8 h (29). In a recent study Wrigge and coworkers showed in a pig model with X-ray computer-assisted tomography that end-expiratory lung volume increased after 4 h of spontaneous breathing as compared with ventilation with equal airway pressure without spontaneous breathing. This recruitment was seen as a larger amount of normally aerated lung in dependent lung regions (30). In our study we noticed improved PaO_2/FiO_2-ratios in the APRV-group, albeit not significant, after 24 h, but there were no differences after the fourth day.

Airway pressure release ventilation has been previously compared with totally controlled ventilatory support in one prospective, randomized clinical trial by Putensen and coworkers (8). In that trial, the study population was multiple trauma patients at risk for ARDS. In the treatment group, APRV was employed very early (6 h) after the beginning of ventilatory support. In our study with confirmed ARDS patients the delay to the start of ventilatory treatment under study was much longer (mean 39 h). Alveolar collapse, which is the hallmark of severe ARDS, develops early in the disease process. Once dependent collapse and consolidation have developed, they might be very resistant for measures to recruit alveoli (31). Also the type of lung injury might have had an impact (32). In the Putensen's study patients had secondary or an indirect type of lung injury (8). In some studies it has been shown that lung with secondary injury is more easily recruitable than lung with direct or primary injury; the type of injury most of our patients had (33, 34). Another major difference between our study and Putensen's study was the non-ventilatory management of the control group. In our study sedation policy was the same in both groups and long-term muscle paralysis was not used in either group; both factors which could *per se* have impacted on outcome variables such as length of mechanical ventilation, length of ICU stay, and even mortality. In analgosedation we found no differences, which could be explained by the fact that the control group also had the possibility of triggering the ventilator and it was not suppressed with sedation.

Our study has some methodological limitations. Either the ventilator used in this study or the spirometry technique could not measure accurately the amount of spontaneous ventilation. Measuring the amount of spontaneous breathing precisely during partial ventilatory support is difficult and requires the measurement of esophageal pressure, which would not have been feasible in a long-term clinical trial. However, it care was meticulously taken that patients in the APRV-group maintained spontaneous breathing and this was verified by observing the flow and pressure tracings of the ventilator. Due to variability in inspiratory pressures and in inspiratory times because of the use of pressure support in the SIMV-group, it was impossible to compare the true mean airway pressures between the study groups. Therefore, we cannot rule out the possibility that the mean airway pressure might have been different between the groups.

At the time of recruiting patients to the study prone position was a part of standard treatment of ARDS in our unit. In both groups the prone position was used as a prophylactic maneuver and it might have prevented dependent alveolar derecruitment, consequent ventilation-perfusion mismatch, and development of severe hypoxemia. Although there was no difference in the times nursed prone between the groups, this is a confounding factor in assessing the effects of the two ventilatory modes on gas exchange. We have reported earlier that during the two first prone episodes, unsupported spontaneous breathing and prone position, had a synergistic, positive effect on gas exchange (21).

In prospective studies with cardiac surgery patients (4) and with trauma patients (8, APRV has been shown to decrease the consumption of analgesics and sedatives when compared with controlled ventilation. In our study we found no difference in analgosedation between the ventilatory strategies under investigation. The possibility for patient's initiated breaths also with SIMV-pressure support could have dissolved the differences between ventilatory modes in adaptation to the ventilator. We did not use any sedation scale and therefore we cannot rule out that we might have been achieved a different level of sedation in the groups.

We planned this study before the ARDS network-study was published (35). In our patients, the mean tidal volume per body weight was larger than that used for the treatment-group in the ARDS net-study. However, plateau pressures in both groups in our trial were significantly less than 35 cmH_2O, as recommended by consensus conference in 1993 (36). Recently, also criticism towards the use of a very low tidal volume have been presented (37). Very low tidal volumes may be harmful, especially to patients without severely impaired lung compliance.

North American-European consensus criteria for ARDS were developed to include patients in clinical trials (16). These criteria have been criticized because the oxygenation criteria do not determine the ventilator setting when the PaO_2/FiO_2-ratio is measured. In our trial the patients were stabilized with a standardized protocol, and diagnostic criteria for ARDS were evaluated at the end of this phase. This practice confirmed that patients really had severe failure of gas exchange and that the oxygenation failure was not due to, for example, temporary atelectasis or inappropriate ventilator settings. However, this stabilization phase delayed randomization and the start of the ventilatory protocol.

Our sample size was based on a power analysis with the assumption of a decrease in ventilator-free days by 15% with APRV. However, the study was terminated for futility on the basis of an interim analysis, when two-thirds of the estimated 80 patients were included. The decision to terminate the study was also based on slow recruitment of the patients and on the need to change several general principles of care. The difference in ventilator-free days between the groups in the 58 patients included was 9% (1.2 days) in favor of APRV, which is not statistically significant. However, in order to evaluate the possibility of too small a sample size, we calculated the 95% confidence interval for the difference in ventilator-free days between the groups. This analysis showed that the upper limit of the confidence interval was 5.7 days, i.e. a 43% increase in ventilator-free days with APRV as compared with SIMV with PS. This indicates that we cannot definitely exclude the possibility of a clinically significant difference between the ventilatory modes and that our study was not powered enough to answer the hypothesis posed.

In conclusion, the 1-year mortality in our study, 21% of the whole material, was below the range of recently published mortality rates (from 31 to 70%) in clinical trials with ARDS patients (38–40). Thus, a ventilatory strategy utilizing partial ventilatory support with either unsupported spontaneous breathing (APRV) or pressure-supported ventilation (SIMV) together with prophylactic prone positioning was a feasible treatment strategy for ARDS patients. However, we were unable to demonstrate any difference between the two strategies, APRV and SIMV with PS, regarding the primary endpoint of the study; i.e. the number of ventilator-free days.

Acknowledgements

We are indebted to the intensive care nurses and physicians at Helsinki University Hospital, as well as our patients and their families, who supported this trial.

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