

Ventilatory Support by Continuous Positive Airway Pressure Breathing Improves Gas Exchange as Compared with Partial Ventilatory Support with Airway Pressure Release Ventilation

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In acute lung injury, airway pressure release ventilation (APRV) with superimposed spontaneous breathing improves gas exchange compared with controlled mechanical ventilation. However, the release of airway pressure below the continuous positive airway pressure (CPAP) level may provoke lung collapse. Therefore, we compared gas exchange and hemodynamics using a crossover design in nine pigs with oleic acid-induced lung injury during CPAP breathing and APRV with a release pressure level of 0 and 5 cm H₂O. At an identical minute ventilation (\dot{V}_E 8 L/min) spontaneous breathing averaged 55%, 67%, and 100% of \dot{V}_E during the two APRV modes and CPAP, respectively. Because of the concept of APRV, mean airway pressure was highest during CPAP and lowest during APRV with a

release pressure of 0 cm H₂O. Shunt was reduced to almost half during CPAP (6.6% of Q_t) compared with both APRV-modes (13.0% of Q_t). Cardiac output and oxygen consumption, in contrast, were similar during all three ventilatory settings. Thus, in our lung injury model, CPAP was superior to partial ventilatory support using APRV with and without positive end-expiratory pressure. This may be attributable to beneficial effects of spontaneous breathing on gas exchange as well as to rapid lung collapse during the phases of airway pressure release below the CPAP level. These findings may suggest that the amount of mechanical ventilatory support using the APRV mode should be kept at the necessary minimum.

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Improved oxygenation and increased cardiac output result from the interaction of spontaneous breathing and mechanical ventilation (1–3). Interestingly, these beneficial effects of spontaneous breathing were observed only during airway pressure release ventilation (APRV) but not during pressure support ventilation (1,3). APRV is a unique approach to ventilatory support because ventilation is achieved by a periodic pressure release from a preset continuous positive airway pressure (CPAP) level to a lower airway pressure (P_{aw}), rather than by increasing P_{aw} intermittently higher than CPAP as performed during more conventional forms of mechanical ventilation (4,5). APRV can provide full ventilatory support for patients who are not capable of spontaneous breathing and is then identical to pressure-controlled ventilation.

APRV can also be used for partial ventilatory support with the unique possibility of unrestricted spontaneous breathing throughout the whole ventilatory cycle. Finally, if equal inspiratory and expiratory airway pressures are chosen, APRV is identical to CPAP. APRV was introduced for the treatment of patients with severe acute lung injury (4) and has been studied in experimental lung injury (1,2,5) as well as in clinical trials (3,6–8). Two studies have shown that lung collapse may occur rapidly during each expiration, followed by recruitment during the succeeding inspiration (9,10). These observations call for an analysis of the effects on respiratory mechanics and gas exchange of the short pressure releases during APRV with and without the application of positive end-expiratory pressure (PEEP).

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Material and Methods

Study Protocol

After approval of the local animal ethics committee, 15 healthy pigs (mixed Swedish country breed, weight 33 ± 5 kg) were anesthetized and mechanically ventilated. In nine pigs (Study group) baseline values

were obtained 30 min after instrumentation, followed by induction of lung injury with oleic acid injected via a central venous catheter. After a stabilization period of 120 min measurements were repeated, then three ventilatory settings were sequentially applied for 1 h each in random order. Thereafter, mechanical ventilation was studied once more to assess any change in lung function over time (Fig. 1). Hemodynamic and ventilatory measurements were performed at the end of each study period; thereafter the pigs were paralyzed for a brief period to measure compliance of the respiratory system and the amount of mechanical ventilation during partial ventilatory support. Controlled mechanical ventilation with PEEP 20 cm H₂O and an inspiratory pressure of 50 cm H₂O followed each study period for 5 min to have a consistent volume history before each study mode.

In a second group of 6 pigs the stability of our lung injury model over time was evaluated during mechanical ventilation after induction of lung injury (Time Control group). Handling of animals and data collection were performed as in the Study group. This resulted in a total study period of approximately 8 h.

Anesthesia

Forty mg azaperonum (Stresnil[®], Janssen, Belgium) were given IM as premedication before transport from the farm. General anesthesia was induced with atropine (0.04 mg · kg⁻¹), tiletamin/zolazepam (Zoletil[®], Reading, Carros, France) (6 mg · kg⁻¹), and xylazin (Rompun[®], Bayer, Leverkusen, Germany) (2.2 mg · kg⁻¹) IM, followed by a constant infusion of 400 mg · h⁻¹ clomethiazole (Heminevrin[®], Astra, Södertälje, Sweden), 100 µg · h⁻¹ fentanyl, 200 µg · h⁻¹ ketamine, and 6 mg · h⁻¹ xylazin. The animals were endotracheally intubated with a cuffed tube and connected to the ventilator.

Before baseline measurements, 1000 mL Ringer's acetate (Pharmacia AB, Stockholm, Sweden) at body temperature was infused; thereafter, fluid replacement was aimed at a constant hemoglobin value and a stable systemic arterial blood pressure. This resulted in an average infusion rate of 20–30 mL · h · kg⁻¹ after induction of lung injury.

Ventilation

Mechanical ventilation was initiated using the BIPAP mode of the Evita 4 ventilator (Drägerwerke, Lübeck, Germany) with an F_{IO₂} = 0.5, a respiratory rate of 20 breaths · min⁻¹, and an inspiratory:expiratory ratio (I:E) of 1:2. The expiratory airway pressure (Paw_{low}) was set to 0 cm H₂O, and the inspiratory airway pressure (Paw_{high}) was chosen so that tidal volumes (V_T) were in the range of 10 mL · kg⁻¹. Paw_{high} was then increased until all spontaneous breathing efforts stopped as assessed from the simultaneously displayed curves of gas flow and airway pressure. During the course of the

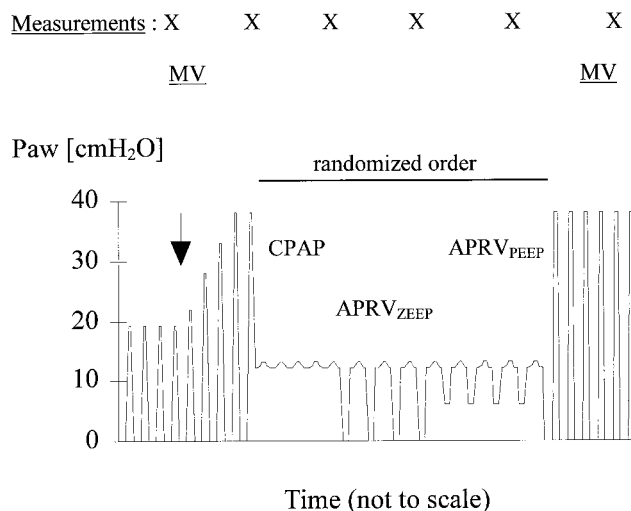


Figure 1. Study protocol of the Study group. Measurements (X) include hemodynamics, mixed venous and arterial blood samples, and ventilatory variables. The ventilation-perfusion distribution was studied using the multiple inert gas elimination technique during all measurements, except for the second period of mechanical ventilation (MV). The arrow indicates the induction of lung injury with oleic acid injection. Note that the mean airway pressure was equal during MV after induction of lung injury and during CPAP breathing. In the Time Control Group (not shown) pigs were kept on MV during the whole study period.

study Paw_{high} was further adjusted if either spontaneous breathing efforts appeared during mechanical ventilation periods or if minute ventilation \dot{V}_E increased >10% because of a change of respiratory mechanics.

After lung injury was established, mechanical ventilation as described above was always chosen as a first and last ventilatory mode to assess the degree of lung injury induced by oleic acid injection, and to evaluate any change in lung function over time. In between, the following three ventilatory settings with different pressure release levels were compared using the BIPAP mode and an F_{IO₂} of 0.5.

- 1) APRV with pressure release to ambient airway pressure (APRV_{ZEEP}). The time intervals for Paw_{high} and Paw_{low} were set to 2 and 1 s, respectively. Thus, the rate of mechanically delivered breaths was 20 · min⁻¹ with an I:E ratio of 2:1. Paw_{high} matched the mean airway pressure (Paw_{mean}) of mechanical ventilation whereas Paw_{low} was set to 0 cm H₂O to obtain the greatest possible inspiratory-expiratory pressure difference and thus the greatest possible mechanical ventilatory support for a given Paw_{high} and respiratory rate.
- 2) APRV with pressure release to 50% of the CPAP level (APRV_{PEEP}). The time intervals of Paw_{high} and Paw_{low} as well as the pressure level of Paw_{high} were identical as during APRV_{ZEEP}. Paw_{low} was decreased to the value that was 50% of Paw_{high} to provide less ventilatory support

compared with APRV_{ZEEP}. If Paw_{high} was an uneven number, Paw_{low} was increased to the next integer (e.g., if Paw_{high} was 11 cmH₂O, Paw_{low} was set to 6 cmH₂O).

- 3) CPAP. The respiratory rate, I:E ratio and Paw_{high} were identical as during APRV_{ZEEP}, but Paw_{low} was chosen identical to Paw_{high}. Thus, the ventilator generated no pressure swings, so these ventilator settings were actually identical to CPAP.

Lung Injury

Oleic acid (Apoteksbolaget, Göterborg, Sweden) 0.1 mL/kg suspended in 20 mL isotonic saline was slowly (over 20 min) injected via the central venous catheter. If the Sao₂ decreased to less than 85% during the injection, no further oleic acid was given. During injection blood pressure was stabilized with titrated doses of adrenaline.

Ventilatory Variables

For measurements of V_T and Paw, the readings of the ventilator were used. The amount of spontaneous breathing during APRV was estimated as \dot{V}_E - mechanical ventilation, with the amount of mechanical ventilation being determined during complete muscle paralysis. Compliance (C_{rs}) of the total respiratory system was estimated as V_T/Paw_{high} during complete paralysis, with Paw_{high} and Paw_{low} set to match the values during mechanical ventilation. Because mechanical ventilation and APRV resulted in a nearly instantaneous increase and decrease of Paw, mean airway pressure (Paw_{mean}) was estimated as $(Paw_{high} \cdot t_{insp} + Paw_{endexpiration} \cdot t_{exp}) \cdot (t_{insp} + t_{exp})^{-1}$, where t_{insp} and t_{exp} denote the time intervals of Paw_{high} and Paw_{low}, respectively.

Hemodynamics

For pressure measurement and arterial blood sampling, an 18-gauge catheter was inserted into the left carotid artery together with a thermistor-tipped fiberoptic catheter (Pulsioath 4F FT PV 2024; Pulsion Medical System, Munich, Germany) that was advanced into the descending aorta for measurements of cardiac output (Qt) and intrathoracic blood volume (ITBV). A Swan-Ganz catheter and an 18-gauge catheter were introduced into the right external jugular vein. The position of catheters was confirmed by pressure tracing.

Systemic, pulmonary arterial and central venous pressures were displayed on a bedside monitor together with the oxyhemoglobin saturation (Sao₂) (Series 7010, Tram; Marquette Electronics Inc.) and recorded with reference to atmospheric pressure at midthoracic level at end-expiration. Qt and ITBV were

calculated automatically (Pulsion COLD Z-021; Pulsion Medical System) after injecting 8-10 mL of 1 mg/mL indocyanine green (ICG) (Pulsion Medical System) mixed in sterile water (temperature ca. 5°C-7°C), randomly within the respiratory cycle (11,12). The mean of triplicate measurements was calculated and used for statistical evaluation. Oxygen delivery ($\dot{D}O_2$), oxygen consumption ($\dot{V}O_2$), systemic vascular resistance, and pulmonary vascular resistance were calculated with standard equations.

Gas Exchange and Ventilation Perfusion Relationship

Arterial and mixed venous blood gas samples were analyzed with ABL 300 and OSM 3 Hemoximeter (Radiometer, Copenhagen, Denmark).

Determination of the ventilation-perfusion distribution (\dot{V}_A/\dot{Q}) was done with the multiple inert gas elimination technique (13) in the Study group during all measurements except for the second period of mechanical ventilation. In the Time Control group, the multiple inert gas elimination technique was performed in 5 animals (one animal was excluded because of technical problems) at baseline, 2 and 6 h after induction of lung injury. The standard deviations of the logarithmic distribution of perfusion (Logsd \dot{Q}) and ventilation (Logsd \dot{V}) were calculated as measures of the dispersion (mismatch) of the blood flow and ventilation distribution, respectively.

Statistics

All data are presented as mean \pm SD if not stated otherwise. $P < 0.05$ was chosen as the level of significance. Not all data were normally distributed as tested with the Shapiro-Wilk's-W-Test, therefore a Friedman ANOVA was used to analyze differences between the ventilatory settings, followed by Wilcoxon's signed rank test, if significant differences were detected. Calculations were performed with the software package Statistica[®] on a personal computer.

Results

At baseline, the Study group and Control group had similar characteristics except for an increased heart rate in the Control group. Oleic acid injection affected hemodynamics, oxygenation and respiratory mechanics significantly and caused a comparable degree of lung injury in both groups as shown in Tables 1 and 2.

Ventilatory Variables and Hemodynamics

Spontaneous breathing accounted for 8.1 ± 1.8 L/min during CPAP, 5.5 ± 1.9 L/min ($66.6 \pm 13.9\%$ of \dot{V}_E) during APRV_{PEEP} and 4.6 ± 2.0 L/min ($56.3 \pm 14.9\%$ of \dot{V}_E) during APRV_{ZEEP} ($P < 0.001$ for differences

Table 1. Mechanical Ventilation in the Study Group

Variables	Baseline	Lung injury 2h	Lung injury 6h
HR (bpm)	107 ± 12	101 ± 13	117 ± 11†
MAP (mm Hg)	97 ± 10	94 ± 17	86 ± 12
CVP (mm Hg)	5 ± 3	8 ± 2*	6 ± 2†
SVR (dyn · s · cm ⁻⁵)	1388 ± 198	1422 ± 348	1345 ± 247
MPAP (mm Hg)	18 ± 3	36 ± 4*	28 ± 4†
PCWP (mm Hg)	7 ± 3	9 ± 3*	7 ± 2†
PVR (dyn · s · cm ⁻⁵)	185 ± 52	469 ± 154*	346 ± 69†
Q _t (L/min)	5.2 ± 0.5	4.9 ± 1.0	4.8 ± 0.4
ITBV (mL)	615 ± 60	588 ± 81	547 ± 29
Hb (g/L)	91 ± 7	95 ± 6*	92 ± 7
PaO ₂ (mm Hg)	211 ± 16	99 ± 39*	122 ± 34
SaO ₂ (%)	98.0 ± 0.3	92.8 ± 5.1*	96.3 ± 1.6
DO ₂ (mL/min)	620 ± 87	574 ± 103	579 ± 52
VO ₂ (mL/min)	188 ± 35	244 ± 45*	200 ± 38
SvO ₂ (%)	67.9 ± 5.8	52.6 ± 9.3*	62.8 ± 7.4†
V _E (L/min)	10.3 ± 1.7	11.8 ± 1.1*	12.1 ± 1.8
PaCO ₂ (mm Hg)	36 ± 2	43 ± 7*	40 ± 9
Paw _{high} (cm H ₂ O)	19 ± 3	37 ± 11*	35 ± 9
Paw _{mean} (cm H ₂ O)	6 ± 1	12 ± 5*	11 ± 5
Compliance (mL/cmH ₂ O)	28 ± 4	17 ± 5*	18 ± 4

Values are given as mean ± SD.

Lung injury 2h = measured 2 h after induction of lung injury; Lung injury 6h = measured 6 h after induction of lung injury; HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; SVR = systemic vascular resistance; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; Q_t = cardiac output; ITBV = intrathoracic blood volume; Hb = hemoglobin; PaO₂ = arterial oxygen tension; SaO₂ = arterial oxygen saturation; DO₂ = oxygen delivery; VO₂ = oxygen consumption; SvO₂ = mixed venous oxygen saturation; V_E = minute ventilation; PaCO₂ = arterial carbon dioxide tension; Paw_{high} = inspiratory airway pressure; Paw_{mean} = mean airway pressure.

* $P < 0.05$ compared with baseline; † $P < 0.05$ compared with lung injury 2h.

between groups). V_E (8 L/min) and respiratory rate of mechanical and spontaneous breaths combined (26 breaths/min), in contrast, were almost identical during CPAP and both APRV patterns. Thus, the decrease of Paw during APRV_{PEEP} from 12 ± 4 cm H₂O to 7 ± 2 cm H₂O (Fig. 1) allowed the lungs to expire passively 135 ± 50 mL per breath whereas the further decrease of Paw_{low} from 7 ± 2 cm H₂O to 0 cm H₂O during APRV_{ZEEP} increased V_T only by additional 36 mL to 171 ± 49 mL. Crs tended to be higher during CPAP compared with both APRV patterns (19 ± 4 versus 17 ± 4 mL/cm H₂O; $P = 0.17$), but the application of PEEP had no influence on Crs. Hypercapnia (PaCO₂ 60 mm Hg) developed during CPAP and both APRV patterns, whereas a PaCO₂ between 35–45 mm Hg was necessary to completely override spontaneous breathing efforts during mechanical ventilation.

Hemodynamic variables such as Q_t, systemic and pulmonary arterial pressure as well as DO₂ were similar during CPAP and both APRV modes.

Ventilation-Perfusion Matching

In the Study and Control groups, oleic acid injection increased shunt and V_A/Q-mismatch, as indicated by LogSDQ̇ (Tables 2 and 4), whereas perfusion of poorly ventilated lung areas was minor before and after induction of lung injury (Fig. 2).

Shunt and V_A/Q-mismatch were lower during CPAP-breathing than APRV (Table 3). Thus, PaO₂ was significantly increased ($P < 0.01$) with CPAP compared with both APRV patterns and the application of PEEP = 7 cm H₂O had only minor effects on gas exchange as compared with APRV_{ZEEP} (Fig. 3). However, no close correlation was found between the amount of spontaneous breathing and venous admixture, shunt, or LogSDQ̇. Alveolar ventilation decreased by approximately 40% when ventilation changed from mechanical ventilation to CPAP or APRV and dead space ventilation (% of V_E) increased significantly. In contrast, no difference in dead space was noted, whether or not spontaneous breathing was supported by cyclic airway pressure release.

Stability of the Lung Injury Model

In the Study group, lung injury tended to improve over time. Compared with the measurements performed 2 h after induction of lung injury, pulmonary vascular resistance was significantly decreased (469 ± 154 versus 426 ± 69 dyn · s · cm⁻⁵) and mixed venous oxygen saturation was significantly increased (52.6 ± 9.3 versus 62.8 ± 7.4%) 4 h later. Furthermore, oxygenation was slightly better ($P = 0.086$) after 6 than 2 h (PaO₂ 122 ± 34 versus 99 ± 39 mm Hg, $P = 0.086$) and Paw_{high} could be reduced by 2 cm H₂O. In the Control group, in contrast, lung injury was more or less stable during the 6-h observation period (Table 2).

Table 2. Mechanical Ventilation in the Control Group

Variables	Baseline	Lung injury 2h	Lung injury 6h
HR (bpm)	127 ± 10 [†]	105 ± 18	124 ± 14
MAP (mm Hg)	98 ± 12	92 ± 14	86 ± 14
CVP (mm Hg)	4 ± 2	6 ± 1* [‡]	6 ± 2
MPAP (mm Hg)	18 ± 6	30 ± 6*	32 ± 7
PCWP (mm Hg)	5 ± 1	7 ± 2*	6 ± 2
Q _t (L/min)	5.4 ± 0.8	4.6 ± 1.0*	5.3 ± 1.3
Hb (g/L)	93 ± 10	97 ± 11	90 ± 5
Pao ₂ (mm Hg)	190 ± 50	73 ± 19*	67 ± 27
Svo ₂ (%)	68.9 ± 6.4	50.2 ± 13.6*	49.9 ± 13.1
V _E (L/min)	9.3 ± 1.3	9.6 ± 1.6 [‡]	10.3 ± 2.8
Paw _{mean} (cm H ₂ O)	7 ± 1	11 ± 2*	12 ± 4
V _A /Q Data			
Shunt (V _A /Q < 0.005) (% Q _t)	6.3 ± 6.4	25.1 ± 8.1*	30.1 ± 11.9
0.005 < V _A /Q < 0.1 (% Q _t)	0	0.7 ± 1.4	1.0 ± 1.4
LogSDQ	0.67 ± 0.07	0.96 ± 0.19*	1.10 ± 0.29
Dead space (100 < V _A /Q) (% V _E)	34.3 ± 1.9	42.2 ± 4.5	43.6 ± 5.7
Mean V	1.72 ± 0.34	2.51 ± 0.54*	2.87 ± 1.27
LogSDV	0.69 ± 0.08	0.75 ± 0.03	0.80 ± 0.04

Baseline readings and data obtained 2 h and 6 h after induction of lung injury are shown (n = 6) except for V_A/Q measurements n = 5). Values are given as mean ± SD.

HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; Q_t = cardiac output; Hb = hemoglobin; Pao₂ = arterial oxygen tension; Svo₂ = mixed venous oxygen saturation; V_E = minute ventilation; Paw_{mean} = mean airway pressure; V_A/Q = ventilation to perfusion ratio; mean V = Mean of the ventilation distribution; LogsdQ = log standard deviation of perfusion distribution; LogsdV = log standard deviation of ventilation distribution.

* P < 0.05 compared with baseline; † P < 0.05 compared with the Study group at baseline; ‡ P < 0.05 compared with the Study group 2 h after induction of lung injury.

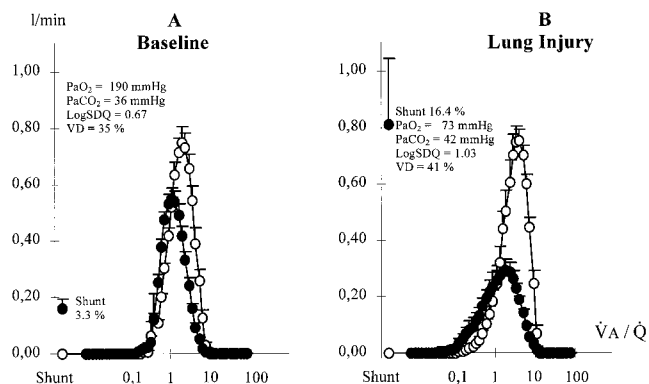


Figure 2. Baseline and lung injury ventilation-perfusion distribution (V_A/Q) by multiple inert gas elimination technique. The continuous distributions of ventilation and blood flow are plotted versus the ventilation-perfusion ratio. Data are shown as mean + SEM. Panel A shows the data obtained during baseline measurements and panel B shows data obtained at the end of the stabilization period after the induction of lung injury. Shunt increased from 3.3% during Baseline to 16.4% after induction of lung injury. Perfusion of poorly ventilated lung areas (V_A/Q ratio < 0.1) was minimal before and after induction of lung injury. Thus, the decrease of Pao₂ after oleic acid injection is mainly explained by the increase of shunt. LogsdQ, logarithmic standard deviation of perfusion distribution; Vd, dead space ventilation.

Discussion

During APRV, mechanical ventilatory support achieved by decreasing Paw periodically below the CPAP level (which causes a decrease of Paw_{mean}) was associated with increased shunt as compared with

CPAP breathing, even though a short pressure release time of only one second was used. In addition, application of PEEP 7 cm H₂O had only minor effects on gas exchange and did not change compliance compared to APRV without PEEP. No difference was found for dead space ventilation between CPAP and APRV. Therefore, the cyclic release of airway pressure should be confined to the minimum necessary to avoid respiratory muscle fatigue. However, compared with mechanical ventilation all modes with spontaneous breathing, APRV and CPAP, increased Qt without any measurable effect on oxygen consumption.

Gas Exchange

Paw_{mean} has an important influence on oxygenation and is usually closely related to mean alveolar pressure (14). It has even been suggested that oxygenation is simply a function of Paw_{mean}, irrespective of the ventilatory mode used, including CPAP (15). Because of the concept of APRV (4), mechanical ventilatory support is achieved by periodically decreasing Paw below the CPAP level and thereby decreasing Paw_{mean}. Thus, the increased shunt and ventilation perfusion mismatch, indicated by an increased LogsdQ, during APRV compared with CPAP may in part be explained by differences in Paw_{mean}. Other groups, however, reported that oxygenation was similar (16) or even better (17) with CPAP than mechanical ventilation, when the end-expiratory airway pressure was equal, and when Paw_{mean}; thus, should have

Table 3. Continuous Positive Airway Pressure (CPAP) versus Airway Pressure Release Ventilation (APRV)

Variables	CPAP	APRV _{PEEP}	APRV _{ZEEP}
HR (bpm)	122 ± 14	121 ± 20	127 ± 10
MAP (mm Hg)	98 ± 10	102 ± 8	98 ± 6
CVP (mm Hg)	8 ± 2	7 ± 2	7 ± 3
SVR (dyn · s · cm ⁻⁵)	1235 ± 220	1284 ± 313	1174 ± 158
MPAP (mm Hg)	29 ± 5	30 ± 4	28 ± 4
PCWP (mm Hg)	11 ± 2	11 ± 2	10 ± 1
PVR (dyn · s · cm ⁻⁵)	245 ± 98	259 ± 90	227 ± 49
Q _t (L/min)	5.9 ± 0.9	6.1 ± 1.0	6.2 ± 0.8
ITBV (mL)	632 ± 71	658 ± 55	663 ± 122
Hb (g/L)	90 ± 5	90 ± 7	91 ± 6
PaO ₂ (mm Hg)	165 ± 48	136 ± 42*	124 ± 50‡
SaO ₂ (%)	96.5 ± 1.6	95.7 ± 2.2*	93.1 ± 6.0‡
DO ₂ (mL/min)	687 ± 84	701 ± 122	702 ± 85
VO ₂ (mL/min)	219 ± 38	224 ± 48	216 ± 40
S _v O ₂ (%)	65.7 ± 4.8	64.9 ± 5.2	64.6 ± 7.2
V _E (L/min)	8.1 ± 1.8	8.2 ± 1.5	8.1 ± 1.5
SB (% V _E)	100	67 ± 14*	56 ± 15‡
RR (bpm)	27 ± 9	26 ± 7	26 ± 8
Paco ₂ (mm Hg)	58 ± 8	60 ± 10	59 ± 10
Paw _{high} (cm H ₂ O)	12 ± 4	12 ± 4	12 ± 4
Paw _{mean} (cm H ₂ O)	12 ± 3	10 ± 3*	8 ± 2‡
Compliance (mL/cm H ₂ O)	19 ± 4	17 ± 4	17 ± 4

Values are given as mean ± sd.

HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; SVR = systemic vascular resistance; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; Q_t = cardiac output; ITBV = intrathoracic blood volume; Hb = hemoglobin; PaO₂ = arterial oxygen tension; SaO₂ = arterial oxygen saturation; DO₂ = oxygen delivery; VO₂ = oxygen consumption; S_vO₂ = mixed venous oxygen saturation; V_E = minute ventilation; SB = spontaneous breathing; Paco₂ = arterial carbon dioxide tension; Paw_{high} = inspiratory airway pressure; Paw_{mean} = mean airway pressure; PEEP = positive end-expiratory pressure; ZEEP = zero end-expiratory pressure.

* P < 0.05 compared with CPAP; † P < 0.05 compared with APRV_{PEEP}; ‡ P < 0.05 compared with CPAP.

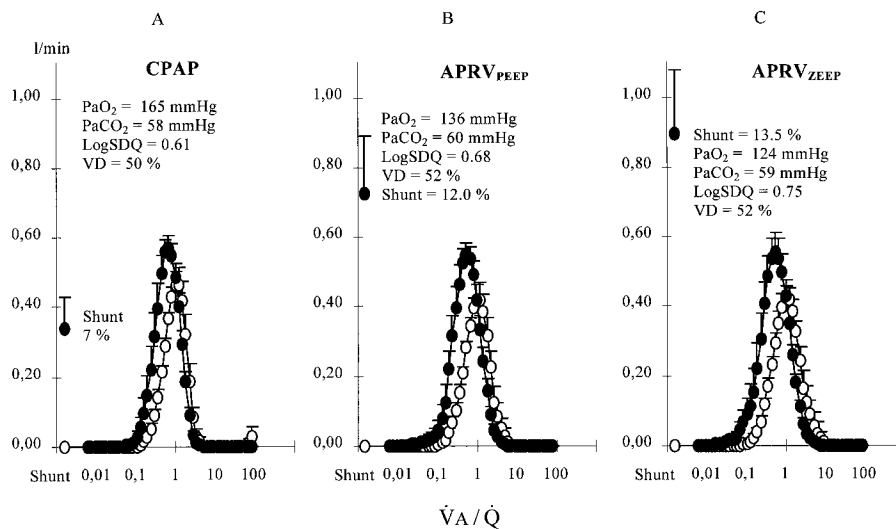


Figure 3. Ventilation-perfusion distribution (\dot{V}_A/\dot{Q}) during CPAP, APRV_{PEEP}, and APRV_{ZEEP}. The continuous ventilation-perfusion distributions of ventilation and blood flow are plotted versus the ratio. Data are shown as mean + SEM. Panel A shows data for CPAP breathing, panel B for partial ventilatory support with APRV using an average PEEP = 7 ± 2 cmH₂O and panel C for partial ventilatory support with APRV and no PEEP (ZEEP). During APRV the upper airway pressure was always identical to the CPAP pressure. Shunt was significantly higher during both APRV patterns compared with CPAP, whereas CPAP and both APRV patterns reduced LogsdQ, which is a measure for ventilation perfusion mismatch, to a similar degree compared with controlled mechanical ventilation. APRV_{PEEP}, APRV setting with a positive end-expiratory pressure that was approximately half of the CPAP level; APRV_{ZEEP}, APRV setting without positive end-expiratory pressure; LogsdQ, Logarithmic standard deviation of perfusion distribution; (\dot{V}_A/\dot{Q} , ventilation-perfusion ratio; VD, dead space ventilation.

been decreased during CPAP. In our study, Paw_{mean} was equal or even less during the spontaneous breathing modes than during mechanical ventilation, but

still oxygenation was slightly or significantly improved with spontaneous breathing. Thus, oxygenation is not solely dependent on Paw_{mean}.

Table 4. Inert Gas Data in the Study Group

Variables	Baseline	Lung injury 2h	Randomized order		
			CPAP	APRV _{PEEP}	APRV _{ZEEP}
Shunt ($\dot{V}_A/\dot{Q} < 0.005$) (% \dot{Q}_t)	3.3 ± 2.3*	16.4 ± 12.1†	6.6 ± 5.6*	12.0 ± 7.2	13.5 ± 8.6
0.005 < $\dot{V}_A/\dot{Q} < 0.01$ (% \dot{Q}_t)	0.1 ± 0.1	0	0	0	0
0.005 < $\dot{V}_A/\dot{Q} < 0.01$ (% \dot{Q}_t)	0.1 ± 0.1	0	0	0	0
0.01 < $\dot{V}_A/\dot{Q} < 0.1$ (% \dot{Q}_t)	0.2 ± 0.5	1.7 ± 3.3	0.4 ± 1.1	1.3 ± 3.5	2.1 ± 4.2
0.1 < $\dot{V}_A/\dot{Q} < 1$ (% \dot{Q}_t)	48.5 ± 4.2*	35.5 ± 12.1†	73.6 ± 11.3*	69.3 ± 12.7*	67.2 ± 13.1*
1 < $\dot{V}_A/\dot{Q} < 10$ (% \dot{Q}_t)	48.0 ± 5.6	46.2 ± 9.4	19.5 ± 10.0*	17.4 ± 8.1*	17.2 ± 9.6*
10 < $\dot{V}_A/\dot{Q} < 100$ (% \dot{Q}_t)	0	0.2 ± 0.3	0	0	0
10 < $\dot{V}_A/\dot{Q} < 100$ (% \dot{Q}_t)	0	0.2 ± 0.3	0	0	0
Mean \dot{Q}	1.07 ± 0.12	1.15 ± 0.31	0.63 ± 0.16*	0.58 ± 0.17*	0.58 ± 0.21*
LogSD \dot{Q}	0.67 ± 0.13*	1.03 ± 0.30†	0.61 ± 0.15*	0.68 ± 0.20*	0.75 ± 0.21*
Dead space (100 < \dot{V}_A/\dot{Q}) (% \dot{V}_E)	34.5 ± 3.7	40.8 ± 7.1	50.1 ± 7.7*	52.1 ± 6.7*	51.8 ± 5.0*
0.005 < $\dot{V}_A/\dot{Q} < 0.01$ (% \dot{V}_E)	0	0	0	0	0
0.005 < $\dot{V}_A/\dot{Q} < 0.01$ (% \dot{V}_E)	0	0	0	0	0
0.01 < $\dot{V}_A/\dot{Q} < 0.1$ (% \dot{V}_E)	0	0	0	0.1 ± 0.2	0.1 ± 0.2
0.1 < $\dot{V}_A/\dot{Q} < 1$ (% \dot{V}_E)	16.6 ± 2.0*	7.2 ± 2.5	29.5 ± 8.1*	27.5 ± 7.5*	26.1 ± 8.1*
1 < $\dot{V}_A/\dot{Q} < 10$ (% \dot{V}_E)	48.9 ± 4.1	51.2 ± 7.3	20.1 ± 6.0*	20.3 ± 8.5*	21.9 ± 7.4*
10 < $\dot{V}_A/\dot{Q} < 100$ (% \dot{V}_E)	0	0.7 ± 1.0	0.4 ± 1.2	0	0
Mean \dot{V}	1.65 ± 0.13*	2.75 ± 0.470	0.95 ± 0.26*	0.92 ± 0.24*	1.02 ± 0.39*
LogSD \dot{V}	0.64 ± 0.07*	0.78 ± 0.10	0.68 ± 0.26	0.64 ± 0.14*	0.70 ± 0.13*

Values are given as mean ± sd.

\dot{V}_A/\dot{Q} = ventilation to perfusion ratio; \dot{Q}_t = cardiac output; mean \dot{Q} = mean of perfusion distribution; LogSD \dot{Q} = log standard deviation of perfusion distribution; Mean \dot{V} = mean of the ventilation distribution; LogSD \dot{V} = log standard deviation of ventilation distribution; \dot{V}_E = minute ventilation; lung injury 2h = 2 h after induction of lung injury; CPAP = continuous positive airway pressure; APRV = airway pressure release ventilation; PEEP = positive end-expiratory pressure; ZEEP = zero end-expiratory pressure.

* $P < 0.05$ compared with lung injury 2h; † $P < 0.05$ between CPAP, APRV_{PEEP}, and APRV_{ZEEP} by Friedman analysis of variance.

The end-expiratory lung volume is another important factor that influences gas exchange and end-expiratory lung volume is dependent on the PEEP level. Thus, the periodic pressure release lower than CPAP during APRV may have facilitated atelectasis formation. Lung collapse occurs rapidly within the first second of an expiration, even when higher PEEP levels were used (9,10). Thus, the rather small increase of V_T (36 mL), when Paw_{low} was decreased from 7 (APRV_{PEEP}) to 0 cm H₂O (APRV_{ZEEP}), indicates that parts of the lung were most likely flooded or collapsed at end-expiration during APRV_{PEEP}, so that the additional decrease of Paw to ambient pressure during APRV_{ZEEP} resulted in little further exhalation. This may also explain why Crs was unaffected whether or not PEEP was applied during APRV. However, during mechanical ventilation and APRV_{ZEEP} no PEEP was used, but the alveolo-arterial oxygen difference was significantly less ($P < 0.05$) during APRV_{ZEEP} (163 ± 44 mm Hg) compared with mechanical ventilation (208 ± 37 mm Hg). Therefore, differences of the end-expiratory airway pressure do not fully explain differences of gas exchange observed with CPAP, APRV and mechanical ventilation in the present study.

In experimental lung injury (1,2) and acute respiratory distress syndrome patients (3,18), spontaneous breathing reduces shunt when combined with APRV. The mechanisms by which this is achieved are not fully elucidated. Diaphragmatic contractions reduce the size of atelectasis in dependent lung areas during

general anesthesia (19), and in subjects lying supine, the dorsally located parts of the diaphragm move more during spontaneous breathing than during mechanical ventilation (20). Spontaneous breathing may therefore reopen atelectasis that is preferentially located in dependent areas and could thereby improve gas exchange.

Hemodynamics

Compared with mechanical ventilation, CPAP and APRV increased \dot{Q}_t in the present study, but the magnitude of this increase was independent from the amount of spontaneous breathing. A better cardiac performance with CPAP than mechanical ventilation has previously been reported (16,17,21), and may be explained by improved venous return of blood to the heart during CPAP, because intrathoracic pressure decreases during spontaneous inspirations. However, conflicting results have also been published (15,22). This discrepancy may be explained by differences of the arterial carbon dioxide tension among the ventilatory modes compared. An increase of the $Paco_2$ is associated with a decrease of the systemic vascular resistance and an increase of the \dot{Q}_t (23,24), and may thus explain the higher \dot{Q}_t during CPAP and APRV compared with mechanical ventilation in the present study. However, Putensen et al. (1-3) showed that \dot{Q}_t increased in the presence of spontaneous breathing with APRV, even though $Paco_2$ was unchanged or

even less after animals or patients started to breath spontaneously. Thus, the higher \dot{Q}_t during CPAP and both APRV patterns than during mechanical ventilation may be explained by both hypercapnia and spontaneous breathing *per se*.

Oxygen Cost of Spontaneous Breathing

Spontaneous breathing associated with CPAP and APRV did not increase $\dot{V}O_2$ compared with mechanical ventilation. This is in accordance with numerous previous reports (CPAP (16,17,21,22), APRV (1-3,8)). Apparently, the oxygen cost of spontaneous breathing is so small compared with the total body oxygen consumption that measurements of $\dot{V}O_2$ have a poor signal-to-noise ratio to detect changes of the metabolic activity of respiratory muscles.

Stability of the Lung Injury Model

In pigs, oleic acid-induced lung injury is stable for several hours (25-27). The finding that lung injury improved somewhat over time in our Study group was therefore unexpected, and no such change was observed in the Control group. Thus, it seems reasonable to believe that the use of CPAP and/or APRV had a favorable influence on the degree of lung injury. Lefevre et al. (27) demonstrated that variability of V_T and respiratory rate improves oxygenation during mechanical ventilation. Such variability or other aspects of spontaneous breathing may explain this finding. However, because we did not evaluate the degree of lung injury before and after each APRV pattern and CPAP separately, we cannot draw definite conclusions in this regard.

In conclusion, in our acute lung injury model, oxygenation was better with CPAP breathing compared with partial ventilatory support with APRV. Because of the concept of APRV, airway pressure is decreased below the CPAP level when ventilatory support is initiated during APRV. This may promote lung collapse, even during short expiratory time intervals. In addition, Paw_{mean} , which is one important determinant of oxygenation, decreases when mechanical ventilatory support increases during APRV. Thus, mechanical ventilatory support during APRV should be confined to the necessary minimum needed to compensate for the increased workload of breathing associated with acute respiratory failure, so that respiratory muscle fatigue is prevented. Nevertheless, compared with controlled-mechanical ventilation, both CPAP and APRV increased \dot{Q}_t and tended to increase $\dot{D}O_2$ at an equal or lower Paw_{mean} .

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