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An experimental randomized study of five different ventilatory modes in a piglet model of severe respiratory distress

M. Lichtwarck-Aschoff[2], J.B. Nielsen[1], U.H. Sjöstrand[1] and E.L. Edgren*

[1]Department of Anesthesiology and Intensive Care, University Hospital, Uppsala, Sweden
[2]Institute of Anesthesiology and Surgical Intensive Care Medicine, Zentralklinikum Augsburg, Augsburg, FRG

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Abstract. *Objectives:* To characterize different modes of pressure- or volume-controlled mechanical ventilation with respect to their short-term effects on oxygen delivery (DO_2). Furthermore to investigate whether such differences are caused by differences in pulmonary gas exchange or by airway-pressure-mediated effects on the central hemodynamics. *Design:* After inducing severe respiratory distress in piglets by removing surfactant, 5 ventilatory modes were randomly and sequentially applied to each animal. *Setting:* Experimental laboratory of a university department of Anesthesiology and Intensive Care. *Animals:* 15 piglets after repeated bronchoalveolar lavage. *Interventions:* Volume-controlled intermittent positive-pressure ventilation (IPPV) with either 8 or 15 cmH_2O PEEP; pressure-controlled inverse ratio ventilation (IRV); pressure-controlled high-frequency positive-pressure ventilation (HFPPV) and pressure-controlled high frequency ventilation with inspiratory pulses superimposed (combined high frequency ventilation, CHFV). The prefix (L) indicates that lavage has been performed. *Measurements and results:* Measurements of gas exchange, airway pressures, hemodynamics, functional residual capacity (using the SF_6 method), intrathoracic fluid volumes (using a double-indicator dilution technique) and metabolism were performed during ventilatory and hemodynamic steady state. The peak inspiratory pressures (PIP) were significantly higher in the volume-controlled low frequency modes (43 cmH_2O for L-IPPV-8 and L-IPPV-15) than in the pressure-controlled modes (39 cmH_2O for L-IRV, 35 cmH_2O for L-HFPPV and 33 cmH_2O for L-CHFV, with PIP in the high-frequency modes being significantly lower than in inverse ratio ventilation). The mean airway pressure (MPAW) after lavage was highest with L-IRV (26 cmH_2O). In the ventilatory modes with a PEEP > 8 cmH_2O PaO_2 did not differ significantly and beyond this "opening threshold" MPAW did not further improve PaO_2. Central hemodynamics were depressed by increasing airway pressures. This is especially true for L-IRV in which we found the highest MPAW and at the same time the lowest stroke index (74% of IPPV). *Conclusions:* In this model, as far as oxygenation is concerned, it does not matter in which specific way the airway pressures are produced. As far as oxygen transport is concerned, i.e. aiming at increasing DO_2, we conclude that optimizing the circulatory status must take into account the circulatory influence of different modes of positive pressure ventilation.

Key words: Respiratory failure – Lung lavage – Pressure-controlled ventilation – Inverse ratio ventilation – High frequency ventilation – Functional residual capacity – Extravascular lung water

We have previously characterized a stable piglet lung lavage model with ARDS-like properties and compared in this model three different modes of ventilation [1]. This included pressure-controlled high-frequency positive-pressure ventilation (HFPPV) [1–5] and pressure-controlled inverse ratio ventilation (IRV) [1, 2, 6–8]. We now studied 5 modes of ventilation in this model, adding one pressure-controlled high frequency ventilation mode with superimposed inspiratory pulses (combined high frequency ventilation, CHFV) [2, 9–16] and another volume-controlled intermittent positive-pressure ventilation (IPPV) with 15 cm H_2O PEEP to the three previous modes. IPPV with 15 cm H_2O PEEP was added in order ot study differences in externally applied PEEP and intrinsic PEEP which all, except the IPPV mode before lavage and the L-IPPV-8 mode after lavage, thus had a comparable PEEP level of about 15 cm H_2O.

Much like drugs the most important effects and "side-effects" of new ventilatory modes should be investigated [17] and described in terms of gas exchange, airway pressures and resulting oxygen transport the latter being a central parameter to describe the immediate effects of a ventilatory mode. In the future this will help to tailor ventilatory modes to the specific requirements of individual patients.

* *Present address:* Department of Anesthesiology, Bassett Hospital, One Atwell Road, Cooperstown, NY 13326, USA

For the time being it is technically impossible to continuously follow up lung structural changes with direct imaging techniques [18–20]. Thermal-dye-dilution determination of intrathoracic blood volume (ITBV) and extravascular lung water (EVLW) provide an indirect picture of structural damages and of changes in these intrathoracal compartements [21–26] caused by different ventilatory modes.

The following study aims at improving our understanding of the following questions concerning conditions of severe respiratory distress:

1) Are there significant differences in oxygen transport between different modes of positive pressure ventilation, the modes being adjusted to equal ventilation in terms of arterial PCO_2 and comparable PEEP (either extrinsic or intrinsic)?

2) If there are such differences, are they caused by differences in pulmonary gas exchange or by airway-pressure-mediated effects on the central hemodynamics?

Materials and methods

Two papers describing the methods in detail have been published previously [1, 2]. The main differences compared to the previous experimental protocol were the following:

1) The use of ketamine instead of clomethiazole as a major anesthetic. This diminished vasodilation and improved cardiovascular stability.

2) Following collapse of the lung during controlled ventilation (without PEEP), the subsequent therapeutic mode was introduced by instant application of a peak inspiratory pressure of 55 cm H_2O for 5 to 10 minutes. Adjustment to PaCO2 of 4 kPa was then performed through down-regulation of ventilatory pressure or volume (as applicable). This helped avoid exposing the animal to varying times of hypoxic episodes while titrating volumes or pressures upward until the (often precipitous) opening of the collapsed lung.

Animals

Healthy piglets (15) of Swedish country breed were examined. Mean weight was 24.3 kg (0.8 SEM).

The experiments were performed at the experimental laboratory of the Department of Anesthesiology and Intensive Care in Uppsala. The local ethics comittee for animal experimentation reviewed and consented to the protocol.

Experimental procedure

Following anesthesia and preparation the animal was placed in the prone position. Baseline values were obtained after stabilization, i.e. $PaCO_2$ of 4 kPa and hemodynamic steady state were established. Lavage was performed by the method of Lachmann [27] and five ventilatory modes were randomly and sequentially applied to each animal. Each mode was applied for at least half an hour and all measurements were done under conditions of ventilatory and hemodynamic steady state. Between the experimental ventilatory modes a control mode of ventilation (IPPV without PEEP) was interposed, in order to reproduce alveolar collapse. Except from the preparation period an inspired oxygen fraction of 1.0 was used.

Anesthesia and fluid management

Premedication: Pentobarbital 15 mg/kg+0.5 mg atropine intraperitoneally 15 min pre-induction. *Induction and anesthesia:* 500 mg ketamine and 0.5 mg atropine i.v., followed by a ketamine infusion at 10 mg/kg·h. In addition to this, i.v. morphine was given up to 20 mg during initial preparation of tracheostomy and catheter introductions. *Relaxant:* pancuronium bromide 0.26 mg/kg·h. The animals were tracheostomized and ventilated through a 8 mm diameter double lumen (1:10 lumen ratio) Hi Lo jet endotracheal tube (Mallinckrodt Inc., Glens Falls, NY, USA).

A Siemens Servo ventilator 900C (Siemens Elema, Solna, Sweden) was used. A pediatric humidifier and heated circuit with a compression volume of 590 ml and an internal static compliance of 0.7 ml/cm H_2O was employed (Fisher and Paykel, New Zealand [1, 2]). With the tidal volumes (V_t) of this equipment, the compression volume (V_c) to tidal volume ratio (V_c/V_t) was improved compared to a previous study [2] in normal piglets. Due to this reduction in V_c/V_t ratio there is a relatively rapid build-up of the force of insufflation, whereby inspiratory flow reaches its maximum value rather instantaneously thus making the ventilator system more efficient [1–5]. The production of a breathing pattern with superimposed inspiratory pulses was performed by an additional device (Servo HFV 970).

Fluid replacement was titrated according to intrathoracic blood volume (ITBV). An ITBV of 20 ml/kg was aimed for before lavage, assuming normovolemia at this point. To this end 0.9% NaCl with 2.5% glucose (Rehydrex, Pharmacia Infusion AB, Uppsala, Sweden) was infused up to 40 ml/kg·h. If required a 100 ml bolus of dextran (Macrodex 70, Pharmacia Infusion AB, Uppsala, Sweden) was given to achieve the required ITBV.

A thermostatically controlled heating pad and an infrared heating lamp were used to keep the animal's body at normal.

Monitoring

Intravascular catheters were placed surgically for the measurement of central venous, pulmonary artery (via internal jugular vein) and aortic pressures (via carotid artery). A thermo-dye COLD Computer (Pulsion Medizintechnik KG, München, West Germany) was used. The fiberoptic catheter was introduced via the femoral artery and advanced to the descending aorta. The recordings of the hemodynamic pressures were made on a 4 channel rectilinear heat pen recorder (MX 412, Devices Instruments Ltd, Welwyn Garden City, UK). Continuous monitoring of ECG was performed and intermittent analysis of arterial and mixed venous blood gases at 37 °C was made (ABL2 Radiometer, Copenhagen, Denmark).

Oxygen saturation was calculated using the PO_2 value obtained in the ABL2 at 37 °C according to [38], taking into account the P50 value for the pigs blood. The calculated oxygen saturation (suffix "calc" in Table 1) had to be used as the saturation measurement in the hemoximeter available (Radiometer OSM2, one wavelength only) is influenced by the cardiogreen.

Ventilatory volumes were obtained using the readings form the Servo ventilator as we in previous experiments had demonstrated a good correlation to the values measured when using a spirometer. Carbon dioxide production was recorded by a metabolic monitor (Datex Deltatrac, Datex Instrumentation Corp., Helsinki, Finland).

Thermo-dye-dilution

The indicator bolus, i.e. indocyanine green (dye) mixed in ice-cold glucose 5% (thermal indicator), was injected manually within 1 sec into the vena cava superior or right atrium [21–26]. The dilution curves for dye and temperature were recorded simultaneously in the descending aorta with the thermistor-tipped fiberoptic catheter. The dye and the thermal curve recorded in the femoral artery were used for the calculation of CO, intrathoracic blood volume (ITBV) and extravascular lung water (EVLW, measured as extrathermal volume ETV). The dye stays intravascularly during one passage through the cardiopulmonary system, whereas cold both diffuses and is convected into the extravascular space depending on time, vascular surface, heat conductivity and capacity. Thus an intravascular volume IVV_{MTT} and a thermal distribution volume TV_{MTT} can be calculated:

$$IVV_{MTT} = Q_D \cdot MTT_D \quad (1)$$

where Q_D is the dye dilution flow and MTT_D is the mean transit time of the dye indicator, and

$$TV_{MTT} = Q_T \cdot MTT_T \quad (2)$$

Table 1. Results obtained in 15 piglets under general anesthesia ventilated with 100% oxygen under steady state conditions as specified in the text

Parameter	Mode of ventilation											
	[1] IPPV-8		[2] L-IPPV-8		[3] L-IPPV-15		[4] L-IRV		[5] L-HFFPV		[6] L-CHFV	
1. Ventilation												
MPAW	11		17		22		26		19		18	
[cmH_2O]	0.16		0.5		0.43		1.5		1.01		0.91	
		**1		**1		**1		**1		**1		
				**2		**2						
						**3		**3		**3		
								**4		**4		
PIP	22		43		43		39		35		33	
[cmH_2O]	0.46		1.9		1.7		2.61		2.68		2.64	
		**1		**1		**1		**1		**1		
								**2		**2		
								**3		**3		
										**4		
PEEP	8		8		16		16		17		17	
[cmH_2O]			0.15		0.35		0.69		0.99		0.69	
				**1		**1		**1		**1		
				**2		**2		**2		**2		
MV	6507		12667		9473		9780		15527		14727	
[ml]	197		779		568		552		998		1037	
		**1		**1		**1		**1		**1		
				**2		**2		**2				
								**3		**3		
								**4		**4		
TV	13.5		26.5		19		20.2		10.7		14	
[ml/kg]	0.3		1.7		1		1.2		0.8		0.8	
		**1		**1		**1		**1		**1		
				**2		**2		**2				
								**3		**3		
								**4		**4		
Compliance	39.4		24.3		21.2		22.9		20.2		20.8	
[ml/cmH_2O]	1.2		1.4		1.2		1.6		2.5		1.7	
		**1		**1		**1		**1		**1		
2. Gas exchange												
PaO_2	70		40		57		58		52		52	
[kpa]	2		6		6		4		5		6	
		**1		**1		**1		**1		**1		
				**2		**2		**2		**2		
$PaCO_2$	5.0		4.03		4.51		3.91		4.0		4.35	
[kpa]	0.47		0.21		0.28		0.21		0.18		0.22	
		**1		*1		**1		**1		**1		
				*2		**3		*3		*4		
SaO_{2calc}	99.9		97.8		99.1		99.6		99.1		98.6	
[%]	0.01		0.9		0.6		0.2		0.5		1.1	
3. Hemodynamics												
MAP	106		116		114		113		120		124	
[mmHg]	4.7		4.9		5		3.7		5.2		5.2	
								*1		**1		
CVP	5		7		9		10		9		9	
[mmHg]	0.4		0.6		0.6		0.8		0.7		0.6	
		**1		**1		**1		**1		**1		
				**2		**2		*2		*2		
								*3		*3		
PCWP	10		13		14		16		14		14	
[mmHg]	0.8		0.9		1		1.5		1.1		1.3	
		*1		**1		**1		**1		**1		
				*2		**2						
PAP	21		33		37		37		35		37	
[mmHg]	0.8		1.5		2.1		2.2		2		2	
		**1		**1		**1		**1		**1		
				*2		*2				*2		
SvO_{2calc}	84.8		73.9		81.2		76.5		76.6		76.8	
[%]	1.6		2		2.6		2.4		2.2		2.9	
		**1				*1		*1		*1		

Table 1 (continued)

Parameter	Mode of ventilation											
	[1] IPPV-8		[2] L-IPPV-8		[3] L-IPPV-15		[4] L-IRV		[5] L-HFFPV		[6] L-CHFV	
Qs/Qt_{calc}	10		20		15		13		16.5		15.9	
[%]	1.2		2		3		1.8		1.4		2.9	
		**1		*1		*1		*1		*1		
				**2		**2		**2		**2		
SVI	50		44		40		37		43		40	
[ml/beat·m^2]	2.4		2.1		2.2		2.7		2.7		2.9	
		*1		**1		**1		**1		**1		
						**2		*3				
CI	6.6		6.2		5.8		5.5		6.1		5.8	
[l/min·m^2]	0.3		0.2		0.3		0.3		0.3		0.3	
				*1		**1				*1		
						*2		*4				
SVRI	1249		1437		1485		1564		1506		1620	
[dyn·s·cm^{-5}·m^{-2}]	72		89		66		90		102		85	
				*1		**1		**1		**1		
4. Intrathoracic volumes												
ITBV	22		20		18		18		19		18	
[ml/kg]	0.8		1.1		0.8		0.9		0.8		1	
		*1		**1		**1		**1		**1		
EVLW (ETV)	9		21		23		21		21		21	
[ml/kg]	0.7		2.6		2.6		1.9		2.7		2.5	
		**1		**1		**1		**1		**1		
5. Metabolism												
DO_2I_{calc}	800		721		723		669		750		732	
[ml/min·m^2]	29.6		25		30.4		39		37		35	
VO_2I_{calc}	194		205		179		197		212		201	
[ml/min·m^2]	6.7		15.5		12.3		13		14		10	
VCO_2	217		241		218		228		217		226	
[ml/min]	6		10		9		7		7		8	
		**1		**2				**2		*2		

Mean and SEM $n = 15$. Multi-comparison significance level for one factor in the analysis of variance (ANOVA) the difference to ventilatory mode 1, 2, 3, 4 or 5 being: * = significant at 95%, ** = significant at 99%

where Q_T is the thermodilution flow and MTT_T is the mean transit time of the thermal indicator. IVV_{MTT} corresponds to the intrathoracic blood volume ITBV, TV_{MTT} corresponds to the sum of the intravascular blood volume IVV_{MTT} and the extravascular heat accessible volume. Thus the extravascular thermal volume ETV_{MTT}, defined as

$$ETV_{MTT} = TV_{MTT} - IVV_{MTT} \quad (3)$$

can be calculated. With the calculation of ETV the measurement of extravascular lung water (EVLW) as physical property for quantification of lung damage is possible. The temperature of the injectate was corrected for catheter dead space, taking into consideration the different portions of the catheter that lay intravascularly and outside the animals body.

Airway pressures

The airway pressures were obtained from the Servo 900C ventilator digital display. In earlier experiments [1, 2] in order to measure distal tracheal pressure variations, a tip transducer (Camino mod 420, Camino Laboratories, San Diego, CA, USA) was introduced through the insufflation channel of the double lumen endotracheal tube (measurement level approximately 2 cm above carina). The peak pressures obtained from the tip transducer were compared with the peak pressures obtained from the Servo 900C ventilator. The values from the tip transducer measurements were only slightly lower, but with much more variation, than the readings from the Servo ventilator. This can probably be explained by secretion and interference from the tracheal wall. Due to the homogeneity of the peak pressure readings from the ventilator these were used. The mean airway pressures obtained from the tip transducer signals, were identical with the pressure readings from the Servo ventilator.

The static chest-lung compliance was calculated according to the formula: Tidal volume/(endinspiratory pressure − endexpiratory pressure). When the end inspiratory and end expiratory pressures were measured the hold functions of the Servo 900C ventilator were used (i.e. no flow, pressure equilibrium in the lungs, airways and ventilator circuit was established).

FRC

For the measurement of FRC the method described by Larsson et al. was used [28–30]. The measurement system (Siemens Elema, Solna, Sweden), connected to and synchronized with the signals from the Servo 900C ventilator, includes a SF_6 dispensing unit, a heated Fleisch pneumotachograph with a differential pressure transducer, and infrared SF_6 analyzer with the transducer placed over a cuvette in the airway, and a computer. During wash in the microprocessor-controlled dispensing device delivered SF_6 into the airway in proportion to instantaneous inspiratory flow so that the inspiratory concentration was held constant at 0.5% regardless of inspiratory flow pattern. SF_6 was washed in for 3–8 min until the expiratory concentration curve had the shape of an horizontal plateau, the height of which was stable from breath to breath. Washout was started by stopping tracer gas infusion between two inspirations and was considered complete when the mean expired SF_6 concentration of the last five breath was $<0.001\%$. During washout, instantaneous expiratory SF_6 flow was calculated by the computer from the expiratory flow and the SF_6 signals. Inspired and expired tidal volumes as well as tidal and total volumes were obtained by integration.

FRC was calculated as the total volume of SF_6 washed out divided by the alveolar concentration at the end of wash in.

The FRC measurement was only studied in 4 modes of ventilation (– the superimposed inspiratory pulses in L-CHFV bypassing the SF_6-containing gas delivered "conventionally" by the Servo 900C –) and in 7 animals. We therefore did not perform statistical analysis on these data and in the results section they are only given as mean of 7 observations in 7 experiments.

Lavage

The lavage was performed in the way already described [1, 27]. Surfactant was removed by a series of 10–12 instillations of 37 °C normal saline, each of 1–1.5 l volume. In order to improve surfactant depletion and reduce the periods of hypoxemia during the lavage procedure we modified the ventilation modality compared to the previous study. Thus we used IPPV with 5 cm H_2O PEEP in the intervals between the single lavage procedures and increased the tidal volumes as soon as the arterial oxygen tension did not come up following a lavage instillation.

Ventilatory modes

Baseline measurements and the study of the various ventilatory modes were performed with the animals in the prone position and with FiO_2 1.0. As previously described [1, 2] each mode was used for at least 30 min, achieving a steady state defined as stable end-tidal carbon dioxide and hemodynamic values for at least 5 min. Following each experimental ventilatory mode the lungs were permitted to collapse under IPPV without PEEP ("control mode") in order to confirm the tendency to alveolar collapse and provide a similar starting point for each experimental mode. The following ventilatory modes were examined:

IPPV (before lavage): Volume-controlled intermittent positive-pressure ventilation with a frequency of 20 breaths per min (bpm), inspiratory time 25%, inspiratory pause 10% and expiratory time 65% which results in an inspiration : expiration (I : E) ratio of 1 : 2. An external PEEP set at 8 cm H_2O was used to avoid atelectases as consequences of anesthesia and/or artificial ventilation.

IPPV-control: A control mode ventilation with ventilator settings as IPPV mentioned above, but without PEEP ("collapse mode"). In the lavage lung model the absence of PEEP permitted alveolar collapse. Even with a FiO_2 1.0, the PaO_2 and the arterial saturation dropped dramatically. This mode was used before and after each experimental ventilatory mode, but in order to minimize the risk of inadvertent hypoxic damage the control periods were kept as brief as possible.

After lavage, 5 ventilatory modes were applied in random sequence to each animal following the above control mode. The prefix (L) indicates that lavage has been performed.

L-IPPV-8: Identical to IPPV described above, but after lavage

L-IPPV-15: As above but with 15 cm H_2O PEEP

L-IRV: Pressure-controlled inverse ratio ventilation with 20 bpm, inspiratory time 67%, expiratory time 33% (I : E 2 : 1), external PEEP valve at 8 cm H_2O, no inspiratory pause

L-HFPPV: Pressure-controlled high-frequency positive-pressure ventilation, 60 bpm, inspiratory time 50%, expiratory time 50% (I : E ratio 1 : 1), external PEEP at 8 cm H_2O, no inspiratory pause

L-CHFV: A L-HFPPV (above) but with superimposed inspiratory pulses of 10 Hz during the inspiratory cycle. The pulses had themselves a duty cycle of 20%. This resulted in a 75% "conventional" volume and a 25% "pulsed" volume.

As described above the introduction of each experimental mode was made at a peak inspiratory pressure (PIP) of 55 cm H_2O. This opened collapsed alveolar units rapidly and thus minimized the hypoxic episodes during the experimental procedure, compared to our earlier practice of upward titration of pressure or volume until opening occurred [1]. The lungs were considered "open" when arterial oxygen tension approached baseline measurements. From this "opening point" the ventilation was adjusted down to a $PaCO_2$ of ≥ 4 kPa.

Calculations and statistics

Calculations were made according to standard formulae, some of which have been described in detail in our previous articles [1, 2]. Values are given as mean and standard error of the mean (SEM). One-way analysis of variance (ANOVA) for repeated measures was used for all pair-wise comparisons within each variable. Statistical significance was considered to be achieved only if Fisher's and Scheffé's criteria both were significant at the 95% level $p \leq 0.05$ or at the 99% level $p \leq 0.01$. Regression analysis was applied where appropriate, and a $p \leq 0.05$ was considered statistically significant. For the statistical analysis we used the STAT VIEW™ software.

Results

The results are condensed in Tables 1–3 and Fig. 1–3.

1. Ventilation

Following lavage airway pressures and extravascular lung water increased and compliance and oxygenation parameters fell.

The highest peak inspiratory pressures (PIP) of 43 cm H_2O were found in the volume-controlled low frequency modes L-IPPV-8 and L-IPPV-15, while in the pressure-controlled high frequency modes PIP was lower (lowest in L-CHFV with 33 cm H_2O).

Mean airway pressure (MPAW) was highest in the inverse ratio mode L-IRV (26 cm H_2O) while in the high frequency modes L-HFPPV (19 cm H_2O) and L-CHFV (18 cm H_2O) MPAW was lower than in L-IRV. A MPAW of 17 cm H_2O in L-IPPV-8 was insufficient to maintain patency of the airways (cf., oxygenation parameters).

In the pressure-controlled modes an "intrinsic" PEEP of 8 cm H_2O (L-IRV) and 9 cm H_2O (L-HFPPV and L-CHFV) was generated by the relative short expiration periods.

Following lavage the minute ventilation and tidal volumes (TV) required for a $PaCO_2$ of 4 kPa differed markedly between the different modes of ventilation. Compared to baseline the volume requirement after lavage using conventional IPPV with 8 cm H_2O PEEP doubled (MV 12.7 l/min, TV 26.5 ml/kg). The high frequency modes tripled minute volume (MV 15.5 l/min and 14.7 l/min, TV 10.7 and 14 ml/kg with and without inspiratory pulses, respectively). The inverse ratio ventilation required the lowest minute volume (9.8 l/min, TV 20.2 ml/kg) which produced the lowest $PaCO_2$

Table 2. Correlation factors R for the relationship between cardiac filling pressures and volume indicators for 15 piglets each ventilated with five different ventilatory modes (* = $p \leq 0.05$; ** = $p \leq 0.01$)

	CI	SVI	ITBV	DO_2I
CVP	−0.136	−0.238**	−0.263*	−0.186
PCWP	−0.284**	−0.414**	−0.289**	−0.43**
CI		0.763**	0.508**	0.803**
SVI	0.763**		0.675**	0.556**
ITBV	0.508**	0.675**		0.449**
DO_2I	0.803**	0.556**	0.449**	

Table 3. Key parameters for functional conditions of the lung after surfactant depletion in the present study compared to previous study [1] (Mean ± SEM)

Parameter		Mode of ventilation			
		IPPV	L-IPPV-8	L-IRV	L-HFFPV
MPAW [cmH_2O]	present study	11 ± 0.16	17 ± 0.50	26 ± 1.50	19 ± 1.01
	study ref [1]	10.5 ± 0.1	15.8 ± 0.5	26.2 ± 1.2	17.9 ± 0.8
PIP [cmH_2O]	present study	22 ± 0.46	43 ± 1.90	39 ± 2.61	35 ± 2.68
	study ref [1]	19.6 ± 0.4	39.8 ± 1.6	39.2 ± 1.9	34.3 ± 1.8
Compliance [ml/cmH_2O]	present study	39.4 ± 1.2	24.3 ± 1.4	22.9 ± 1.6	20.2 ± 2.5
	study ref [1]	42 ± 3	22 ± 2	23 ± 1	18 ± 1
PaO_2 [kpa]	present study	70 ± 2	40 ± 6	58 ± 4	52 ± 5
	study ref [1]	73.7 ± 1.4	35.6 ± 4.8	67.6 ± 4.2	50.9 ± 5.1
EVLW [ml/kg]	present study	9 ± 0.7	21 ± 2.6	21 ± 1.9	21 ± 2.7
	study ref [1]	7.5 ± 1.06	18.0 ± 2.69	22.1 ± 1.91	18.7 ± 2.32

(3.9 kPa) of all modes after lavage. The relative hyperventilation was a result of our efforts to avoid alveolar collapse which occured at lower volumes [1, 7] as discussed in the materials and methods section.

Compared to the pre-lavage baseline level of 70 kPa, arterial oxygen tension was significantly lower in all ventilatory modes, lowest in L-IPPV 8 with 8 cm H_2O PEEP.

2. *Hemodynamics*

The central hemodynamics were significantly depressed during all experimental modes as reflected by the stroke volume index (SVI). The most striking depression of SVI and cardiac index (CI) was seen during inverse ratio ventilation (IRV) (CI from 6.6 l/min·m^2 pre-lavage to 5.5 l/min·m^2 in L-IRV, SVI from 50 ml·beat/m^2 pre-lavage to 37 ml/beat/m^2 in L-IRV). Significant increases in systemic vascular resistance indices were generally seen during the experimental modes. The pulmonary shunting Qs/Qt was increased from baseline (12%), most pronounced during L-IPPV-8 (to 24%). Elevations of CVP and PCWP were significant compared to baseline-maximal values in L-IRV (CVP 10 mmHg and PCWP 16 mmHg).

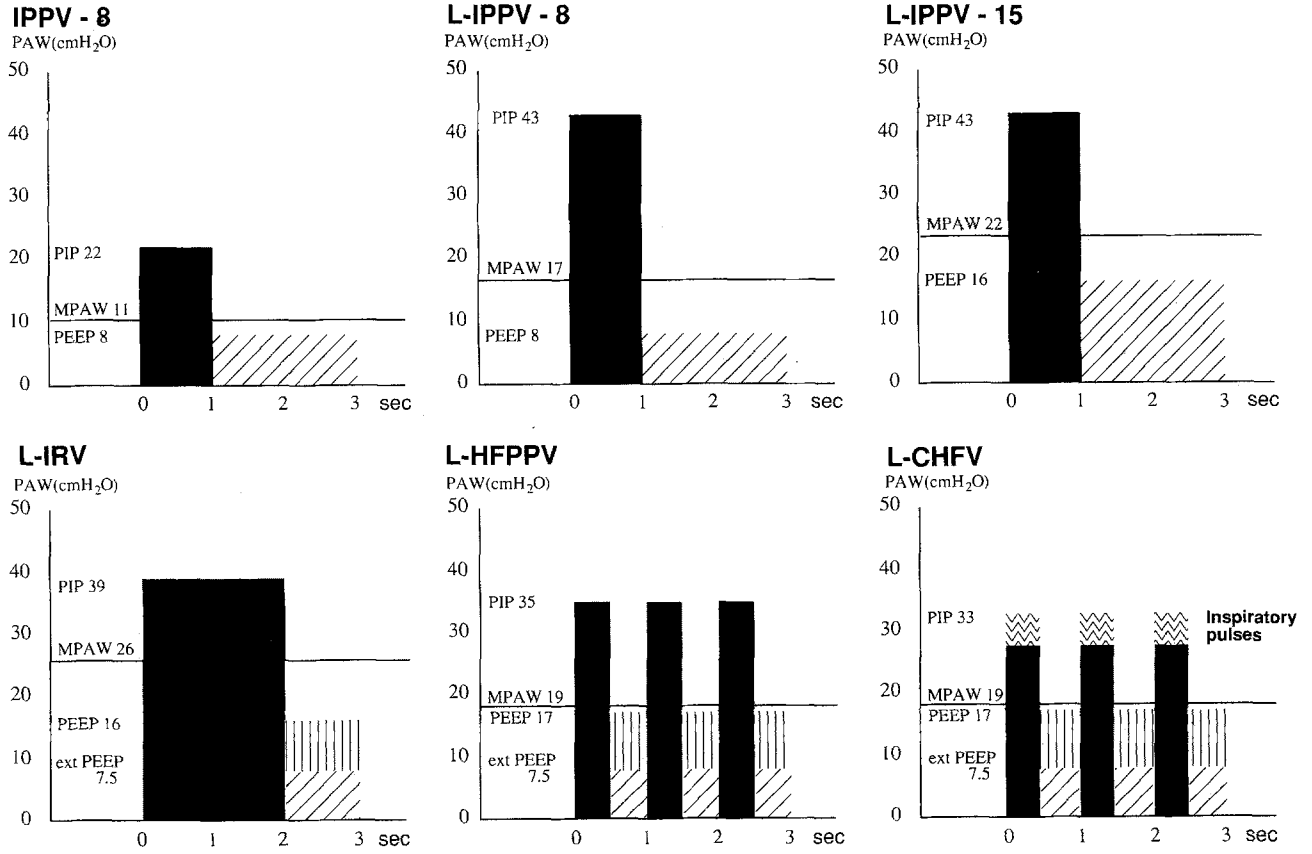

Fig. 1. Schematics of the ventilatory pattern used. L denotes ventilation after lavage, i.e. under conditions of severe respiratory distress. (*PIP* = Peak inspiratory pressure; *MPAW* = Mean airway pressure; *ext PEEP* = PEEP adjusted at the external valve of the respirator)

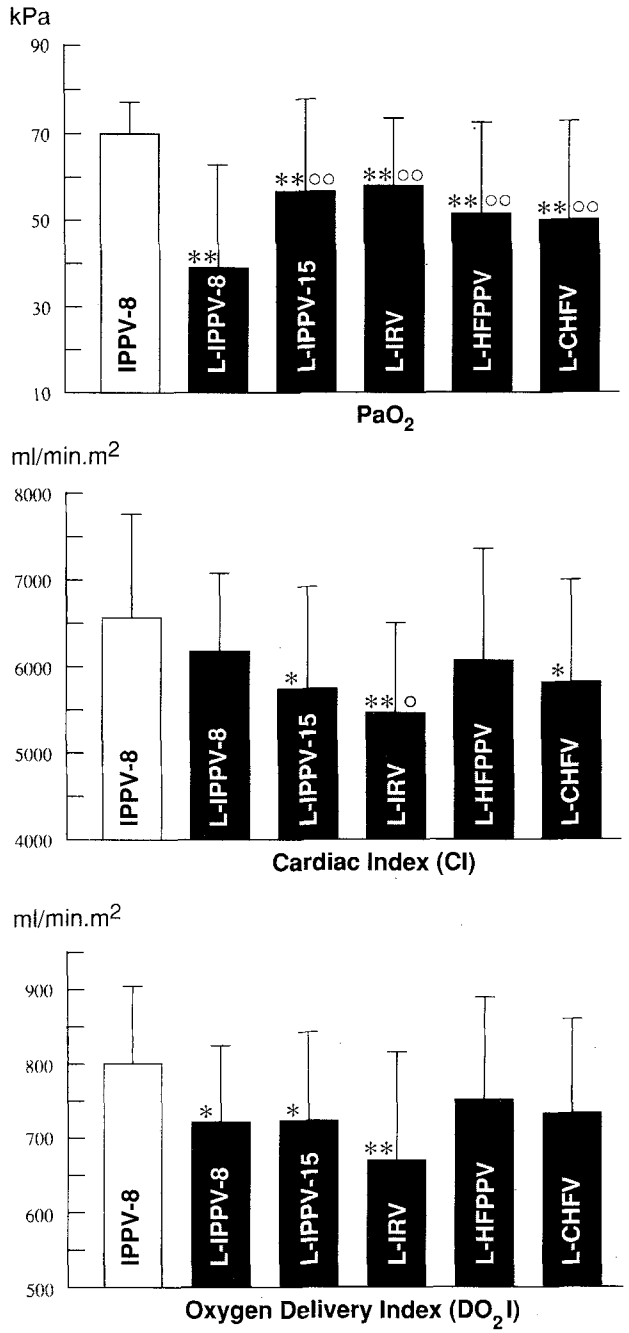

Fig. 2. PaO_2, CI and DO_2I in 15 piglets before (IPPV-8, *white column, left*) and after lavage ventilated with 5 different modes of ventilation. Difference to IPPV-8: *: $p \leq 0.05$; **: $p \leq 0.01$. Difference to L-IPPV-8: °: $p \leq 0.05$; °°: $p \leq 0.01$

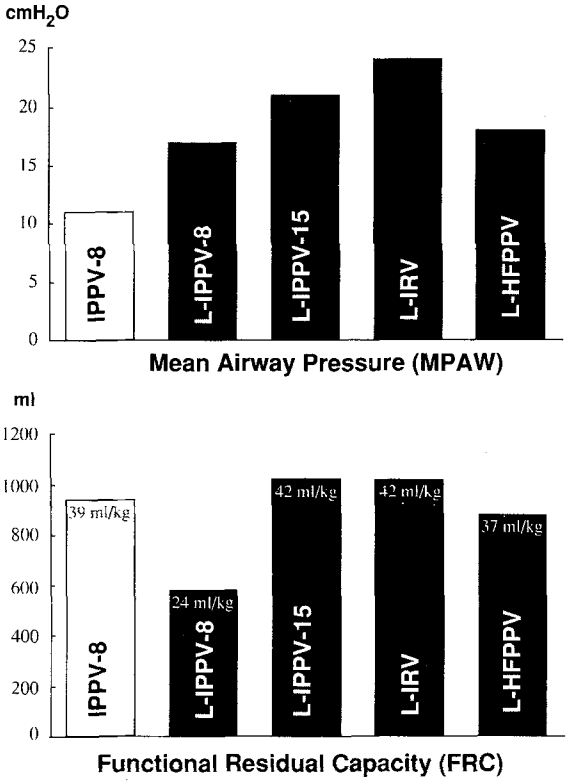

Fig. 3. Mean airway pressure (*MPAW*) and functional residual capacity (*FRC*) in 7 pigs ventilated with 4 different modes of ventilation

Using regression analysis (Table 2) no correlation between the cardiac filling pressures (CVP and PCWP) and parameters usually taken as volume status indicators (stroke index and cardiac index) could be found, whilst the correlation factor R for the relationship between intrathoracic blood volume (ITBV) and stroke volume index (SVI) was 0.675 ($p \leq 0.01$).

3. Intrathoracic fluid volumes

The extravascular lung water (EVLW) was at a mean of 9 ml/kg before lavage. It elevated to at least 21 ml/kg following lavage and remained high independent of the ventilatory mode used. Intrathoracic blood volume, indicating normovolemia pre-lavage (22 ml/kg), after lavage fell slightly but significantly. This reduction of ITBV was independent of ventilatory mode.

4. Oxygen transport

The calculated oxygen transport was 800 ml/min·m^2 before lavage and did not display any significant differences.

5. FRC

In the 7 animals in which FRC measurement was available, FRC (measuring 937 ml pre-lavage) increased with MPAW exceeding even pre-lavage level in L-IPPV-15 (1023 ml) and L-IRV (1018 ml) (see Fig. 3).

Discussion

Reproducibility of the lavage model

In a previous study [1] we could demonstrate that the lavage model is reasonably stable with time. Using this same model under different conditions we now found that the model moreover is reasonably reproducible by function. This can be seen when comparing the key parameters for functional conditions of the lung after surfactant depletion [1]. The values for airway pressures, compliance, arterial oxygen tension and extravascular lung water reflecting the lung after lavage (see Table 3) are very similar in the present study to the values obtained in

the previous study despite a different type of anesthesia was used (ketamine instead of clomethiazole), and volemia and alveolar ventilation differed.

Airway pressures

Comparing different modes of ventilation, ideally this should be done at the same alveolar ventilation, mean airway pressure and sufficient steady state conditions. At the time when the present study was designed it was not known to us the relative ability of IPPV, IRV, HFPPV and CHFV to open the lungs. For that reason, apart from L-IPPV-8, we aimed at the level of 15 cm H_2O of PEEP. The additional increase in MPAW necessary to open the collapsed lung was then achieved by increasing alveolar ventilation. This resulted in different MPAW and slightly differing $PaCO_2$ for the ventilatory modes under study.

Peak inspiratory pressure (PIP) was low in the high frequency pressure-controlled models. This confirmed the known benefit of pressure-controlled ventilatory settings in respect to PIP [7]. However, to obtain a $PaCO_2$ of 4 kPa higher minute volumes were necessary in the high frequency modes L-HFPPV and L-CHFV compared to L-IRV [1]. The peak inspiratory pressures produced by a ventilatory mode could be of clinical interest. Clinical [31–33] and experimental studies [34, 35] indicate, that high peak inspiratory pressures damage lung structure and by itself result in ARDS-like histological alterations when applied to healthy lungs over a period of time. In addition, as indicated by the results in Fig. 3, in all modes of ventilation but L-IPPV-8 the FRC was established to the level of pre-lavage conditions. Thus ventilatory modes with low peak inspiratory pressures and the ability to re-establish FRC could avoid further aggravating the pathologic mechanisms induced by acute lung injury [33, 35].

PaO_2 was significantly lower in L-IPPV-8, whilst the ventilatory modes in which PEEP was at least 15 cm H_2O or higher did not differ in the resulting PaO_2 (irrespective of "external" or "intrinsic" PEEP). Once opening was achieved and expiratory reclosure prevented by higher airway pressures – which was the case in all ventilatory modes with a PEEP exceeding 8 cm H_2O – PaO_2 could not be further augmented by increasing MPAW. Thus beyond this "opening threshold" MPAW did not further improve PaO_2.

In the ventilatory modes with a PEEP > 8 cm H_2O, PaO_2 did not differ significantly. Thus we conclude that as far as oxygenation in this model is concerned it does not matter in which specific way the airway pressures are produced. In other words: Whether PEEP was applied by the external valve or intrinsically created by the I : E ratio and by the ventilatory frequency did not significantly influence PaO_2.

Volume status and hemodynamics

The cardiac filling pressures CVP and PCWP, which are useful indicators of circulating blood volume in spontaneously breathing individuals, may mislead volume status interpretation in mechanically ventilated individuals [36]: The increase of intrathoracic pressure caused by mechanical ventilation with positive airway pressure compresses the low pressure capacitance system. Right ventricular filling thus is decreased because of reduced venous return, though an improvement of cardiac filling by the elevated CVP thus induced would seem to imply the opposite. Keeping this in mind clinicians often try to get an impression of circulatory filling with CVP and/or PCWP measurements by removing PEEP. It is of real interest to verify the changes of the cardiac preload related to the changes of positive airway pressure. In fact only the intrathoracic part of the total blood volume contributes to gas exchange. Hence the intrathoracic blood volume is a major determinant of oxygen transport. This relationship we could also confirm: The cardiac index CI and the stroke index SVI correlated to the intrathoracic blood volume ITBV, R being 0.508 for ITBV/CI and 0.675 for ITBV/SVI. CI and SVI did not correlate to the cardiac filling pressures CVP and PCWP.

Clomethiazole anesthesia was used in our previous study [1]. Together with a more restrictive fluid replacement this produced hypovolemic and vasodilated animals (intrathoracic blood volume 15 ml/kg). In the present study we used ketamine anesthesia and replaced fluid vigorously. This resulted in normovolemic animals (ITBV 21.7 ml/kg). Thus the airway pressures influenced ITBV (and hence DO_2I) less profoundly ($R = 0.347$ for the correlation between ITBV and DO_2I compared to $R = 0.734$ in the hypovolemic animals). Viewed in this light (see Fig. 2) the impressive elevation of PaO_2 that could be obtained by high PEEP in a conventional volume-controlled ventilatory pattern, or by reversing the I : E ratio, probably were of little use to the animal's tissues, whereas a more moderate increase in PaO_2 combined with less depression of the central hemodynamics (as with the high frequency modes) may have been more beneficial in terms of oxygen delivery to the tissues [37].

If extrapolated to the clinical setting and in line with the clinical findings by Fusciardi et al. [39, 40] it may then be assumed that application of optimal modes of ventilation might be of greater importance in patients with compromized cardiocirculatory status which can not be always corrected in an easy way. Once normovolemia is achieved, the increased airway pressures depress central hemodynamics and hence oxygen transport less profoundly. In this favourable situation the ventilatory modes may then be chosen and adapted to reestablish FRC and by minimizing peak inspiratory pressures reduce the risk of barotrauma.

Conclusion

Optimizing the circulatory status, i.e. aiming at increasing DO_2I, must take into account the circulatory influence of different modes of positive pressure ventilation.

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U.H. Sjöstrand, MD, PhD
Department of Anesthesiology
and Intensive Care
University Hospital
S-75185 Uppsala, Sweden