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An experimental study of different ventilatory modes in piglets in severe respiratory distress induced by surfactant depletion*

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Abstract. In 19 anesthetized piglets 3 ventilatory modes were studied after inducing pulmonary insufficiency by bronchoalveolar lavage by the method of Lachmann. The lavage model was considered suitable for reproduction of severe respiratory distress. This model was reproducible and stable with respect to alveolar collapse, decrease in static chest-lung compliance and increase in extravascular lung water. The ventilatory modes studied were volume-controlled intermittent positive-pressure ventilation (IPPV), pressure-controlled inverse ratio ventilation (IRV), and pressure-controlled high-frequency positive-pressure ventilation (HFPPV). The 3 ventilatory modes were used in random sequence for at least 30 min to produce a ventilatory steady state. Ventilation with no PEEP, permitting alveolar collapse, was interposed between each experimental mode. The ability to open collapsed alveoli, i.e. alveolar recruitment, was different. The recruitment rate for IPPV was 74%, but for IRV and HFPPV it was 95%, respectively. Although IRV provided the best PaO_2, this was at the expense of high airway pressures with circulatory interference and reduced oxygen transport. In contrast to this, HFPPV provided lower airway pressures, less circulatory interference and improved oxygen transport. In the clinical setting there might be negative effects on vital organs and functions unless the ventilatory modes are continuously and cautiously adapted to the individual requirements in different phases of severe respiratory distress. Therefore, one ventilatory strategy could be to "open the airways" with IRV, but then switch to HFPPV in an attempt to maintain the airways open with lesser risk of barotrauma and with improved oxygen transport.

Key words: Respiratory failure – Lung lavage – Intermittent positive-pressure ventilation – Pressure-controlled ventilation – Inverse ratio ventilation – High frequency ventilation – Airway pressures – Oxygen transport

During recent years there has been much debate about optimal ventilatory patterns for patients in acute respiratory failure (ARF) and adult respiratory distress syndrome (ARDS) [1]. The present ideology is that the ventilatory mode should open and maintain the patency of the airways with the lowest possible risk of barotrauma [2] in order to obtain optimal oxygen transport. One of the methods suggested is conventional volume-controlled positive-pressure ventilation with PEEP [3] created by an external valve mechanism (external PEEP). Another method is inverse ratio ventilation (IRV), which was originally suggested and studied by Reynolds [4] and has also been advocated by Lachmann et al. [2] for almost 10 years. IRV creates an "intrinsic" PEEP, i.e. the PEEP is created by short expiratory times trapping gas in the lungs, and thus expandig the alveolar membranes during expiration even in the absence of external PEEP valves. A third alternative, which has not yet been fully explored, is high-frequency positive-pressure ventilation (HFPPV) [5, 6], where high breathing frequencies create short expiration times. This may create gas trapping ("intrinsic" PEEP), the size of which will strongly depend on the inspiration/expiration (I : E) ratio. Thus it may be anticipated that the combination of a high ventilatory frequency and an adapted I : E ratio can create an "intrinsic" PEEP similar to that of IRV [7]. We considered that the above strategies justified a study in piglets with induced severe respiratory distress. An animal study would also provide important information necessary for the design of a prospective clinical study.

To achieve the pulmonary dysfunction, i.e. severe respiratory distress, we chose the bronchoalveolar lavage model developed by Lachmann and collaborators [8].

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This model was particularly attractive for the following reasons [9]: it reliably produces alveolar collapse due to surfactant depletion; the surfactant depletion does not damage the alveolar microstructure; a fall in pulmonary compliance has been demonstrated.

The stability of this model, which was essential when studying sequential randomized ventilatory modes, was studied in 5 Beagle dogs [2] without any statistical test mentioned. In contrast to dogs (and humans) piglets lack collateral ventilation. Species with collateral ventilation [10] have an auxilary respiratory mechanism protecting them under certain circumstances from regional alveolar hypoxia [11]. It is not known whether the lavage procedure in the above model introduces an interstitial edema detectable by measurement of extravascular lung water (EVLW). Nor is it known whether the EVLW would remain stable throughout a testing sequence of various breathing patterns. Therefore the aim of the study was to clarify the following questions: is the lavage lung model suitable for sequential studies of different ventilatory modes in piglets; is it possible to confirm the stability of the lung model further, by adding EVLW measurements; what are the corresponding ventilatory and hemodynamic parameters (with special attention to oxygen transport) for 3 ventilatory modes applied to this lavage lung model.

The results of studies in 19 piglets are presented, and give the background to possible future strategies of ventilation in clinical practice. A preliminary report has been presented recently [12].

Material and methods

Animals

Nineteen healthy domestic piglets of Swedish origin were studied. Mean weight was 24.3 kg. The experimental procedure was reviewed and accepted by the local ethical committee for animal experimentation.

Experimental procedure

Following anesthesia and preparation, the animal was placed in the prone position and baseline values were obtained after stabilization, i.e. normoventilatory and hemodynamic steady state. Lavage was performed by the method of Lachmann, and 3 ventilatory modes were randomly and sequentially applied. Each mode was used for at least half an hour, and all measurements were performed under conditions of ventilatory and hemodynamic steady state. Between the experimental ventilatory modes a control mode of ventilation was interposed in order to reproduce alveolar collapse. Except for the preparation period an inspired oxygen fraction (FiO_2) of 1.0 was used.

Anesthesia

Premedication was performed with pontobarbital 15 mg/kg i.p. and atropine 0.5 mg i.p. After 15 min, anesthesia was induced by intravenous injection of ketamine 500 mg and atropine 0.5 mg. Following induction, anesthesia was maintained by continuos infusion of chlormethiazole (64 mg/kg/h) with pancuronium bromide (0.26 mg/kg/h).

Intermittent doses of morphine up to a maximum total of 20 mg were given as necessary. Tracheostomy was performed immediately. An 8 mm diameter double lumen (1 : 10 lumen ratio) HiLo Jet endotracheal tube (Mallinckrodt Inc., Glens Falls, NY) was inserted. Ventilation was performed throughout with a Servo ventilator 900C (Siemens-Elema AB, Solna, Sweden). A pediatric humidifier and heated circuit (Fisher and Paykel, New Zealand) with low compressible volume was employed [5, 6, 13, 14]. During preparation, before lavage was started, ventilation was performed with humidified oxygen and air heated to body temperature (FiO_2 0.3). In addition to this a thermostatically controlled heating pad and an infrared heating lamp were used to keep the animals' body temperature normal. Initially a continuous infusion of 0.9% sodium chloride in 2.5% glucose (Rehydrex, Pharmacia Infusion AB, Uppsala, Sweden) was given at 5 ml/kg/h. For 10 of the 19 piglets in the study this amount of fluid was increased to 40 ml/kg/h when intrathoracic blood volume determination became available [15] (see the Monitoring section).

Monitoring

Continuous monitoring of ECG was performed. Blood gas status and oxygen saturation were analysed by an automatic blood laboratory and a hemoximeter (ABL2 and OSM2, Radiometer, Copenhagen, Denmark) at 37 °C. Ventilatory volumes were obtained using the readings from the Servo ventilator. In previous experiments we had demonstrated similarity with the values measured when using a spirometer (Bear VM90, Bear Medical Systems Inc., Riverside, CA). An indwelling urinary catheter was inserted surgically for measurement of urine volume.

Measurements were made of central venous and pulmonary artery pressures using a triple lumen catheter and a Swan-Ganz catheter (Edwards Inc., Santa Ana, CA) introduced through the internal jugular vein. Arterial pressure was measured in the carotid artery. The recordings were made on a 4-channel rectilinear heat pen recorder (MX 412, Devices Instruments Ltd, Welwyn Garden City, UK). A catheter was placed in the descending aorta via the femoral artery for extravascular lung water (EVLW) measurements.

Cardiac output (CO) and EVLW were calculated using two different lung water computers. Both computers use the thermal-green double indicator dilution technique, described in detail in other publications [16–20]. The calculations of EVLW accord to the equation ETV = CO * (MTT thermo − MTT dye), where MTT is the mean transit time. ETV means extravascular thermo-volume and is similar to EVLW [20]. In 9 piglets an Edwards lung water computer (Edwards Inc., Santa Ana, CA) was used. The Edwards computer uses the thermistor in the tip of the Swan-Ganz catheter and the termistor in the tip of the aortic catheter for "thermal dilution" measurements (MTT thermo). The dye dilution is measured by a densitometer connected to the catheter in the descending aorta (MTTdye). In 10 piglets a COLD Z-02 computer (Pulsion Medizintechnik KG, München, FRG) was used for the CO and EVLW measurements. The COLD Z-02 equipment is described by Pfeiffer et al. [21, 22]. With the COLD Z-02 the dye dilution is measured using a fiberoptic catheter in the descending aorta; there is therefore no time difference in the measurements of MTT thermo and MTTdye. The Edwards and COLD computers have been evaluated recently by Wickerts et al. [23]. According to Pfeiffer [21, 22], the EVLW values measured and calculated are 25% higher than the values obtained from the Edwards system, but the CO measurements are similar. Therefore the EVLW values obtained by the Edwards computer were recalculated to fit the COLD computer values. In the COLD computer additional hemodynamic variables can be calculated through additional algorithms. For instance, intrathoracic blood volume (ITBV) can be calculated according to the formula: ITBV = CO × MTTdye. In addition by using the downslope method described by Newman [19], the pulmonary blood volume (PBV) can be calculated. It is also possible to calculate the prepulmonary blood volume (PPBV), i.e. the sum of the end-diastolic volumes of the right heart. It is possible to evaluate functional performance of the right heart with the dimensionless quotient PPBV/CI, i.e. the prepulmonary blood volume (PPBV) in relation to the cardiac index (CI). As long as the function of the right heart is intact, the PPBV changes in parallel with the CI, thus with increasing PPBV the CI increases, and vice versa with decreasing PPBV. This means that with intact function of the right heart the value of the quotient PPBV/CI is unchanged with changing values of CI. In the case of a functional decrease in right heart performance, the end-diastolic volumes increase due to the failing Frank-Starling mechanism. Consequently the value of the quotient PPBV/CI increases to higher values in relation to the reduction in right heart performance.

Airway pressures

During the early experiments, in order to measure distal tracheal pressure variations, a tip transducer (Camino mod. 420, Camino Laboratories, San Diego, CA) 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 is probably 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, a fact also shown in previous experiments [24].

Compliance

The static chest-lung compliance was calculated according to the formula: Tidal volume/(end-inspiratory pressure − end-expiratory 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.

Oxygen consumption (VO_2) and carbon dioxide production (VCO_2)

A metabolic computer (Datex Deltatrac, Datex Instrumentation Corp., Helsinki, Finland) using the working principle of indirect calorimetry with an open circuit technique, paramagnetic O_2 sensor and Haldane transformation, facilitated measurements of VO_2, VCO_2, respiratory quotient (RQ) and energy expenditure. In this study, due to the working principle and algorithms of this computer, inaccuracies in the calculated values could be expected. FiO_2 values > 0.6 and high pressures in the respirator circuit were the main reasons for these inaccuracies. Therefore, the VCO_2 values were only used for estimating ventilatory steady state. Due to ventilation with an FiO_2 of 1.0, VO_2 had to be calculated from arterial and mixed venous blood gas analysis according to the Fick principle (for the haemoglobin-oxygen affinity a factor of 1.39 ml/g was used).

Lavage procedure

Before lavage was started, FiO_2 was changed to 1.0. Lavage was performed with microwave-heated 0.9% saline at body temperature. In our previous experiments in healthy piglets the functional residual capacity (FRC) was shown to be 1 – 1.5 l in piglets of the pertinent size. A volume of saline corresponding to FRC was fed through the endotracheal tube from a height of approximately 75 cm and immediately poured out again; ventilation with pure oxygen was resumed. Prolonged exposure to the high intrathoracic pressures created by the lavage fluid proved to be deleterious to the circulatory stability of the model. Therefore, if arterial systolic blood pressure dropped below 100 mmHg the instillation of saline was immediately interrupted and the saline removed. Our previous experiments had indicated that 10 – 12 of such washouts were necessary in order to establish a stable condition of surfactant depletion. The absence of foam in the lavage liquid was taken as an indicator of an effective surfactant washout. The total amount of saline used during the lavage procedure and the total residual amount of saline/surfactant fluid regained were measured.

Early in the study, ventilation between lavages was performed as volume-controlled intermittent positive-pressure ventilation (IPPV) with a frequency of 20 breaths per minute (bpm), inspiration to expiration (I : E) of 1 : 2, inspiratory pause 10%, no PEEP and with a ventilatory volume providing normoventilation in the animal before lavage. Later in the study it became clear that increasing the tidal volume and adding a PEEP of 5 cm H_2O during the lavage sequence improved the animals's over-all condition in terms of oxygenation, circulation and acid-base balance. Apart from the ventilatory volume and PEEP the ventilator settings were the same.

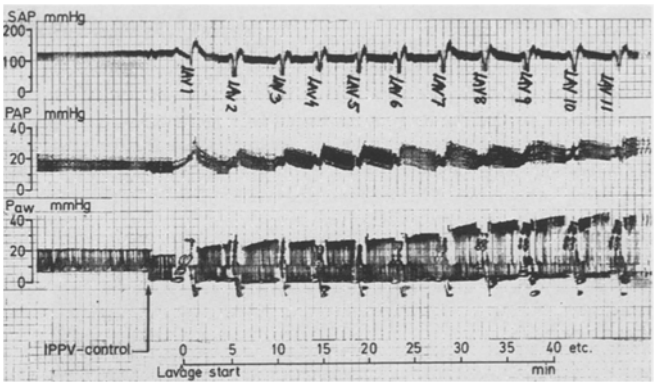

Fig. 1. The consequences of the lavage procedure on arterial pressure (*SAP*), pulmonary arterial pressure (*PAP*) and airway pressure (*Paw*) in one piglet. A tip transducer catheter was used for the airway pressure measurement. Control ventilation (*IPPV-control*) with pure oxygen and constant tidal volume was started before the lavage sequence was initiated

After terminating the lavage procedure, the pulmonary dysfunction was demonstrated by a pronounced decrease in PaO_2 and compliance during ventilation with IPPV-control (cf. Ventilatory modes). A pronounced increase in airway pressures and pulmonary arterial pressures were noted during lavage (Fig. 1).

Three animals were sacrificed using a perfusion fixation procedure permitting the subsequent light and electron microscopic analysis of pulmonary tissue [25]. In 1 animal chest radiographs were obtained at baseline and 5 h subsequent to lavage (Fig. 2).

Ventilatory modes

Baseline measurements and the study of the various ventilatory modes were performed with the animals in the prone position and with $FiO_2 = 1.0$. Each mode was used for at least 30 min, achieving a steady state defined as stable VCO_2 and hemodynamic values for at least 5 min. Following every experimental ventilatory mode an alveolar collapse was permitted under intermittent positive-pressure ventilation *without* PEEP (IPPV-control). The alveolar collapse was demonstrated by arterial blood gas analysis and compliance measurement.

As shown in Fig. 3 the following ventilatory modes were examined.

- *IPPV (before lavage)*: Volume-controlled positive-pressure ventilation, with a frequency of 20 bpm, inspiratory time 25%, inspiratory pause 10% and expiratory time 65% (I : E 1 : 2) and tidal volume resulting in normoventilation before lavage was used. External PEEP at 7.5 cm H_2O was used to avoid atelectasis as a consequense of anesthesia and artificial ventilation.
- *IPPV-control*: A control mode ventilation with ventilator settings like IPPV mentioned above, but without PEEP. In the lavage lung model the absence of PEEP permitted alveolar collapse, and even with an $FiO_2 = 1.0$, the PaO_2 and 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.

Three ventilatory modes were applied in random sequence to each animal. The prefix (L) indicates that lavage has been performed.

- *L-IPPV*: Identical to IPPV described above, but after lavage.
- *L-IRV*: Pressure-controlled inverse ratio ventilation with 20 bpm, inspiratory time 67%, expiratory time 33%. (I : E 2 : 1) and external PEEP of 7.5 cm H_2O.
- *L-HFPPV*: Pressure-controlled high-frequency positive-pressure ventilation with 60 bpm, inspiratory time 50%, expiratory time 50% (I : E 1 : 1) and external PEEP of 7.5 cm H_2O.

During all ventilatory modes the aim was normocapnea. The "opening" procedure was as follows: The airway pressure was increased in increments (in the volume-controlled mode by increasing tidal volumes) until opening of the collapsed alveoli occurred. Due to the risk of baro-

trauma, inflation pressures exceeding 55 cm H_2O were avoided as higher pressures would not be applicable in the clinical situation.

The reversal of alveolar collapse was usually a rapid phenomenon occuring at a specific pressure level individual to each animal. In both pressure-controlled modes with intrinsic PEEP (see end-expiratory pressure, Table 1) it proved very difficult to avoid hyperventilation. This may be a consequence of the titrated approach of the ventilation when "opening" the lungs. Down-regulating ventilation in order to avoid hyperventilation frequently precipitated alveolar collapse and inadequate oxygenation ensued.

For these reasons the lower limit of $PaCO_2$ was set at 3.0 kPa. Further hyperventilation was not accepted, however, despite the common presence of partial alveolar collapse and reduction of PaO_2.

Consequently, in spite of aiming at normoventilation in all modes, unfortunately a certain degree of hyperventilation *had* to be accepted. As shown in Table 1 this was more pronounced with the pressure-controlled ventilatory modes inducing intrinsic PEEP.

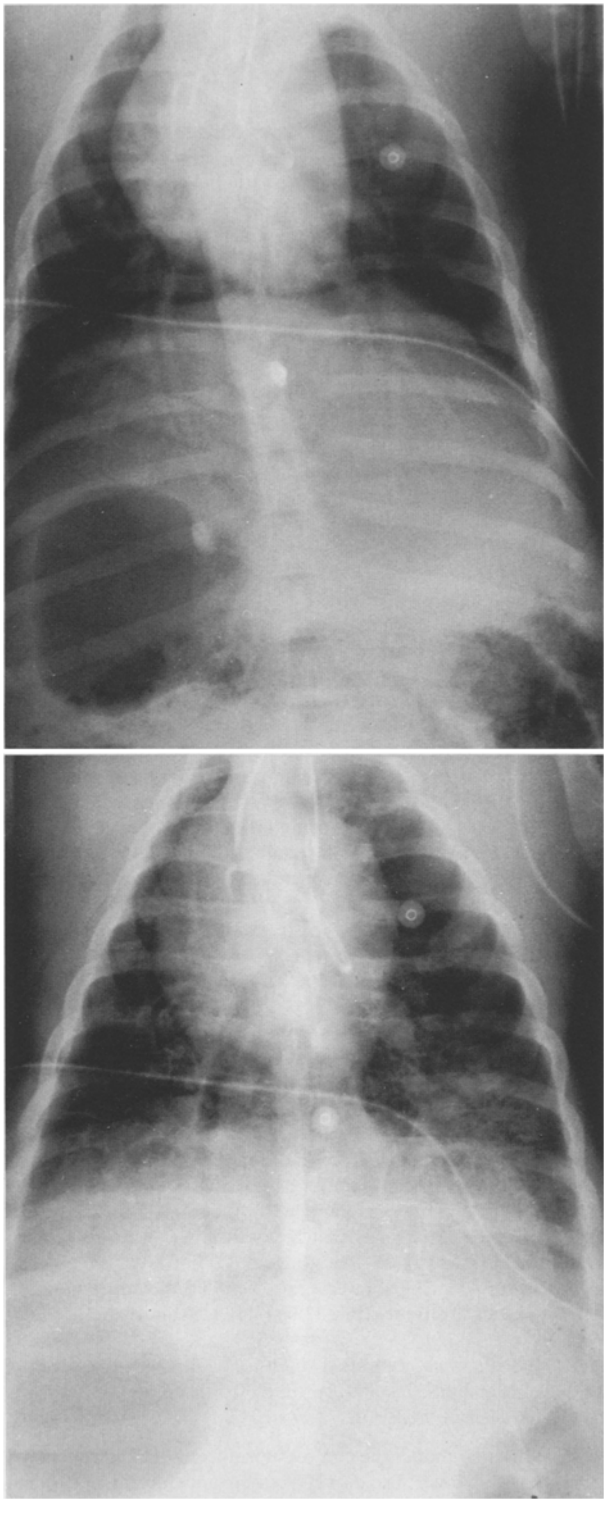

Fig. 2. Chest X-rays before (*top*) and 5 h subsequent to lavage (*bottom*)

Calculations

All values given as mean and standard error of the mean (SE).

Ventilatory volume readings from the Servo ventilator were calculated to BTPS.

Compliance, VO_2 and VCO_2:	(see Monitoring section).
Shunt (Qs/Qt):	$Qs/Qt = (Cc'O_2\text{-}CaO_2)/(Cc'O_2\text{-}CvO_2)$ $Cc'O_2$ is the ideal capillary oxygen content.
Systemic vascular resistance (SVR):	$SVR = ((MAP\text{-}CVP)/CO)\times 80$. The denomination is $dynes\times s\times cm^{-5}$
Pulmonary vascular resistance (PVR):	$PVR = ((PAPmean - PAPdia)/CO)\times 80$. The denomination is $dynes\times s\times cm^{-5}$.

Pulmonary vascular resistances were calculated substituting PCWP with diastolic pulmonary arterial pressures (PAPdia) as PCWP could not always be obtained due to the prevailing experimental conditions. The high heart rates in this study often resulted in a slight inaccuracy in calculations which use the PAPdia.

See the monitoring section in the text regarding cardiac output (CO), extravascular lung water (EVLW), prepulmonary blood volume (PPBV), intrathoracic blood volume (ITBV), prepulmonary blood volume/cardiac index (PPBV/CI). For further details the reader is referred to previous studies [16–23].

Statistics

Analysis of variance (ANOVA) for repeated measures was used. This test uses Fisher's and Scheffe's criteria for statistical significance. Statistical significance was considered to be achieved only if both criteria were significant at the 95% level ($p \leq 0.05$).

Results

In Table 1 the complete results are shown for all 19 piglets studied. In Table 2, blood gas data and static chest-lung compliance are given for the control mode ventilation (IPPV-control) within 300 min after lavage of the 10 piglets in which the COLD-computer was used. The EVLW values in Table 2 are means of all EVLW values obtained in these 10 piglets; ventilation 300–600 min after lavage was performed with either L-IPPV, L-IRV or L-HFPPV in 3 piglets for a prolonged study period.

The lavage lung model (Table 2)

As mentioned in the Monitoring section, in order to re-establish the alveolar collapse created by the lavage procedure, the IPPV-control mode of ventilation was used before and after each experimental mode of ventilation. The stability of the model was evaluated using IPPV-control ventilation 5–300 min after lavage in the 10 piglets in which the COLD-computer was used (see Table 2).

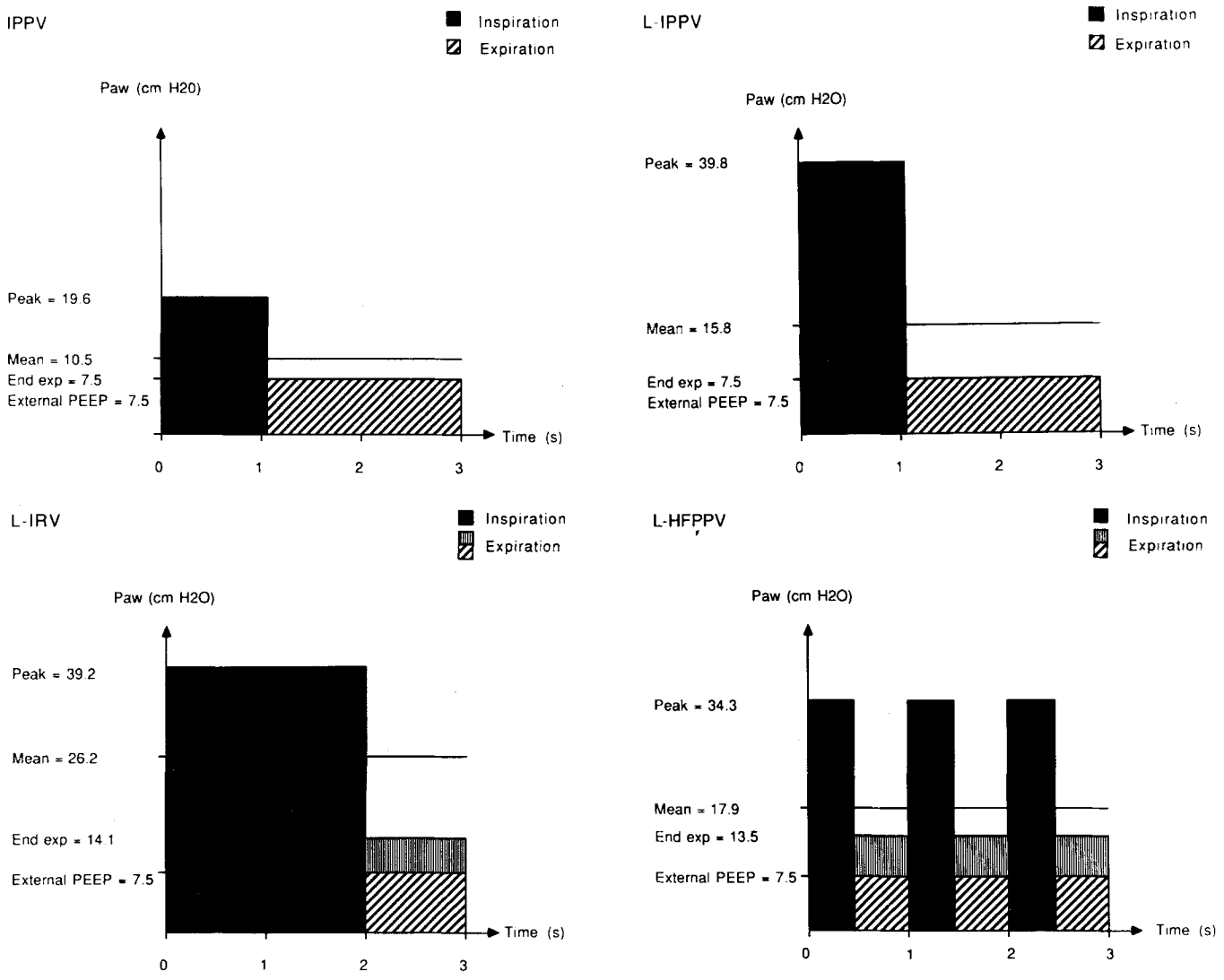

Fig. 3. Schematics of the ventilatory patterns used. *L* denotes ventilation after lavage and under conditions of severe respiratory distress

The EVLW was 6.7 ml/kg at baseline and increased to approximately 26 ml/kg after lavage. The EVLW after lavage was found to remain essentially constant during the whole experimental procedure. The PaO_2 decreased from an average of 74.4 kPa to approximately 7.5 (range 6.1–8.0) after lavage. Similarily, the compliance decreased from 43 ml/cm H_2O to 14 ml/cm H_2O and remained constant during the 5 h test period. The values given in Table 2 were obtained from the 10 piglets in which the COLD equipment was used. In all 19 piglets the reproducability of the alveolar closure was illustrated by the mean values obtained from all the IPPV-control modes used throughout the study ($n = 76$). These values were: PaO_2 11.6 kPa±1.1, $PaCO_2$ 6.9 kPa±0.2 and compliance 12.9 ml/cm H_2O±0.3.

By the measurement of saline used for lavage, the volume of saline/surfactant fluid regained and the weight of the animal after terminating the experiment, an accumulation of third space fluid was demonstrated. This third space accumulation seemed to be initiated by, and was most pronounced during the lavage (at minimum 8–12% of the lavage volume), but fluid accumulation continued throughout the experiments (it totalled a minimum of 5% of the body weight/h).

Pathological anatomy and chest X-ray

One normal pig and 2 pigs with severe respiratory distress were sacrified with fixation fluid while still under anesthesia. Six tissue blocks from different parts of the lungs were removed from each pig and examined by light and electron microscopy to determine morphological signs of severe respiratory distress 5 h after the lavage sequence. The fixation procedure proved satisfactory and the preservation of lung tissues was generally very high. Under light microscopy the normal pig lungs presented no clear difference from those with severe respiratory distress. Under electron microscopy, however, the respiratory membrane diameter was seen to be significantly increased in the pigs with severe respiratory distress, most prominently in the basal parts of the lungs. This was interpreted as edema. Furthermore, slightly dilated lymphatic vessels were demonstrated in the respiratory distress pigs. Alveolar and perivascular cells demonstrated normal morphol-

Table 1. Results obtained in 19 piglets under general anesthesia and ventilation with 100% oxygen under steady state conditions as specified in the text

Ventilation	Ventilatory modes			
	(IPPV)	(L-IPPV)	(L-IRV)	(L-HFPPV)
PIP (cmH_2O)	19.6 ± 0.4	39.8 ± 1.6	39.2 ± 1.9	34.3 ± 1.8[a,b]
Paw endinsp. (cmH_2O)	15.0 ± 0.5	30.9 ± 1.2	36.5 ± 1.8[a]	28.4 ± 1.5[b]
MPAW (cmH_2O)	10.5 ± 0.1	15.8 ± 0.5	26.2 ± 1.2[a]	17.9 ± 0.8[a,b]
Paw endexp. (cmH_2O)	7.5 ± 0	7.5 ± 0	14.1 ± 0.6[a]	13.5 ± 0.8[a]
VE BTPS (ml/kg·min)	272 ± 7	472 ± 14	459 ± 13	736 ± 23[a,b]
$PaCO_2$ (kPa)	4.9 ± 0.1	4.7 ± 0.4	3.5 ± 0.2[a]	3.8 ± 0.2
Compliance (ml/cmH_2O)	42 ± 3	22 ± 2	23 ± 1	18 ± 1[a,b]
Oxygenation				
PaO_2 (kPa)	73.7 ± 1.4	35.6 ± 4.8	67.6 ± 4.2[a]	50.9 ± 5.1[b]
SaO_2 (%)	97.1 ± 0.3	89.3 ± 4.6	96.9 ± 1.5	96.5 ± 1.2
Qs/Qt (%)	12.2 ± 1.0	27.1 ± 4.8	9.6 ± 2.5[a]	15.7 ± 1.8
Hemodynamics				
MAP (mmHg)	102 ± 5	104 ± 3	89 ± 4[a]	97 ± 4
CVP (mmHg)	3.0 ± 0.5	5.1 ± 0.7	6.8 ± 1.1[a]	5.4 ± 0.9[b]
PAP mean (mmHg)	17.9 ± 1.0	30.8 ± 2.4	31.8 ± 1.6	28.7 ± 1.4
PCWP (PAP dia) (mmHg)	11.0 ± 1.0	20.8 ± 2.1	22.1 ± 1.5	19.7 ± 1.6
SvO_2 (%)	68.6 ± 1.8	55.0 ± 4.5	49.1 ± 3.2	58.9 ± 3.0[b]
CO (ml/kg·min)	175 ± 8	161 ± 8	105 ± 7[a]	139 ± 5[b]
SV (ml/kg·beat)	1.09 ± 0.05	0.90 ± 0.06	0.54 ± 0.05[a]	0.73 ± 0.04[a,b]
O_2-transport (ml/kg·min)	23.3 ± 1.1	19.4 ± 1.1	13.7 ± 0.8[a]	18.3 ± 0.8[b]
SVR ($dyn \cdot s \cdot cm^{-5}$)	2087 ± 104	2311 ± 206	2976 ± 186[a]	2412 ± 149[b]
PVR ($dyn \cdot s \cdot cm^{-15}$)	147 ± 15	220 ± 23	358 ± 71	237 ± 19
Intrathoracic volumes				
EVLW (ETVmtt ml/kg) ($n = 19$)	7.5 ± 1.06	18.0 ± 2.69	22.1 ± 1.91	18.7 ± 2.32
PPBV (ml/kg)($n = 10$)	8.2 ± 0.56	7.90 ± 0.70	6.13 ± 0.66	6.81 ± 0.69
ITBV (ml/kg) ($n = 10$)	18.3 ± 1.55	18.32 ± 1.74	12.68 ± 1.31[a]	14.01 ± 0.79[a]
PPBV/CI ($n = 10$)	1.5 ± 0.095	1.443 ± 0.111	2.077 ± 0.214[a]	1.675 ± 0.084
Metabolism				
VO_2 (ml/kg·min)	6.7 ± 0.4	7.5 ± 0.4	6.5 ± 0.3	7.1 ± 0.4
VCO_2 (ml/kg·min)	10.6 ± 0.4	11.7 ± 0.04	11.2 ± 0.3	12.1 ± 0.4

Mean ± SE
[a] Different from L-IPPV, $p \leq 0.05$
[b] Different from L-IRV, $p \leq 0.05$

ogy. No hyaline membranes and no necrosis of bronchial epithelium were seen in any of the pigs. The chest X-ray obtained at baseline was normal, but 5 h subsequent to lavage the chest radiogram demonstrated an ARDS-like picture, with bilateral irregular densities and bronchogram (Fig. 2).

Ventilation

In the IRV mode, end-inspiratory, mean and end-expiratory airway pressures were significantly higher than in the conventional L-IPPV mode ($p < 0.05$). Using L-IRV, the peak inspiratory pressure (PIP) was on average 39 cm H_2O with an end-inspiratory pressure of 37 and end-expiratory pressure of 14 cm H_2O (this entails external PEEP of 7.5 cm H_2O + intrinsic PEEP). The IRV-induced mean airway pressure (MPAW) was 26 m H_2O which was significantly higher than with L-IPPV (16 cm H_2O) or L-HFPPV. The latter produced an intermediate MPAW level of 18 cm H_2O. With L-HFPPV, oxygen transport was 18 ml/kg/min, i.e. of the same magnitude as with L-IPPV which gave 19 ml/kg/min, while L-IRV produced only 14 ml/kg/min. The PaO_2 levels, however, followed the mean airway pressures more closely. L-IRV with high PIP and MPAW gave a PaO_2 of 67.6 kPa. L-HFPPV gave a PaO_2 of 50.9 kPa but L-IPPV only produced 35.6 kPa. Despite these differences in PaO_2, L-IPPV – being less detrimental to cardiac output – produced a similar level of oxygen transport to L-HFPPV, both being significantly higher than with inverse ratio ventilation (IRV) with its high airway pressures during both inspiration and expiration (Fig. 4).

Hemodynamics

During L-IRV a lower cardiac output (CO) was observed than during either the L-IPPV or the L-HFPPV modes. The intrapulmonary shunt Qs/Qt was elevated from 12% before lavage to 27% during L-IPPV. The shunt was significantly lower with L-IRV (10%) than during L-HFPPV, which produced a shunt of 16%. The systemic vascular resistance (SVR) was significantly higher during L-IRV than during L-IPPV or L-HFPPV. The pulmonary vascular resistance was the same for all 3 modes of ventilation.

Table 2. Stability of the lavage lung model ($n = 10$) in the 10 piglets in which the COLD-computer was used. In the columns the statistical test refers to the values in italics

Time	EVLW (ETVmtt ml/kg)	PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	SaO_2 (%)	Compliance (ml/cm H_2O)
5 min before lavage	6.7±0.99	74.4±1.9	5.1±0.1	7.44±0.01	96±1	43±2
5 min after lavage		*6.1*±0.54	*8.8*±0.4	*7.16*±0.09	*52*±1	*14*±1
125 min after lavage	*26.2*±2.73	6.8±0.5	6.3±0.5*	7.32±0.03	59±6	15±1
185 min after lavage	23.7±2.58	8.0±0.7	7.1±0.5	7.28±0.03	71±6*	13±1
245 min after lavage	26.1±3.10	7.6±0.9	7.2±0.5	7.30±0.03	65±8*	13±1
300 min after lavage	24.7±2.38	7.5±0.8	6.6±0.6	7.33±0.03	70±8*	13±1
360 min after lavage[a]	22.5	48.3	4.1	7.48	97	12
420 min after lavage[a]	22.3	47.9	4.0	7.46	95	12
480 min after lavage[a]	27.9	49.9	4.1	7.46	93	12
540 min after lavage[a]	25.8	70.8	3.7	7.48	95	12
600 min after lavage[a]	21.8	63.5	3.7	7.51	97	12

Mean±SE, $*p \leq 0.05$

[a] Not enough measurements for statistical calculations (in 3 piglets with a prolonged study period of L-IPPV, L-IRV or L-HFPPV)

The intrathoracic blood volumes (ITBV) also indicated that higher MPAWs had the effect of preventing blood from entering the thorax (see Table 1). Thus the modes producing intrinsic PEEP (L-IRV and L-HFPPV) gave ITBVs of around 13–14 ml/kg, which was lower (L-IRV, $p<0.05$) than with L-IPPV, which permitted an average of 18 ml/kg of blood to remain in the thoracic cavity. The significantly higher PPBV/CI value during L-IRV (2.077 compared to 1.477 in L-IPPV; $p<0.05$) indicated less efficient function of the right heart with this ventilatory pattern.

Metabolism

As mentioned in the Monitoring section, an inaccuracy in the absolute values of VCO_2 measurements had to be accepted. These values were ony used to estimate ventilatory steady state. Evaluated by the oxygen consumption the metabolism remained stable throughout the experiment, but RQ calculations were impossible.

Discussion

Following recent debate concerning strategies of suitable modes of ventilation [1, 6, 9, 12–14, 26–28], we considered a randomized sequential study in an animal model of severe respiratory distress might resolve some of the unclear points concerning the efficacy of different ventilatory modes. Several previously described models of severe respiratory distress, such as infusion of endotoxins or live bacteria, were considered not particularly suitable for a study of sequentially applied ventilatory modes. These models entail a high mortality and are difficult to reproduce and maintain reliable with respect to stability and a suitable level of hypoxemia [17, 29–33]. Other models of pulmonary damage, such as hydrochloride instillation, infusion of oleic acid or similar substances, give reproducible damage, but displays such pronounced time-dependent changes that randomized sequential comparisons are difficult. Lachmann and co-workers have published models of respiratory distress by surfactant depletion through broncho-alveolar lavage in rodents, rabbits and dogs [2, 8, 9].

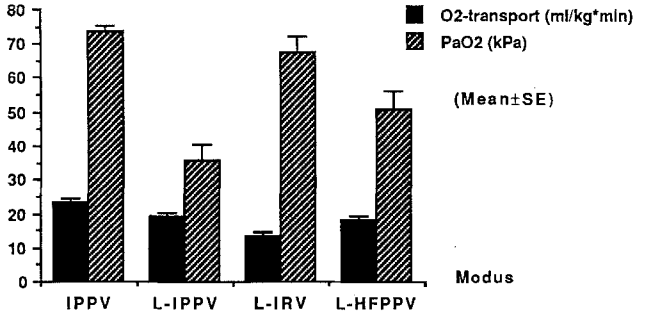

Fig. 4. PaO_2 and oxygen transport

The lavage model was considered suitable for reproduction of severe respiratory distress. We wished to characterize this model when it was employed in piglets for sequential analysis following lavage. We have become satisfied that this model is reproducible and stable for at least 5 h following lavage with respect to liability to alveolar collapse, decrease in static chest-lung compliance and increase in extravascular lung water (see Tables 1 and 2).

Paraphrasing Lachmann et al. [9], efficient modes of ventilation must overcome forces related to increased surface tension in the airways (recruitment of the airways). This requires inspiratory pressures which overcome a critical opening pressure. This opening pressure must be exceeded or maintained during inspiration for a sufficiently long period of time and expiration must permit efficient exhalation with minimal airway closure. Thus, inspiratory and expiratory phases should allow sufficient airway pressures, gas flows and lung volumes with the least possible "barotrauma" and circulatory impairment.

If successful recruitment was judged in terms of sufficient alveolar ventilation, 14 of the 19 piglets could be ventilated with L-IPPV, 18 of 19 piglets with L-IRV and 18 of 19 piglets with L-HFPPV, respectively (Fig. 5). However, under conditions of successful alveolar recruitment the airway pressures and circulatory interference were substantially different. The L-IRV mode provided the best PaO_2, but with the expense of high airway pres-

Table 3. Oxygnation. Airway pressures and circulatory interference after eliminating differences in alveolar ventilation

Parameter	Ventilatory modes			$PaCO_2$ range 3.0 – 4.0 kPa		
	(L-IPPV)	(L-IRV)	(L-HFPPV)	(L-IPPV)	(L-IRV)	(L-HFPPV)
Number of measurements	17	19	18	8	16	12
$PaCO_2$ (kPa)	4.7 ± 0.44	3.5 ± 0.20[a]	3.8 ± 0.15	3.6 ± 0.07	3.3 ± 0.06	3.5 ± 0.08
MPAW (cmH_2O)	15.8 ± 0.5	26.2 ± 1.2[a]	17.9 ± 0.8[a,b]	14.9 ± 0.5	26.5 ± 1.3[a]	17.2 ± 0.9[b]
PIP (cmH_2O)	39.8 ± 1.6	39.2 ± 1.9	34.3 ± 1.8[a,b]	35.9 ± 1.6	39.7 ± 2.1	32.4 ± 1.8
PaO_2 (kPa)	35.6 ± 4.8	67.6 ± 4.3[a]	50.9 ± 5.1	42.9 ± 6.8	70.4 ± 3.0[a]	62.6 ± 3.9
O_2-transport (ml/kg·min)	19.4 ± 1.1	13.7 ± 0.8[a]	18.3 ± 0.8[b]	20.9 ± 1.4	13.7 ± 0.9[a]	18.2 ± 0.8[a]
SvO_2 (%)	55.0 ± 4.5	49.1 ± 3.2	58.9 ± 3.0[b]	63.6 ± 2.0	49.3 ± 3.3	64.0 ± 2.1

Mean ± SE
[a] Different from L-IPPV, $p \leq 0.05$
[b] Different from L-IRV, $p \leq 0.05$

sures and consequent circulatory interference expressed by reduced oxygen transport and reduced mixed venous saturation (Table 1).

It can be speculated, that the "opening"-procedure of lungs with alveolar closure neither is, nor can be, standardized, i.e. the ventilatory volumes, the airway pressures and circulatory interference depend on the ventilator settings. However, in Table 1, which includes the results from all 19 pigs, it can be seen that only for L-IPPV the $PaCO_2$ value is statistically different, and that the standard errors of the mean for all $PaCO_2$ values are relatively small. For further standardization, and in order to eliminate the differences in $PaCO_2$, we have isolated the measurements, in which the $PaCO_2$ values were within the range 3.0 to 4.0 kPa (Table 3). Obviously the statistical differences are not exactly the same, but it must be taken into consideration that the statistical test is also influenced by the low number of measurements. Despite this, these statistical differences as well as the numerical values, are essentially the same.

Extrapolating from these studies, it may be reasoned that in the early treatment of acute respiratory distress, high peak inspiratory pressure (PIP) and fairly high MPAW can be desirable components of a ventilatory mode, as both components seem closely related to recruitment of collapsed alveoli. On the other hand, in clinical practice the use of high PIP and MPAW is somewhat limited by at least 2 perceived risks: one is barotrauma, and the other is the risk of reduced cardiac output with reduction in oxygen transport. As recently stressed by Hickling [34], an additional aspect is the risk of increasing the lung damage by the use of high airway pressures, especially PIP. Consequently, lower airway pressures may be obtained with low tidal volumes, which may then improve the outcome for patients in severe respiratory distress [35].

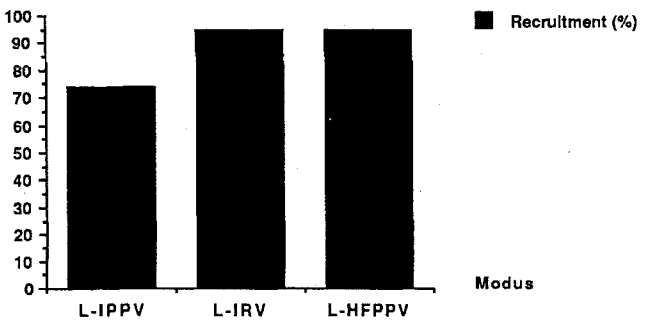

Fig. 5. Recruitment rate

If alveolar recruitment and oxygen transport are viewed as main factors determinating the efficacy of ventilation, in the present study HFPPV seems to be the mode with the lowest risk of barotrauma still providing sufficient oxygen delivery (Table 1).

In the clinical setting there might be negative effects on vital organs and functions unless the ventilatory modes are continuously and cautiously adapted to the individual requirements in different phases of severe respiratory distress. Therefore, one ventilatory strategy could be to "open the airways" with IRV, but then switch to HFPPV in an attempt to maintain the airways open with lesser risk of barotrauma and with improved oxygen transport.

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