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EXPERIMENTAL

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Tracing best PEEP by applying PEEP as a RAMP

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Abstract *Objective:* The aim of this study was to show the feasibility of a slow, continuously increasing level of positive end-expiratory pressure (PEEP) (ramp manoeuvre) in selecting best PEEP and to evaluate whether best PEEP, as definded by maximal oxygen transport, coincides with best systemic arterial oxygenation or best compliance.
Design: In 11 anaesthetized piglets, PEEP was increased between 0 cmH_2O (zero end-expiratory pressure; ZEEP) and 15 cmH_2O ($PEEP_{15}$) with a constant rate of 0.67 $cmH_2O \cdot min^{-1}$. This ramp manoeuvre was performed both under normal conditions and after induction of an experimental lung oedema. During the ramp manoeuvre, haemodynamic and pulmonary variables were monitored almost continuously.
Results: During the rise in PEEP, cardiac output declined in a non-linear way. In the series with normal conditions, best PEEP was always found at ZEEP. In the series with experimental lung oedema, best PEEP, as defined by maximum oxygen transport, was found at $PEEP_{1-6}$, as defined by maximal compliance, at $PEEP_{7.5}$ and by maximal arterial oxygen tension (PaO_2) at $PEEP_{10-14}$.
Conclusions: Best PEEP according to oxygen transport is lower than best PEEP according to compliance and PaO_2; the use of PEEP as a ramp might prevent unnecessarily high levels of PEEP.

Key words (Best) PEEP · Haemodynamics · Oxygen transport · Pulmonary edema

Introduction

Mechanical ventilation with positive end-expiratory pressure (PEEP) is still the usual therapy for patients with the acute respiratory distress syndrome. Since the paper by Ashbaugh et al. [1], many others have demonstrated the beneficial effect on arterial oxygen tension (PaO_2) [2–7]. PEEP leads to the augmentation of an abnormally low functional residual capacity (FRC) [4, 7–9]. This increase in FRC is due to recruitment of collapsed alveoli [6, 7, 10], or to hyperinflation [7, 11]. Care should be taken when applying PEEP, because the latter mechanism increases the risk of barotrauma. Furthermore, PEEP may have a negative effect on cardiac output, because it decreases venous return to the heart through an increase in right atrial pressure [12, 13].

As oxygen transport is the product of the oxygen content of arterial blood and cardiac output, it will be obvious that a decrease in cardiac output will counteract the beneficial effect of PEEP on arterial oxygen content. The PEEP level, where oxygen transport is maxi-

mal, has been called "best PEEP" [5]. Because of the negative influence on the circulation and the risk of barotrauma, "best PEEP" should be as low as possible [14]. Others stress the importance of preventing the collapse of recruited alveoli ("keep the lung open") as a means of preventing lung damage caused by mechanical ventilation [15]. These different goals can result in different "best PEEP" levels. Because the ultimate goal is the delivery of oxygen to the tissues, we chose maximal oxygen transport as the end-point for best PEEP. Suter et al. [5] found that the PEEP level of maximum oxygen transport coincided with the highest compliance.

In previous papers [16–18], the haemodynamic responses to PEEP, applied as a ramp in time, were found to be non-linear in piglets. Cardiac output and aortic pressure decreased in three phases, with the sharpest decline with a PEEP between 3 and 10 cmH_2O (phase II). These non-linear responses were attributed to a combination of three mechanisms. Firstly, to a linear decrease in venous return, caused by the rise in intrathoracic pressure and the concomitant rise in central venous pressure (CVP), secondly, to cardiovascular compensatory mechanisms, evoked by the fall in arterial pressure [16], and thirdly, to a lung stretch depressor reflex (phase II), inducing systemic vasodilatation and a decrease in heart rate [17]. When PEEP is applied in steps, followed by blood gas analysis and cardiac output determination, which is the usual practice, such non-linearity might be missed. This might result in a higher best PEEP level than necessary. The objective of this study in piglets was to evaluate the haemodynamic and pulmonary responses as a function of PEEP during conditions of experimentally induced pulmonary oedema. To be maximally informed on the haemodynamic changes due to PEEP at all levels between 0 and 15 cmH_2O, we applied PEEP as a continuous rising function, as a ramp. A previous study [16] has shown that cardiac output and CVP follow this PEEP ramp closely and that these variables do not change during interruptions of the ramp at different levels of PEEP.

Besides tracing best PEEP in terms of oxygen transport, the purpose of this study was to evaluate whether indicators, other than oxygen transport, could be used to identify this best PEEP level during the continuous rise in PEEP.

Materials and methods

All experiments were performed according to the *Guide for the Care and Use of Laboratory Animals,* published by the National Institutes of Health (NIH publication 85-23, revised 1985) and approved by the Animal Care Committee of Erasmus University Rotterdam, The Netherlands.

Eleven piglets (5–7 weeks old, 7–11 kg) were anaesthetized with pentobarbital sodium (30 $mg \cdot kg^{-1}$ intraperitoneally) and placed in the supine position. Rectal temperature was maintained at about 38 °C on a thermocontrolled operating table. A tracheostomy was performed. Anaesthesia was maintained by a continuous intravenous infusion of pentobarbital 7.5 $mg \cdot kg^{-1} \cdot hr^{-1}$. The animals were paralysed with d-tubocurarine (0.1 $mg \cdot kg^{-1}$) administered over a period of 3 min followed by a continuous infusion of 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ to avoid spontaneous breathing during the experimental procedures. The animals were ventilated with room air with a volume ventilator with a sinusoidal inspiratory flow pattern and an inspiratory : expiratory ratio of 4 : 5. The respiratory rate was 10 breaths $\cdot$ min^{-1} and the tidal volume was adjusted to an arterial CO_2 tension ($PaCO_2$) between 38 and 45 mm Hg. Tidal volume was then kept constant during the experiment.

Two polyethylene catheters were inserted into the right common carotid artery: one, a double-walled injection catheter (1.14 mm i.d.), was placed with the tip 2.5–3.0 cm beyond the aortic valve into the left ventricle, the other (1.14 mm i.d.), with a thermistor at its tip, was positioned in the aortic arch near the origin of the brachiocephalic artery. A flow-directed pulmonary artery catheter (5 F) was inserted via the right internal jugular vein into the pulmonary artery. A four-lumen catheter (7 F) was placed through the right internal jugular vein in the superior caval vein at the level of the right atrium for the administration of anaesthetics, muscle relaxants and fluids and for CVP measurement. Loss of blood was compensated for with 6% dextran (Macrodex).

Measurements

Airway pressure was measured in a short, wide-bore (i.d. 8 mm) tracheal cannula. Mean aortic pressure (MAP), mean pulmonary artery pressure (MPAP) and CVP were also continuously monitored. Cardiac output was determined by both the thermodilution technique and the direct Fick method for O_2 [20]. For the estimation by thermodilution, 0.5 ml saline at room temperature was injected automatically into the left ventricle through the double-walled catheter. The injection was given at a fixed moment in the ventilation cycle about at the end of spontaneous expiration (i.e. 60% of the cycle from the beginning of inspiration), which provides, for any level of PEEP, a representative estimate of the mean cardiac output [20]. For the direct Fick method, CO_2 production and O_2 consumption were calculated from the ventilatory variables and the inspired and mixed expired CO_2 and O_2 concentrations. CO_2, O_2 and N_2 concentrations in air were measured with a mass spectrometer (Perkin-Elmer type MGA 1100). PaO_2 and $PaCO_2$ were measured in arterial and mixed venous blood samples of 0.5 ml by means of an automatic blood gas analyser. O_2 saturation and haemoglobin values were measured with an oximeter (Radiometer). In four animals instantaneous PaO_2 was continuously measured with a catheter provided with a Clark electrode, positioned via the carotid artery into the aorta. This PaO_2 was matched with the PaO_2 measured by the blood gas analyser.

Oxygen transport was calculated, using the formula: oxygen transport = cardiac output × oxygen content, in which oxygen content in ml per 100 ml of blood is

$$SaO_2 \times Hb \times 0.013 + PaO_2 \times 0.003 \quad (1)$$

in which arterial O_2 saturation (SaO_2) is expressed in whole numbers from 0–100, haemoglobin (Hb) in g $\cdot$ dl^{-1} and PaO_2 in mmHg.

Oxygen saturation was derived from an adjusted Kelman's formula, in which oxygen saturation is a function of the partial pressure of oxygen, with adjustments for pH and partial pressure of carbon dioxide [21, 22]. This adjusted formula was derived from a separate series of experiments in pigs, in which oxygen dissociation curves were constructed.

Table 1 Control data for each series[a]

	Series 1 (control): $FIO_2 = 0.21$			Pre-oedema: $FIO_2 = 0.40$ ZEEP	Series 2 (oedema): $FIO_2 = 0.40$		
	$ZEEP_1$	$PEEP_{15}$	$ZEEP_2$		$ZEEP_1$	$PEEP_{15}$	$ZEEP_2$
PaO_2 (mm Hg)	78.3 (6.5)	84.7 (7.8)*	78.9 (5.5)	156.5 (12.8)	60.3 (19.5)***	154.0 (28.3)**	58.7 (15.3)***
$PaCO_2$ (mm Hg)	43.7 (1.9)	42.9 (2.5)	43.2 (1.9)	42.9 (2.5)	53.2 (4.2)***	44.4 (3.4)**	50.9 (4.0)***
CO (Fick) $ml \cdot s^{-1} \cdot kg^{-1}$	2.65 (0.37)	1.29 (0.25)**	2.61 (0.39)	–	2.43 (0.58)	1.20 (0.21)**	2.12 (0.63)*

* $p < 0.01$ and ** $p < 0.001$ compared to $ZEEP_1$ of the same series, *** $p < 0.001$ compared to the pre-oedemic value with $FIO_2 = 0.40$

[a] Values are means ± SD ($n = 11$) taken before the positive ramp ($ZEEP_1$), during the 8-min interval ($PEEP_{15}$) and after the reversed ramp ($ZEEP_2$). Before the induction of lung oedema, FIO_2 was raised to 0.40

Experimental procedure

A control PEEP ramp was established before the induction of lung oedema (series 1). Before the ramp at zero end-expiratory pressure ($ZEEP_1$), cardiac output was determined by the thermodilution technique and the direct Fick method. With thermodilution, cardiac output was taken as the mean of five successive measurements. The Fick method was used to estimate cardiac output at ZEEP and at $PEEP_{15}$ (at 15 cmH_2O), whereas the thermodilution technique was used for the cardiac output changes during the PEEP ramp. Immediately after the control measurements at ZEEP, the end-expiratory pressure was linearly increased by moving the expiratory line at constant speed into a water seal down to 15 cmH_2O in 22.5 min. Thus PEEP was applied as a positive ramp with a velocity of 0.67 $cmH_2O \cdot min^{-1}$.

During the ramp procedure, thermodilution measurements were performed at intervals of 30 s. At the same time, the mean vascular pressures over the cardiac cycle and other variables were determined at end-expiration. At the end of the positive ramp, $PEEP_{15}$ was maintained for 8 min. Then a reversed ramp was established with the same velocity. During maintenance of $PEEP_{15}$, and at ZEEP after the reversed ramp ($ZEEP_2$), cardiac output was determined again by both methods.

Next, lung oedema was induced by the intravenous administration of both alloxan (75 $mg \cdot kg^{-1}$) [23, 24] and oleic acid (0.05 $ml \cdot kg^{-1}$) [3, 25]. Cardiac output was restored to its pre-oedemic value at ZEEP with 6% dextran (Macrodex). Before the induction of lung oedema, fractional inspired oxygen (FIO_2) was raised to 0.40. After a stabilization period of 30 min, cardiac output was measured by both methods, and the same PEEP ramp procedure, positive and reversed, was carried out again (series 2).

Data analysis and statistics

The end-expiratory value of the mean CVP of each experiment during ZEEP ventilation in the initial control phase in series 1 and 2 was reset to zero. All other measured pressures were related to this zero level.

Previously, it was shown that the changes in mean CVP (ΔCVP) by PEEP are equal to the changes in mean intrathoracic pressure (ΔP_{it}) [16]. Therefore ΔCVP was used for the calculation of transmural MPAP ($MPAP_{tm}$) changes, with CVP reset to 0 at end-expiration at ZEEP.

With the objective of data reduction, cardiac output and the other variables corresponding in time plotted against PEEP are the means of three successive measurements. Because the measurements were performed every 0.5 min and the velocity of the PEEP ramp was 0.67 $cmH_2O \cdot min^{-1}$, these mean values represent a 1-cm PEEP interval. Statistical analyses were done with Student's t-test for paired variables. A statistical program, Timvar [26], was used for each animal to test for a non-linear relationship between the change in cardiac output with PEEP. This program analyses regression over time. Because PEEP increased linearly with time, cardiac output responses could be tested against PEEP. Values are presented as mean ± SD.

Results

Stability of the model

Table 1 presents the results of the steady-state measurements of the 11 experiments before the induction of lung oedema (series 1) and after the induction of lung oedema (series 2), at $ZEEP_1$, at $PEEP_{15}$, and after the reversed ramp at $ZEEP_2$. In each series, there was no difference in PaO_2 or $PaCO_2$ at ZEEP before and after the PEEP ramp procedure. Cardiac output in series 1 was similar at $ZEEP_1$ and $ZEEP_2$. In series 2, cardiac output, which was restored to its pre-oedemic value with dextran 9.5 ± 4.1 $ml \cdot kg^{-1}$ body weight, did not return to its baseline values after the PEEP ramp procedure; a small difference ($p < 0.01$) remained.

In series 1, there was a small but significant ($p < 0.01$) increase in PaO_2 at $PEEP_{15}$, compared to ZEEP. $PaCO_2$ was not influenced by PEEP in series 1. Before the induction of lung oedema FIO_2 was increased to 0.40, which resulted in a large increase in PaO_2, while $PaCO_2$ remained stable. After the induction of oedema, PaO_2 decreased, and $PaCO_2$ increased significantly ($p < 0.001$) compared to the pre-oedemic values at $FIO_2 = 0.40$.

At $PEEP_{15}$ in series 2, PaO_2 and $PaCO_2$ were significantly increased and decreased, respectively ($p < 0.001$), compared to the values at $ZEEP_1$ and were restored to their pre-oedemic values.

Ramp procedures

In series 1, tracheal peak pressure ($P_{T,p}$) (Fig. 1) increased over the whole range of PEEP. In series 2, $P_{T,p}$ was significantly ($p < 0.02$) higher compared to the corresponding values for series 1 up to $PEEP_{5,5}$. Above

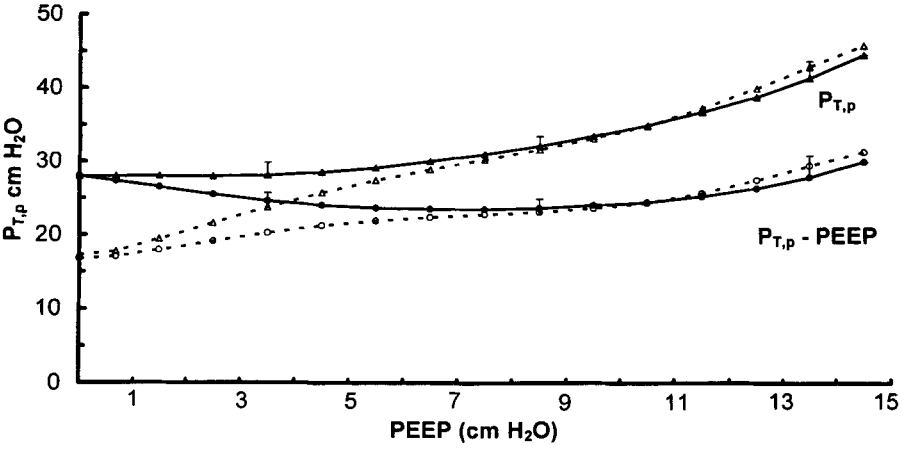

Fig. 1 Tracheal peak pressures $P_{T,p}$, *triangles* and tracheal peak pressures minus PEEP $P_{T,p}$ – *PEEP, circles* in series 1 *dashed lines, open symbols* and series 2 *solid lines, closed symbols* during the positive PEEP ramp. Values are means ± SD; $n = 11$

$PEEP_{5.5}$, the peak pressures were not significantly different from series 1. When the PEEP level was subtracted from the tracheal peak pressure ($P_{T,p}$ – PEEP), this pressure difference increased over the whole range of PEEP in series 1 (Fig. 1). But in series 2, $P_{T,p}$ – PEEP declined significantly up to $PEEP_{7.5\pm1.5}$ ($p < 0.01$) and increased above $PEEP_{7.5}$.

Cardiovascular responses

The cardiac output measured by thermodilution yielded a non-linear relation with PEEP (Fig. 2 A). By means of regression analysis the response can be divided into three parts: phase I from ZEEP to $PEEP_3$, phase II from $PEEP_3$ up to $PEEP_{10}$ and phase III from $PEEP_{10}$ up to $PEEP_{15}$. During phase II there is a significantly ($p < 0.05$) sharper decline in cardiac output compared with that during phases I and III. There were no differences in cardiac output between the two series (Fig. 2 A). MAP also decreased over the three pases, with the sharpest decline in phase II, with no significant differences between the two series (Fig. 2 B).

In series 1, $MPAP_{tm}$ did not change. In series 2, $MPAP_{tm}$ was significantly higher over the whole range of PEEP compared to series 1 ($p < 0.01$). In series 2, $MPAP_{tm}$ at end-expiration decreased up to $PEEP_{7.5}$ and remained constant during a further increase of PEEP.

CVP at end-expiration increased nearly linearly with PEEP in series 1. In series 2, mean CVP at ZEEP was 2 mm Hg higher, but was reset to 0 for each animal individually (Fig. 2 D). From ZEEP to $PEEP_{8.5}$, the increase in CVP with PEEP was significantly less in series 2 compared to the control group ($p < 0.05$). At PEEP values higher than $PEEP_{8.5}$, the increase of CVP was similar in both groups.

Oxygen transport

Four animals with continuous PaO_2 measurements showed a similar cardiac output response to the application of PEEP as the whole group. In these four animals, PaO_2 decreased after the induction of lung oedema. This decrease was not uniform; in two animals, PaO_2 decreased substantially (to 35 and 38 mm Hg, respectively), whereas in the other two animals the decrease was moderate (to 63 and 67 mm Hg). In all animals, PaO_2 increased with PEEP (Fig. 3 A).

The effect of PEEP on oxygen transport in these individual animals is shown in Fig. 3 B. Oxygen transport in the two animals with the higher PaO_2 did not benefit from PEEP, but in the two animals with the initial low PaO_2, PEEP clearly improved oxygen transport.

Discussion

The animal model

In both series, gas exchange before and after the PEEP ramp was identical. In series 1, cardiac output returned to baseline values after the reversed ramp. In series 2, a small difference remained between cardiac output values at $ZEEP_1$ and $ZEEP_2$ (Table 1), but this was regarded as physiologically insignificant. Therefore, it is reasonable to suppose that the animal model was satisfactorily stable for this study. The stability of this animal model has been confirmed by other studies [16, 25, 27], and indicates that the effects of PEEP are reversible. Stable cardiac outputs were found during periods of arrested PEEP at the same velocity of the PEEP ramp [16]. Also, CVP was adapted at this speed. These results indicate that the control mechanisms of cardiac output are adapted completely at the applied velocity of 0.67 $cmH_2O \cdot min^{-1}$. How-

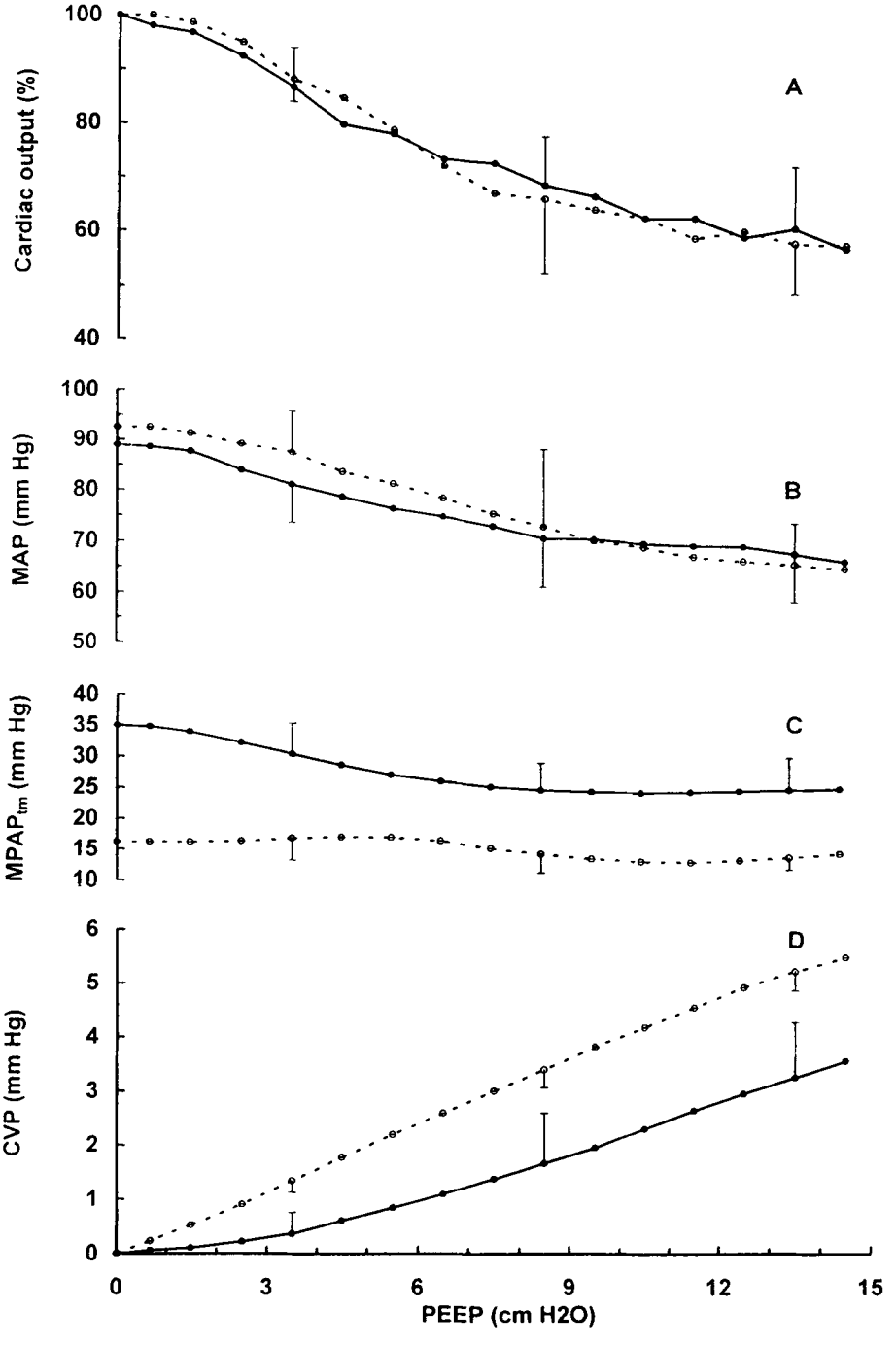

Fig. 2 Haemodynamic variables during the positive PEEP ramp. Series 1: preoedema *dashed lines;* series 2: oedema *solid lines.* **A** Cardiac output relative to the cardiac output at ZEEP. **B** Mean aortic pressure *MAP.* **C** Mean transmural pulmonary artery pressure at end-expiration $MPAP_{tm}$. **D** Change in mean central venous pressure at end-expiration ΔCVP. Values are means ± SD; $n = 11$

ever, $MPAP_{tm}$ decreased during the first 15 min [16]. This delayed vascular response was ascribed to either a decrease of hypoxia in atelectatic regions, or to vasoactive influences. Peak airway pressure also decreased during the first 15 min after the arrest in PEEP, which was ascribed to either diminished recoil forces in the pulmonary tissue or a decrease in atelectatic regions, or both [16].

Cardiac output and aortic pressure

This study confirms earlier results that individual responses of cardiac output and aortic pressure to PEEP, applied as a ramp, are non-linear, characterized by three phases [16–18]. Although the averaged response curve has the same three-phase pattern, it is smoothed due to individual differences, especially to the differences in

the PEEP range and steepness of phase II. Thus, the mechanisms, to which we attributed this non-linearity, compensating cardiovascular reflexes and the lung stretch depressor reflex [16], were operative in both the control and oedema series. In clinical practice, the fall in cardiac output and systemic arterial pressure will be compensated for by intravascular volume expansion and by infusion of inotropic drugs. The aim of this animal study was to evaluate the physiological variables without these interventions.

Central venous pressure

In series 1, CVP rose nearly linearly with PEEP. Because changes in CVP equal changes in P_{it} [16], one might conclude that the non-oedematous lungs were expanded by PEEP. After the induction of lung oedema, mean CVP at end-expiration was increased with 2 mm Hg. It can be hypothesized, that the total lung volume (fluid + air) was increased by the induction of oedema, resulting in a higher intrathoracic pressure. The increase in CVP at ZEEP might also be explained by a rise in right ventricular afterload [28], because mean pulmonary artery pressure markedly increased, probably as a result of the lung oedema and vasoconstriction [19]. However, the lower increase in CVP during the PEEP ramp contradicts right ventricular failure due to an increased right ventricular afterload. Moreover, in a former study, the increase in CVP in hypervolaemic animals during the PEEP ramp was similar compared to a control series, while $MPAP_{tm}$ in the hypervolaemic animals was markedly increased [18]. Thus, the increase in CVP is caused by an increase in lung volume and not by an increase in right ventricular afterload.

The lower increase in CVP in the oedema series up to $PEEP_{8.5}$ can be explained by decreased lung compliance. This will impair lung expansion, resulting in a smaller increase in P_{it} and, consequently, in CVP [16]. Above $PEEP_{8.5}$, the change in CVP was similar for the control and lung oedema series (Fig. 2 D). In both series, we think that an increase in CVP was caused by an increase in lung volume and thus in P_{it}. Using the deflection point (i.e. the PEEP value from which the rise in CVP in series 2 parallelled that in series 1) as an indicator for best PEEP, best PEEP in the oedema series, derived from the change in CVP, is at $PEEP_{8.5}$.

Gas exchange

The decrease in PaO_2 and the increase in $PaCO_2$ after induction of pulmonary oedema is the result of intrapulmonary shunting and ventilation–perfusion mismatch. The increase in PaO_2 with PEEP in these animals is a typical phenomenon and is attributed to recruitment of collapsed alveoli, reducing this shunt [6, 7, 10]. Normalization of the $PaCO_2$ with PEEP in the oedema group also indicates a restoration of alveolar ventilation. In the oedema series, best PEEP, defined according to maximal PaO_2 [29], was found at $PEEP_{10-14}$ (Fig. 3 A).

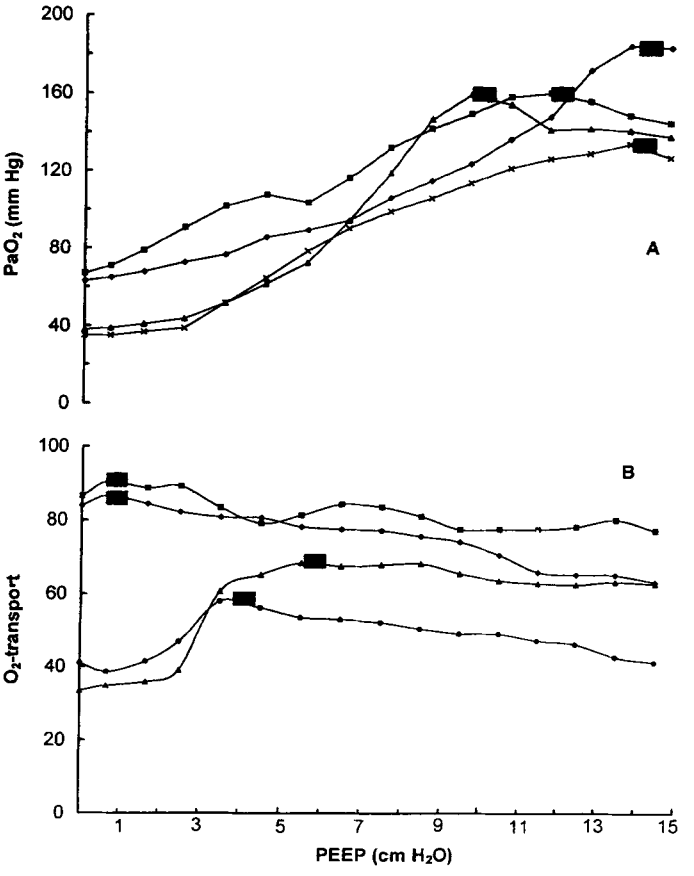

Fig. 3 Series 2 (oedema): four animals with continuous PaO_2 measurement. **A** PaO_2 in the individual animals during the positive ramp. **B** Oxygen transport in the individual animals during the positive ramp, in arbitrary units. PaO_2: ■ 67, ◆ 63, ▲ 38 and ● 35 mm Hg at $ZEEP_1$. *Black rectangles* "best PEEP" (see text)

Tracheal peak pressure

We ventilated the animals with a sinusoidal flow pattern with a fixed volume (co-sinusoidal volume pattern), i.e. with an airflow of zero at both the beginning and end of inflation. At these times, the airway resistance part of the tracheal pressure (flow × resistance) equals zero, and only the compliant part of the pressure remains. Therefore, the difference between the pressures at the end of inflation and the end of expiration is a measure of lung compliance.

$P_{T,p}$ in the pre-oedema group rose during the whole PEEP ramp. This could indicate overstretching of al-

ready ventilated alveoli. In the oedema group, the higher $P_{T,p}$ at the same tidal volume indicates an increased stiffness of the lungs. During the PEEP ramp, $P_{T,p}$ remained constant up to $PEEP_4$, followed by a slight increase up to $PEEP_{7.5}$. This rise was less than the applied PEEP. Thus, $P_{T,p}$ minus PEEP declined up to $PEEP_{7.5}$, implicating an increase in compliance due to recruitment of alveoli. We ascribe the increase in $P_{T,p}$ – PEEP above $PEEP_{7.5}$ to a stretching of ventilated alveoli. Therefore, according to the $P_{T,p}$ – PEEP, mean best PEEP should be at $PEEP_{7.5}$.

Oxygen transport

Because in series 1 the rise in PaO_2 with PEEP hardly increased oxygen content (Formula 1) while cardiac output decreased with PEEP, oxygen transport decreased with PEEP. Thus, in the pre-oedema series, under the conditions of controlled ventilation with room air, best PEEP is at ZEEP.

In the two animals with lung oedema and continuous PaO_2 measurements with the lowest PaO_2 at ZEEP, best PEEP was found at $PEEP_{5-6}$ (Fig. 3B). In the other two animals, in which the PaO_2 decrease had been moderate (Fig. 3A), best PEEP was observed at a lower level of PEEP (Fig. 3B). This difference in best PEEP levels is mainly due to the shape of the oxygen saturation curve. Raising PaO_2 when PaO_2 is near normal already, which was the case in two animals with lung oedema and continuous PaO_2 measurements, hardly influences oxygen content.

In conclusion, best PEEP, according to maximal PaO_2, was found at $PEEP_{10-14}$. However, best PEEP, derived from compliance ($P_{T,p}$ – PEEP), and from the rise in CVP, was observed at $PEEP_{7.5}$ and at $PEEP_{8.5}$, respectively. Best PEEP, in terms of oxygen transport, was observed at even lower levels, at $PEEP_{1-6}$. Searching for best PEEP by the continuous measurement of arterial PaO_2, or oxygen content, and cardiac output is not an easy task in a clinical setting. In addition, the fall in cardiac output and systemic arterial pressure is often counteracted by intravascular volume expansion and by the infusion of inotropic drugs. Even then, the application of PEEP as a ramp procedure might be advisable, as cardiac output remaining constant, maximum oxygen transport coincides with maximum oxygen content.

References

1. Ashbaugh DG, Bigelow DB, Petty TH, Levine BE (1967) Acute respiratory distress in adults. Lancet II: 319–323
2. Kumar A, Falke KJ, Geffin B, Aldredge CF, Laver MB, Lowenstein E, Pontoppidan H (1970) Continuous positive-pressure ventilation in acute respiratory failure. N Engl J Med 283: 1430–1436
3. Cheney FW, Martin WE (1971) Effects of continuous positive pressure ventilation on gas exchange in acute pulmonary edema. J Appl Physiol 30: 378–381
4. Falke JK, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver MB (1972) Ventilation with end-expiratory pressure in acute lung disease. J Clin Invest 51: 2315–2323
5. Suter PM, Frisley HB, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292: 284–289
6. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin R, Mascheroni D, Torressin A (1988) Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology 69: 824–832
7. Ranieri VM, Eissa NT, Corbeil C, Chassé M, Braidy J, Matar N, Milic-Emili J (1991) Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome. Am J Respir Crit Care Med 145: 544–551
8. Rose DM, Downs JB, Heenan TJ (1981) Temporal responses of FRC and oxygen tension to changes in PEEP. Crit Care Med 9: 79–182
9. Katz JA, Ozanne GM, Zinn SE, Failey HB (1981) Time course and mechanics of lung-volume increase with PEEP in acute pulmonary flow. Anesthesiology 54: 9–16
10. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Am J Respir Crit Care Med 136: 730–736
11. Valta P, Takala J, Eissa NT, Milic-Emili J (1993) Does alveolar recruitment occur with positive end-expiratory pressure in ARDS patients? J Crit Care 8: 34–42
12. Cournand A, Motley HL, Werkö L, Richards DW Jr (1948) Physiological studies of the effects of intermittent positive-pressure breathing on cardiac output in man. Am J Physiol 152: 162–174
13. Guyton AC, Lindsey AW, Abernathy B, Richardson T (1957) Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol 189: 609–615
14. Albert RK (1985) Least PEEP: primum non nocere. Chest 87: 2–3
15. Marini JJ (1994) Pressure-targeted, lung-protective ventilatory support in acute lung injury. Chest 105 (Suppl): 109S–115S
16. Schreuder JJ, Jansen JRC, Bogaard JM, Versprille A (1982) Hemodynamic effects of positive end-expiratory pressure applied as a ramp. J Appl Physiol 53: 1239–1247
17. Schreuder JJ, Jansen JRC, Versprille A (1984) Contribution of lung stretch depressor reflex to nonlinear fall in cardiac output. J Appl Physiol 56: 1578–1582
18. Schreuder JJ, Jansen JRC, Versprille A (1985) Hemodynamic effects of PEEP as a ramp in normo-, hyper- and hypovolemia. J Appl Physiol 59: 1178–1184
19. Grotjohan HP, Van Der Heijde RMJL, Wagenvoort CA, Wagenvoort N, Versprille A (1993) Pulmonary vasoconstriction in oleic acid induced lung injury. A morphometric study. Int J Exp Pathol 74: 347–355

20. Jansen JRC, Schreuder JJ, Bogaard JM, Van Rooyen W, Versprille A (1981) Thermodilution for measurement of cardiac output during artificial ventilation. J Appl Physiol 51: 584–591
21. Kelman GR (1966) Digital computer subroutine for the conversion of oxygen tension into saturation. J Appl Physiol 21: 1375–1376
22. Bartels H, Harms H (1959) Sauerstoffdissoziationskurven des Blutes von Säugetieren. Pflugers Arch 268: 334–365
23. Kawada T, Kambara K, Arakawa M, Segawa T, Ando F, Hirakawa S, Emura S (1992) Pretreatment with catalase or dimethyl sulfoxide protects alloxan-induced acute lung edema in dogs. J Appl Physiol 73: 1326–1333
24. Clark WR, Nieman G, Hakim TS (1990) Distribution of extravascular lung water after acute smoke inhalation. J Appl Physiol 68: 2394–2402
25. Grotjohan HP, Van der Heijde RMJL, Jansen JRC, Wagenvoort CA, Versprille A (1996) A stable model of respiratory distress by small injections of oleic acid in pigs. Intensive Care Med 22: 336–344
26. Brown RL, Durbin J, Evans JM (1975) Techniques for testing the constancy of regression relationships over time. J R Statist Soc Ser B 37: 149–163
27. Berglund JE, Halden E, Jakobson S, Svensson J (1994) PEEP ventilation does not cause humorally mediated cardiac output depression in pigs. Intensive Care Med 20: 360–364
28. Calvin JE, Quinn B (1989) Right ventricular pressure overload during acute lung injury: cardiac mechanics and the pathophysiology of right ventricular systolic dysfunction. J Crit Care 4: 251–265
29. Dall'ava-Santucci J, Armaganidis A, Brunet F, Dhainaut JF, Nouira S, Morisseau D, Lockhart A (1990) Mechanical effects of PEEP in patients with adult respiratory distress syndrome. J Appl Physiol 68: 843–848