Intensive Care Med (1996) 22: 329–335

ORIGINAL

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Oxygenation remains unaffected by increased inspiration-to-expiration ratio but impairs hemodynamics in surfactant-depleted piglets

Received: 14 March 1994
Accepted: 30 August 1995

This study was supported by the Swedish Medical Research Council (project 4252), the Swedish Heart-Lung Foundation, Stockholm, Sweden, and the Laerdal Foundation for Acute Medicine, Stavanger, Norway

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Abstract *Objectives:* Prolongation of inspiratory time is used to reduce lung injury in mechanical ventilation. The aim of this study was to isolate the effects of inspiratory time on airway pressure, gas exchange, and hemodynamics, while ventilatory frequency, tidal volume, and mean airway pressure were kept constant.
Design: Randomized experimental trial.
Setting: Experimental laboratory of a University Department of Anesthesiology and Intensive Care.
Animals: Twelve anesthetised piglets.
Interventions: After lavage the reference setting was pressure-controlled ventilation with a decelerating flow; I:E was 1:1, and PEEP was set to 75% of the inflection point pressure level. The I:E ratios of 1.5:1, 2.3:1, and 4:1 were applied randomly. Under open lung conditions, mean airway pressure was kept constant by reduction of external PEEP.
Measurements and results: Gas exchange, airway pressures, hemodynamics, functional residual capacity (SF_6 tracer), and intrathoracic fluid volumes (double indicator dilution) were measured. Compared to the I:E of 1:1, $PaCO_2$ was 8% lower, with I:E 2.3:1 and 4:1 ($p \leq 0.01$) while PaO_2 remained unchanged. The decrease in inspiratory airway pressure with increased inspiratory time was due to the response of the pressure-regulated volume-controlled mode to an increased I:E ratio. Stroke index and right ventricular ejection fraction were depressed at higher I:E ratios (SI by 18% at 2.3:1, 20% at 4:1; RVEF by 10% at 2.3:1, 13% at 4:1; $p \leq 0.05$).
Conclusion: Under open lung conditions with an increased I:E ratio, oxygenation remained unaffected while hemodynamics were impaired.

Key words Pressure-controlled inverse ratio ventilation · End-inspiratory pressure · Intrinsic PEEP · Functional residual capacity · Hemodynamics

Introduction

A growing body of evidence exists that high airway pressures should be avoided during mechanical ventilation to avoid further aggravation of the underlying lung injury [1–3]. To achieve this goal, prolongation of the inspiratory time to the point of inverting the inspiration-to-expiration (I:E) ratio seems promising [4–9]. Controlled trials in patients have been published

[9–12], and, as pointed out by Marini and Kelsen [13], additional prospective controlled trials in patients are needed. To investigate the effects of prolonged inspiratory time we chose an animal experimental model. The aim of this study was to isolate the effects of inspiratory time on airway pressure, gas exchange, and hemodynamics, while keeping mean airway pressure constant. Under open lung conditions, no improvement in oxygen tension was expected when mean airway pressure was kept constant, but prolongation of the inspiratory time was anticipated ultimately to impair hemodynamics.

Material and methods

Preparation of the animals

Two papers describing in detail the methods used have been previously published [14, 15]. Twelve healthy piglets of a Swedish country breed (25.4 ± 1.9 kg) were examined. Premedication consisted of 15 mg/kg pentobarbital and 0.5 mg atropine administered intraperitoneally 15 min prior to induction. Induction was achieved with 500 mg ketamine and 0.5 mg atropine i.v. followed by 20 mg morphine and ketamine i.v. at 20 $mg\,kg^{-1}\,h^{-1}$. Pancuronium bromide (0.26 $mg\,kg^{-1}\,h^{-1}$) was used as relaxant. The animals were tracheostomized and ventilated through an 8-mm endotracheal tube (Mallinckrodt, Glens Falls, N.Y., USA) with a Servo 300 ventilator (Siemens-Elema, Solna, Sweden). A thermostatically controlled heating pad was used to keep the animal's temperature at 37.6° ± 0.6 °C.

The investigations were performed at the experimental laboratory of the Department of Anesthesiology and Intensive Care at the University Hospital in Uppsala. The local ethics committee for animal experimentation reviewed and approved the protocol.

Monitoring

Intravascular catheters were surgically placed for the measurement of central venous, pulmonary artery pressure (via the external jugular vein), and aortic pressure (via the carotid artery). The exact position of catheters was confirmed by pressure tracing. All pressures were displayed on a bedside monitor (Siemens Sirecust) and recorded with reference to the middle thorax, and end-expiration. Heart rate, arterial and venous blood gases were all recorded (ABL 300, Radiometer A/S, Copenhagen, Denmark). Carbon dioxide production was recorded by a metabolic monitor (Datex Deltatrac, Datex Instrumentation, Helsinki, Finland).

The estimation of cardiac output was performed using the COLD system (Pulsion Medizintechnik, Munich, Germany). A fiberoptic catheter was introduced via the femoral artery and advanced to the descending aorta. The thermistor in the femoral artery catheter connected to the COLD system detects the temperature signal in the descending aorta from which cardiac output is calculated [16]. Right ventricular end-diastolic volume was measured according to the technique described previously [17]. Extravascular lung water (EVLW) and intrathoracic blood volume were measured using double indicator dilution as described in detail elsewhere [16, 18]. The double indicator consisted of 10 mg indocyanine green mixed in 10 ml 5% dextrose in water at a temperature of 5°–7 °C and was injected as a bolus into the superior vena cava. The dilution curves for dye and temperature were recorded simultaneously in the descending aorta with the thermistor-tipped fiberoptic catheter. EVLW was calculated as the difference between the volume accessible to the thermal indicator and the volume accessible to the intravascular indicator, indocyanine green. Intrathoracic blood volume was calculated as the product of cardiac output and the mean transit time of indocyanine green between the injection and detection points.

Airway pressures were obtained from the Servo 300 digital displays. Before starting the study the pressure and flow transducers of the Servo 300 were calibrated with independent devices. Every morning a functional check was performed according to the procedure given in the operating manual of the Servo 300.

Static chest-lung compliance was calculated according to the formula: tidal volume/(end-inspiratory pressure – end-expiratory pressure). When end-inspiratory pressure and total PEEP were measured, the hold functions of the Servo 300 were used for 5 s before the equilibrium values were noted. In this study total PEEP was defined as the sum of external PEEP (set by the PEEP valve of the ventilator) and intrinsic PEEP. Total PEEP was measured by the end-expiratory hold procedure.

The SF_6 tracer gas wash-out-method was used to measure functional residual capacity (FRC); (for details see [19]). The SF_6 equipment was available only for ten animals; therefore all FRC data presented in this study refer to ten animals.

Opening procedure

Immediately after and 3 h after lavage the surfactant-deficient lungs were recruited with the external PEEP set to the level which generated a peak inspiratory pressure of 50 cmH_2O and I:E ratio of 1:1 for 5 min.

Inflection point

The pressure/volume loop was generated using a constant inspiratory flow of 0.15 l/s and tidal volume of 1200 ml. From this loop the inflection point was determined by inspection [20, 21] immediately after lavage and 3 h after lavage (Fig. 1).

Inspiratory flow pattern

The Servo Ventilator 300 provides a pressure-regulated volume-controlled mode (Siemens-Elema, Solna, Sweden). This mode provides the set tidal volume by regulating the inspiratory pressure to

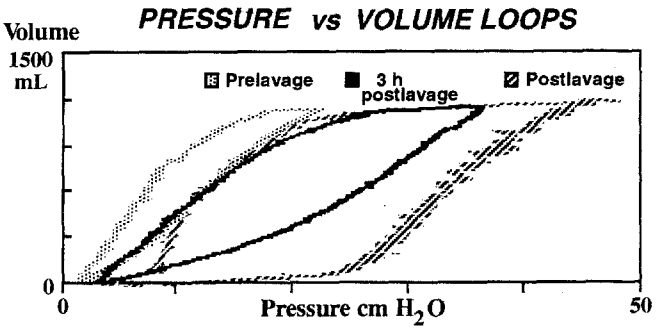

Fig. 1 Pressure-volume loops before, immediately after, and 3 h after lavage in one of the piglets

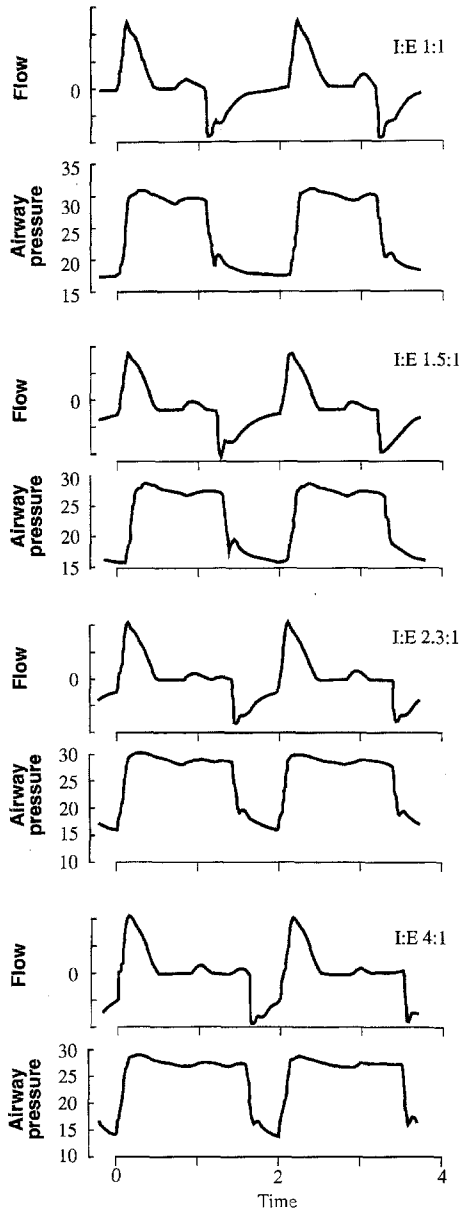

Fig. 2 Original experimental record of gas flow and airway pressure for two breaths at 30 bpm and with (*top to bottom*) increasing I:E ratios. The pressure-regulated volume-controlled mode provided the set tidal volume (by regulating the inspiratory pressure to a value based on the pressure/volume conditions for the previous breath). Adjusting the drive gas pressure between each breath provided decelerating inspiratory flow and constant tidal volume for all settings. Time is given in seconds, airway pressure in cmH_2O, and flow in a relative scale

a value based on the pressure/volume conditions of the previous breath. Allowing the drive gas pressure to be adjusted between each breath maintains the set tidal volume within limits given by the set upper pressure limit and pressure differences between breaths not exceeding 3 cmH_2O. Decelerating inspiratory flow was therefore delivered together with a constant tidal volume for all settings (Fig. 2).

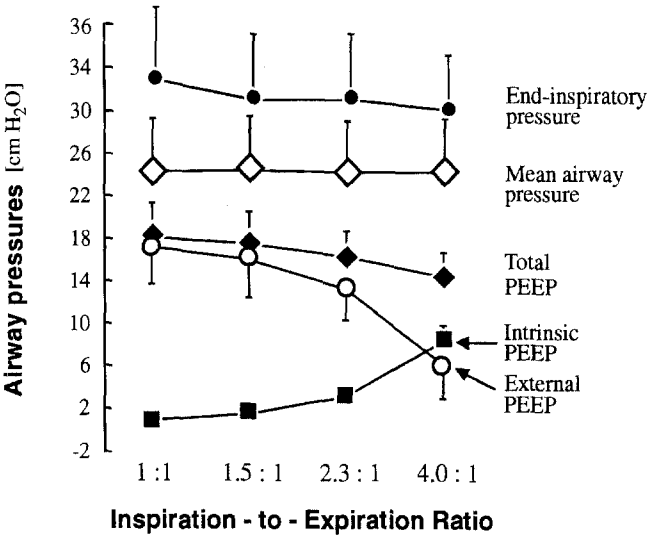

Fig. 3 End-inspiratory and mean airway pressures, the relationship between external and intrinsic PEEP, and the resulting total PEEP, with stepwise inversed I:E ratio while mean airway pressure was kept constant (see Discussion: Methodological considerations). Levels of significance are given in Table 1

Experimental procedure

Following anesthesia and preparation the animals were placed in prone position. Lavage was performed with a series of 10 or 11 instillations of 37 °C normal 0.9% saline, each of 1–1.5 l volume (for details see [15, 22]). Postlavage a first opening procedure was performed. Thereafter the inflection point of the inspiratory limb of the pressure/volume loop was determined, followed by a second opening procedure. Ventilation was resumed 30 min after lavage, with the external PEEP set to 100% of the inflection point value. External PEEP was then reduced to 75% of the inflection point value [23], which maintained open lung conditions. The latter setting was then used as the reference setting with the I:E ratio at 1:1. Three different I:E ratios – 1.5:1, 2.3:1, and 4:1 – were then applied randomly for 30 min to achieve a ventilatory and hemodynamic steady state when measurements were taken.

The reference setting included the following: decelerating inspiratory flow, ventilatory frequency 30 bpm, I:E ratio 1:1 and FIO_2 0.5. Based on previous experimental studies in the same animal model, external PEEP was set to 75% of the inflection point (PEEP 17 ± 4 cmH_2O). Tidal volume was adjusted to 9 ± 1 ml/kg to achieve a $PaCO_2$ of 5.5 ± 0.3 kPa. Prolonged inspiratory times generated increasing intrinsic PEEP, and to keep mean airway pressure constant external PEEP therefore had to be reduced.

Presentation and statistical analysis of data

Values are given as mean $\pm$ 1 standard deviation. A standard statistics package was used (STATWIEV). Differences between the ventilatory settings were evaluated with a one-way analysis of variance for factorial measures for all paired comparisons within each variable using Scheffe's F test. If significant differences were detected, a post hoc test was performed to verify the significances detected in the analysis of variance. Figure 3 presents data according to increasing I:E ratio, although I:E 1.5:1, 2.3:1, and 4:1 were applied at random rather than in sequence with increasing I:E ratios. For easier reading they are connected by a spline.

Table 1 Pulmonary function parameters

Inspiration time (s)	1.00	1.20	1.40	1.60
I:E ratio	1:1	1.5:1	2.3:1	4:1
Modus (A–D)	A	B	C	D
End-inspiratory pressure	32 ± 7	30 ± 6	30 ± 6	29 ± 5
Peak inspiratory pressure	32 ± 7	30 ± 7	30 ± 6	29 ± 6
Mean airway pressure	24 ± 5	24 ± 5	24 ± 5	24 ± 5
Total PEEP	18 ± 3	18 ± 3	16 ± 2 A*, B*	14 ± 2 A*, B*, C*
External PEEP	17 ± 4	16 ± 4	13 ± 3 A*, B*	6 ± 3 A*, B*, C*
Intrinsic PEEP	1 ± 1	2 ± 1 A*	3 ± 1 A*, B*	8 ± 1 A*, B*, C*
Compliance	18 ± 4	20 ± 6	20 ± 5	21 ± 7
Functional residual capacity (ml)	1620 ± 371	1633 ± 392	1618 ± 360	1525 ± 307
$PaCO_2$	5.67 ± 0.31	5.52 ± 0.28	5.21 ± 0.31 A**, B*	5.24 ± 0.48 A**
PaO_2	33 ± 5	35 ± 2	36 ± 2	35 ± 3
CO_2 production ($ml\,m^{-2}\,min^{-1}$)	268 ± 35	254 ± 31	255 ± 25	257 ± 28

Pulmonary function parameters with stepwise inversed I:E ratio. Values are mean ± 1 SD; $n = 12$ (for FRC: $n = 10$). A, significant difference from I:E 1:1; B, from I:E 1.5:1; C, from I:E 2.3:1; $^*p \leq 0.05$, $^{**}p \leq 0.01$. Airway pressures are given in cmH_2O and partial pressures in kPa.

Table 2 Hemodynamic function parameters

Inspiration time (s)	1.00	1.20	1.40	1.60
I:E ratio	1:1	1.5:1	2.3:1	4:1
Modus (A–D)	A	B	C	D
SvO_2 [%]	62 ± 9	61 ± 9	60 ± 8	60 ± 7
Pulmonary arterial pressure (mmHg)	28 ± 4	34 ± 8 A*	34 ± 6 A*	34 ± 7 A*
Cardiac index ($ml\,m^{-2}\,min^{-1}$)	5175 ± 1059	4675 ± 1422	4475 ± 1014 A**	4292 ± 973 A**
Stroke index ($ml\,m^2$)	40 ± 10	34 ± 9	33 ± 8 A*	32 ± 6 A*
Shunt (%)	10 ± 1	11 ± 1	11 ± 1	11 ± 2
Intrathoracic blood volume ($ml\,kg^{-1}$)	23 ± 6	21 ± 4	20 ± 4	20 ± 4
Extravascular lung water ($ml\,kg^{-1}$)	19 ± 3	17 ± 3 A*	16 ± 3 A*	16 ± 3 A*
RV end-diastolic volume ($ml\,m^2$)	120 ± 23	126 ± 25	115 ± 19	117 ± 23
RV ejection fraction (%)	31 ± 5	28 ± 5	28 ± 6 A*	27 ± 5 A*
Oxygen delivery ($ml\,m^{-2}\,min^{-1}$)	571 ± 125	553 ± 146	521 ± 109 A*	509 ± 82

Hemodynamic function parameters with stepwise inversed I:E ratio. Values are mean ± 1 SD; $n = 12$. $^*p \leq 0.05$, $^{**}p \leq 0.01$. A, significant difference from I:E 1:1; B, from I:E 1.5:1; C, from I:E 2.3:1.

Results

Results are presented in Tables 1 and 2 and Figs. 1–3.

Effects of lavage

Lavage reduced compliance from 26 ± 4 to 11 ± 2 ml/cmH_2O and FRC from 674 ± 167 to 180 ± 43 ml. With FIO_2 1.0 and zero PEEP ventilation PaO_2 was reduced from 76 ± 4 prelavage to 7 ± 2 kPa postlavage, and EVLW increased from 5 ± 1 to 19 ± 3 ml/kg. The inflection point was 23 ± 2 cmH_2O immediately after lavage and had disappeared at the pressure/volume loop measurement 3 h postlavage (Fig. 1).

Airway pressures

In the reference setting (I:E 1:1) external PEEP was set to 17 ± 4 cmH_2O. Intrinsic PEEP increased with prolongation of inspiratory time. To maintain mean airway pressure constant at 24 ± 5 cmH_2O external PEEP had to be reduced to 16, 13, and 6 cmH_2O (Fig. 3). Total PEEP was 18, 18, 16, and 14 cmH_2O. The decrease in peak and end-inspiratory pressure (32 ± 7 cmH_2O with 1:1) paralleled the decrease in total PEEP (Fig. 3).

Ventilation, gas exchange, compliance, and lung volumes

Prolongation of inspiratory time did not affect PaO_2. Compared to the I:E ratio of 1:1 $PaCO_2$ was lower with I:E 2.3:1 and 4:1 (5.21 ± 0.31, and 5.24 ± 0.48, respectively). Compliance remained at the level of 18–21 ml/cmH_2O in the postlavage settings. FRC (reference: 1620 ± 371 ml) was reduced to 1525 ± 307 ml with the I:E ratio at 4:1. EVLW was 19 ± 3 ml/kg with the first postlavage reference setting (I:E 1:1), and it was lower in all other settings ($p \leq 0.05$).

Hemodynamics and oxygen delivery

Cardiac and stroke indices and right ventricular ejection fraction all decreased with I:E 2.3:1 and 4:1 ($p \leq 0.05$). With constant arterial PO_2, oxygen delivery was reduced only when I:E was 2.3:1 ($p \leq 0.05$).

Discussion

Under open lung conditions, the present study revealed no improvement in PO_2 when mean airway pressure was kept constant, but prolongation of the inspiratory time impaired hemodynamics.

Methodological considerations

In the ventilator used mean airway pressure was calculated – like in most modern ventilators – by computing the time-weighted value of the pressure measured in the ventilator circuit. To measure and calculate the time ("intrapulmonary") mean airway pressure during ventilation with intrinsic PEEP, the prevailing total PEEP should be utilized by means of intratracheal pressure measurements (not available in this study).

During the experiments there was a definite decrease in EVLW. As the I:E ratio of 1:1 was studied immediately postlavage, and was always used prior to the randomly applied settings, the largest amount of EVLW was present when I:E was 1:1. Therefore, timing may evidently bias the comparison between the I:E ratio of 1:1 and the other I:E ratios. On the other hand, the model was stable with respect to compliance, PaO_2, and FRC.

In the present study the inflection point of the inspiratory limb of the pressure/volume loop was determined by inspection. The projection on the airway pressure axis of the vertex of the lower curved section was defined as the inflection point pressure. As such a procedure entails low accuracy, we have since searched for more accurate methods.

In previous studies in the same lung model [23] PEEP corresponding to 100% impaired hemodynamics (unpublished data). Therefore, during ventilation with the reference setting (I:E at 1:1) in the present study, external PEEP was set to 75% of the inflection point.

Lung mechanics

Peak and end-inspiratory airway pressure displayed identical values, which was expected with pressure-controlled ventilation and a decelerating inspiratory flow (see Fig. 1). The decrease in inspiratory pressures from 32 to 29 cmH_2O with increasing I:E ratio was due to the pressure-regulated volume-controlled mode and its adaptation to the increased inspiratory time. This finding contradicts results by Lessard et al. [24], and by Mercat and coworkers [25], who found no reduction in inspiratory pressures using pressure-controlled ventilation.

Compared to the reference setting, FRC was reduced by 100 ml with an I:E ratio of 4:1, which is explained by the lower total PEEP (Fig. 3). We limit this statement to the 30-min period of investigation, as

extended application time of reduced total PEEP might produce a change in FRC [26].

Gas exchange

$PaCO_2$ decreased in parallel with increasing inspiratory time. This is a uniform finding in a number of studies [6, 8, 26], but the mechanisms responsible for this improved CO_2 elimination are not entirely clear [27] and could not be clarified in the present study. The virtually unchanged FRC in the present study does not, however, exclude recruitment of previously closed alveoli as a possible explanation.

In contrast to the present results, other investigators have found increased arterial PO_2 with prolonged inspiratory times [5, 6, 9, 10]. In these studies, however, FRC was neither measured nor matched. It is, therefore, conceivable that in these earlier studies prolonged inspiratory times increased PaO_2 by producing intrinsic PEEP and raising total PEEP, thereby preventing end-expiratory alveolar closure and/or recruiting alveolar units. In the reference mode of the present study (I:E 1:1) PEEP was set to a level which kept the lung open during the entire respiratory cycle. As mean airway pressure was kept constant, there was no improvement in PaO_2. Cole and coworkers [8], however, studying volume-controlled ventilation at matched FRC in patients, found increased oxygen transfer when inspiratory time was prolonged with I:E between 1.1:1 and 1.7:1. The increased oxygen delivery in their clinical study was, therefore, probably related more to the prolonged inspiratory time than to increased FRC.

Hemodynamics

Stroke index was lower with I:E ratios of 2.3:1 and 4:1. Right ventricular end-diastolic volume, reflecting diastolic function of the right ventricle, was unaffected. On the other hand, right ventricular ejection fraction, reflecting systolic function of the right ventricle, was compromised with 1:E ratios of 2.3:1 and 4:1. These observations correspond to the decreased stroke index and increased pulmonary artery pressure (increased right ventricular afterload), respectively. Other investigators have demonstrated [29] that hemodynamic performance may be influenced by longer inspiratory times even with constant mean airway pressure.

Conclusion

We conclude that under open lung conditions, in the surfactant-depleted porcine lung and increased I:E ratio, arterial oxygenation remained unaffected while hemodynamics were impaired.

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