INFLUENCE OF HIGH FREQUENCY VENTILATION AT DIFFERENT END-EXPIRATORY LUNG VOLUMES ON THE DEVELOPMENT OF LUNG DAMAGE DURING LUNG LAVAGE IN RABBITS

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Several investigators have used the lung lavage model for testing different modes of ventilatory treatment in the surfactant-depleted lung. Different patterns, including variations in PEEP, I:E ratio and frequency have been examined, usually after lung damage had already occurred. Little information is available on the application of different ventilatory patterns during the lavage itself. Lachmann and colleagues briefly reported that a pressure controlled inverse ratio ventilation (I:E ratio of 4:1) prevented the deleterious effects of surfactant depletion on lung function when this mode of ventilation was initiated during the period of lavage [1].

High frequency ventilation (HFV) using different exciting systems has also been used in the treatment of postlavage lung failure. It was claimed that high frequency jet ventilation (HFJV) represents a superior ventilatory pattern by maintaining a higher end-expiratory lung volume because of intrinsic PEEP mechanisms [2, 3]. However, during high frequency oscillation (HFO), lung volume can be adjusted and measured independently of other ventilatory settings. With this mode of ventilation, a marked improvement in oxygenation was described when lungs were hyperinflated immediately before the onset of HFO [4]. The gain in lung volume caused by these sustained inflations (SI) could then be maintained with HFO. There has been much discussion on the impact of frequency-related phenomena on these observations. Less attention has been paid to the role of tidal volume during HFV.

The aim of this study was to determine the effects of a small tidal volume, high frequency, pressure-controlled ventilation (frequency 120 b.p.m.) in combination with sustained inflations, on both the functional and morphological changes of the lungs in the rabbit lung lavage model when this type of ventilation was applied during the period of lavage.

SUMMARY

The effects of high frequency ventilation in combination with sustained inflations was studied in the surfactant-deficient lungs of 18 New Zealand White rabbits (weight 1.9–2.1 kg) during anaesthesia with urethane and neuromuscular block with pancuronium. Lung damage was induced by repeated lung lavage. In nine rabbits (group I) baseline ventilator settings were maintained constant throughout the study and airway pressure was readjusted to achieve a constant tidal volume. In the other nine rabbits (group II), ventilation was re instituted after lung lavage with one period of four sustained inflations followed immediately by high frequency ventilation. In group I there was a significant decrease in gas exchange for oxygen and deterioration in pulmonary mechanics, whereas in group II there was little change in baseline blood-gas values or pulmonary mechanics. These data suggest that, with adequate ventilatory management during the period of lung lavage, the lung damage produced by this manoeuvre may be obviated.

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MATERIALS AND METHODS

Investigations were carried out in 18 male New Zealand White rabbits (weights 1.9–2.1 kg). After application of a topical anaesthetic to the skin, a 22-gauge cannula was inserted into an ear vein. Anaesthesia was induced with 20% urethane 6 ml kg\(^{-1}\) and maintained throughout the experiment with supplementary doses of urethane 1 ml kg\(^{-1}\) given as indicated by changes in arterial pressure or salivation. After the rabbit was placed in the supine position, tracheotomy was performed. The trachea was cannulated with a 3.5–4.0 mm i.d. uncuffed tracheal tube and secured with ligatures to prevent air leaks. Mechanical ventilation was provided by a modified high frequency jet ventilation technique (high frequency pulsation (HFP)) using a specially developed adaptor, described in detail previously [5]. Although a jet is the driving mechanism in this breathing circuit, it is converted into pressure pulses by an injector. The pressure and flow patterns supplied to the airway opening are very similar to those of a time-cycled, pressure-controlled ventilator. Initial adjustments were made to a frequency (\(f\)) of 120 b.p.m., an inspiratory:expiratory (I:E) ratio 1:2, a peak airway pressure (\(P_{aw,max}\)) to achieve a tidal volume (\(V_T\)) of 7 ml kg\(^{-1}\) and \(FIO_2\) 0.5. PEEP of 3.7 mm Hg was generated by an external PEEP device on the expiratory limb. Neuromuscular paralysis was produced with pancuronium 0.5 mg kg\(^{-1}\) i.v. and maintained with repeated bolus doses (0.5 mg kg\(^{-1}\)). Eighteen-gauge carotid arterial and jugular venous catheters were inserted for continuous monitoring of systemic arterial and central venous pressures. Repeated bolus injections of 5% glucose solution 2 ml kg\(^{-1}\) were given i.v. until mean central venous pressure remained stable at 2–3 mm Hg. An oesophageal temperature probe was inserted to register body temperature which was maintained greater than 38 °C by use of a warming blanket. Following instrumentation, all rabbits were placed in the right lateral decubitus position.

Lung damage was induced in all rabbits by repeated lung lavage using a technique modified slightly from that described originally by Lachmann, Robertson and Vogel [6]. The lungs were lavaged five times over a 45-min period with normal saline at 37 °C. The second lavage procedure was 5 min after the first one. The remaining three lavages were performed at 10-min intervals. In order to guarantee that each rabbit's lungs were washed with a standardized volume, 80% of the rabbit's lung volume above FRC at a transpulmonary pressure of 22 mm Hg (calculated from the baseline volume-pressure curve) was taken as the lung lavage volume in ml. This volume was injected with a syringe. Tracheal pressures were maintained less than 18.7 mm Hg. Fluid was recovered solely by passive lung recoil in order to avoid negative airway pressures caused by suction.

The rabbits were allocated to two groups; different ventilation was applied during the periods between the lung lavage procedures. \(FIO_2\) was kept constant at 0.5 throughout the experiment. In group 1, ventilation was reinstituted after lavage with HFP by using the initial ventilator settings. \(V_T\) was kept constant at 7 ml kg\(^{-1}\) throughout the study by readjusting the driving pressure of the high frequency ventilator. PEEP was held constant at 3.7 mm Hg. In group 2, ventilation was reinstituted after lavage with one period of four sustained inflations (4 × SI at \(P_{aw,max}\) 22 mm Hg, \(f\) 12 b.p.m., I:E 9:1 (4.5 s:0.5 s), PEEP 6 mm Hg) using the same breathing circuit. At the end of the fourth SI the ventilatory mode was changed immediately to HFP (\(f\) 120 b.p.m., I:E 1:2, \(FIO_2\) 0.5). HFV was continued at the new PEEP of 6 mm Hg.

Blood samples for the determination of blood-gas (BG) tensions and volume-pressure (PV) curves for determination of lung mechanics obtained before the first lavage (BG1, PV1) were used as baseline data and those obtained 10 min after the fifth lavage (BG2, PV2) were used as end of experiment data. Airway pressures and tidal volume were monitored continuously throughout the study. After end of experiment data had been obtained, sternotomy was performed and a specimen of inflated lung tissue was taken from the right lower lobe while the lungs were ventilated continuously at the final ventilator settings. Finally, after disconnection from the ventilator, both lungs were removed and the wet weight determined immediately.

All specimens of lung tissue were placed in the inflated state in formaldehyde solution. After fixation they were embedded in paraffin, sectioned and stained with haematoxylin and eosin. Each section was examined under light microscopy (×100 and ×400 magnification) by a histologist who was unaware of the ventilation mode to which each section belonged.
Arterial blood-gas tensions and haemoglobin concentrations were measured immediately after withdrawal from the carotid arterial catheter. \(P_{aw}\) was measured continuously with a pressure transducer (Gould P50, Bilthoven, NL) close to the proximal end of the tracheal tube, which was assumed to be the location with the highest pressure in our breathing system. Gas flow was measured by a Fleisch pneumotachograph (Gould, Godart) placed between the HFP adaptor and the proximal end of the tracheal tube and integrated electronically for both inspiratory and expiratory volumes. The pressure–volume (PV) curve was recorded by a syringe technique. The syringe was flushed initially with pure oxygen. Volume steps of 10 ml were added to the lungs at intervals of 3 s until a pressure of 22 mm Hg was reached. After that procedure, the lungs were deflated in the reverse manner down to an airway pressure of zero. The whole process was fully automated. Timing and piston displacement were controlled by computer (Atari STF 1040), which also plotted the digitized pressure and volume signals as an \(x-y\) diagram. To describe the stability of lung expansion we used a numerical index [7]:

\[
L = \frac{(2 - V5 + V10 - 3 - V0)}{(2 - V30 - 2 - V0)}
\]

where \(V0, V5, V10 \text{ and } V30\) are the measured lung volumes on the expiratory limb at the corresponding pressures (0, 3.7, 7.5, 22 mm Hg). This index gives an expression of how much lung volume is captured at various pressures on the expiratory limb related to total volume at 22 mm Hg. According to Gruenwald [7], indices greater than 0.81 represent good surface properties, an intermediate range from 0.80 to 0.71 is defined as borderline normal, and values less than 0.70 are typical for poor surface properties.

All results are expressed as mean (SD). The data were analysed statistically using an unpaired \(t\) test.

**RESULTS**

Gas exchange and pulmonary mechanics were significantly different in both groups. For the ventilatory management of group 1, the anticipated decrease in these two assessments of lung function was produced, whereas in group 2 the regimen maintained almost baseline values (table I).

**Arterial blood-gas tensions** (fig. 1). A significant decrease in arterial partial pressure of oxygen, \(P_{aO_2}\) from baseline value was found in group 1 at the end of the experiment. In contrast, no significant changes in \(P_{aO_2}\) was observed in group 2 at the same observation point. \(P_{aCO_2}\) could be kept within the normal range for both groups and was not influenced by the different modes of ventilation.

**Airway pressures** (fig. 2). Airway pressures required for target tidal volume of 7 ml kg\(^{-1}\) were similar for both groups before induction of lung damage. After the first lung lavage (LL1), \(P_{aw,max}\) had to be increased from 9.7 mm Hg to approximately 15 mm Hg in both groups. Only slight individual changes in \(P_{aw,max}\) were necessary subsequently. PEEP was kept at 3.7 mm Hg in group 1, but was increased from 3.7 to 6 mm Hg after the first lung lavage in group 2. As a result of this different setting, \(P_{aw,mean}\) was significantly greater in group 2 (10.4 (1.1) mm Hg) compared with group 1 (8.5 (1.1) mm Hg).

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**Table I.** Arterial blood-gas tensions, lung stability index, wet lung weight, recovery rate and unrecovered lavage fluid before and after five lung lavage procedures in rabbits (mean values (SD)). Baseline = Values obtained before first lung lavage. End of experiment = values obtained 10 min after fifth lung lavage. *Significantly different from corresponding mean baseline value (\(P < 0.01\)). †Data obtained from two healthy rabbits sacrificed after baseline measurements.

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<th>Group 1</th>
<th>Group 2</th>
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<td></td>
<td>Baseline</td>
<td>End of experiment</td>
</tr>
<tr>
<td>(P_{aO_2}) (kPa)</td>
<td>30.8 (1.3)</td>
<td>6.3 (2.9)*</td>
</tr>
<tr>
<td>(P_{aCO_2}) (kPa)</td>
<td>5.5 (0.6)</td>
<td>5.6 (0.9)</td>
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<tr>
<td>Lung stability index (L) [7]</td>
<td>0.69 (0.04)</td>
<td>0.38 (0.09)*</td>
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<tr>
<td>Wet lung weight (g kg(^{-1}))</td>
<td>4.15 (0.49)*</td>
<td>9.65 (1.99)</td>
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<tr>
<td>Recovery rate (%)</td>
<td>98.8</td>
<td>96.6</td>
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<tr>
<td>Unrecovered lavage fluid (ml kg(^{-1}))</td>
<td>-1.9 (5.5)</td>
<td>-6.8 (5.8)</td>
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mm Hg). Although Paw,max did not differ significantly from one group to the other at the end of the experiment, the pressure change (Paw, max—PEEP) in group 1 was greater (13.6 (2.8) mm Hg) than in group 2 (9.7 (3.1) mm Hg) because of a lower PEEP.

Tidal volumes (fig. 3). Tidal volumes were almost identical at the beginning of the experiment. In group 1, VT was maintained constant at 7.9 (0.6) ml kg⁻¹ throughout the study. In order to avoid exceeding a Paw,max of 15 mm Hg in group 2, there was a reduction of VT to 5.1 (0.6) ml kg⁻¹ after LL1. During the following four lung lavage procedures, VT recovered to a final value of 7.1 (0.7) ml kg⁻¹.

Pressure-volume curves (fig. 4). In group 1 there were signs of a severe deterioration in pulmonary mechanics (high opening pressure, reduction in total lung volume, flat expiratory limb). The numerical index of the stability of lung expansion (L) calculated from the expiratory limbs of the pressure-volume curves 10 min after the fifth lung lavage procedure showed a significant decrease below 50% of its baseline value (table I). There was hardly any inflection point in

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**FIG. 1.** Effects of different ventilatory management on arterial blood-gas tensions before (bl) and 10 min after (ee) five lung lavage procedures. Large triangles are mean (SD) values and small triangles are individual data.

**FIG. 2.** Effects of different ventilatory management on airway pressures during five lung lavage procedures. △, Δ = Paw,max; ○, O = Paw,mean; □, □ = PEEP. bl = Baseline; LL1-LL5 = values registered before the next lung lavage procedure; ee = end of experiment.

**FIG. 3.** Tidal volumes resulting from the adjusted airway pressures during ventilatory management in group 1 (○: VT = 7 ml kg⁻¹) and group 2 (○: Paw,max = 15 mm Hg).
FIG. 4. Effects of ventilatory management on the pressure—volume curves after five lung lavage procedures. Original recordings of three individual curves by means of a syringe technique. Left: PV1 recorded before first lung lavage at $L = 0.72$. Middle: PV2 recorded from a group 1 rabbit 10 min after fifth lung lavage at $L = 0.34$. Right: PV2 recorded from a group 2 rabbit 10 min after fifth lung lavage at $L = 0.63$. $L =$ Numerical index of the stability of lung expansion $((2 \cdot V_5 + V_{10} - 3 \cdot V_0)/(2 \cdot V_30 - 2 \cdot V_0))$ [7].

Our results indicate that, with an adequate ventilatory management during the lavage period, lung damage following lavage may be prevented. Furthermore, we showed that the strategy required to avoid this damage may be close to a conventional type of ventilation.

Lavage fluid losses (table I). Recovery rate with our modified lavage technique was high. The amount of unrecovered lavage fluid was only 1.9 (5.5) ml kg$^{-1}$ in group 1 rabbits and 6.8 (5.8) ml kg$^{-1}$ in group 2 rabbits, for a total lung lavage fluid volume applied during LL1 to LL5 of approximately 160 ml kg$^{-1}$.

Lung histology. The histological findings in the two groups differed markedly. In group 1, lung histology showed the typical changes described after lung lavage, such as overdistended terminal airways in combination with large areas of atelectasis. Moreover, diffuse bronchoalveolar haemorrhage, interstitial and alveolar oedema and cellular infiltration in alveolar septa were present. In contrast with these findings, the group 2 rabbits did not develop atelectasis and their lungs revealed a tight alveolar epithelium with tall, but distended, alveolar septa. However, no ruptured septa were seen, although the lungs seemed to have been fixed at a high degree of inflation.

DISCUSSION

Our results indicate that, with an adequate ventilatory management during the lavage period, lung damage following lavage may be prevented.
of lavage. Nevertheless, two important changes were made influencing the end-expiratory lung volume in group 2. PEEP was increased from 3.7 to 6 mm Hg and sustained inflations were performed after each lavage to recruit and maintain alveolar surface area. The efficiency of such a manoeuvre in terms of gain in lung volume during HFO has been demonstrated by several authors [4, 10]. In a similar lung lavage model and greater values of PEEP, sustained inflations were reported to have no effect during HFJV. Although gas exchange in these experiments was significantly better in the HFJV group compared with CMV, lung pathology was not improved by HFJV [3]. It seems important to us that the change from SI to the high-frequency mode was made without an expiratory pause. This may explain our HFO findings in gas exchange and in lung pathology. However, we have no explanation for the identical gain in lung weight in each group. We could not identify the site of possible fluid accumulation in any histological specimen in group 2.

As a marked opening pressure was not present in group 2, an increase in PEEP of only 2.2 mm Hg compensated for the increased lung recoil pressure after lavages. The greater adjusted Paw, max after LL1 was necessary in order to overcome increased flow resistance of the airways; compliance did not change as demonstrated by the pressure–volume curves (fig. 4, left and right). If significant opening pressures are allowed to build up during the lavage period as in group 1 (fig. 4, middle: inflection point at about 11 mm Hg), much greater values of PEEP are required to reopen atelectatic areas and restore oxygenation [9].

A further possible reason why the pattern of ventilation is suitable to preserve alveolar stability may be the relatively low VT used in our experiments. More than 20 years ago, it was shown in the excised lungs of dogs without surfactant deficiency that mechanical ventilation with tidal volumes of 30% of maximum lung volume or greater result in continuous loss of expiratory lung stability with duration of ventilation. By either reducing VT to 10% of maximum lung volume or adding PEEP of 2.2 mm Hg, this deterioration could be inhibited [11]. Later experiments on lung stability in cats confirmed these findings and showed increased minimum surface tension of lung extract from such lungs [12]. If lung surface area is not subject to large changes throughout the ventilatory cycle, ability of surfactant to produce low surface tension during expiration is not really stressed. Under these conditions, lung stability can be maintained at almost constant surface tension close to its "equilibrium value". Thus the improved response of surfactant-depleted lungs to HFV is more likely to be related to small volume excursions of the lungs than to any particular frequency-dependent mechanism if end-expiratory lung volume is maintained.

REFERENCES