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EXPERIMENTAL

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Pressure-limited ventilation with permissive hypercapnia and minimum PEEP in saline-lavaged rabbits allows progressive improvement in oxygenation, but does not avoid ventilator-induced lung injury

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Abstract *Objective:* To determine whether pressure-limited intermittent mandatory ventilation with permissive hypercapnia and positive end-expiratory pressure (PEEP) titrated to arterial oxygen tension (PaO_2) prevents or reduces acute lung injury, compared to conventional ventilation, in saline-lavaged rabbits.
Design: Prospective randomised trial.
Setting: University animal laboratory.
Subjects: 18 New Zealand White rabbits.
Interventions: Following five sequential saline lung lavages, anaesthetised rabbits were randomly allocated in pairs to receive either of two ventilation protocols using intermittent mandatory ventilation. The study group had peak inspiratory pressure limited to 15 cm H_2O and arterial partial pressure of carbon dioxide ($PaCO_2$) was allowed to rise. The control group received 12 ml/kg tidal volume with rate adjusted for normocarbia. PEEP and fractional inspired oxygen (FIO_2) were adjusted to maintain PaO_2 between 8 and 13.3 kPa (60 and 100 mm Hg) using a predetermined protocol. At 10 h or following death, lung lavage was repeated and lung histology evaluated.
Measurements and main results: The mean increase in lavage cell counts and protein concentration and hyaline membrane scores were not significantly different between the groups. Oxygenation progressively improved more in the study group ($p = 0.01$ vs control for PaO_2/FIO_2 ratio and alveolar-arterial oxygen tension gradient ($AaDO_2$)). PEEP was similar and the mean airway pressure higher in the control group, suggesting that this probably resulted from less ventilator-induced injury in the study group. Four deaths occurred in the control group (three due to pneumothorax and one to hypoxaemia) and none in the study group ($p = 0.08$).
Conclusions: This ventilatory protocol may have failed to prevent lung overdistension or it may have provided insufficient PEEP to prevent injury in this model; PEEP greater than the lower inflection point of the pressure-volume curve has been shown to prevent injury almost entirely.

Key words Adult respiratory distress syndrome · Artificial respiration · Permissive hypercapnia · Peak inspiratory pressure · Ventilator-induced lung injury · Saline lavage

Introduction

It has been demonstrated in a variety of animal models that controlled mechanical ventilation with a high peak lung volume, or with a low end-expiratory volume in surfactant-depleted lungs, can result in acute lung injury characterised by hyaline membranes, granulocyte infiltration and ultimately fibrosis [reviewed in 1–3]. The lung injury appears to cause an inflammatory response; increased systemic vascular permeability was associated with ventilator-induced lung injury in the saline-lavaged rabbit model [4], and Burger et al. [5] demonstrated that indomethacin or thromboxane-A2 receptor blockade prevented the pulmonary hypertension which otherwise occurred. High volume ventilation in rats increased the concentration of interleukin 1-beta in lung lavage fluid [6] and, following an endotoxin challenge, high volume ventilation up-regulated the production of tumour-necrosis factor alpha in the lung [7]. The activation of an inflammatory response as a result of ventilator-induced injury in patients with adult respiratory distress syndrome (ARDS) could possibly augment the development of multiple organ failure and could potentially have an important effect on mortality from causes other than respiratory failure.

In the saline-lavaged rabbit model, lung injury has been demonstrated using a tidal volume (Vt) as low as 12 ml/kg and peak inspiratory pressure (PIP) as low as 20 cm H_2O [4, 8] if ventilation occurs with a low end-expiratory volume. The avoidance of phasic lung distension using apnoeic oxygenation and extracorporeal CO_2 removal, almost completely prevents lung injury in this model [8]. Positive end-expiratory pressure (PEEP) greater than the pressure at the lower inflection point of the respiratory static pressure-volume curve also appears to protect against lung injury during mechanical ventilation in this model [9–11], possibly by maintaining the patency of small airways throughout the respiratory cycle and preventing shear forces produced during the repetitive opening of closed airways and alveoli [9, 12].

Pressure-limited ventilation with permissive hypercapnia has been suggested as a possible method of minimising ventilator-induced lung injury in ARDS [13–16], but has not yet been adequately evaluated in controlled clinical trials. This study was undertaken to determine whether ventilator-induced injury in the saline-lavaged rabbit model is avoided, or reduced in comparison to that produced by conventional ventilation, by a protocol in which PIP is limited to 15 cm H_2O and PEEP titrated to maintain arterial oxygen tension (PaO_2) more than 8 kPa (60 mm Hg) with fractional inspired oxygen (FIO_2) of 0.6 or less.

Methods

Overall study design

Animals were studied in pairs. Following anaesthesia, instrumentation, saline lavage of the lungs and baseline measurements, one animal from each pair was randomly allocated to the pressure-limited permissive hypercapnia group and the other to the control group. Ventilation continued for 10 h or until death, when a final lung lavage was performed. Study endpoints were change in cell counts and protein concentration from initial to final lung lavage, lung histology, arterial oxygen tension to inspired oxygen fraction (PaO_2/FIO_2) ratio, alveolar to arterial oxygen tension gradient ($AaDO_2$), respiratory index ([mean airway pressure × $AaDO_2$/PaO_2]/100) [17] and death.

Ventilators used

Bear Cub ventilators (Bear Medical Systems, Inc., Riverside, California) were used for this study. These paediatric ventilators provide a constant flow rate of air-oxygen mixture, which is delivered to the animal when the expiratory valve is closed and continues to flow in the circuit when the expiratory valve is open. The delivered Vt is the gas flow rate multiplied by the set inspiratory time. A pressure relief valve diverts the fresh gas flow to atmosphere if the inspiratory pressure limit is exceeded, in which case Vt is reduced by the amount of diverted gas. When the inspiratory pressure limit is exceeded, spontaneous inspiratory effort can increase Vt and lung distension by increasing the inspiratory flow to the animal, thus decreasing the amount of diverted gas through the pressure relief valve. When the inspiratory pressure is below the pressure limit, the preset inspiratory gas flow rate can not be exceeded, and the effect of inspiratory effort is then to reduce the inspiratory pressure without altering Vt. Spontaneous breaths can occur with an inspiratory flow rate not exceeding that of the continuous gas flow.

Animal preparation

Adult New Zealand White rabbits (3–4 kg) were anaesthetised with halothane in 100% oxygen and a 3.5 mm endotracheal tube was inserted 3 cm into the trachea through a tracheostomy incision. The endotracheal tube was cut at the 12 cm mark and tied firmly to prevent any air leak. Cannulae were inserted into a carotid artery for pressure monitoring and blood sampling and a jugular vein for intravenous fluid replacement. Normal saline was infused at 3 ml/kg per h. The animals were ventilated using a flow rate of 5 l/min, an inspiratory time of 0.7 s, a mandatory rate of 30 breaths/min, a FIO_2 of 1.0, and 3 cm H_2O PEEP. The inspiratory pressure limit was set to give a peak inspiratory pressure of 15 cm H_2O. The lungs were then lavaged with 15 ml/kg of normal saline at 37 °C using a modification of the technique described by Lachmann et al. [18] and the aspirated saline was evaluated by cell counting and cytospin for differential cell counts (see below), and for total protein concentration. The lavage procedure was repeated a further 4 times at 5-min intervals. The animals were ventilated with an FIO_2 of 1.0 between lavages. Arterial blood (0.4 ml) was then sampled for blood gas analysis. The lungs were inflated with 100% oxygen from a syringe to a volume of 12 ml/kg, and the airway pressure at this volume recorded. One animal from each pair was then randomly allocated to the study group and the other to the control group.

Ventilation protocols

In the study group animals ventilation was continued with the inspiratory pressure limit set at 15 cm H_2O, an inspiratory time of

0.7 s, mandatory rate of 30/min, inspiratory flow of 5 l/min, and PEEP of 3 cm H_2O. The inspiratory pressure limit was always reached, so that inspiratory effort could increase Vt and lung distension during mandatory breaths. Arterial partial pressure of carbon dioxide ($PaCO_2$) was allowed to rise; if the $PaCO_2$ fell below 8 kPa (60 mm Hg) the mandatory rate was decreased incrementally to a minimum of 4/min and if it exceeded 13.3 kPa (100 mm Hg) the rate was increased incrementally to a maximum of 40/min.

In the control group animals the inspiratory time was set at 0.7 s, PEEP at 0 cm H_2O, and the flow rate was then adjusted to obtain a peak inspiratory pressure the same as the pressure obtained at a volume of 12 ml/kg following the sequential lung lavages, thus obtaining an estimated Vt of 12 ml/kg. PEEP was then set at 3 cm H_2O and the mandatory rate at 20/min. The inspiratory pressure limit was set at 28 cm H_2O (the PIP was limited to 28 cm H_2O in order to prevent early deaths from pneumothorax, which occurred in most animals during a pilot study when using a higher PIP). The mandatory rate was subsequently adjusted to maintain the $PaCO_2$ in the range of 4.6–6 kPa (35–45 mm Hg) when possible, with a minimum rate of 4/min and a maximum of 60/min. The actual Vt would be somewhat less than 12 ml/kg as the PIP was set during flow; we were unable to obtain an end-inspiratory pause with these ventilators. However, the flow rates used were relatively low and we do not believe that the Vt would have been substantially less than 12 ml/kg. The exact Vt was not critical in this study, and other studies with this animal model have shown the development of severe lung injury at similar levels of PIP [4, 5].

In both groups PEEP and FIO_2 were subsequently adjusted to maintain PaO_2 in the range of 8–13.3 kPa (60–100 mm Hg) when possible, using a predetermined algorithm; to increase PaO_2, the FIO_2 was increased incrementally to 0.6, PEEP was then increased incrementally from 3 to 15 cm H_2O, and FIO_2 was increased incrementally from 0.6 to 1; to decrease PaO_2 the same sequence was followed in reverse order. In both groups an additional 5 ml of saline was administered if the animal became hypotensive (systolic pressure < 60 mm Hg, and not corrected by reduced halothane). Anaesthesia was maintained throughout the study with halothane at a concentration of 0.5–2%.

Measurements

Blood gases and physiological parameters were recorded at baseline, following lavage, every 30 min for 4 h, every hour for the next 4 h and at 10 h. After 10 h, surviving animals were sacrificed using intravenous pentobarbitone. Immediately after death the lungs were again lavaged with 15 ml/kg of normal saline at 37 °C, and the aspirated fluid was evaluated for total and differential cell counts (see below) and total protein concentration. The lungs were then inflated with formalin via the endotracheal tube to a pressure of 25 cm H_2O for 20 min, excised, the trachea ligated and the lungs immersed in formalin for 12 h. The lungs were then prepared for histology using standard methods, and sections from each lung were scored for hyaline membranes (see below).

Processing of lavage fluid

After gentle mixing, aliquots of unfiltered lavage fluid were placed in a Nebauer haemocytometer and total nucleated cell counts undertaken in duplicate. Aliquots of 3 ml of lavage fluid were then spun at 2000 rpm for 10 min and the supernatant frozen at -80 °C for later biochemical analysis. Cytospin preparations were made following red cell lysis and stained with Wrights-Geimsa. Differential cell counts were performed in duplicate by one observer. The results for total and differential cell counts are expressed as a change from baseline (i.e. final lavage minus initial lavage data).

Protein analysis

The total protein concentration in the initial and final lavage fluid was measured using the Bio-Rad protein assay (Bio-Rad, Richmond, California, USA).

Histological scoring

After fixation with 10% formol saline, a complete section of each lobe of the lungs was processed routinely and embedded in paraffin wax for light microscopy. Each lobe was sectioned from the hilum through the greatest part of the lobe. The sections were stained with haematoxylin and eosin, and examined morphometrically for hyaline membrane formation as follows: a 2 mm square grid was drawn on the cover slip, which was then placed over the section so that all the section was covered by the grid. In each square of the grid the microscopic field to be examined was centred in the grid square with the 10x objective lens, and the objective then changed to the 40 × lens for morphometric assessment. This provided a random selection of microscopic fields covering the entire section of each lobe. A Weibel type 2 eyepiece graticule was used to quantify the hyaline membranes by counting all points at which a free alveolar wall crossed a graticule line. Normal alveolar septa and those covered by a layer of hyaline membrane were scored separately, and the frequency of hyaline membrane intersects compared with uninvolved alveolar intersects. An average of 149 high power fields (× 400 magnification) were evaluated per rabbit (range 99–230, depending on the area of the sections). The observer was blinded to the group allocations.

Statistical analysis

The differences between groups in hyaline membrane frequency and the increase in cell counts and protein concentration from the initial to the final lung lavage were compared using students *t*-tests. Differences in PaO_2/FIO_2 ratio, PEEP, mean airway pressure, $PaCO_2$ and pH over the first 6 h were compared using repeated measures analysis of variance. Missing data due to deaths precluded comparison after 6 h with repeated measures ANOVA. The SAS procedure GLM (general linear model) was used for the ANOVA analyses [19]. Deaths in the two groups were compared using Fisher's exact test.

In order to take account of the early deaths in the control group and of unequal variances between groups, data for PaO_2/FIO_2 ratio, $AaDO_2$ and respiratory index were also analysed using an approach based on fitting individual regression curves to each animal, followed by averaging these estimates over animals to produce an estimated mean regression curve. Using this approach, the possibility that animals who died prematurely differed systematically from survivors with respect to their time profile is allowed for by regressing the individual regression estimates on survival time. The mean regression curve is then taken to be the regression curve predicted by the second stage regression, at the mean survival time. This approach thus allows for the possibility that the time course of the indices of oxygenation differed in survivors and non-survivors, and is described in detail elsewhere [20, 21].

In this study there were no early deaths in the study group, so in that group the mean regression curve was defined by the unweighted average of the individual regression estimates. However in the control group, in which four animals died prematurely, the mean regression curve is an appropriately weighted average of the individual estimates, with allowance also for the possible dependency of the individual estimates on survival time. We used model robust estimates of the variances of the mean regression parameter estimates

[22]. These robust variance estimates appear to protect against misspecification of the between-animal variance. Our experience to date suggests that such misspecification is possible using the inter-individual variance estimation strategy proposed in Wu and Bailey [19] and adapted from Vonesh and Carter [23]. We tested between group differences in mean regression curves using standard multivariate Wald chi-squared statistics. Since we found that cubic models were required for the individual curves in order to accommodate the observed individual time profiles, the Wald chi-squared tests had three degrees of freedom, the intercept terms being excluded from the testing procedure.

The results are presented as the mean and 95% confidence intervals (dashed lines on Figs. 1 and 2) or standard deviation (error bars on other figures).

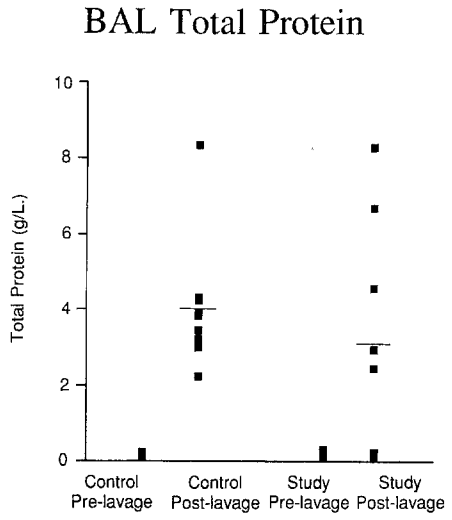

Fig. 1 Total protein concentration in study and control groups in initial (pre-lavage) and final (post-lavage) lavage fluid. The difference between groups in the increase from initial to final lavage is not significant

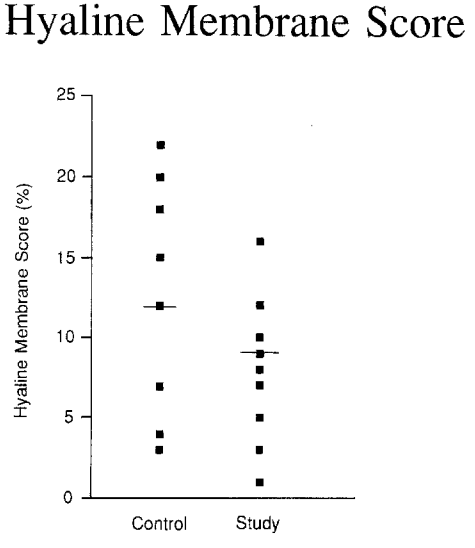

Fig. 2 Frequency of hyaline membranes for study and control groups expressed as the ratio of hyaline membranes to hyaline membranes + alveolar septa. The difference between groups is not significant

The study was approved by the Animal Ethics Committee of the Christchurch School of Medicine.

Results

BAL cell counts and lung histology

The increase in granulocyte count and total cell count from the initial to final lavage was not significantly different between the groups. Figures 1 and 2 show the values of total protein concentration in the initial and final lung lavage and the frequency of hyaline membranes expressed as the ratio of hyaline membranes to alveolar septa + hyaline membranes. The differences between the groups was not significant, but the mean values for all were lower in the study group.

Ventilation and gas exchange

Mean values for PaO_2/FIO_2 and $AaDO_2$ and the estimated mean regression curves in each group are shown in Figs. 3 and 4. The values were initially similar in each group, but study group animals showed a progressive increase in PaO_2/FIO_2 and decrease in $AaDO_2$, and the difference between the groups was significant

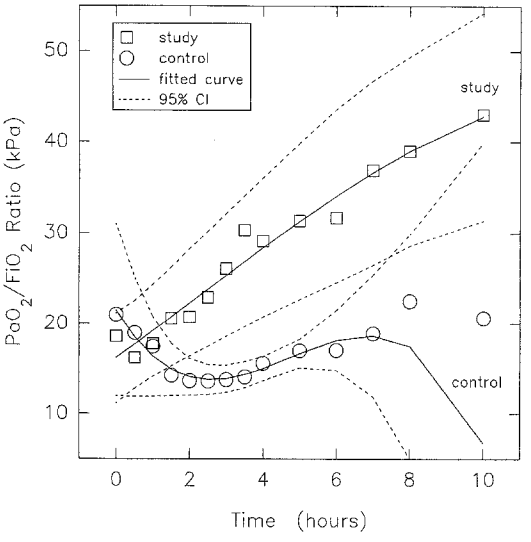

Fig. 3 Mean PaO_2/FIO_2 ratio. The difference between groups is significant ($p = 0.02$). Observed mean values at each time point are shown by *squares* (study group) and *circles* (control group). The estimated mean regression curves for each group are shown with *continuous lines*, and the 95% confidence intervals for the curves with *broken lines*. The estimated mean regression curve for the control group diverges from the mean observed data points after 6 h as a result of deaths in control group animals (see "Statistical methods")

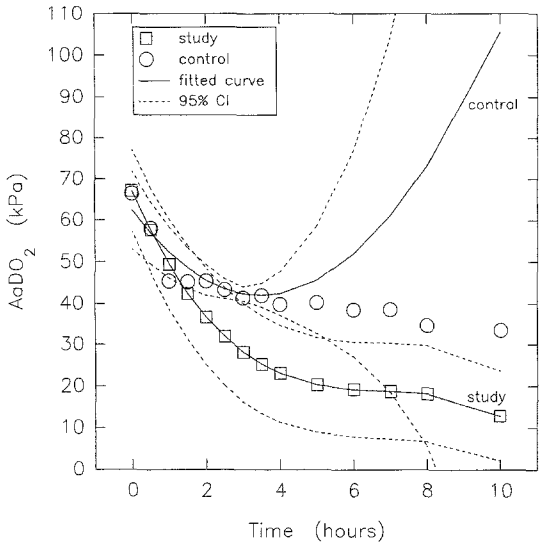

Fig. 4 Mean alveolar to arterial oxygen tension gradient ($AaDO_2$). The difference between groups is significant ($p = 0.01$). Observed mean values at each time point are shown by *squares* (study group) and *circles* (control group). The estimated mean regression curves for each group are shown with *continuous lines*, and the 95% confidence intervals for the curves with *broken lines*. The estimated mean regression curve for the control group diverges from the mean observed data points after 6 h as a result of deaths in control group animals (see "Statistical methods")

($p = 0.01$ for PaO_2/FIO_2 and for $AaDO_2$; with ANOVA $p = 0.05$ for PaO_2/FIO_2). The time profile of mean respiratory index was also more favourable in the study group but the difference did not reach significance ($p = 0.07$). The mean level of PEEP required to maintain PaO_2 at the predetermined levels, and the mean airway pressure, are shown in Fig. 5. There was no significant difference in PEEP between the groups. The reduction in mean PEEP in control group animals after 6 h resulted partly from the death of animals requiring high levels of PEEP at the times shown, but three surviving animals required less PEEP after 6 h. The difference between groups in the time profile of mean airway pressure was significant over the first 6 h ($p = 0.04$). The mandatory ventilation rate was progressively reduced to a mean of 5.4 in the study group and increased to a mean of 44 in the control group. Mean $PaCO_2$ and pH are shown in Fig. 6. The overall difference in $PaCO_2$ between groups was significant ($p = 0.03$). In the control group the requirement for increasing PEEP over the first 4 h to maintain oxygenation, with a constant Vt, resulted in all animals reaching the inspiratory pressure limit of 28 cm H_2O by 4 h. Further increases in PEEP then resulted in a reduction of Vt as part of the inspiratory gas flow was vented through the pressure relief valve, and increasing the ventilator rate to the maximum failed to achieve normocarbia in most animals. The subsequent fall in $PaCO_2$ after 6 h was related partly to the death of animals with severe lung injury and a high $PaCO_2$, and partly to reduced PEEP requirement in some surviving animals; the PIP then fell below the inspiratory pressure limit again, and Vt was restored to the initial value. The rise in $PaCO_2$ of study group animals was limited by spontaneous ventilation to a variable extent, although five animals reached a $PaCO_2$ of more than 10.7 kPa (80 mm Hg) for a period of time. The subsequent fall in $PaCO_2$ in the study group was probably mainly related to increased spontaneous ventilation as lung function improved.

Mortality

Four of nine control group animals died during the experimental protocol (3 from pneumothorax, 1 from progressive respiratory failure without pneumothorax), whereas none of the nine study group animals died during the study ($p = 0.08$). The deaths occurred at 3.3, 6.3, 7.4 and 8.4 h.

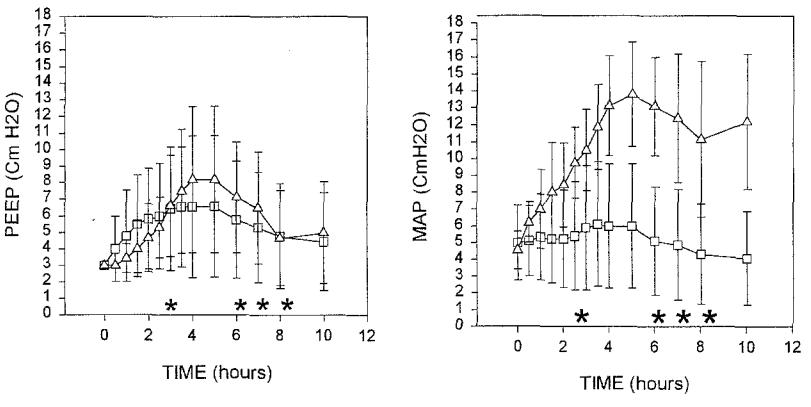

Fig. 5 Mean PEEP (*left*) and mean airway pressure (*right*) in study (—□—) and control group (—△—). The difference in PEEP is not significant; mean airway pressure is significantly lower in the study group ($p = 0.002$). Error bars show standard deviation; * indicates the time of death of a control group animal

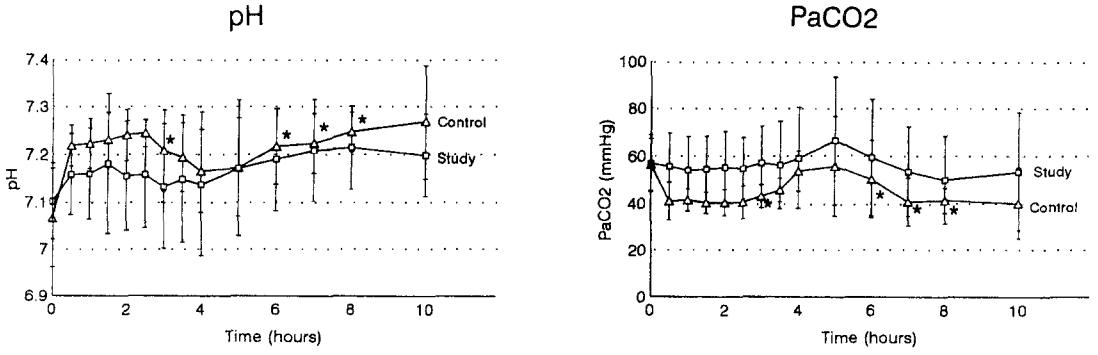

Fig. 6 Mean pH and $PaCO_2$ in study and control group. The difference in time profile and overall difference for $PaCO_2$ is significant ($p = 0.03$ for both); the difference in pH is not significant. Error bars show standard deviation; * indicates the time of death of a control group animal

Other data

There was no significant difference in haemoglobin concentration, base excess or mean blood pressure between groups at any time.

Discussion

Although study group animals showed significantly greater improvement in oxygenation during the 10 h study than the control group, the study group protocol did not prevent lung injury; there was no significant difference between the groups in protein concentration or cell counts in lung lavage fluid at the end of the study, or in hyaline membrane scores.

The PaO_2/FIO_2 ratio and $AaDO_2$ were initially similar in each group following saline lavage, but the study group showed significantly greater improvement of these parameters during ventilation than the control group. Mean airway pressure was significantly lower in the study group over this period and the mean level of PEEP was not significantly different. The difference in mean airway pressure would favour improved oxygenation in the control group, so the results suggest that the observed greater improvement of oxygenation in the study group occurred as a result of reduced lung injury from the ventilatory protocol in this group. Dorrington et al. [5] showed in this model that, if the animals were supported by extracorporeal CO_2 removal and apnoeic oxygenation to prevent ventilator-induced lung injury, oxygenation gradually improved, whereas with controlled mechanical ventilation it progressively deteriorated. The findings in our study are similar. It is conceivable that the higher mean airway pressure in the control group caused a fall in cardiac output and thus a reduced mixed venous oxygen saturation, and if a reduction in intrapulmonary shunt did not occur this would result in a lower PaO_2/FIO_2 ratio and higher $AaDO_2$. However, in acute lung injury or pulmonary oedema, an increase in mean airway pressure usually reduces intrapulmonary shunt and increases the PaO_2/FIO_2 ratio, and that has been shown to occur in this animal model [24]. It was also our invariable experience during pilot work with this model, as well as during the study, that increasing PEEP and mean airway pressure initially increased the PaO_2/FIO_2 ratio. Thus we do not believe it is likely that the higher mean airway pressure in the control group caused the lower PaO_2/FIO_2 ratio through this mechanism; greater ventilator-induced injury seems a more likely explanation.

The mean $PaCO_2$ in the control group increased between 3 and 6 h as described in the results section. This was a result of our use of an inspiratory pressure limit of 28 cm H_2O, so that Vt fell with increasing PEEP after this inspiratory pressure limit was reached. We chose to use this pressure limit, in the knowledge that we would not maintain normocapnia in all animals, in order to prevent too many early deaths from pneumothorax; this occurred in most animals during pilot work if a higher pressure limit was used. Frequent early death from pneumothorax in the control group would have reduced the probability of showing a difference in acute parenchymal lung injury between the groups. Thus the occurrence of some hypercapnia in the control group was expected, and does not affect the comparison of the two ventilation protocols.

The reduction in death from pneumothorax in the study group is not surprising or unexpected. Other studies have shown a high incidence of death from pneumothorax in this model [25] and that can be avoided by other ventilatory strategies such as extracorporeal CO_2 removal and apnoeic oxygenation, or high frequency ventilation [8, 25]. We are unable to determine whether death from progressive hypoxaemia without pneumothorax would have been reduced if the experimental protocol had been continued for a longer period of time. Hamilton et al. [25] showed that when

conventional ventilation was continued for 20 h in this model all animals died from progressive hypoxaemia or pneumothorax. Differences between the groups for the other indicators of lung injury (hyaline membranes, BAL protein and BAL granulocytes) all favoured the study group but none reached statistical significance. It is possible that the final lung lavage may have removed some of the proteinaceous material forming the hyaline membranes as well as inflammatory cells, and may therefore have modified the lung histology. The effect should be similar in both groups, but it is possible that it could have reduced the magnitude of any difference between the groups. We believed that lung lavage would provide an additional, and perhaps more sensitive, indicator of lung injury.

The results of this study therefore suggest some reduction of lung injury in the study group, but substantial injury still occurred. This may have been because even a PIP of 15 cm H_2O is sufficient to cause overdistension lung injury when spontaneous breaths are superimposed on the pressure-limited mandatory breaths, thus increasing transpulmonary pressure and lung distension. Indeed even spontaneous breathing without mechanical ventilation has been shown to cause lung injury if Vt is sufficiently high [26]. The animals did appear to have a high respiratory drive following lavage, at which time the respiratory rate was frequently more than 70/min. However, the lung injury in this model using a moderate Vt and PIP may not be related to lung overdistension; it may be related entirely to lung derecruitment with each breath and repeated opening of closed airways and alveoli and the related shear forces. If this is the case, then even extreme reduction of Vt and PIP may not prevent lung injury if some ventilation continues. It has been shown in several studies of saline lavaged rabbits that ventilator-induced lung injury can be largely prevented by the use of PEEP greater than the lower inflection point of the thoracopulmonary static pressure-volume curve [9–11], possibly by preventing end-expiratory collapse and re-expansion of airways and alveoli during each respiratory cycle. Thus it may be necessary to use higher levels of PEEP in this model to prevent lung injury. Alternatively, more extreme limitation of phasic lung distension by the use of paralysis and a very low Vt could perhaps prevent injury even with more moderate levels of PEEP. We are presently undertaking a further study to evaluate such extreme hypoventilation using neuromuscular blockade and low PEEP in this animal model.

It is not possible to extrapolate these results directly to clinical practice, but they do suggest the possibility that the widely used practice of titrating PEEP against oxygenation may not be optimal for the prevention of ventilator-induced injury, and this requires further study.

References

1. Parker JC, Hernandez LA, Peevy KJ (1993) Mechanisms of ventilator-induced lung injury. Crit Care Med 21: 131–143
2. Hickling KG (1990) Ventilatory management of ARDS: can it affect the outcome? Intensive Care Med 16: 219–226
3. Hickling KG (1992) Low volume ventilation with permissive hypercapnia in the Adult Respiratory Distress Syndrome. Clin Intensive Care 3: 67–78
4. Kawano T, Mori S, Cybulsky M, Burger R, Ballin A, Cutz E, Bryan AC (1987) Effect of granulocyte depletion in a ventilated surfactant-depleted lung. J Appl Physiol 62: 27–33
5. Burger R, Fung D, Bryan AC (1990) Lung injury in a surfactant deficient lung is modified by indomethacin. J Appl Physiol 69: 2067–2071
6. Valenza F, Ribeiro S, Slutsky A (1995) High volume low pressure mechanical ventilation up-regulates IL1-beta production in an ex-vivo lung model (Abstract). Am J Respir Crit Care Med 151: A552
7. Valenza F, Ribeiro S, Slutsky A (1995) Large volume high pressure mechanical ventilation up-regulates the production of tumor-necrosis factor alpha in an ex-vivo rat septic lung model (Abstract). Crit Care Med 23: A159
8. Dorrington KL, McRae KM, Gardaz JP, Dunhill MS, Sykes MK, Wilkinson AR (1989) A randomised comparison of total extracorporeal CO_2 removal with conventional mechanical ventilation in experimental hyaline membrane disease. Intensive Care Med 15: 184–191
9. Muscedere JG, Mullen JBM, Gan K, Slutsky AS (1994) Tidal ventilation at low airway pressures can cause pulmonary barotrauma. Am J Respir Crit Care Med 149: 1327–1334
10. Sandhar BK, Niblett DJ, Argiras EP, Dunhill MS, Sykes MK (1988) Effects of positive end-expiratory pressure on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome. Intensive Care Med 14: 538–546
11. Argiras EP, Blakeley CR, Dunhill MS, Otremski S, Sykes MK (1987) Reduction of hyaline membrane formation by the use of high PEEP. Br J Anaesth 59: 1278–1283
12. Froese AB, Bryan AC (1987) High frequency ventilation. Am Rev Respir Dis 135: 1363–1374
13. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16: 372–377
14. Hickling KG, Henderson S, Walsh J et al. (1994) Low mortality using low volume pressure limited ventilation with permissive hypercapnia in ARDS: a prospective study. Crit Care Med 22: 1568–1578
15. Slutsky A (1993) ACCP Consensus Conference: Mechanical Ventilation. Chest 104: 1833–1859
16. Bidani A, Tzouanakis AE, Cardenas VJ, Zwischenberger JB (1994) Permissive hypercapnia in acute respiratory failure. JAMA 272: 957–962

17. Zobel C, Kuttnig M, Trop M, Grubbauer HM (1990) A respiratory severity index for children with ARDS. Clin Intensive Care 1: 17–21
18. Lachmann B, Robertson B, Vogel J (1980) In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesia Scand 24: 231–236
19. SAS Institute Inc. SAS/STAT User's Guide release 6.03 edition (1988) Cary, North Carolina, USA
20. Wu MC, Bailey KR (1989) Estimation and comparison of changes in the presence of informative right censoring: conditional linear model. Biometrics 45: 939–955
21. Wu MC, Bailey KR (1988) Analysing changes in the presence of informative right censoring caused by death and withdrawal. Stat Med 7: 337–346
22. Royall RM (1986) Model robust confidence intervals using maximum likelihood estimators. Int Stat Rev 54: 221– 226
23. Vonesh EF, Carter RL (1987) Efficient inference for random coefficient growth curve models with unbalanced data. Biometrics 43: 617–628
24. McCulloch PR, Forkert PG, Froese AB (1988) Lung volume maintenance prevents lung injury during high frequency oscillation in surfactant-deficient rabbits. Am Rev Respir Dis 137: 1185–1192
25. Hamilton PP, Onayemi A, Smith JA, Gillan JE, Cutz E, Froese AB, Bryan AC (1983) Comparison of conventional and high frequency ventilation: oxygenation and lung pathology. J Appl Physiol 55: 131–138
26. Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, Buckhold D (1988) Acute respiratory failure following pharmacologically induced hyperventilation: an experimental study. Intensive Care Med 15: 8–14