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A lung recruitment maneuver immediately before rescue surfactant therapy does not affect the lung mechanical response in immature lambs with respiratory distress syndrome

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Background: In animals with acquired surfactant-deficiency, a recruitment maneuver by increased tidal volumes enhances the effect of exogenous surfactant. In contrast, in the preterm lamb model, hyperinflation early after birth impairs the effect of surfactant prophylaxis. Here we examined whether a lung recruitment maneuver just before surfactant would affect the response to rescue treatment in immature lambs with established respiratory distress syndrome (RDS).
Methods: Five pairs of preterm twin lambs with gestational age 127 days were delivered by cesarean section and supported by pressure-limited mechanical ventilation for 4 h. At 30 min of age, when all the lambs were in severe respiratory failure, they were treated with porcine surfactant, 200 mg kg^{-1}. One lamb in each pair was subjected to a lung recruitment maneuver consisting of five sustained inflations of 20 ml kg^{-1} just before surfactant instillation.
Results: At 10 min after surfactant treatment, all the lambs showed a large improvement in oxygenation and an increase in inspiratory capacity and static compliance. Except for a transiently better oxygenation after surfactant therapy in the recruitment group ($P < 0.05$), there was no significant between-group differences in gas exchange or lung mechanics at any time point during the study. There was no difference in *post mortem* intrapulmonary air volume or alveolar expansion in histologic lung sections between groups.
Conclusion: This small study does not show any positive or negative effect of a lung recruitment maneuver on the response to rescue surfactant therapy in immature animals with RDS.

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Key words: Animals, newborn; lung recruitment; pulmonary surfactants; respiratory distress syndrome.

It is generally believed that prophylactic surfactant administration to preterm infants at risk of developing respiratory distress syndrome (RDS) results in a better outcome than selective use of surfactant in babies with established RDS (1). Even so, a substantial number of preterm infants are given so-called 'rescue' treatment, e.g. because they did not fulfill the criteria for prophylaxis, were not in respiratory distress at birth or were thought to benefit from a trial of nasal continuous distending pressure. At the time of intubation, such infants may have a strong tendency to lung collapse and hypoxia, and it would seem logical to stabilize the baby with a period of manual ventilation with high inspiratory pressures before surfactant instillation.

If, in such infants, collapsed air spaces are indeed recruited by the application of a sufficiently high end-inspiratory pressure, then the subsequently instilled surfactant would be expected to spread into a larger part of the lung, and the net result might be an improved effect of treatment. In two animal models of surfactant depletion (lung-lavaged piglets and young rabbits), Krause et al. demonstrated that a volume recruitment maneuver, consisting of an approximate doubling of tidal volumes (up to 16–17.5 ml kg^{-1}), improved the response to natural surfactant in terms of gas exchange and lung mechanics (2, 3). In piglets, lung recruitment also resulted in a more homogenous surfactant distribution (3). However, similar effects have not been demonstrated in animal models of neonatal RDS.

It has been questioned whether the lungs of preterm infants with established RDS are as easily recruitable as those of animals with acquired surfactant depletion (4). Infants with severe RDS not only have a decreased lung stability, but also a very limited inspiratory capacity (5), implying that ventilation with large tidal volumes may easily lead to overdistension and perhaps lung injury (6). We have previously shown in immature lambs that a few large lung inflations (16–32 ml kg^{-1}) given immediately at birth blunt the response to subsequent surfactant instillation (7, 8). The aim of this study was to investigate whether similar inflations, given before rescue surfactant treatment in immature lambs with established RDS, would in any way influence the therapeutic response.

Materials and methods

Overview of the study

Preterm twin lambs were delivered by cesarean section and mechanically ventilated for 4 h. At 30 min of age, when all lambs were in severe respiratory failure, they were treated with surfactant. In addition, one twin in each pair was given five sustained lung inflations of 20 ml kg^{-1}, to mimic a vital capacity lung recruitment maneuver, just before surfactant instillation. The response to surfactant was assessed by blood gases, pulmonary mechanics and histologic examination of the lungs.

The study was approved by the local review board for animal research.

Procedures

Caesarean section was carried out in date-mated ewes carrying twins at 127 days after conception. Anesthesia was as previously described (7). The head of the lamb was exteriorized, and a 3.5- or 4.0-mm inner diameter tube was inserted through an incision in the trachea, so that the tip was located well above the carina. The tube was secured with ligatures around the trachea to prevent any leakage. To simulate the lung liquid elimination that would have occurred during a spontaneous vaginal delivery, 10 ml of tracheal fluid was removed by syringe. Additional tracheal fluid was then allowed to drain passively into a bag-and-tube system connected to the endotracheal tube. Catheters were inserted into a jugular vein and a carotid artery. The lamb was given 8 mg of ketamine and 0.4 mg of pancuronium intravenously just before the umbilical cord was cut. The lamb was then weighed and placed in an open incubator.

All lambs were mechanically ventilated with a Servo Ventilator 900C (Siemens-Elema, Solna, Sweden). This was set in pressure control mode with a ventilatory rate of 50 min^{-1}, inspiratory time 50% of the cycle, and positive end-expiratory pressure (PEEP) 4 cm H_2O. These settings were kept unchanged during the course of the experiment. Inspiratory pressure was initially set at 29 cm H_2O (25 cm H_2O + PEEP). Fraction of inspired oxygen (FiO_2) was initially 0.9. Airway pressure was monitored with a VenTrak model 1500 respiratory monitoring system (Novametrix, Wallingford, Connecticut, CT) using a Hans Rudolph model 8411 neonatal pneumotachograph (Hans Rudolph, Kansas City, Missouri, MO). Anesthesia was given by an infusion of ketamine, 1 mg ml^{-1} in glucose 50 mg ml^{-1}, at a rate of 4 ml kg^{-1} h^{-1}.

At 30 min of age, all lambs were treated with surfactant. With the lamb held lying on its back, 200 mg kg^{-1}(2.5 ml kg^{-1}) of modified natural porcine surfactant (Curosurf; Chiesi Farmaceutici, Parma, Italy) was instilled as a single rapid bolus through the endotracheal tube.

One lamb in each pair was randomly assigned to receive a standardized recruitment maneuver consisting of five sustained inflations of 20 ml kg^{-1} immediately before surfactant instillation. A large syringe filled with the requisite volume of air was connected to the tracheal tube via airtight tubing and emptied into the lungs. The inflation lasted 1–2 s and was followed by a 5-s postinspiratory pause. The lungs were thereafter allowed to empty passively into the atmosphere, while the syringe was refilled, and the procedure was repeated four times. Airway pressures obtained during the inflations were recorded with the VenTrak monitor. The pressure at the first and last points of no flow during the sustained inflation was taken from the stored VenTrak curves.

At 40 min of age (i.e. 10 min after surfactant) FiO_2 was lowered to 0.5. If during the further course of the experiment PaO_2 was below 4 kPa, FiO_2 was increased stepwise to 0.7 and at most 0.9. Peak inspiratory pressure was adjusted with the aim of keeping $PaCO_2$ around 6–6.5 kPa; the maximal allowed peak pressure was 39 cm H_2O.

Lung function in vivo

Arterial blood gases (ABL 300, Radiometer, Denmark) were measured at 10, 20, 40, 90, 135, 195 and 225 min of age, and at the same time points the pressures from the VenTrak monitor were noted. Oxygenation was assessed as PaO_2 (kPa)/FiO_2 (=PF-ratio). Oxygenation index (OI) was calculated as [mean airway pressure (cm H_2O) × FiO_2 × 100]/[PaO_2 (kPa) × 7.5]. The measures at 20 min of age were taken to represent gas exchange before surfactant treatment. In the first pair of lambs, blood gases at 20 min were not taken, and the values obtained at 10 min of age were used instead.

Static expiratory pressure-volume (P-V) diagrams of the respiratory system (5) were recorded at 10, 40, 135, and 225 min after birth. Using a large syringe, the lungs were inflated with room air to an airway pressure of 35 cm H_2O. After maintaining this pressure for 15 s, the lungs were allowed to empty passively into the atmosphere through a flowmeter and an electronically operated occluder, which cyclically interrupted the expired flow for 80 ms and let it through for 80 ms. The slow expiration, which lasted 10–15 s, continued until airway pressure was less than 0.5 cm H_2O. A computer recorded the pressure at the later part of each flow interruption and used the flow signal to calculate the volume decrement between successive interruptions so that a static P-V diagram could be drawn. At each stage of the experiment, three to four diagrams were made.

Two measures were extracted from the P-V curves: inspiratory capacity (IC), measured as the expired volume between 30 and 0 cm H_2O, and maximal static deflation compliance of the respiratory system (Crs_{max}), i.e. the steepest slope of the P-V curve. The means from the last two acceptable curves obtained at each stage were used for the numerical analysis. The values were corrected for body weight.

Post mortem investigations

At 4 h, the lamb was killed with an intravenous injection of thiopental and the lungs were prepared as previously described (8). After examination for pneumothorax, the heart-lung preparation was removed *en bloc*. Intrapulmonary air volume at 30 cm H_2O distending pressure was estimated by subtracting the weight of the preparation (in g) from its total volume (in ml). Perfusion fixation with formaldehyde through the pulmonary artery was then carried out while the lungs were kept distended at an airway pressure of 10 cm H_2O.

Large paraffin sections from all lung lobes, stained with hematoxylin and eosin, were examined by one of the authors (B.R.), with particular reference to the alveolar expansion pattern, bronchiolar epithelial injury, alveolar hyaline membranes, and recruitment of granulocytes to the airspaces. The assessment of the histologic findings was performed in a blinded fashion, i.e. the examiner was unaware of both the treatment given and the results of lung function measurements. The histologic response to surfactant was quantified as percent of the alveoli estimated to be air-expanded.

Statistics

Differences in quantitative parameters over time and between twins were assessed by paired comparison *t*-tests. Results are given as mean ± SD unless otherwise noted. P-values <0.05 were taken to indicate statistical significance.

Results

We had originally planned to examine eight pairs of twin lambs. However, after having studied five pairs, we realized that the chance of finding a significant difference in outcome between twins was very small, and the study was terminated.

Before receiving surfactant, all the lambs were in severe respiratory failure with $PaCO_2$ 12.5 ± 3.5 kPa, PF-ratio 5.7 ± 3.4 kPa, and OI 48 ± 26. There were no significant differences in gas exchange or lung mechanics (IC and Crs_{max}) between the groups before surfactant treatment.

In the lambs subjected to a recruitment maneuver before surfactant treatment, pressure during the first inflation was 62 ± 9 cm H_2O at the first and 39 ± 11 cm H_2O at the last point of no flow. The corresponding figures for the last inflation were 56 ± 4 and 40 ± 9 cm H_2O (not significant).

All lambs responded to surfactant therapy with a marked increase in oxygenation (PF-ratio) and a decrease in OI (both $P < 0.001$). However, the PF-ratio at 10 min after surfactant was higher in the lambs subjected to a recruitment maneuver before receiving surfactant than in the controls (52 ± 12 vs. 38 ± 9.7 kPa; $P = 0.04$). Similarly, at 10 min after surfactant treatment, OI was 3.9 ± 1.3 in the lambs subjected to a lung recruitment maneuver vs. 5.7 ± 1.6 in the controls (not significant). During the further course of the study, there was a successive fall in the PF-ratio and an increase in OI. At 225 min of age, the PF-ratio and OI were not significantly different from the values obtained before surfactant treatment. At this time point, all except one lamb in each group were again on 90% oxygen. $PaCO_2$ at 225 min was 8.4 ± 3.4 kPa and peak inspiratory pressure 31 ± 6.3 cm H_2O. Except for the higher PF-ratio at 40 min in the recruitment group, there was no significant between-groups difference in any measure of gas exchange at any time point after surfactant treatment.

In all lambs, IC and Crs_{max} increased immediately after surfactant treatment (Figure 1). At 10 min after surfactant treatment, IC had increased by $128 \pm 46\%$ and Crs_{max} by $162 \pm 80\%$ (both $P < 0.001$). The highest mean values for IC and Crs_{max} were seen at 135 min of age. During the latter part of the experiments, these parameters tended to fall again or remained unchanged. At 225 min, IC and Crs_{max} were still significantly higher than before surfactant treatment ($P = 0.002$ and $P = 0.01$, respectively).

There was no significant difference in IC and Crs_{max} at any time point between the lambs subjected to a recruitment maneuver before receiving surfactant and those who were not. The values at 4 h varied widely, but tended to be similar within each pair of twins (Figure). A multivariate analysis with IC at 4 h as the dependent variable showed that litter contributed significantly to IC ($P < 0.001$) while the recruitment maneuver did not. A similar result was obtained for Crs_{max} ($P < 0.01$ for litter). Simply, this means that each lamb tended to have a similar outcome as its sibling, and this was not significantly influenced by the different treatment protocols.

There was a significant correlation between the lung mechanical parameters (IC and Crs_{max}) at 4 h and the *post mortem* parameters (intrapulmonary air volume and alveolar expansion). Similarly, there was a significant inverse relation between peak inspiratory pressure and $PaCO_2$ at 4 h and the *post mortem* measures (all $P < 0.05$). *Post mortem* intrapulmonary air volume at 30 cmH_2O distending pressure was $32 \pm 14\ ml\ kg^{-1}$ in the lambs subjected to a recruitment maneuver before surfactant and $43 \pm 22\ ml\ kg^{-1}$ in the controls (not significant). The estimated percent expanded alveoli in histologic sections varied widely (from 3% to 90%), but again tended to be similar between twins. Bronchiolar epithelial necrosis and hyaline membranes were observed mainly in poorly expanded lung fields, and was in four animals associated with mild recruitment of granulocytes to the interstitium and alveolar spaces. Focal discrete interstitial and/or intra-alveolar hemorrhage was present in four animals. There was no obvious relation between the treatment and the histologic findings.

Discussion

This small study shows that in immature lambs with RDS, a recruitment maneuver consisting of five sustained inflations of $20\ ml\ kg^{-1}$ at 30 min of age does not affect the response to subsequent rescue surfactant treatment.

Wada et al. (9) showed that preterm lambs delivered at 129 days' gestation and ventilated with a tidal volume of $20\ ml\ kg^{-1}$ for 30 min before surfactant treatment subsequently had lower compliance of the respiratory system and lower ventilatory efficiency

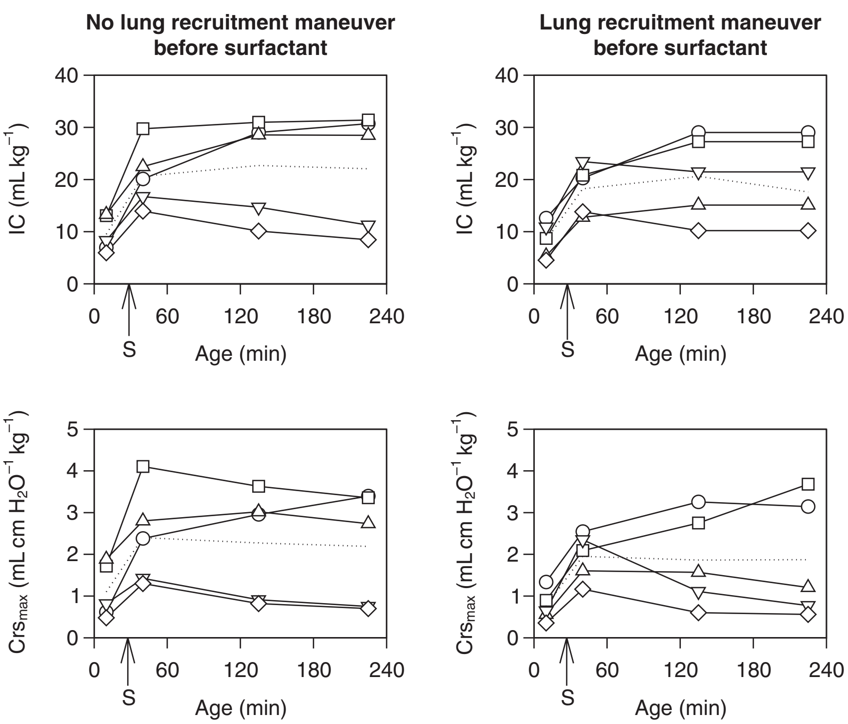

Fig. 1. Inspiratory capacity of the lungs (IC; upper graphs) and maximal deflation compliance of the respiratory system (Crs_{max}; lower graphs). Graphs on the left show control lambs and those on the right show lambs subjected to a volume recruitment maneuver before receiving surfactant. Each unbroken line represents one individual lamb. Twins have the same symbols in each set of graphs. The dotted lines show mean values. The arrow shows the time when surfactant (S) was given. There were no significant between-groups differences in the illustrated parameters at any time point during the study. The lung mechanical response tended to be similar within each pair of twins.

than had lambs initially ventilated with a tidal volume of 5 ml kg^{-1}. We have previously showed that, in lambs delivered at 127 days gestation, only a few large lung inflations were needed to blunt the response to exogenous surfactant, if these inflations were given immediately at birth (8). In the present study, when such inflations were given at 30 min of age, no negative effect was demonstrated, although the airway pressures obtained during the inflations were similar.

The explanation for these seemingly discrepant findings is probably that the surfactant-deficient lung is most sensitive to hyperventilation very early after birth. Even without surfactant, our lambs showed some improvement in gas exchange and presumably lung expansion during the first 30 min of mechanical ventilation. Thus, the PF-ratio was significantly higher and OI significantly lower at 20 than at 10 min of age (both $P < 0.05$) although $PaCO_2$ remained unchanged. We suggest that the partly expanded but unstable lung at 30 min can cope more easily with a few *supra*-physiologic lung inflations than the fluid-filled lung at birth.

It could be argued that the recruitment maneuver was suboptimal, and that a positive effect would have been seen if another method had been used. We believe that the 5×5-s inflations should be adequate to open up most atelectatic areas of the lung. The maneuver did result in a transiently better oxygenation, suggesting that at least some collapsed lung parts were recruited and remained open for some time after surfactant treatment. In the piglet model, Krause et al. (3) found that large tidal volumes was the best way to enhance the effect of surfactant treatment, and the inflation volumes used in our study were similar to those used by that group. In contrast to the protocol applied by Krause's group, our lambs were disconnected from the ventilator during the recruitment maneuver, and airway pressure fell to zero between inflations, decreasing the chance that a recruitment effect would be sustained. However, our method mimics the way such recruitment maneuvers are often carried out in clinical practice with the use of an ordinary resuscitation bag.

Another possibility is that lung collapse was less important in these lambs than, e.g., alveolar edema, and that therefore the lung was to a large extent not recruitable with large inflation volumes. Finally, it could be argued that the lambs already at 30 min of age had so severe RDS that small effects of the recruitment maneuver were hidden by the prominent improvement in lung function obtained with surfactant supplementation.

No clinical inferences should be drawn from this small study. However, there is no evidence from randomized clinical trials suggesting that outcome after surfactant therapy is influenced by any specific ventilatory maneuvers at the time of surfactant instillation. We can not presume that maneuvers involving the application of large tidal volumes or high pressures are harmless and, consequently, we believe such maneuvers are best avoided.

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