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Incomplete protection by prophylactic surfactant against the adverse effects of large lung inflations at birth in immature lambs

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Abstract *Objective:* To investigate whether preceding surfactant instillation prevents the harmful effect of large lung inflations at birth in immature lambs, and, if not, to find out for how long the immature lung remains sensitive to large inflations. *Design:* In an exploratory study, 12 preterm lambs given surfactant at birth were randomized to receive five large lung inflations at four different times: at birth just before or immediately after surfactant treatment; at 10 min; or at 60 min of age. In a confirmatory study, 10 pairs of preterm lamb twins were all given surfactant before the first breath. One lamb in each pair was randomised to receive large lung inflations immediately after surfactant while the other twin underwent similar inflations at 10–15 min of age. *Setting:* Animal laboratory. *Experimental animals:* Anaesthetized lambs delivered by cesarean section at a gestational age of 127 days. *Interventions:* Surfactant supplementation at birth. Five sustained lung inflations of 16 ml/kg at different times in relation to surfactant instillation. Pressure-limited mechanical ventilation for 4 h. *Measurements and results:* The response to surfactant was assessed by ventilator settings, lung mechanics and lung histology. Preceding surfactant supplementation did not prevent the adverse effect of large lung inflations at birth on ventilatory efficiency and lung mechanics, but seemed to protect against severe lung injury. No adverse effect was seen from large lung inflations given at 10 min of age or later. *Conclusion:* Prophylactic surfactant supplementation does not fully protect against the harmful effect of large lung inflations during a short sensitive period immediately after birth.

Keywords Respiratory distress syndrome · Pulmonary surfactants · Resuscitation · Lung recruitment · Animals · Newborn

Introduction

During resuscitation of asphyxiated full-term newborn infants, manual ventilation is the most important therapeutic measure. Vigorous inflation of the lungs with relatively high pressures often results in immediate release of reflex inhibition of circulation and breathing and a rapid recruitment of lung volume [1]. In very preterm infants who fail to establish efficient respiration at birth, a similar course of action may seem intuitively beneficial. Indeed, in many centres, the majority of such infants are intubated and subjected to manual ventilation at birth; however, retrospective clinical studies have indicated that such an aggressive respiratory management early in life increases the risk of chronic lung disease [2, 3, 4, 5], and it has been suggested that attempts to rapidly recruit lung volume at birth in preterm infants may be harmful [6, 7].

In immature lambs, a period of hyperventilation [8, 9, 10] or even only a few large lung inflations at birth [11, 12] may blunt the response to subsequent surfactant treatment and result in lung injury. Mechanical ventilation of the surfactant-deficient lung results in heterogeneous lung expansion. Overdistension of structurally immature lung regions may cause epithelial disruption, proteinaceous oedema and surfactant inactivation. Previous animal studies have indicated that this injury sequence can be prevented by preceding surfactant supplementation [13], giving experimental support for the use of prophylactic surfactant in preterm human infants.

Surfactant treatment at birth promotes synchronous expansion of air spaces [13]; however, even after prophylactic surfactant instillation, resorption of fetal lung fluid and the establishment of a normal lung capacity probably occurs much slower in very preterm than in full-term newborns. In immature lambs receiving surfactant before the first breath and then undergoing mechanical ventilation, a maximal inspiratory capacity of 35–40 ml/kg was not established until around 1 h of life [11, 12]. We therefore hypothesized that the immature lung would remain sensitive to ventilation with large inflation volumes for some time after surfactant instillation simply because the lung would still be partly fluid-filled with limited room for air entry. In the preterm lamb model, we have previously shown that the response to prophylactic surfactant treatment will be suboptimal if the instillation is preceded by large inflations of the lungs (five inflations of 16 ml/kg) [12]. We now examined the effect of the same inflation manoeuvre given at various time intervals (0–60 min) *after* surfactant treatment.

Materials and methods

Overview of the study

The work reported herein was done in two stages: an exploratory stage (study A) and a confirmatory stage (study B). Premature lambs (127 days GA) delivered by caesarean section were used.

Study A

In study A, 12 lambs (three pairs of twins and six singletons; body weight 3004±727 g) were randomly assigned to four different treatment groups with three lambs in each group. All lambs received surfactant shortly after birth, while the timing of a standardized large inflation manoeuvre, consisting of five sustained lung inflations of 16 ml/kg, varied:

Group 1:
Five lung inflations shortly after birth, immediately followed by surfactant instillation.

Group 2:
The order was reversed, i.e. surfactant instillation before the first breath, immediately followed by lung inflations.

Group 3:
The same as in group 2, except that 10 min of pressure-limited mechanical ventilation preceded the large lung inflations.

Group 4
The same as in group 2, except that the large lung inflations were given 60 min after birth.

The lambs in groups 1 and 2 were thus given "early inflations" (i.e. shortly after birth), while those in groups 3 and 4 were given "late inflations" (at 10 min of age or later).

Study B

In the confirmatory study, 10 pairs of twin lambs (body weight 2694±530 g) were studied (S1). All 20 lambs received surfactant before the first breath. In one lamb in each pair five large lung inflations were given immediately after surfactant (see group 2 above), while in the other lamb identical size inflations were given 10–15 min after surfactant (at 10 min in the first four pairs and at 15 min in the following six pairs; see group 3 above). Randomisation was arranged so that there were an equal number of first and second twins in the two groups.

All lambs in both studies were mechanically ventilated in the pressure control mode for 4 h (S2). Surfactant response was assessed by blood gases (S3), in vivo lung mechanics and post-mortem investigations. The study was approved by the local review board for animal research, and the NIH "Principles of laboratory animal care" were followed.

Procedure and measurements

Anaesthesia of the ewes was as previously described [11]. Details on the preparation and care of lambs can be found in the electronic supplement (S4).

An outline of the study is shown in a figure in the electronic supplement (S5). In all lambs, surfactant was given within a few minutes after birth. None of the lambs breathed spontaneously before receiving surfactant. In 29 lambs surfactant was given before any gas was allowed to enter the lungs and in three lambs (group 1 in study A) it was given just after the lung inflation manoeuvre (see above). With the lamb held lying on its back, 200 mg/kg (2.5 ml/kg) of modified natural porcine surfactant (Curosurf, Chiesi Far-

maceutici, Parma, Italy) was instilled as a single rapid bolus through a feeding tube, inserted to reach the lower trachea just beyond the tip of the endotracheal tube.

The lambs were subjected to a standardised lung inflation manoeuvre consisting of five sustained inflations of 16 ml/kg at different time points as indicated above. 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 post-inspiratory pause. The lungs were thereafter allowed to empty passively into the atmosphere, while the syringe was refilled, and the procedure was repeated four times. The pressure at the first point of no flow during the sustained inflation was used for statistical calculations (S6).

Static expiratory pressure–volume (P–V) diagrams of the respiratory system [14] were recorded at 15, 40, 105, 135, 170 and 240 min after birth (S7).

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 curves of acceptable quality at each stage were used for the numerical analysis. The values were converted from ATPS to BTPS conditions by multiplying with 1.09 and were divided by body weight.

In study A, functional residual capacity (FRC) was measured at 15, 40, 170 and 240 min after birth with a washin–washout technique, using sulphur hexafluoride as tracer gas [15]. At each stage, FRC was measured two to five times at 5 cm H_2O PEEP, and a mean value was calculated and corrected for body weight. When study B was done, the equipment for measuring FRC was not functioning.

At 4 h, the lamb was killed with intravenous sodium thiopental, 250 mg. Intrapulmonary air volume at 30 cm H_2O airway pressure was measured and perfusion fixation of the lungs was done as previously described [12] (S8).

Statistical methods are reported in the electronic supplement (S9).

Results

Exploratory study: study A

Significantly higher airway pressures were generated by the large lung inflations in the lambs given "early inflations" (groups 1 and 2) than in those given "late inflations" (groups 3 and 4; Fig. 1, left panel). The "early inflation" lambs were then more difficult to ventilate and needed significantly higher peak inspiratory pressures at all time points from 40 min onwards (Fig. 2, left panel; Table 1). The IC and Crs_{max} increased during the first hours in the "late inflation" lambs but remained almost unchanged in the lambs subjected to "early inflations"(Fig. 3, left panel). The FRC was significantly higher in the "late inflation" lambs at all time points when it was measured (Fig. 4). At 4 h, IC, Crs_{max} and FRC were all approximately two times higher in the "late inflation" than in the "early inflation" lambs (Table 1).

Post-mortem intrapulmonary air volume at 30 cm H_2O airway pressure was significantly larger in the "late inflation" lambs (Table 1). All six "late inflation" lambs had a satisfactory response to surfactant, as judged by the histological findings (at least 75% of alveoli estimated to be air expanded). In contrast, only one of six "early inflation" lambs had a clearly satisfactory response ($p<0.05$), and two such lambs had a very unsatisfactory response (40% and <10% alveolar expansion, respectively).

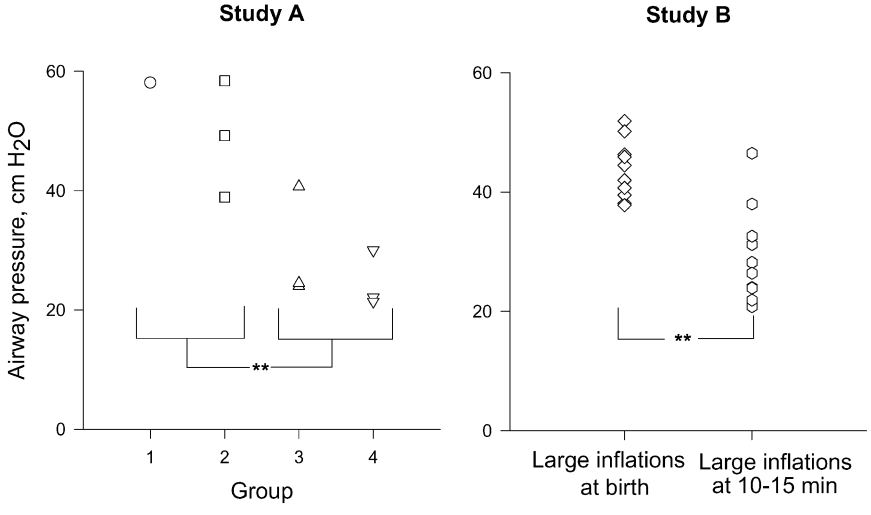

Fig. 1 Airway pressure during the inflation manoeuvres. *Symbols* represent the pressure at the first point of no flow during the first inflation in each lamb. $^{**}p<0.01$. Study A is exploratory study: all lambs were given surfactant shortly after birth, i.e. as prophylaxis, and in all except group 1, surfactant was given before the first breath. Group 1, five large inflations (16 ml/kg) just before surfactant instillation; group 2, large inflations just after surfactant; group 3, large inflations at 10 min of age; group 4, large inflations at 60 min of age. In group 1, the pressure measurement failed in two out of three lambs. The significance level represents a comparison between the "early inflation" lambs (groups 1 and 2) and the "late inflation" lambs (groups 3 and 4), as indicated. Study B is confirmatory study: all lambs were given surfactant before the first breath. Large lung inflations were given either immediately after surfactant instillation or at 10 or 15 min of age

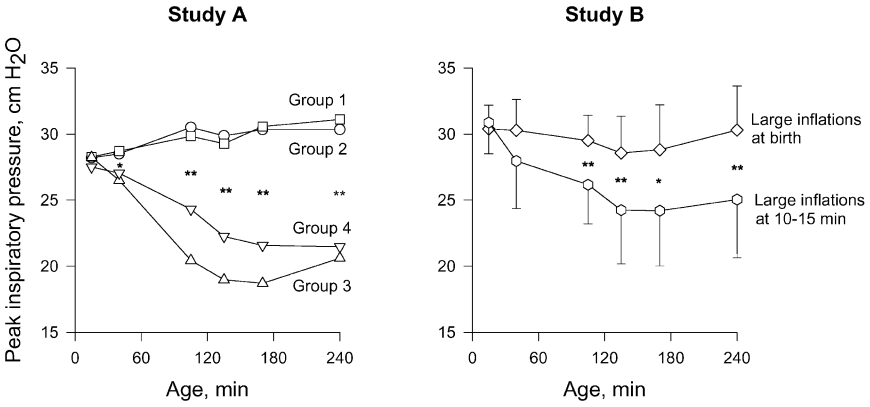

Fig. 2 Peak inspiratory pressure at different time points during 4 h of mechanical ventilation. Ventilator pressure was adjusted to keep $PaCO_2$ around 6 kPa. *p<0.05, **p<0.01. *Group symbols* are the same as in Fig. 1. In study A significance levels represent a comparison between lambs subjected to early (groups 1 and 2) vs late (groups 3 and 4) inflations. There is one missing value in group 4 at 15 min, one in group 2 at 40 min, one in group 4 at 135 min and one in group 3 at 170 min. In study B *error bars* show standard deviation

Table 1 Ventilatory efficiency and lung mechanics in vivo at 240 min of age and post-mortem lung volume. *PIP* peak inspiratory pressure, *IC* inspiratory capacity, Crs_{max} maximal compliance of the respiratory system, *FRC* functional residual capacity, *IPAV* post-mortem intrapulmonary air volume at 30 cm H_2O inflation pressure

Study A	PIP	$PaCO_2$	IC	Crs_{max}	FRC	IPAV
	(cm H_2O)	(kPa)	(ml/kg)	(ml/cm H_2O/kg)	(ml/kg)	(ml/kg)
Early inflations (groups 1 and 2)	30.4 (5.2)	8.0 (1.5)	21.2 (10.0)	1.6 (0.8)	10.0 (4.7)	40 (16)
Late inflations (groups 3 and 4)	21.3 (1.4)	6.9 (1.1)	38.6 (7.0)	3.7 (0.7)	20.0 (3.9)	62 (18)
p value	<0.05	n.s.	<0.05	<0.05	<0.05	<0.05
Study B	PIP	$PaCO_2$	IC	Crs_{max}	FRC	IPAV
	(cm H_2O)	(kPa)	(ml/kg)	(ml/cm H_2O/kg)	(ml/kg)	(ml/kg)
Inflation at birth	30.3 (3.3)	6.2 (0.8)	20.3 (6.4)	1.7 (0.6)	–	47 (12)
Inflation at 10–15 min	25.6 (4.6)	6.6 (0.7)	28.3 (7.3)	2.9 (1.4)	–	55 (12)
p value	<0.05	n.s.	<0.05	<0.05		n.s.

Numbers are mean with SD in parentheses

Table 2 Oxygenation index in the confirmatory study (study B)

	5 min	15 min	40 min	120 min	240 min
Inflations at birth	9.6 (0.7)	4.5 (1.4)	5.2 (2)	7.6 (4)	15.3 (12)
Inflations at 10–15 min	5.2 (0.5)	5.0 (0.5)	4.8 (2)	7.9 (6)	11.4 (12)
p value	n.s.	n.s.	n.s.	n.s.	n.s.

Numbers are mean with SD in parentheses

Confirmatory study: study B

Airway pressures during the lung inflation manoeuvres

Airway pressure at the first point of no flow during the first inflation was 44±5 cm H_2O in the group subjected to large inflation at birth and 29±8 cm H_2O in the group given same size of inflations at 10–15 min (p<0.01; Fig. 1, right panel). Corresponding values for the fifth inflation were 51±8 cm H_2O and 29±8 cm H_2O (p<0.001).

Lung function in vivo

Throughout the study, there was a marked within-group variation in PaO_2. There was no significant difference between the groups in PaO_2 or oxygenation index (OI; Table 2) at any time point.

During the 4 h of mechanical ventilation, peak inspiratory pressure was adjusted to keep $PaCO_2$ around 6 kPa. Consequently, after the first hour, there was no significant difference in $PaCO_2$ between the groups (Table 3). There was no difference in tidal volumes between the groups after the first 15 min (Table 4); however, the lambs subjected to large lung inflations at birth needed signifi-

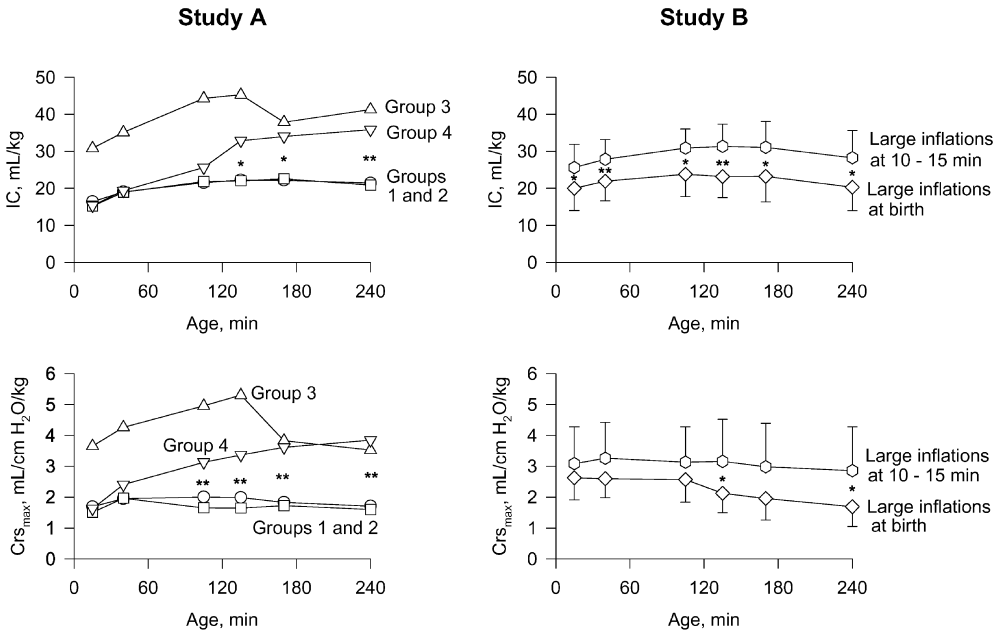

Fig. 3 Group means for inspiratory capacity (*IC*) and maximal static deflation compliance (Crs_{max}) at different time points in the two studies. Group *notations* and *symbols* are the same as in previous figures. In the exploratory study (*left panel*), the high mean values for IC and Crs_{max} in group 3 were caused by one twin lamb that had an unusually good lung mechanical response to surfactant; the other twin was in group 2

Table 3 $PaCO_2$ values (in kPa) in the confirmatory study (study B)

	15 min	40 min	105 min	135 min	170 min	240 min
Inflations at birth	8.6 (3.7)	6.8 (2.2)	5.3 (1.2)	6.0 (1.2)	6.3 (0.9)	6.2 (0.8)
Inflations at 10–15 min	6.7 (4.0)	4.7 (1.7)	4.4 (1.1)	5.9 (1.0)	6.3 (1.1)	6.6 (0.7)
p value	n.s.	0.03	n.s.	n.s.	n.s.	n.s.

Numbers are mean with SD in parentheses

Table 4 Tidal volumes (in ml/kg) in the confirmatory study (study B)

	15 min	40 min	105 min	135 min	170 min	240 min
Inflations at birth	7.9 (2.1)	8.9 (1.4)	8.7 (1.0)	7.9 (1.3)	8.0 (1.2)	8.4 (1.1)
Inflations at 10–15 min	10.9 (1.8)	9.7 (1.8)	8.7 (1.8)	7.1 (1.4)	7.4 (1.3)	7.1(2.8)
p value	<0.01	n.s.	n.s.	n.s.	n.s.	n.s.

Numbers are mean with SD in parentheses

cantly higher peak inspiratory pressures to obtain these tidal volumes than the lambs given large inflations at 10 or 15 min (significant at all time points after the first hour; Fig. 2, right panel; Table 1).

The IC and Crs_{max} were less in the lambs given large inflations immediately after surfactant than in those with inflations postponed until 10 or 15 min of age (Table 1; Fig. 3, right panel). In the lambs given large inflations at birth, Crs_{max} fell significantly over the 4-h study period ($p<0.01$), whereas in the other group, it was unchanged.

Post-mortem observations

None of the lambs had pneumothorax at post-mortem examination. The intrapulmonary air volume at 30 cm H_2O inflation pressure was 47±12 ml/kg in the lambs given large inflations at birth and 55±12 ml/kg in lambs given same size inflations at 10 or 15 min ($p=0.11$; Table 1).

Five of ten lambs given large inflations after surfactant at birth had a satisfactory histological response to surfactant, compared with seven of ten lambs given large inflations at 10 or 15 min (not significant). Focal bronchiolar necrosis and mild recruitment of granulocytes to the airspaces were observed in most animals, particularly in poorly expanded areas, and discrete hyaline membranes in a few, without difference between the groups.

Discussion

We have previously shown that a few large lung inflations given shortly after birth to immature lambs blunt the lung mechanical response to subsequent surfactant instillation and may cause lung injury [11, 12]. The adverse effect was related to the size of lung inflations but was evident

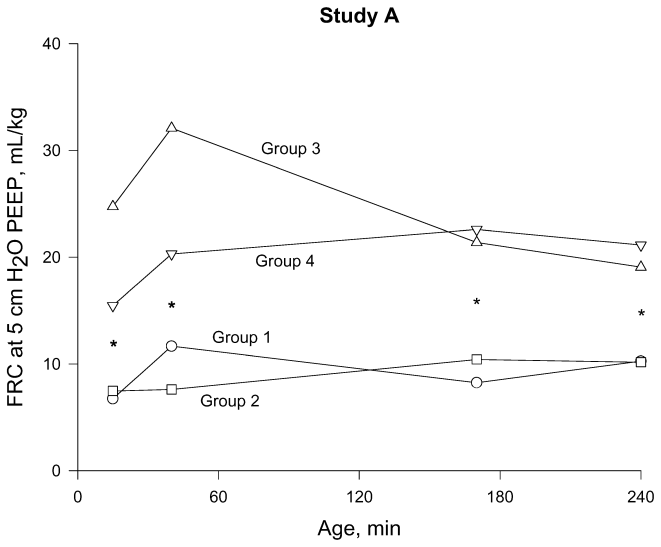

Fig. 4 Group means for functional residual capacity (*FRC*) measured during mechanical ventilation with 5 cm H_2O PEEP in the exploratory study (study A). Group *notations* and *symbols* are the same as in previous figures. There is one missing value in group 1 at 15 min, one in group 3 at 40 min, one in group 1 at 170 min, and one in group 3 at 240 min. The high mean values for FRC in group 3 were caused by one lamb that had an unusually good lung mechanical response to surfactant (see Fig. 3). In the confirmatory study (study B), FRC was not measured

also with relatively modest volumes, and occurred even if surfactant was given immediately after the large inflations [12]. The present article examines whether large inflations are harmful even when given after surfactant treatment, and in that case, for how long after surfactant instillation the lung remains sensitive to such inflations.

An exploratory study (study A) seemed to give clear-cut results. Five sustained lung inflations (each 16 ml/kg) severely blunted the lung mechanical response to surfactant no matter if surfactant was given immediately before or immediately after the large inflations. In contrast, lambs given same size lung inflations at 10 or 60 min of age had significantly higher IC, FRC and Crs_{max} at 4 h of age and were easier to ventilate. The lungs of the latter lambs also had significantly better alveolar expansion in histological sections. These findings suggested that preceding surfactant instillation would not protect against the harmful effect of large inflations at birth, but that the sensitive period was probably very short as large inflations at 10 min of age did not seem to cause any harm.

This first study included a small number of lambs from seven different litters and there was a considerable within-group variation in lung mechanics. In our experience, a large variation in lung physiology can be seen in lambs born at the same gestational age but from different litters, increasing the risk of chance findings, and emphasizing the need for twin controls. We therefore made a confirmatory study (study B) using twin lambs, where one twin was given large lung inflations immediately after prophylactic surfactant and the other twin was given same size inflations at 10 min (4 lambs) or 15 min (6 lambs) of age. There was no difference in the response to large inflations at 10 vs 15 min of age, so the results from all twin pairs were pooled.

Study B did confirm an adverse effect of giving large lung inflations immediately after surfactant, but the effect was less prominent than suggested by the findings in study A; thus, the response to surfactant in lambs given large inflations at birth was not completely blunted but still unsatisfactory both in terms of lung mechanics and ventilatory efficiency. There was no significant difference in alveolar expansion in histological sections, and signs of lung injury and inflammation were relatively minor.

In both studies, the between-group differences in lung function became more pronounced over time. It may be argued that the 4 h of ventilator treatment with possible tidal opening and closing of lung units contributed to this, especially as the lambs subjected to large inflations at birth were later ventilated with higher peak inspiratory pressures; however, these higher pressures should primarily be regarded as a sign of lung function derangement, not as its cause. The target for ventilation in terms of $PaCO_2$ was the same in all lambs. The lambs given large inflations at birth needed higher ventilator settings to reach this target, but they did not have larger tidal volumes, and were thus not subjected to a more severe volutrauma after the initial stage of the study. It is more probable that the large lung inflations at birth triggered an injury sequence that manifested itself during the following hours of mechanical ventilation. Maybe the consequences of the initial trauma could have been mitigated if a more protective mode of mechanical ventilation had been used, but that question was not addressed in the present study.

Previous animal studies have demonstrated that prophylactic administration of surfactant can protect the lung against ventilation-induced injury. Grossmann et al. [13] showed that, in preterm newborn rabbits, treatment with natural surfactant at birth prevented the ultrastructural lung injury that was seen in untreated littermate controls already after a few minutes of mechanical ventilation with a peak pressure of approximately 35 cm H_2O. This protection was effective even though surfactant-treated animals were ventilated with much larger tidal volumes (31 vs 13 ml/kg). Wada et al. [10] showed that preterm lambs (gestational age 126–127 days) given bovine surfactant (Survanta, Abbott Laboratories, North Chicago, Ill.) at birth could be ventilated (pressure-control mode, PEEP 4 cm H_2O) for 30 min with ventilator pressure around 40 cm H_2O and a target tidal volume of 20 ml/kg without developing lung injury. Our present study shows that if similar volumes are forced into the lung immediately following surfactant instillation at

birth, the effect of surfactant is blunted, though not to the same extent as when such inflations are given before surfactant [12].

Structural immaturity, surfactant deficiency and immature fluid clearance pathways probably all contribute to making the preterm lung particularly sensitive to large inflations immediately after birth. The poorly developed elastic structures of the immature lung offers little protection against overstretching. Surfactant treatment at birth promotes uniform lung expansion [13], but even though the surfactant that we used (Curosurf) is known to spread very rapidly, it still takes about 1 min for it to reach its final destination [16], which is probably a prerequisite for a full effect. The lung is fluid-filled at birth and, even if undisturbed, the process of lung liquid absorption and the establishment of an air-filled lung is not an immediate event [11, 12, 17, 18]. Forcing a large volume of gas into the lung before the corresponding volume of liquid has cleared will produce very high transpulmonary pressures (as demonstrated in the lambs subjected to large inflations at birth; Fig. 1) and probably cause a heterogenous expansion pattern with gross overdistension of some lung regions while others remain fluid-filled. This might create considerable shear forces and epithelial disruption, in turn triggering an injury sequence with fluid leak to air spaces (proteinaceous oedema), progressive loss of lung volume, invasion of granulocytes and inhibition of surfactant.

In view of the above, our finding that large inflations at birth cause lung function impairment, even if preceded by surfactant instillation, is hardly surprising. It is more remarkable that the sensitive period is so short. Already 10 min after surfactant treatment, the lungs could be inflated with equally large volumes without creating alarmingly high airway pressures (approximately 30 cm H_2O; Fig. 1) and apparently without adverse effect. This implies that during the first 10 min of post-surfactant pressure-limited ventilation, lung capacity had increased substantially, probably mainly by resorption of lung liquid.

It is often taught that, during resuscitation at birth, the lungs should be immediately expanded to increase oxygenation. This can be achieved with a self-expanding resuscitation bag, perhaps with the pressure pop-off valve inactivated so that distinct chest movements can be seen, resulting in ventilation without PEEP and often without any control of volumes inflated or pressures obtained. This non-physiological way to initiate respiration is usually well tolerated by asphyxiated full-term babies, but our results suggest that it may cause lung function impairment if applied to preterm subjects, even if surfactant has been instilled before the first inflation. Although findings in animal models cannot be directly translated to the clinical setting, an overall objective must be to do no harm, and we believe that a more gentle approach to resuscitation is feasible and probably equally effective.

It is currently debated whether the very preterm infant should be intubated and given surfactant immediately at birth or instead be allowed to establish spontaneous respiration aided by nasal continuous positive airway pressure [19]. Even if the former approach is chosen, high inspiratory pressures are usually not needed [20] and can probably be avoided by using appropriate devices [21]. Stenson [20] observed that less than 20% of preterm infants given prophylactic surfactant needed inflation pressures above 20 cm H_2O during resuscitation, and none needed pressures above 30 cm H_2O. The idea of trying to rapidly recruit lung volume after surfactant administration by using large inflations is not in line with current knowledge, and the present study suggests that it is inappropriate.

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