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Blood Gases and Pulmonary Blood Flow During Resuscitation of Very Preterm Lambs Treated With Antenatal Betamethasone and/or Curosurf: Effect of Positive End-Expiratory Pressure

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ABSTRACT: Resuscitation of very premature lambs with positive end-expiratory pressure (PEEP) improves oxygenation and reduces pulmonary blood flow (PBF). However, the effects of PEEP on blood gases and PBF have not been studied in preterm lambs receiving antenatal corticosteroids or postnatal surfactant. Lambs were delivered at 125 d of gestation (term 147 d) and ventilated with a tidal volume (V_T) of 5 mL/kg using different levels of PEEP. Four treatment groups were studied: (1) antenatal betamethasone 24 and 36 h before delivery; (2) postnatal Curosurf; (3) antenatal betamethasone and postnatal Curosurf; (4) untreated controls. Blood gases, PBF, and ventilator parameters were recorded during the first 2 h. Increasing PEEP improved oxygenation even after antenatal betamethasone and postnatal Curosurf, without adverse effects on arterial P_{CO_2}. Increasing PEEP reduced PBF; this effect was not altered by betamethasone and/or Curosurf. In very preterm lambs ventilated with fixed V_T, increasing levels of PEEP improved oxygenation after antenatal glucocorticoids and/or postnatal surfactant. These treatments do not alter the deleterious effects of high levels of PEEP on PBF. **(*Pediatr Res* 62: 37–42, 2007)**

During ventilation of very preterm infants, PEEP helps maintain end-expiration lung volumes, conserves surfactant, reduces lung injury, and improves oxygenation (1–3). Therefore, PEEP may promote lung aeration and help maintain lung volume in the resuscitation period immediately after birth. However, PEEP is not commonly recommended and rarely used during the immediate resuscitation of very premature infants (4–6), although it is now recognized that lung injury may have its origins at this time (7,8). In a recent study aimed at improving gas exchange and minimizing V_T in the postnatal resuscitation period, we found that a PEEP of 8 cm H_2O halved the alveolar to arterial difference in oxygen tension ($AaDO_2$) after 10 min of ventilation of very premature lambs without affecting arterial pressure or P_{CO_2} (9). However, these lambs were not treated with antenatal corticosteroids or postnatal surfactant treatment. It is possible that antenatal steroids and postnatal surfactant could alter the effects of PEEP.

Gas exchange after birth is facilitated by a large decrease in pulmonary vascular resistance (PVR) and an increase in PBF. When PEEP is applied to normal lungs, it can constrain the heart and reduce PBF (10). We have shown that PEEP reduces PBF during the early ventilation of very premature lambs by increasing PVR (11); when PEEP was increased from 4 to 8 cm H_2O and from 4 to 12 cm H_2O, PBF fell by approximately 20% and 41%, respectively. Despite this reduction in PBF, increasing the level of PEEP improved oxygenation without adverse effects on systemic blood pressure or heart rate. The adverse effects of high levels of PEEP on PBF and PVR shortly after birth may impair pulmonary gas exchange in very preterm infants.

Although most very premature infants receive antenatal corticosteroids and postnatal surfactant (12), lambs in our previous studies (9,11) were not treated with antenatal corticosteroids or postnatal surfactant and, therefore, had structurally and mechanically very immature lungs. As both of these treatments increase lung compliance, it is possible that they alter the relationship between PBF, oxygenation, and PEEP levels. Therefore, it is critical to further examine the relationship between PBF and airway pressure in the most immature lung and in a lung that has altered lung structure and/or tissue mechanics as a result of antenatal steroid and/or postnatal surfactant treatment. In the clinical trials that demonstrated the beneficial effects of antenatal corticosteroids and prophylactic postnatal surfactant, the majority of infants would not have received PEEP during resuscitation (13,14). Thus, there is little information about the individual or combined effects of these treatments on blood gases and PBF when infants are

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Abbreviations: $AaDO_2$, alveolar to arterial difference in P_{O_2}; **C_{RS},** compliance of the respiratory system; **Fio_2,** fraction of inspired oxygen; **MAP,** mean arterial pressure; **$Paco_2$,** partial pressure of carbon dioxide in arterial blood; **Pao_2,** partial pressure of oxygen in arterial blood; **PBF,** pulmonary blood flow; **PEEP** positive end-expiratory pressure; **PIP,** peak inspiratory pressure; **PVR,** pulmonary vascular resistance; **Sao_2,** percent oxygen saturation; **V_T,** tidal volume

resuscitated using PEEP. It is important to identify the level of PEEP that maximizes oxygenation of very preterm infants without injuring their lungs or adversely affecting the changes in pulmonary physiology that are essential for the transition to air breathing at birth. Our specific objective was to assess the effects of different levels of PEEP on blood gases and PBF in very preterm lambs treated with antenatal corticosteroids and/or postnatal surfactant. We studied lambs over a 2-h period after delivery at an age that corresponds to approximately 26 wk of human gestation. The broad goal of our studies is to obtain data that could lead to improved management of very premature infants immediately after birth using methods that would minimize pulmonary volutrauma.

METHODS

Experimental protocol. All animal procedures were approved by the Monash University Animal Ethics Committee, according to the guidelines of the National Health and Medical Research Council of Australia Code of Practice for the Care and Use of Animals for Scientific Purposes. Aseptic surgery was conducted on 23 pregnant Border-Leicester × Merino ewes at 122 ± 1 d of the 147-d gestation (11). Catheters were inserted into a fetal carotid artery and jugular vein, the amniotic sac, and left pulmonary artery; a 4-mm ultrasonic flow probe (Transonic Systems, Ithaca, NY) was placed around the left pulmonary artery. Before delivery, fetal arterial blood Po_2 (Pao_2), Pco_2 ($Paco_2$), pH, and percentage of oxygen saturation (Sao_2) were monitored (ABL30, Radiometer, Denmark). Surgery was performed prenatally rather than following the cesarean delivery to avoid extensive thoracic surgery after birth, which would have the potential to influence the respiratory and cardiovascular measurements made immediately at and after the onset of ventilation.

At 124 ± 1 d of pregnancy, ewes were randomly assigned to one of four treatment groups: 1) maternal i.m. injection of betamethasone (11.4 mg, Celestone Chronodose; Schering-Plough, Australia) 36 and 24 h before the planned cesarean delivery, $n = 5$; 2) postnatal Curosurf 2 mL/kg (160 mg/kg, Chiesi Pharmaceuticals, Parma, Italy) *via* the endotracheal tube 5 min after delivery, $n = 6$; 3) antenatal betamethasone and postnatal Curosurf (doses as above), $n = 6$; 4) untreated controls, $n = 6$.

Six hours before the planned cesarean delivery, control recordings were made of fetal systemic and pulmonary arterial pressures, left pulmonary artery blood flow, and heart rate. At 126 ± 1 d of gestation, ewes and fetuses were anesthetized and the fetal head and neck exposed *via* cesarean section. The trachea was intubated with a 3.5-mm cuffed tube and lung liquid was drained passively before the umbilical cord was clamped and cut. The lambs were then delivered, dried, weighed, placed under a radiant heater, and ventilated with a Babylog 8000+ ventilator (Dräger, Lübeck, Germany) using volume guarantee mode with a set expired V_T of 5 mL/kg, at 60 inflations/min, a variable fraction of inspired oxygen (Fio_2) and a PEEP of 4 cm H_2O. The expiratory time and Fio_2 were altered to maintain arterial pH between 7.30 and 7.45, $Paco_2$ between 35 and 60 mm Hg, and Sao_2 between 90% and 95%.

After delivery lambs received 5% dextrose (i.v.) and were sedated (pentobarbitone, i.v.) to prevent spontaneous breathing. All lambs were ventilated for 120 min, divided into 20-min epochs each with a different level of PEEP. Lambs in the Curosurf group received it 5 min after ventilation started. For the betamethasone- and/or Curosurf-treated lambs, PEEP started at 4 cm H_2O and was changed to 0, 8, or 10 cm H_2O in a random order, returning to 4 cm H_2O between the other PEEP levels. In the control group, a maximum PEEP of 12 cm H_2O was initially used, but due to the development of pneumothoraces in these lambs, we decided to ventilate all further lambs at a maximum of 10 cm H_2O PEEP. Control animals did not receive 10 cm H_2O PEEP.

Systemic and pulmonary arterial pressures, left PBF, peak inspiratory pressure (PIP), PEEP, breathing frequency, V_T, and heart rate were continuously recorded using a data acquisition system (Powerlab/8SP, ADI, Castle Hill, Australia). Rectal temperature was maintained at 39°C. After the 2-h ventilation period, lambs were killed by an overdose of sodium pentobarbitone (130 mg/kg i.v.). The lungs were inspected for pneumothoraces before they were excised and weighed.

PBF and PVR analysis. Six-minute recordings were analyzed at the 4 cm H_2O baseline PEEP level and then after the PEEP was changed to 0, 8, or 10 cm H_2O; there was 5 min of stabilization before making recordings at each level of PEEP. PVR was calculated using the formula PVR = Ppa − Pla/Qp, where Ppa is pulmonary arterial pressure, Pla is left atrial pressure, and Qp is flow through the left pulmonary artery; Pla was assumed to be 9 mm Hg based on previous studies (11,15).

Physiological and ventilator parameters. Arterial blood gas tensions were measured every 5 min for the first 20 min and then every 10 min. The oxygenation status was calculated as the $AaDO_2$. Respiratory system compliance (C_{RS}) and minute ventilation were recorded from the ventilator every 10 min. After delivery, the arterial blood gas status of lambs was maintained within the physiological range by altering the ventilator parameters and inspired oxygen content (Fio_2).

Data analysis. Statistical analyses were performed using SigmaStat (SPSS, Chicago, IL). A two-way analysis of variance (ANOVA) for repeated measures was used to determine the effect of treatment (betamethasone, Curosurf, betamethasone + Curosurf, or Control) and PEEP level on PBF, oxygenation, and all other physiological and ventilator parameters. As appropriate, one-way repeated-measures ANOVA and least significant difference (LSD) for *post hoc* pairwise comparisons were used to confirm the effects of different PEEP levels identified by the two-way repeated-measures ANOVA. Data are presented as mean ± SEM. Statistical significance was accepted at $p < 0.05$.

RESULTS

Fetal physiological status. There were no significant differences between fetal arterial pH, Pco_2, Po_2, or Sao_2 for all groups before anesthesia. All ewes were healthy during the prenatal period with no signs of labor.

Neonatal oxygenation. $AaDO_2$ improved in all groups when ventilated with 4, 8, or 10 cm H_2O PEEP compared with 0 cm H_2O PEEP (Fig. 1*A*). Fio_2 was changed to maintain the Pao_2 and Sao_2 within the target range and was reduced as the level of PEEP increased for all groups (Table 1). The Pao_2 values need to be considered in the knowledge that the Fio_2 was changing (Table 1).

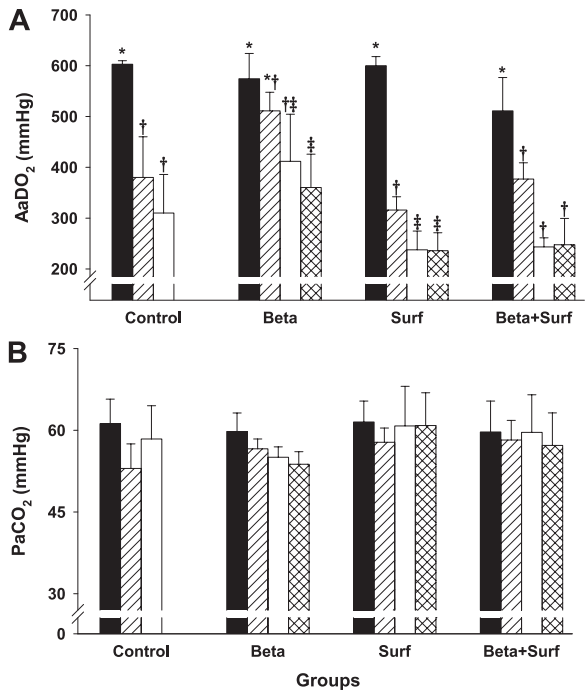

Figure 1. Effects of different levels of PEEP on $AaDO_2$ (*A*) and $Paco_2$ (*B*) in very premature lambs from four treatment groups: control, antenatal betamethasone (Beta), postnatal Curosurf (Surf), antenatal betamethasone + postnatal Curosurf (Beta+Surf). 0 cm H_2O PEEP (■), 4 cm H_2O PEEP (▨); 8 cm H_2O PEEP (□); 10 cm H_2O PEEP (▩). Control lambs ventilated at 12 cm H_2O PEEP had a number of pneumothoraces and thus are not included. In each group, values that do not share a common symbol are significantly different from one another.

Neonatal arterial Pco_2 and pH. There were no significant differences in $Paco_2$ between any of the groups and at each level of PEEP (Fig. 1*B*). Throughout the study, most $Paco_2$ values were at, or just above, the upper end of the target range. Arterial pH values were not significantly different between any of the groups or at any level of PEEP (Table 1). There were no significant differences in minute ventilation between the groups or at any level of PEEP.

Pulmonary artery blood flow, vasculature resistance, and pressure. There were no significant differences in left PBF between the four treatment groups. However, within three of the groups, PBF was significantly affected by the level of PEEP (Fig. 2). PVR increased in all groups with increased PEEP (Table 2). In both the control and betamethasone + Curosurf groups, the pulmonary artery pressure (PAP) was significantly higher ($p = 0.03$) than in the Curosurf group (Table 2); however, at each level of PEEP, there was no difference between groups.

Systemic arterial blood pressure. Mean arterial pressure (MAP) was within the normal range for all groups (Table 2). It was significantly higher in lambs treated with betamethasone and/or Curosurf compared with controls ($p = 0.006$). MAP was slightly but significantly lower in the control group at 8 cm H_2O PEEP ($p < 0.001$) compared with 0 cm H_2O PEEP. Similarly, MAP was lower in the betamethasone + Curosurf group at 10 cm H_2O PEEP compared with 0 cm H_2O PEEP.

Ventilator pressure. The ventilator was set to deliver an expired V_T of 5 mL/kg, and so the PIP was automatically altered for each level of PEEP. In all groups, the mean airway pressure increased significantly ($p < 0.001$) at each level of PEEP (Table 1). The ventilating pressure (PIP − PEEP) was significantly lower ($p = 0.003$) in the betamethasone + Curosurf group compared with the control and Curosurf groups (Table 1).

Respiratory system compliance. C_{RS}/kg was low in all groups and at all levels of PEEP. There was a significant increase in C_{RS}/kg ($p = 0.038$) in the betamethasone + Curosurf group at a PEEP of 4 cm H_2O compared with control and betamethasone groups; no other differences between groups or at any other PEEP level were found.

DISCUSSION

This study has confirmed previous studies (9,11) that showed that the use of PEEP significantly and rapidly improves oxygenation in very premature lambs immediately after birth when V_T is kept constant. The new information that we report is that PEEP still has this effect after the lambs were treated with antenatal corticosteroids and postnatal Curosurf. Our study shows that the effect of 8 cm H_2O of PEEP on oxygenation immediately after birth is larger than the effect of antenatal steroid treatment or postnatal surfactant. This improvement in oxygenation was not at the expense of increased $Paco_2$ or a decrease in blood pressure, both of which were largely unaffected by PEEP. Surprisingly, the effect of PEEP on PBF was essentially unaffected by antenatal steroid treatment or postnatal surfactant.

The dose of betamethasone was chosen to mimic the regimen of antenatal corticosteroids given to women at risk of preterm delivery and was the same dose used to demonstrate fetal sheep lung maturation (16). In preterm animals, antenatal corticosteroids stimulate pulmonary structural maturation, increase the production and secretion of surfactant, and enhance the clearance of lung liquid (17). Previous studies have reported an attenuation of pulmonary interstitial tissue after administration of synthetic corticosteroids (18,19). Therefore, the dose of betamethasone administered in this study would have been sufficient to alter lung structure. We do not have a good explanation for why there was so little effect of antenatal corticosteroids on the functional parameters that we measured. It is possible that these lambs were more immature than those in previous studies or that the treatment interval of 24–36 h before delivery was insufficient to induce the necessary maturational changes. However, a previous study has shown that 15 h is sufficient time to enhance fetal sheep lung maturation (20).

In studies of ventilated very premature infants treated with Curosurf, oxygenation increases within minutes of the treatment (21). Infants in those studies would have all received PEEP as part of the ventilation regimen. In our lambs, oxygenation was inadequate without PEEP even when they had been treated with betamethasone and/or Curosurf. With the application of PEEP, oxygenation was best when it was used in combination with betamethasone + Curosurf or Curosurf alone. Oxygenation levels were similar in these two groups of lambs at 4 and 8 cm H_2O PEEP, whereas in lambs treated with betamethasone alone oxygenation was suboptimal at these levels of PEEP. Consistent with these findings, our previous studies have shown that increasing PEEP significantly improves oxygenation (9,11). Thus, the application of PEEP appears to be more effective than the use of postnatal surfactant in improving oxygenation.

As in our previous studies with fetal and neonatal sheep, increasing the level of PEEP reduced PBF (11). There were some differences between the groups, but the most obvious effect was due to the level of PEEP. Observations of the effect of PEEP on PBF have been made in the lungs of mature animals (22–24), with fluctuating airway pressure having a greater effect than static airway pressure (23), indicating the complexity of the relationship. The exact mechanism for this decrease in PBF with increasing PEEP is unknown, although we postulate that it may result from an increase in the alveolar-capillary transmural pressure causing capillary compression. This suggestion is consistent with the finding that zero PEEP, in fetuses administered Curosurf (with or without betamethasone), increased PBF; an increase in PBF could not be detected in control fetuses. Thus, in the immature noncompliant lung, we hypothesized that increased airway pressure caused by increased PEEP would have less effect on capillary compression than in a mature lung and that increase lung compliance with betamethasone and/or Curosurf would increase the sensitivity of PBF to changes in airway pressure. If this was correct, the effect of increasing PEEP on PBF should be greatest in the most compliant lungs. However, the effect of increasing PEEP on PBF was greatest in control lambs, which

Table 1. *Effect of PEEP on blood gas and ventilation parameters*

	Control			Betamethasone				Curosurf				Betamethasone + Curosurf			
PEEP ($cm H_2O$)	0	4	8	0	4	8	10	0	4	8	10	0	4	8	10
Sao_2 (%)	77.7 ± 4.3[a]	92.9 ± 3.1[b]	94.6 ± 0.8[b]	65.4 ± 10.4[a]	87.7 ± 1.8[b]	94.9 ± 4.8[b]	101 ± 0.7[b]	73.2 ± 7.3[a]	98.2 ± 1.6[b]	96.0 ± 3.5[b]	98.4 ± 2.1[b]	87.8 ± 3.4[a]	100 ± 0.4[b]	97.6 ± 2.6[b]	97.0 ± 2.0[b]
Fio_2	0.98 ± 0.1[a]	0.71 ± 0.1[b]	0.62 ± 0.1[b]	0.93 ± 0.1[a]	0.86 ± 0.1[ab]	0.73 ± 0.1[bc]	0.67 ± 0.1[c]	0.98 ± 0.02[a]	0.62 ± 0.1[b]	0.47 ± 0.1[bc]	0.48 ± 0.1[c]	0.86 ± 0.1[a]	0.71 ± 0.1[b]	0.50 ± 0.03[c]	0.52 ± 0.1[c]
Pao_2 (mm Hg)	32.2 ± 4.2	61.7 ± 9.5	63.6 ± 8.3	26.5 ± 3.5[a]	37.7 ± 3.2[ab]	48.8 ± 7.7[bc]	58.3 ± 1.9[c]	28.6 ± 2.9[a]	65.8 ± 6.8[b]	58.7 ± 10.2[b]	65.5 ± 12.2[b]	36.5 ± 2.9	63.6 ± 5.2	52.1 ± 3.3	61.5 ± 12.8
pH	7.20 ± 0.03	7.25 ± 0.03	7.22 ± 0.04	7.25 ± 0.03	7.26 ± 0.01	7.27 ± 0.01	7.29 ± 0.02	7.19 ± 0.02	7.20 ± 0.02	7.21 ± 0.04	7.21 ± 0.04	7.25 ± 0.05	7.26 ± 0.03	7.28 ± 0.05	7.26 ± 0.05
ΔP ($cm H_2O$)	25.2 ± 2.4†	29.9 ± 2.3†	27.5 ± 3.6†	21.8 ± 2.3	22.3 ± 1.4	22.7 ± 2.1	22.8 ± 1.4	26.1 ± 1.6†	25.5 ± 1.5†	25.6 ± 3.1†	26.9 ± 2.7†	19.3 ± 1.8	17.2 ± 1.4	15.6 ± 1.0	17.7 ± 1.3
P_{aw} ($cm H_2O$)	7.4 ± 1.1[a]	12.2 ± 0.8[b]	16.2 ± 1.8[c]	8.6 ± 1.3[a]	12.1 ± 0.9[b]	16.5 ± 1.2[c]	18.1 ± 0.6[d]	7.7 ± 0.4[a]	11.1 ± 0.6[b]	14.9 ± 0.8[c]	17.5 ± 0.7[d]	6.9 ± 0.7[a]	10.1 ± 0.4[b]	13.7 ± 0.2[c]	16.3 ± 0.4[d]
C_{RS}/kg	0.20 ± 0.01	0.20 ± 0.0*	0.23 ± 0.03	0.24 ± 0.04	0.24 ± 0.02*	0.22 ± 0.03	0.22 ± 0.03	0.21 ± 0.01	0.25 ± 0.02	0.24 ± 0.03	0.22 ± 0.02	0.30 ± 0.03	0.38 ± 0.04	0.36 ± 0.03	0.37 ± 0.02
MV/kg	276 ± 23	281 ± 30	371 ± 51	429 ± 34	391 ± 23	416 ± 30	398 ± 26	383 ± 17	389 ± 18	410 ± 23	410 ± 25	400 ± 19	412 ± 13	430 ± 19	424 ± 11

In each group, values that do not share a common letter are significantly different from one another. MV, minute ventilation; P_{aw}, airway pressure.

* Compliance values at 4 cm H_2O PEEP in control and betamethasone alone groups were significantly lower compared with combined betamethasone and Curosurf group at 4 cm H_2O PEEP ($p = 0.038$).

† ΔP (change in pressure = PIP − PEEP) values were significantly higher in control and Curosurf only groups compared with betamethasone + Curosurf group ($p = 0.003$).

Table 2. *Effect of PEEP on physiological parameters*

	Control			Betamethasone				Curosurf				Betamethasone + Curosurf			
PEEP ($cm H_2O$)	0	4	8	0	4	8	10	0	4	8	10	0	4	8	10
PVR mm Hg $(mL/min)^{-1}$	0.14 ± 0.03	0.13 ± 0.02	0.18 ± 0.03	0.25 ± 0.05	0.23 ± 0.05	0.32 ± 0.08	0.29 ± 0.08	0.16 ± 0.03[a]	0.18 ± 0.02[ab]	0.23 ± 0.03[b]	0.28 ± 0.06[c]	0.17 ± 0.03	0.17 ± 0.06	0.28 ± 0.07	0.23 ± 0.05
Heart rate/min	167 ± 10	159 ± 16	187 ± 9	177 ± 16	178 ± 10	160 ± 8	166 ± 13	180 ± 7	165 ± 7	168 ± 11	160 ± 9	171 ± 6	158 ± 5	160 ± 11	149 ± 9
MAP (mm Hg)	35.5 ± 3.6[a]†	35.4 ± 3.1[a]†	31.3 ± 3.4[b]†	52.9 ± 4.4	51.6 ± 2.0	52.2 ± 2.6	48.8 ± 2.8	44.6 ± 4.2	42.8 ± 3.8	41.3 ± 3.2	43.0 ± 2.9	47.6 ± 3.6[a]	41.6 ± 2.6[ab]	41.5 ± 3.9[ab]	37.3 ± 5.0[b]
PAP (mm Hg)	29.2 ± 4.7*	34.8 ± 4.1*	31.5 ± 4.3*	41.3 ± 5.3	40.4 ± 2.7	39.7 ± 4.5	36.1 ± 4.4	41.1 ± 2.1	41.2 ± 2.9	40.6 ± 2.4	43.7 ± 3.2	33.4 ± 3.5*	30.3 ± 1.4*	29.1 ± 2.0*	25.9 ± 1.8*

In each group, values that do not share a common letter are significantly different from one another.

* PAP (mean left PAP) values in the control and combined betamethasone and Curosurf groups were significantly lower compared with values in the Curosurf alone group ($p = 0.03$).

† MAP values in the control group were significantly lower compared with all other groups ($p = 0.006$).

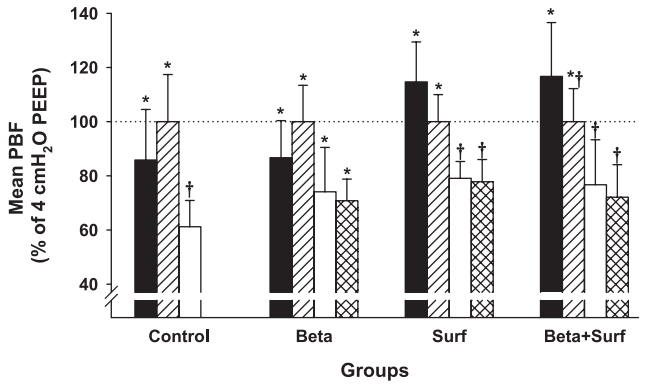

Figure 2. Effects of different levels of PEEP on mean PBF in very premature lambs from four treatment groups: control, antenatal betamethasone (Beta), postnatal Curosurf (Surf), antenatal betamethasone + postnatal Curosurf (Beta+Surf). All PBF values are expressed as the percentage of values measured at a PEEP of 4 cm H_2O immediately before the change in PEEP to 0, 8, or 10 cm H_2O. 0 cm H_2O PEEP (■); 4 cm H_2O PEEP (▨); 8 cm H_2O PEEP (□); 10 cm H_2O PEEP (▩). Coding of bars and use of symbols as in Figure 1. Data from control lambs with pneumothoraces (12 cm H_2O PEEP) are not included.

had the most immature lungs, indicating that the relationship is complex and likely to depend on many factors. For instance, it is possible that the effect of PEEP on PBF is enhanced by the transient increase in interstitial tissue water content associated with airway liquid clearance (25). Delays in the clearance of liquid from the lungs in control fetuses due to lung immaturity may explain this phenomenon and may also explain why all control lambs developed a pneumothorax at high PEEP levels (12 cm H_2O); this was unexpected because the control lungs were relatively noncompliant. Pneumothoraces in control lambs possibly resulted from localized regions of overexpansion caused by reductions in lung gas volume associated with airway liquid retention.

One of the most remarkable changes in lung physiology that occurs within a few breaths after birth is the very large increase in PBF (approximately eightfold) resulting from a rapid and large decrease in PVR (26). The mechanisms responsible for the decrease in PVR immediately after birth are likely to include an increase in oxygenation (27), the release of nitric oxide from the pulmonary vascular bed (28), and an unspecified "effect of ventilation" (15,27). It has been reported that antenatal corticosteroids enhance pulmonary vasodilatation induced by alveolar ventilation at birth in near-term sheep (29). In the present study, increasing the level of PEEP markedly improved oxygenation at the same time as reducing PBF. This was surprising, as increased oxygenation would be expected to promote vasodilatation of the pulmonary vascular bed. It is possible that increasing PEEP led to a gradual decrease in the number of atelectatic regions and therefore improved oxygenation. At the same time, blood flow through these recruited regions could have been reduced due to the compression of capillaries.

Arterial pH remained at the lower end of our target range and $Paco_2$ levels were a little high at all levels of PEEP, which is consistent with our previous findings (9,11), and may have been due to the target V_T chosen for ventilation. It is not surprising that betamethasone and/or Curosurf treatment did not have much effect on arterial pH or $Paco_2$ levels with this ventilator regimen in which V_T was controlled. Arterial pH tended to be higher after betamethasone and betamethasone + Curosurf treatment and in the presence of PEEP. The mild respiratory acidosis may have been eliminated if we had ventilated with a slightly greater V_T. We chose a V_T of 5 mL/kg to prevent lung injury at the higher PEEP levels to maintain consistency between ventilation periods at different PEEP levels and to be consistent with previous studies (9,11). This set V_T is within the range of V_T found in spontaneously breathing premature infants (30) and has been shown to successfully ventilate very premature lambs from birth (9). The ventilator pressures required to appropriately ventilate these lambs varied depending on the treatment group, with lambs in the control and Curosurf alone groups requiring greater pressures. It is unlikely that these pressures were sufficient to induce lung injury as a similar study in our laboratory was unable to detect any evidence of increased expression of proinflammatory mediators (unpublished observation), although others have reported such findings (31).

Although our overall aim was to obtain data that could be used to improve the delivery room management of very premature infants, we used lambs, as it would not be possible to undertake this study in infants. Extrapolation of our lamb data to infants must be made with caution. We believe that although the details may not be the same in infants, the concept that PEEP improves oxygenation immediately after birth regardless of antenatal steroid or postnatal Curosurf treatment is important. This study was purposely designed to investigate the effect of PEEP on very immature animals during the immediate resuscitation period. It may be inappropriate to extrapolate the results to later gestations and other times and clinical circumstances.

In these studies the lambs were anesthetized, delivered by cesarean section without labor, and not spontaneously breathing. This may have influenced the results for several reasons, particularly as it is likely that more lung liquid was present, thereby reducing lung compliance and aeration. Gasping immediately after delivery is an important mechanism for lung aeration, and in the absence of gasping, lung aeration may have been reduced compared with human infants born vaginally or by cesarean section under spinal anesthesia. As the lambs had undergone fetal surgery a few days before delivery, it is possible that this may have caused precocious maturation of the lung and contributed to the apparently reduced effect of antenatal corticosteroids. However, all groups of lambs were exposed to the same surgical intervention, allowing the treatment effects to be directly compared.

Although many clinical and physiological effects of PEEP during resuscitation of the preterm infant have yet to be determined, the present study provides further information on the effects of PEEP, with and without antenatal corticosteroids and/or postnatal surfactant, on neonatal oxygenation and PBF in the immediate newborn period. We conclude that oxygenation of the ventilated, immediately born preterm neonate is improved with increasing PEEP levels (>8 cm H_2O) after treatment with antenatal corticosteroids and/or postnatal surfactant; however, the level of PEEP that was best for oxygen-

ation markedly reduced PBF. These treatments did not affect the significant deleterious effects of high levels of PEEP on PBF.

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