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EFFECTS OF PROSTAGLANDIN E_2 ON THE NEWBORN RESPIRATORY SYSTEM

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To test the hypothesis that prostaglandin (PG) E_2 is a respiratory depressant in the newborn lamb, 12 chronically catheterized, unanesthetized lambs (age 2 to 6 days) were infused with progressively increasing doses of PGE_2 (0.1, 0.5, 1.0 and 5.0 ug/kg/min: 30 min for each dose) into the ascending aorta. PGE_2 caused significant, progressive decrease in ventilation (due to decreased tidal volume and breathing rate) heart rate, blood pressure and percent of the time spent in low voltage electrocortical activity (LVA). PGE_2 also caused respiratory acidosis, hypoxemia and increased frequency and duration of apneic events (> 3 sec). During the infusion, there was a dose related increase in plasma concentration of PGE_2. At 30 min post-infusion, all measured variables showed recovery, although arterial pH carbon dioxide tension and plasma PGE_2 remained significantly different from control values and the percent time in LVA was even higher than during control. Infusion of the vehicle alone (n = 5) caused no significant changes in any of the measured variables. The results, taken in combination with previous fetal studies, indicate that PGE_2 has marked inhibitory effects on breathing movements both before and after birth.

INTRODUCTION

The physiological factors responsible for the control of the fetal breathing movements (FMB) and the onset of continuous breathing and ventilation at birth have not been completely defined, although it is likely that several factors are involved in this process /11,25,32/. In sheep, FBM are intermittent, normally occur only during low voltage

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electrocortical activity (LVA), and are absent during high voltage electrocortical activity (HVA) /8/. Experiments in fetal sheep indicate that prostaglandins (PG), especially PGE_2, may be important in the control of FBM. Infusions of PGE_2 temporarily inhibit FMB: after end of the infusion, there is rapid return of normal FBM /14/. Conversely, infusion of prostaglandin synthetase inhibitors (either meclofenamate or indomethacin) causes a marked decrease in plasma concentration of PGE_2, /19,31,32/ and an associated increase in the incidence and amplitude of FBM /12,13,15,19,32/, so that they occur almost continuously, even during HVA. There is recent evidence that endogenous PGE_2 participates in the regulation of FBM, acting primarily by decreasing the incidence of FBM during HVA /31/. Furthermore, the incidence of FMB correlates inversely with the plasma concentration of PGE_2 both during infusions of different doses of PGE_2 /31/ and during preterm labor induced by administration of ACTH /23/. During spontaneous labor, PGE_2 concentration increases /5/ and the incidence of FBM decreases /1/. At birth when breathing becomes continuous and ventilation is established, the concentration of PGE_2 decreases rapidly to very low level /5,7/.

There is evidence that E-type prostaglandins can affect the control of breathing and ventilation after birth. Apnea has been reported to occur with the infusion of PGE_1 and PGE_2 both in newborn swine /30/ and in human infants with cyanotic heart disease /21/. In addition, PGE_1 decreases the output of the phrenic nerve in newborn swine that have been anaesthetized, paralyzed and maintained with assisted ventilation /16/. However there have been no previous systematic studies of the effects of PGE_2 on ventilation in spontaneously breathing, unanaesthetized newborns.

The present study was designed to determine the effects of PGE_2 infusion on the control of breathing in newborn lambs, more specifically, to test the hypothesis that PGE_2 is a respiratory depressant in newborn lambs.

METHODS

We studied a total of 12 unanaesthetized chronically instrumented newborn lambs.

To be able to perform the experiments as soon as possible after birth, we operated on 7 fetuses (gestational age 140 to 143 days, term 140 ± 5 days) using sterile technique with the ewe and fetus under general anaesthesia /31,32/. Polyvinyl catheters (1.5 mm ID, 75 cm long) were inserted into a carotid artery and an axillary artery, the tip of the carotid catheter was placed in the ascending aorta just above the aortic valve. The catheter tip was localized by pressure measurements, it was advanced into the left ventricle and then withdrawn into the aorta. A balloon-tipped catheter for measurement of intrathoracic pressure was inserted into the pleural space through an incision in the fifth or sixth intercostal space in the midaxillary line. To record the electrocorticogram (ECoG), stainless steel screw electrodes attached to a shielded cable (Cooner Wire Company, California) were inserted through each parietal bone to rest on the dura. The electrodes were insulated from the fetal scalp with dental acrylic compound and grounded to the scalp of the fetus. The vascular catheters were filled with a solution of heparin (1.000 USP units/ml), the catheters and the electrodes were put into a pocket under the fetal skin and exteriorized after birth.

We defined an apneic event as a pause in breathing for 3 or more seconds and we divided the apneic events in three categories: 3 to 6 seconds, 7 to 10 seconds and longer than 10 seconds. We measured heart rate and blood pressure through the axillary arterial catheter connected to a P23DB (Statham) transducer. We recorded ECoG from the subdural electrodes with a preamplifier and we defined LVA as an amplitude less than 40 μv /26/. The recording was analyzed to determine the percent of the time spent in LVA and in HVA. We recorded continuously the cardiorespiratory variables and ECoG on a Devices MX6 polygraph (Devices Instruments Ltd. U.K.). Zero reference point for all pressures was atmospheric pressure at the midchest level of the lamb.

An axillary arterial blood sample (1 ml) was taken every 15 minutes to measure pH, carbon dioxide tension ($PaCO_2$), oxygen tension (PaO_2) and oxygen saturation in a blood gas analyzer (Corning 165 pH/Blood Gas Analyzer, U.K.). The samples were placed on ice immediately and were analyzed within 15 min after collection, values were corrected to 39°C. To measure plasma PGE_2 concentration, another axillary blood sample (5 ml) was taken every 15 minutes and collected in a cold, heparinized syringe, transferred to a cold test tube containing indomethacin (2 μg/ml), and centrifuged at 5°C. Plasma was collected and frozen at -25°C, plasma PGE_2 was later extracted with cyclohexane and ethyl acetate, purified over silicic acid columns, and assayed with specific antibody directed toward PGE_2 /7/. To account for possible losses during extraction /9/, all samples had an internal standard of ^3H-PGE_2. To replace blood withdrawn for measurements of pH, $PaCO_2$, PaO_2 and PGE_2 concentration, the lamb was transfused with 12 ml of maternal blood at the end of each 30 min period.

Infusion: each study lasted 3 hours, the studies were performed between 09.00 to 16.00 h. After a control period of 30 min, all 12 lambs were infused independently of the electrocortical state, with continuous and increasing doses of PGE_2 (Upjohn) through the carotid arterial catheter with the tip above the aortic valve. The doses given were 0.1, 0.5, 1.0 and 5.0 µg/kg/min, each dose was given for 30 min. The amount of PGE_2 needed for each study was dissolved in 100 ml of sodium chloride (9 g/l, pH = 6.84). Variables were also measured during a 30 min post-infusion period. As a control, 5 of these lambs were also infused, on a different day, with sodium chloride (9 g/l) for a similar 3 hour period. These experiments were done at room temperature (approx. 23°C). Plasma PGE_2 concentration was measured in 7 of the 12 lambs infused with PGE_2 and in 4 of the 5 lambs infused with saline.

Data analysis: for statistical analysis of each cardiorespiratory variable, we used the average of the last 3 minutes of each 30 min period for each animal. The reported values of pH and arterial blood gas tensions are the last samples taken during each 30 min period. The time spent in LVA and HVA expressed as percent of time for each of each 30 min period. Apneic events observed in each 30 min period were expressed as apneic events/hour. The plasma concentration of PGE_2 represented an average of the values obtained at 15 and 30 min of each period. Data from post-infusion period were compared to control data using Student's t-test for paired data.

Linear regression analysis was used to determine the relationship of the dose of PGE_2 infused (independent variable) with breathing rate, tidal volume, minute ventilation, arterial pH and blood gas tensions, heart rate, arterial blood pressure, percent of the time spent in LVA and plasma concentration of PGE_2 (dependent variables). For these analyses, the independent variable was transformed as the cube root of the dose, and control period was considered a dose "0". Chi square analysis was used to compare the association between incidence and duration of apnea with the dose of PGE_2 infused and the incidence of apnea during HVA and LVA. Linear regression analysis was also done between the plasma concentration of PGE_2 and the measured variables, where the observations were plotted independently of the period or dose infused. For the lambs infused with the vehicle alone, similar analyses were done using data from the corresponding 30 min periods of the experiments. Statistical analyses were done using the statistical programs "SYSTAT" with an IBM-PC computer and "STATVIEW 512+". with a MACINTOSH computer. The data are expressed as mean $\pm$ SE. A p value < 0.05 was considered significant.

RESULTS

In all 12 lambs, the infusions of PGE_2 had marked effects on the respiratory and the cardiovascular systems (Table I), the maximal effect of each dose occurred between 15 and 30 min after the start of the dose. Ventilation decreased progressively and significantly due to decreases in both the rate of breathing and tidal volume, this resulted in progressive respiratory acidosis and hypoxemia. Blood pressure and heart rate declined progressively throughout the infusions.

ECoG was recorded in 7 lambs. LVA decreased significantly during the infusion periods. The plasma concentration of PGE_2 was measured in 7 of the 12 lambs. During the control period, the concentration of PGE_2 was very low, and 4 of the measurements were below the assay range. In all 7 there was a significant, progressive increase in plasma PGE_2 concentration during the infusion.

By 30 min after the end of the infusion there was recovery of all the measured variables. The post-infusion values for ventilation, breathing rate, tidal volume, PaO_2, oxygen saturation and heart rate were similar to the levels observed during control period. The post-infusion values for pH, $PaCO_2$ and plasma PGE_2 concentration remained significantly different from the control values. The post-infusion value for time spent in LVA was significantly higher than during control.

Infusion of the vehicle caused no significant changes in the measured variables (Table II). In this group, the plasma concentration of PGE_2 was measured in 4 of the 5 lambs. No significant change was observed, 6 of the 24 measurements were below the assay range.

Infusion of progressively increasing doses of PGE_2 also caused a progressive increase in frequency and duration of apneic events (Table III). The most frequent type of apneic events was the shortest (3 to 6 sec), during most of the apneic events, associated hypotension and bradycardia occurred. During the infusion of PGE_2, the apneic events were observed during both LVA and HVA but they were twice as frequent during the time spent in LVA (Table IV). The presence of trembling and diarrhea was also noted during the infusions.

TABLE I

Effects of prostaglandin E_2 infusion on cardiorespiratory variables, incidence of low voltage electrocortical activity and plasma concentration of prostaglandin E_2 in 12 newborn lambs

	Dose of PGE_2 (μg/kg/min)						
	Control	0.1	0.5	1.0	5.0	Post-infusion	rx
Ventilation (ml/kg/min)	506±42	385±26	337±31	292±31	240±22	470±37	-0.64^{++}
Breathing rate (breath/min)	59±6	55±5	49±4	48±4	43±4	55±6	-0.31^{+}
Tidal volume (ml/kg)	9.0±0.6	7.3±0.5	6.8±0.4	6.2±0.4	5.7±0.5	8.7±0.5	-0.55^{++}
pH	7.41±0.01	7.37±0.02	7.35±0.02	7.32±0.02	7.27±0.02	7.35±0.02	-0.66^{++}
$PaCO_2$ (Torr)	47±2	53±3	54±3	60±3	66±4	53±2 q	$+0.54^{++}$
PaO_2 (Torr)	70±3	65±4	58±3	58±3	55±4	68±2	-0.40^{++}
O_2 Saturation (%)	94±1	90±3	86±3	85±3	79±3	92±1	-0.53^{++}
Heart rate (beat/min)	231±9	239±7	215±8	204±9	179±8	236±8	-0.56^{++}

Table I. cont.

Blood pressure							
(torr)	74±4	65±4	61±3	60±4	55±4	70±4 q	-0.44++
LV ECoG							
(% of the time) A	51±8	47±10	39±14	19±5	15±5	78±3 q	-0.54++
Plasma PGE_2							
(PG/ml) B	1.4±0.9	45.0±10.5	71.9±18.1	59.7±14.9	91.5±24.6	14.3±6.7 q	+0.57++

Values are means ± SE LV ECoG, low voltage electrocortical activity. PGE_2, prostaglandin E_2 post-infusion period includes values at 30 min after the end of infusion. A, N = 6 lambs; B, N = 7 lambs. rx, regression value; regression includes control period as dose "0" and it does not include post-infusion period.

\+ $p < 0.05$
++ $p < 0.005$ q $p < 0.05$ for control vs. post-infusion by student's t-test for paired data

TABLE II

Effects of sodium chloride (9 g/l) infusion on cardiorespiratory variables, incidence of low voltage electrocortical activity and plasma concentration of prostaglandin E_2 in 5 newborn lambs

	Duration of infusion (hours)						
	Control	0:30	1:00	1:30	2:00	Post-infusion	rx
Ventilation (ml/kg/min)	467±52	505±152	478±147	483±149	524±165	470±62	0.11
Breathing rate (breath/min)	53±13	52±12	51±13	52±13	56±15	52±5	0.09
Tidal volume (ml/kg)	9.0±0.7	9.7±1.6	9.4±1.7	9.3±1.4	9.4±2.0	9.1±0.8	0.06
pH	7.41±0.02	7.42±0.02	7.41±0.03	7.41±0.03	7.39±0.03	7.40±0.02	-0.27
$PaCO_2$ (torr)	46±5	45±4	46±4	46±6	47±6	47±2	0.08
PaO_2 (torr)	80±4	78±3	80±3	80±5	81±5	79±2	0.09
O_2 Saturation (%)	92±2	91±2	90±4	91±4	90±5	91±1	-0.16
Heart rate (beat/min)	230±9	234±12	239±27	228±26	238±21	224±10	0.10

Table II. cont.

Blood pressure (torr)	72±9	72±10	72±8	73±9	72±9	70±4	0.01
LV ECoG (% of the time) A	40±8	50±10	37±7	52±11	57±9	42±4	0.35
Plasma PGE_2 (pG/ml) B	1.8±0.6	2.2±0.6	1.5±0.4	1.3±0.3	5.9±0.7	3.9±0.7	0.30

Value are means ± SE. LV ECoG, low voltage electrocortical activity. PG, prostaglandin. Post-infusion period includes values at 30 min of the end of infusion. A, N = 3 lambs; B, N = 4 lambs. rx, regression value; regression includes control period as dose "0" and it does not include post-infusion period. None of these results was statistically significant.

TABLE III

Effects of prostaglandin E_2 infusion on incidence of apneic events in 12 newborn lambs

	Prostaglandin E_2 (μg/kg/min)					
Apneic events (sec)	Control	0.1	0.5	1.0	5.0	Total
3 - 6	6	21	146	202	241	616
7 - 10	0	1	22	21	65	109
10	0	0	2	4	12	18
Total	6	22	170	227	318	743

Data are apneic events/hour $x^2 = 22.9$, DF = 8, $p < 0.005$

TABLE IV

Total number of apneic events/hour observed during the different electrocortical stages in 6 newborn lambs infused with prostaglandin E_2

	Prostaglandin E_2 (μg/kg/min)					
Electrocortical stages	control	0.1	0.5	1.0	5.0	Total
High voltage activity	2	6	61	103	72	244
Low voltage activity	4	4	80	153	207	448
Total	6	10	141	256	279	692

Data are total number of apneic events/hour.
Pearson $x^2 = 20.34$, DF = 4, $p < 0.001$

Plasma PGE_2 concentration (42 observations in 7 lambs), plotted independently of the dose infused, showed a significant inverse correlation with ventilation, pH and blood pressure and a significant positive correlation with $PaCO_2$, although the actual data showed variability (Figures 1 and 2). Plasma PGE_2 concentration did not correlate significantly with heart rate (Fig.1), incidence of apneic events ($r = 0.08$, $y = 7 + 0.02x$), PaO_2 ($r = 0.20$, $y = 62 - 0.05x$, or oxygen saturation ($r = -0.10$, $y = 88 - 0.02x$).

In the 4 animals with both ECoG recording and measurements of PGE_2 concentrations, there was a significant inverse correlation of PGE_2 concentration with the incidence of LVA (Fig. 1).

DISCUSSION

Our results indicate that infusion of increasing doses of PGE_2 has marked inhibitory effects on ventilation in newborn lambs. PGE_2 induced a progressive decrease in ventilation (due to decreases in both breathing rate and tidal volume) and increases in the incidence and duration of apneic events. Although there have been no previous systematic studies on the effects of prostaglandins on ventilation in newborn swine /30/ and newborn human infants with cyanotic heart disease /21/, and PGE_1 decreases the output of the phrenic nerve in piglets that have been anesthetized, paralyzed and maintained with assisted ventilation /16/. The inhibitory effects of PGE_2 on ventilation in newborn animals and infants, in the present study and the others quoted above, are analogous to previous studies in fetal sheep where PGE_2 inhibited FBM (14,15,19,20,31). However, these results are in contrast to studies in adults in which E-type prostaglandins caused an increase in ventilation in dogs /28/, rats, cats /17/, guinea pigs /18/ and awake human males /4/. Thus, there appears to be a change in the effects of E-type prostaglandins on ventilation with maturation after birth. The

factors responsible for this change and the age at which it occurs are not known.

In the present study, the inhibitory effects of PGE_2 on ventilation correlated both with the dose infused and with the plasma concentration of PGE_2, these results are similar to those reported for fetal sheep /31/. Of concern is that the measured concentrations of PGE_2 in this study were only about 1/100 of the expected values, based on the amount of PGE_2 infused and an assumed cardiac output of 400 ml/kg/min /27/. The reasons for this discrepancy are not known. Possible explanations include conversion of PGE_2 to PGF_2 in sheep blood /3/, streaming of blood away from the axillary artery in the brachiocephalic trunk or loss of PGE_2 during its extraction and purification /9/.

The site at which PGE_2 exerts its respiratory effects in newborn lambs is not known. In fetal sheep, the site of action on FBM is in the central nervous sytem /32/, most likely in the pons or lower medulla /12,15,20/. Because PGE_2 has an inhibitory effect on breathing both in the fetus and the newborn, it seems reasonable to assume that the site of action is similar in both. However, there are some differences in the effects of PGE_2 on the respiratory system in the newborn compared to he fetus. In fetal sheep, PGE_2 infusion inhibits FBM but does not affect arterial pH or $PaCO_2$ /14,15,19,20), also, PGE_2 does not inhibit FBM stimulated by hypercarbia /15/. Conversely, in the present study in newborn lambs, PGE_2 decreased ventilation and caused hypercarbia and acidosis,

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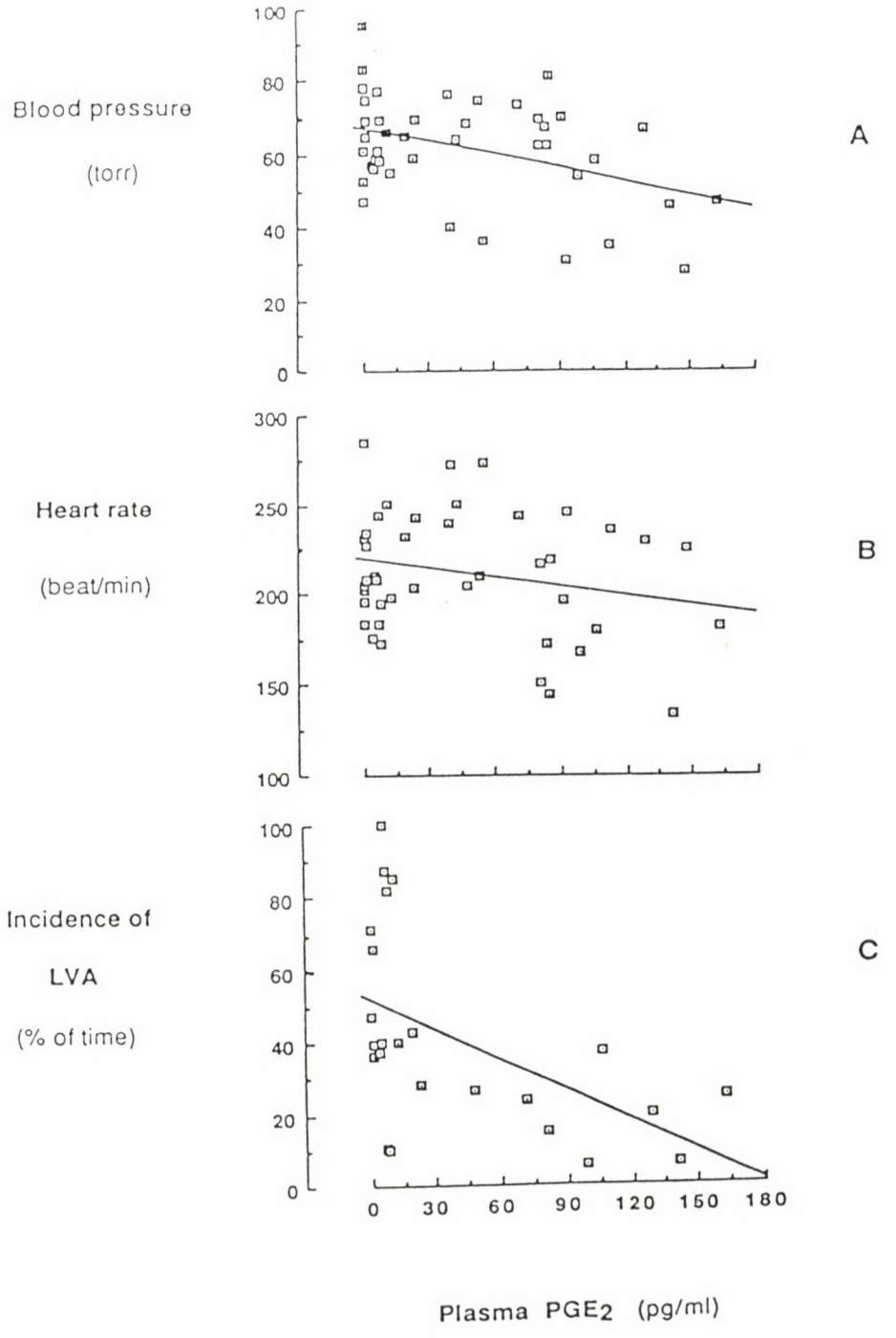
Fig. 1. Relationship of plasma concentration of prostaglandin (PG) E_2 with mean arterial blood pressure (A), and heart rate (B) in 4 lambs, and with the time spent in low voltage electrocortical activity (LVA; C) in lambs. PGE_2 concentration showed significant inverse correlations with blood pressure ($r = -0.41$; $y = 67 - 0.12x$; $p < 0.005$) and incidence of LVA ($r = -0.53$; $y = 52 - -0.28x$; $p < 0.001$), but did not correlate with heart rate ($r = -0.23$; $y = -212 - 0.16x$).


Blood pressure
(torr)
100
80
60
40
20
0
A
Heart rate
(beat/min)
300
250
200
150
100
B
Incidence of
LVA
(% of time)
100
80
60
40
20
0
C
0
30
60
90
120
150
180
Plasma PGE2 (pg/ml)

conditions which normally stimulate ventilation in the newborn /12,25/. Thus, PGE_2 appears to be a potent inhibitor of respiration in the newborn lamb and can overcome the effects of the strong physiological respiratory stimulants, hypercarbia, and acidosis. The mechanism by which PGE_2 affects the respiratory system is not known, although there are some data suggesting that PGE_2 may act as a neurotransmitter or modulate other neurotransmitters /24/.

An unexpected finding in the present study was the marked decrease in incidence of LVA during PGE_2 infusion (Table I), this occurred in association with hypoxemia, hypercarbia and acidosis. These findings differ from the effects of PGE_2, in fetal sheep in which PGE_2 causes only a slight decrease in incidence of LVA from 54 % to 47 % of the time, with no changes in arterial pH or blood gas tensions /20/. Furthermore, in fetal sheep, hypoxemia decreases /2/, hypercarbia increases /2,11/, and acidosis has no effect on the incidence of LVA /10/. The reasons why PGE_2 causes such a marked decrease in incidence of LVA in newborn lambs are not apparent. A possible explanation is that the decrease in LVA is due to a combined effect of PGE_2 and hypoxemia, both of which independently decrease LVA in fetal sheep /2,20/, and this effect is stronger than the tendency for hypercarbia to increase the incidence of LVA. Further studies are needed to resolve this issue.

In this study, PGE_2 caused progressive decreases in heart rate and blood pressure. These effects are similar to those reported by Olley et al /22/. They found that the infusion of

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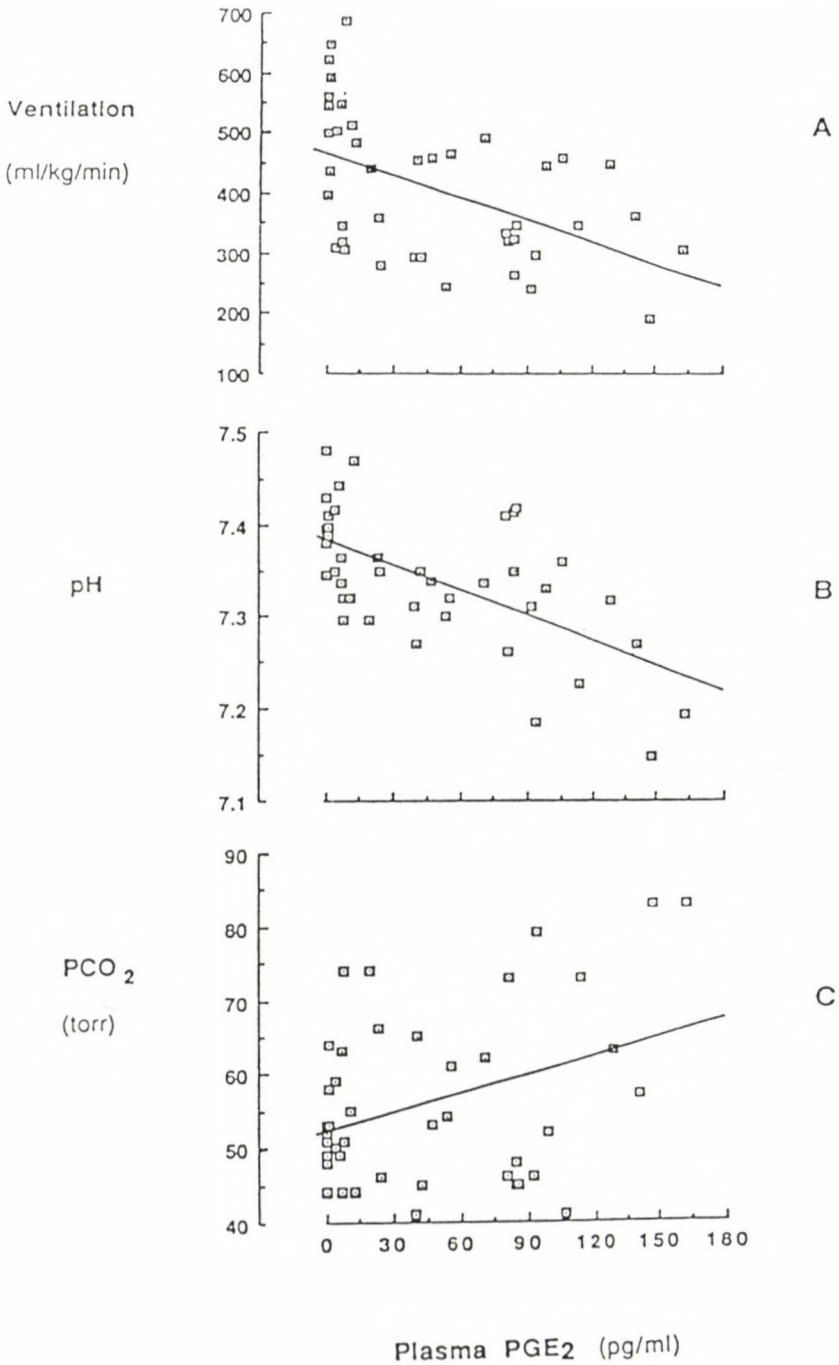
Fig. 2. Relationship of plasma concentration of prostaglandin (PG) E_2 with ventilation (A), arterial pH (B) and PCO_2 PCO_2 (C) in 7 lambs, PGE_2 concentration showed significant inverse correlations with ventilation ($r = -0.50$; $y = 466 - 1.2x$; $p < 0.005$) and pH ($r = -0.63$; $y = 7.39 - 0.001x$; $p < 0.001$), and a significant positive correlation with PCO_2 ($r=0.35$; $y = 52 + 0.08x$; $p < 0.025$).


Ventilation
(ml/kg/min)
700
600
500
400
300
200
100
A
pH
7.5
7.4
7.3
7.2
7.1
B
PCO 2
(torr)
90
80
70
60
50
40
C
0
30
60
90
120
150
180
Plasma PGE2 (pg/ml)

E-type prostaglandins caused a decrease in cardiac output in lambs which were anaesthetized and given assisted ventilation to maintain arterial pH and blood gas tensions in the normal range. These cardiovascular effects may be due to effects on the peripheral vessels, on the myocardium /22/, on the central nervous system /6/, or a combination of these. These findings are in contrast to studies in fetal sheep, in which the infusion of PGE_2 has no effect on heart rate or blood pressure /14/. These differences may be explained by the differences in the circulation of the fetus and the newborn /27/. It is unlikely that the respiratory changes observed during the infusion of PGE_2 were due to these cardiovascular changes. Sola et al reported that, in lambs spontaneously breathing room air, a withdrawal of 50 % of their blood volume caused hypotension, bradycardia, decreased myocardial blood flow and cerebral oxygen delivery, and metabolic acidosis /28/, but these animals were hypocarbic and normoxic, suggesting minute ventilation increased.

In summary, we conclude that infusion of PGE_2 has marked inhibitory effects on ventilation in newborn lambs. These findings taken in combination with previous fetal studies /12,14,15,19,20,31/ indicate that PGE_2 has depressant effects on the respiratory system both in the fetus and in the first few days after birth.

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