Effect of antenatal glucocorticoids on sympathetic nerve activity at birth in preterm sheep

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Segar, Jeffrey L., Eugenie R. Lumbers, Anne Monique Nuyt, Oliva J. Smith, and Jean E. Robillard. Effect of antenatal glucocorticoids on sympathetic nerve activity at birth in preterm sheep. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R160–R167, 1998.—Renal sympathetic nerve activity (RSNA) increases rapidly after delivery of term fetal sheep and parallels the rise in heart rate (HR) and arterial pressure. To examine the RSNA response at birth in immature lambs, experiments were performed in chronically instrumented preterm fetal sheep (118- to 125-day gestation, term 145 days) before and after delivery by cesarean section. HR remained unchanged from fetal values at 1 and 4 h after birth, whereas mean arterial blood pressure (MABP) decreased significantly (P < 0.05) by 4 h after delivery. RSNA significantly decreased after premature birth in all animals studied (n = 6), achieving only 39 ± 17% of fetal RSNA (P < 0.05; all results are mean ± SE). Because cardiovascular function after premature birth is improved by the use of antenatal corticosteroids, we also tested the hypothesis that corticosteroid administration would evade a more pronounced sympathetic response in prematurely delivered lambs (n = 7, 118- to 125-day gestation). After maternal administration of dexamethasone (5 mg im, 48 and 24 h before delivery), RSNA increased after birth in six of seven fetuses to 166 ± 32% of the fetal RSNA value. Dexamethasone treatment also decreased the sensitivity of baroreflex-mediated changes in HR in response to increases in MABP. Because the sympathetic response at birth is depressed in preterm compared with term lambs, we performed an additional study (n = 8) to determine if immature sheep are capable of mounting a sympathetic response to cold. In utero cooling produced rapid and sustained increases in MABP (20 ± 4%), HR (26 ± 6%), and RSNA (282 ± 72%) (all P < 0.05), consistent with a generalized sympathoexcitation. These results suggest that sympathoexcitation is absent after premature delivery despite the presence of functional descending autonomic pathways. Furthermore, exogenous corticosteroids appear to have a maturation effect on the sympathetic response at birth, which may be one mechanism by which maternal steroid administration improves postnatal cardiovascular homeostasis.

renal sympathetic nerve activity; dexamethasone; blood pressure; heart rate; fetus; newborn

NUMEROUS CARDIOVASCULAR, pulmonary, and metabolic adjustments are required at birth to ensure successful adaptation to the extrauterine environment (20). Previous studies have suggested that activation of the sympathoadrenal system, including a surge in adrenal catecholamine release (12, 19) and stimulation of sympathetic nerve activity (25), participates in regulating these physiological responses. Interestingly, preterm animals and human infants have attenuated physiological adaptive responses at birth compared with those delivered at term, despite having greater increases in circulating catecholamine levels (18, 22). Immaturity of neurohumoral systems, receptor mechanisms, and end-organ function may all contribute to impairment of physiological adaptation at preterm birth.

Before birth, there are programmed increases in circulating levels of several neuroendocrine mediators, including cortisol (17). The increasing availability of endogenous glucocorticoids late in fetal development modulates the rate of differentiation of numerous tissues, the most well studied being the lung (3). The enhancement of fetal lung structural and functional maturity by administration of corticosteroids to pregnant women has been extensively reviewed (2). In addition, studies in premature animals (21, 32) and human infants (10) have documented that antenatal corticosteroid administration improves cardiovascular status at birth and lessens the incidence of as well as the morbidity and mortality related to hemorrhagic and ischemic complications (5). The mechanisms by which antenatal corticosteroids facilitate postnatal circulatory function are uncertain but may be related in part to augmented cardiac and peripheral adrenergic (32) and angiotensinergic (34) functions. Corticosteroids may also influence the development of other neurohumoral systems regulating cardiovascular function at birth, including noradrenergic activity (26).

We have recently shown in term fetal sheep that efferent sympathetic nerve activity increases severalfold at birth and likely contributes to the cardiovascular changes after the transition from fetal to newborn life (25). Absence or attenuation of this sympathoexcitatory response may in turn contribute to the impaired cardiovascular responses at birth in preterm lambs. Therefore, the present studies were designed to investigate the sympathetic response at birth in preterm sheep and to determine if the increase in renal sympathetic nerve activity (RSNA) is impaired compared with that seen in term animals. Furthermore, we examined the effects of antenatal glucocorticoid administration on birth-related changes in systemic hemodynamics and RSNA in preterm fetal lambs. Because the sympathetic response at birth was attenuated in preterm lambs, we performed an additional study to determine if immature sheep are capable of mounting a sympathetic response to other stimuli, namely in utero cooling. We compared our results with those previously published in term fetal sheep.
METHODS

Studies were performed in conscious, chronically instrumented fetal sheep at 118- to 125-day gestational age (term 145 days). Pregnant ewes of Dorset and Suffolk mixed breeding were obtained from a local source; gestational ages were based on the induced ovulation technique as previously described (9). Ewes were randomized to receive either saline or dexamethasone (Dex, 5 mg im) 48 and 24 h before delivery.

Surgical preparations. All procedures were performed within the regulations of the Animal Welfare Act and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Briefly, the ewe was fasted for 24 h before surgery and anesthetized using a mixture of halothane (1%), oxygen (33%), and nitrous oxide (66%). For the first series of studies, the uterus was opened under sterile conditions over the fetal hindlimbs, and polyethylene catheters were placed into the fetal femoral arteries and veins bilaterally. A catheter for recording amniotic pressure was also secured to the fetal skin. The left kidney, renal artery, and renal nerves were exposed through a flank incision, and a platinum-coated copper wire, used as a ground wire, was secured in the paravertebral muscle. After isolation of a branch of the left renal nerve bundle, platinum electrodes were secured onto the nerve for recording of RSNA as described previously (30). Function of the renal nerve was tested by audible monitoring of pulse-synchronous bursts of neural activity and by examining oscilloscope tracings during bolus phenylephrine infusion. When function was demonstrated, electrodes were secured using Sil-Gel (Sil-Gel 604A and 604B, Wacker-Chemie, Munich, Germany) and the flank incision was closed in separate layers. Fetal skin incisions were closed, and the fetus was returned to the uterus. Maternal incisions were closed in separate layers. All catheters and tubing were exteriorized through subcutaneous tunnels and placed in cloth pouches on the ewe’s flank. Ampicillin sodium (Wyeth Laboratories) was administered to the ewe intramuscularly before surgery (2 g) and was infused into the amniotic cavity after surgery (2 g).

In the second group of fetuses, the uterus was opened under sterile conditions over the fetal head, and the head, forelimbs, and thorax were exteriorized. Approximately 5 m of tubing from a closed injectate delivery system (model 93–600, Baxter Healthcare, Irvine, CA) was wrapped around the fetal thorax and secured to the skin. A thermistor (Gould 93–600, Baxter Healthcare, Irvine, CA) was wrapped around a series of tubing from a closed injectate delivery system (model 93–600, Baxter Healthcare, Irvine, CA) and was attached to the fetal skin. The left kidney, renal artery, and left renal nerve recording electrode were secured onto the nerve for recording of RSNA as described previously (30). Function of the renal nerve was tested by audible monitoring of pulse-synchronous bursts of neural activity and by examining oscilloscope tracings during bolus phenylephrine infusion. When function was demonstrated, electrodes were secured using Sil-Gel (Sil-Gel 604A and 604B, Wacker-Chemie, Munich, Germany) and the flank incision was closed in separate layers. Fetal skin incisions were closed, and the fetus was returned to the uterus. Maternal incisions were closed in separate layers. All catheters and tubing were exteriorized through subcutaneous tunnels and placed in cloth pouches on the ewe’s flank. Ampicillin sodium (Wyeth Laboratories) was administered to the ewe intramuscularly before surgery (2 g) and was infused into the amniotic cavity after surgery (2 g).

During each experiment, fetal mean arterial blood pressure (MABP) and amniotic pressure were recorded continuously using Statham P23 Db pressure transducers (Spectramed, Critical Care Division, Oxnard, CA) and a Grass 7–24P chart recorder (Grass Instruments, Quincy, MA). Fetal MABP was corrected relative to concomitant amniotic pressure. HR was monitored with a cardiocochmeter triggered from the arterial pressure pulse waves. Temperature (when applicable) was measured continuously using a Gould 13–4615–47 temperature amplifier (Gould, test and measurement group, Valley View, OH).

With the ewe housed inside a Faraday cage, the renal nerve electrodes and ground wire were attached to a high-impedance probe (HIP5, Grass Instruments). The neural signal was amplified (×20,000) and filtered (low-frequency cutoff 100 Hz, high-frequency cutoff 3 kHz) using a Grass P519 voltage amplifier (P519). The output of the amplifier was visually displayed on an oscilloscope (511A, Tektronix, Beaverton, OR) and routed to a Grass AM8 audio monitor. The neural signal was integrated over 1 s using a Grass voltage integrator. The integrated voltage and neurogram signals were stored on videotape (Vetter 4000A PCM, Vetter Digital, Rebersburg, PA), displayed on the recorder, and simultaneously recorded online to a personal computer using Labtech Notebook (version 7.2; Laboratory Technologies, Wilmington, MA).

Experimental protocol. The first series of studies (n = 13) was designed to characterize the changes in systemic hemodynamics, RSNA, and baroreflex function at birth in preterm lambs and to determine the effects of prenatal corticosteroid administration on these autonomic responses. Fetal baseline values for HR, MABP, and RSNA were obtained by recording and averaging those values over a 30-min period. Baroreflex function in the fetus was then determined by producing ramp changes in MABP with a continuous intravenous infusion of progressive doses of phenylephrine (1–30 µg·kg\(^{-1}\)·min\(^{-1}\)) over a 3- to 5-min period using a Harvard infusion pump, while simultaneously recording HR and RSNA. A 30- to 40-min recovery period was allowed for MABP, HR, and RSNA to return to baseline values. After this recovery period, the amount of background noise in the nerve signal was assessed by inhibiting nerve activity using an intravenous infusion of the ganglionic blocking agent tetraethylammonium bromide (10 mg/kg). Integrated RSNA was corrected by subtracting the background noise level obtained in the presence of ganglionic blockade.

After the fetal studies were completed, the ewes were returned to the surgical area and mechanical ventilation was continued. Low spinal anesthesia (1% lidocaine, 10 ml) was administered to the ewe, after which the lamb was delivered by cesarean section. Tracheal intubation of the lamb and administration of exogenous surfactant (100 mg/kg Survanta, kindly provided by Abbott Laboratories, Columbus, OH) was performed before cutting the umbilical cord. Lambs were placed on an infant warmer bed, dried, manually ventilated, and returned to the laboratory. Lambs were then transferred to a sling-frame assembly to maintain them in an upright position and were mechanically ventilated with a time-cycled, pressure-limited infant ventilator. Initial ventilator settings included fractional concentration of inspired O\(_2\) of 1.0, a rate
catecholamines were performed by radioimmunoassay (Uni-
temperature. Measurements of cortisol, AVP, ANG II, and
Lexington, MA). All blood gas values were corrected for fetal
1302 pH/blood gas analyzer (Instrumentation Laboratory,
was collected anaerobically in heparinized syringes, and
end-expiratory pressure of 4 cmH$_2$O, and peak inspiratory
of 40 breaths/min, an inspiratory time of 0.5 s, positive
maintain a partial pressure of O$_2$ in arterial blood of 80–100
mmHg and P CO$_2$ 40–50 mmHg. Diazepam and vecuronium
plasma catecholamine (norepinephrine and epinephrine), ar-
studies were performed after the 1-h recording. At the end of
the study, background noise in the nerve signal was again
examine whether preterm fetal lambs are capable of generat-
the volume of blood sampled from the fetus or newborn was
arginine vasopressin (AVP), angiotensin II (ANG II), and corti-
assessed as described above.
Arterial blood for determination of blood gases and pH and
plasma catecholamine (norepinephrine and epinephrine), ar-
A second set of experiments ($n = 8$) was designed to
to avoid any hemodynamic effects of sampling.
The volume of blood sampled from the fetus or newborn was
arginine vasopressin (AVP), and cortisol levels were obtained before each baroreflex function study. The volume of
blood sampled from the fetus or newborn was replaced immediately with an equivalent volume of maternal
blood to avoid any hemodynamic effects of sampling.
These experiments consisted of four study periods: 1) control, 2) cooling, 3) after rewarming of the fetus, and 4) after delivery by cesarean section. Baseline fetal HR, MABP, and RSNA were initially obtained and averaged over a 15-min period. In utero fetal cooling was performed as previously described (14). Water cooled to 16–20°C was continuously pumped through tubing wrapped around the fetal thorax using a Lauda refrigerating circulator, model RKS-20D (Brinkman Instruments, Westbury, NY). The pump speed was set at its maximum capacity of 15 l/min. The study period was begun 10 min after starting the water pump, at a time when fetal core temperature was decreased by no more than 2°C. Water temperature was then adjusted as necessary to maintain the fetus at the desired temperature. Values for HR, MABP, and RSNA were obtained over 15 min, after which the fetus was rewarmed by increasing the temperature of the circulating water to 42°C. A 1-h equilibration period was then allowed before again obtaining fetal hemodynamic and RSNA values. Finally, the fetus was delivered by cesarean section as described for the first series of studies. Values for HR, MABP, and RSNA were obtained at 1 h after birth. At the completion of each study period, arterial blood was sampled for determination of plasma catecholamine, AVP, ANG II, cortisol, and arterial blood gas values. All blood samples were replaced with an equivalent volume of maternal blood. Background electrical noise in the RSNA signal was determined at the completion of the studies as described above.

Analytic procedures. Arterial blood for pH, P CO$_2$, and Po$_2$ was collected anaerobically in heparinized syringes, and measurements were immediately determined using a BGM 1302 pH/blood gas analyzer (Instrumentation Laboratory, Lexington, MA). All blood gas values were corrected for fetal temperature. Measurements of cortisol, AVP, ANG II, and catecholamines were performed by radioimmunoassay (University of Iowa Cardiovascular Center RIA Core Facility, Donna B. Farley, Director).

Computation and data analysis. RSNA was normalized for each animal and expressed as the percentage of activity observed in the fetus under control conditions. Statistical analyses of differences in HR, MABP, RSNA, plasma hormone concentrations, and arterial blood gas values during the described study periods were performed using a two-way repeated-measures analysis of variance (ANOVA), factoring for treatment group and time. If the F value for the interactive term (group × time) was found to be significant ($P < 0.05$), indicating that differences between groups depend upon what level of time (fetuses vs. 1 h vs. 4 h) is present, pairwise multiple-comparison procedures were performed by the Student-Newman-Keuls method (7). For data exhibiting a lack of homogeneity of variances among groups, nonparametric analysis was applied using the Kruskal-Wallis test.

For determination of baroreflex control of HR, control values of HR were defined as 100%. HR values were collected at 5-mmHg increments from control MABP (~5, 10, and 15 mmHg) for data analysis. Linear regression analysis of the changes in HR (expressed as %control HR) with increasing MABP was performed, with the differences in the slopes of the regression lines determined by analysis of variance. Differences in changes in HR were also analyzed by three-factor ANOVA (factoring for group, age, and change in blood pressure). Differences were considered significant when $P < 0.05$. All results are expressed as means ± SE.

RESULTS

Effect of delivery on arterial blood values. Fetal and newborn arterial blood values before and after delivery are summarized in Table 1. Fetal arterial Po$_2$, P CO$_2$, and pH were similar in preterm control and Dexamethasone (Dex) group. AVP, arginine vasopressin; ANG II, angiotensin II; NE, norepinephrine; Epi, epinephrine. *$P < 0.05$ compared with fetus; †$P < 0.05$ compared with other group at similar time. Statistical differences determined by 2-way repeated-measures analysis of variance or Kruskal-Wallis test.

<table>
<thead>
<tr>
<th>Table 1. Arterial blood values before and after birth</th>
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<tbody>
<tr>
<td>Fetus</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>7.39 ± 0.02</td>
</tr>
<tr>
<td>25 ± 1</td>
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<tr>
<td>40 ± 5</td>
</tr>
<tr>
<td>20 ± 3</td>
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<tr>
<td>160 ± 42</td>
</tr>
<tr>
<td>516 ± 63</td>
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<tr>
<td>69 ± 19</td>
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<tr>
<td>1.69 ± 0.27</td>
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</tbody>
</table>

Values are means ± SE; $n = 6$ in control group, $n = 7$ in dexamethasone (Dex) group. AVP, arginine vasopressin; ANG II, angiotensin II; NE, norepinephrine; Epi, epinephrine. *$P < 0.05$ compared with fetus; †$P < 0.05$ compared with other group at similar time. Statistical differences determined by 2-way repeated-measures analysis of variance or Kruskal-Wallis test.
animals, whereas no differences in newborn PO2 or PCO2 values were seen between the two groups.

No differences were detected in fetal AVP, ANG II, norepinephrine, epinephrine, or cortisol values between control and Dex fetuses. After birth, plasma AVP levels significantly increased in control animals, although no significant difference was seen between newborn control and Dex AVP values. ANG II levels tended to increase in control animals after birth (P = 0.06) and were significantly higher in control than in Dex newborns. Norepinephrine levels significantly increased in both groups after birth, whereas plasma epinephrine values increased only in the control group. Plasma cortisol concentration increased after birth in control but not Dex animals.

Effect of delivery on systemic hemodynamics and RSNA. The changes in HR, MABP, and RSNA occurring with delivery in term and preterm sheep are shown in Fig. 1. Data for the term sheep have previously been published by our group (25) and are presented for comparison with values obtained in preterm sheep. In contrast to term sheep, in which significant increases in HR and MABP occur after birth, preterm sheep failed to demonstrate increases in either HR or MABP after delivery. In fact, by 4 h after birth, HR was significantly less than that seen in the fetus (−31 ± 6%, P < 0.05). Large differences in the sympathetic response at birth were also seen between term and preterm sheep. One hour after delivery, RSNA increased by almost 250% (P < 0.05) in term fetuses, and remained at this level at 4 h after birth. However, in preterm fetuses, RSNA actually decreased after birth, (P < 0.05 at 1 and 4 h) being ~35–40% of the value obtained in utero.

Preterm fetuses receiving antenatal Dex had similar fetal HR and MABP values compared with preterm controls, although there was a tendency for HR to be lower and MABP higher in the Dex group (Fig. 1). However, unlike controls, Dex animals had significant increases in HR (+27 ± 6 beats/min) and MABP (10 ± 2 mmHg) 1 h after birth. The increase in HR was sustained at 4 h, whereas MABP returned to values similar to those in the fetus. Nonetheless, 4-h HR and MABP values were significantly greater in Dex animals than in controls. A large difference in the RSNA response at birth was also seen in the two preterm fetal groups (Fig. 1). RSNA after birth was significantly greater in Dex animals than in controls, the difference being present at both 1 and 4 h. Although the mean value for RSNA in the Dex animals at 1 h is not significantly different from the fetal value, it should be noted that five of seven Dex-treated animals showed an increase in RSNA at birth, whereas all seven of the control animals showed a decrease. The increase in RSNA after birth in Dex animals was significantly less than that previously seen in term sheep.

Effect of antenatal Dex on baroreflex control of HR before and after birth. Progressive intravenous administration of increasing doses of phenylephrine resulted in increases in MABP and pressure-related decreases in HR (Fig. 2). Values for HR after 10- and 15-mmHg increases in MABP were significantly lower in control
animals than in those receiving Dex. Using linear regression analysis, we found significant differences in the slope of the relationship between MABP and HR in Dex and control fetuses (1.8 ± 0.4 vs. 3.5 ± 0.9%/mmHg, respectively). The slope of the baroreflex response for HR was also significantly greater (P < 0.05) in control (4.7 ± 1.0%/mmHg) than in Dex newborns (1.9 ± 0.3%/mmHg). Within each treatment group, no differences were detected in the MABP-HR slope between fetal and newborn values.

In addition to evaluating baroreflex control of HR early during development, we also attempted to assess reflex control of RSNA. It was evident that in several fetuses, increases in MABP resulted in inhibition of RSNA (Fig. 3). However, these RSNA responses were not always reproducible and were not present in all animals. Specifically, in several animals, RSNA appeared dissociated from the reflex-mediated inhibition in HR. Therefore, we were unable to accurately determine measurement of the MABP-RSNA relationship.

Effects of in utero cooling on arterial blood values. Arterial blood values during control conditions and after fetal cooling, fetal rewarming, and delivery are shown in Table 2. Arterial PCO₂ remained unchanged throughout the experiment. Arterial pH was significantly lower after birth compared with all fetal conditions, whereas PO₂ was significantly higher after birth. Plasma AVP, ANG II, and cortisol concentrations remained unchanged throughout the study. Norepinephrine levels were increased (P < 0.05) during the fetal cooling and newborn periods, whereas epinephrine levels increased only after birth.

Table 2. Arterial blood values during fetal cooling and after birth

<table>
<thead>
<tr>
<th></th>
<th>Fetus Control</th>
<th>Fetus Cool</th>
<th>Fetus Rewarm</th>
<th>Newborn (1 h)</th>
</tr>
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<tbody>
<tr>
<td>pH</td>
<td>7.38 ± 0.06</td>
<td>7.39 ± 0.07</td>
<td>7.36 ± 0.05</td>
<td>7.27 ± 0.08*</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>42 ± 3</td>
<td>40 ± 3</td>
<td>46 ± 3</td>
<td>44 ± 4</td>
</tr>
<tr>
<td>PO₂ (mmHg)</td>
<td>21 ± 1</td>
<td>22 ± 1</td>
<td>22 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>AVP (µU/ml)</td>
<td>22.6 ± 3.9</td>
<td>18.4 ± 2.8</td>
<td>28.4 ± 9.2</td>
<td>20.5 ± 12</td>
</tr>
<tr>
<td>ANG II (pg/ml)</td>
<td>58 ± 7</td>
<td>60 ± 10</td>
<td>48 ± 9</td>
<td>70 ± 13</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>399 ± 80</td>
<td>723 ± 112†</td>
<td>372 ± 53</td>
<td>812 ± 147†</td>
</tr>
<tr>
<td>Epi (pg/ml)</td>
<td>226 ± 86</td>
<td>173 ± 22</td>
<td>179 ± 42</td>
<td>465 ± 99*</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>2.21 ± 0.19</td>
<td>2.62 ± 0.27</td>
<td>2.47 ± 0.19</td>
<td>3.61 ± 0.55</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8. * P < 0.05 compared with all fetal values; † P < 0.05 compared with control and Rewarm.

Effects of in utero cooling on systemic hemodynamics and RSNA. Ten to fifteen minutes after the beginning of in utero cooling of the fetus, during which time fetal core temperature decreased by ~2°C, significant increases in HR (26 ± 6%), MABP (20 ± 4%), and RSNA (282 ± 72%) were demonstrated (Fig. 4). Notably, significant changes in systemic hemodynamics and RSNA occurred within minutes after cooling began, before any significant decrease in core temperature. Five minutes after the start of the water pump, at a time when fetal core temperature had decreased by 0.4 ± 0.1°C, HR, MABP, and RSNA had increased by 23, 17, and 259%, respectively. Rewarming of the fetus
returned HR, MABP, and RSNA to values similar to those observed during the control period. The final intervention of the experiment consisted of delivering the fetus by cesarean section. During this period, HR remained similar to that observed during the fetal control period and after rewarming. However, in contrast to fetuses not previously cooled in utero (first series of studies), animals delivered after cooling and rewarming demonstrated significant increases in MABP (10 ± 2 mmHg) and RSNA (145 ± 62%) by 1 h after birth. This increase in RSNA was also significantly greater than that seen in Dex animals at birth.

**DISCUSSION**

In previous experiments in term fetal sheep, we demonstrated that sympathetic outflow, as measured in the renal nerve, increases dramatically at birth and parallels the increases in HR and arterial pressure (25). The present studies were designed to characterize the changes in RSNA at birth in preterm fetal lambs and to investigate the effects of antenatal glucocorticoid administration on the sympathetic response and baroreflex control of HR at birth. The results from these studies indicate that in contrast to lambs delivered at term, a sympathoexcitatory response is absent at birth in preterm sheep. However, preterm fetal sheep of ewes receiving antenatal glucocorticoids had improved cardiovascular and sympathetic function at birth compared with control animals of similar gestational age. Glucocorticoids also decreased the sensitivity of the cardiac baroreflex after birth. The impaired sympathetic response at birth seen in non-Dex-treated fetuses occurred despite the fact that the descending pathways of the sympathetic nervous system appear intact and functional at this stage of development, as demonstrated by the large pressor and sympathoexcitatory response to intrauterine cooling.

Postnatal cardiovascular and metabolic functions are attenuated after premature birth compared with those seen at term (22). These maturational differences cannot be attributed to adrenal unresponsiveness because postnatal circulating catecholamine levels are higher in preterm than term animals (22). Investigators have therefore speculated that immature or incomplete end-organ responses to adrenergic receptor stimulation in target tissues contribute to these impaired responses (21, 32) or that other neurohumoral mechanisms are involved in regulating the physiological adjustments at birth which are not fully developed in the preterm animal. In contrast to our previous observations in term sheep, the present results demonstrate that a sympathoexcitatory response is absent at birth in preterm sheep and that RSNA actually decreases after birth. We speculate that this impaired sympathetic response accompanying premature birth contributes to the attenuated postnatal cardiovascular responses seen with prematurity and suggest that autonomic modulation of circulatory function is of major importance in adaptation to the extrauterine environment.

The effects of corticosteroids on fetal lung development and pulmonary function are well known (2). More recently, it has been appreciated that the use of antenatal glucocorticoids improves cardiovascular function after premature birth (10, 21, 32). Both maternal and direct fetal administration of glucocorticoids improve postnatal blood pressure, cardiac output, and cardiac contractility in prematurely delivered lambs, although the mechanisms regulating these responses are not clearly understood (21, 31, 32). Stein et al. (32) demonstrated that myocardial adenyl cyclase activity is augmented in corticosteroid-treated fetal lambs, although myocardial β-receptor density and affinity were similar in treated and nontreated fetuses. Exogenous cortisol has also been shown in immature fetal sheep to enhance the vascular responsiveness to ANG II, the levels of which increase at birth, but not to norepinephrine (6, 34). Finally, glucocorticoids may also regulate the synthesis of vasoactive compounds, such as prostaglandins (8) or nitric oxide (33), which in turn modulate peripheral vascular reactivity.

It may also be hypothesized that the effect of glucocorticoids on postnatal cardiovascular function is mediated by central mechanisms. In the rat brain, glucocorticoid receptors are present in the fetus and increase in number after birth (16). Studies in a number of species have also shown that glucocorticoid receptors are preferentially concentrated within limbic system structures, the paraventricular nucleus of the hypothalamus (PVN), and the nucleus of the solitary tract (16), these latter two regions being strongly implicated as cardiovascular control centers (13). Maternal administration of Dex accelerates development of central noradrenergic function in newborn rats, as measured by norepinephrine turnover (26), and enhances noradrenergic synaptogenesis (27). At a biochemical level, glucocorticoids increase phenylethanolamine N-methyltransferase (PNMT) within the brain stem and hypothalamus of fetal and newborn rats (36). Increased PNMT activity within the central nervous system has been postulated to raise blood pressure by increasing sympathetic activity, although the data are not consistent (11). Interestingly, a number of studies suggest that in adult animals with glucocorticoid hypertension, sympathetic activity appears reduced or unchanged (40, 41). In addition, in adult rats, central administration of Dex exerts a blood pressure-lowering effect, whereas intracerebroventricular injection of a glucocorticoid antagonist increases blood pressure (35, 39). Whether similar effects of central glucocorticoids are present in the developing animal has not been investigated.

The finding that the gain of the HR baroreflex response was reduced in the Dex animals provides additional evidence that glucocorticoids exert an effect on the autonomic nervous system. It is not known whether the effects on the baroreflex were mediated by afferent (within the carotid sinus) or central or efferent (responsiveness of the sinoatrial node) mechanisms. Within the carotid sinus, glucocorticoids may alter the release of endothelial factors that have been shown to contribute to baroreceptor resetting (4). As previously mentioned, glucocorticoid receptors are present in high density within the nucleus of the solitary tract, the initial component of the central baroreflex pathway, as well as the PVN. Alteration of the baroreflex by glucocor-
ticotropin-releasing hormone, and neuropeptide Y activity are in turn inhibited or downregulated. Acute cold stress alters the level and biosynthesis of a number of neuropeptides and neurohormones, including γ-aminobutyric acid, thyrotropin-releasing hormone, corticotropin-releasing hormone, and neuropeptide Y within the hypothalamus, including the PVN (1, 15, 23, 37, 42). Changes in the expression of these neuropeptides may in turn augment the sympathoexcitatory response at birth.

Perspectives

The mechanisms regulating the numerous physiological adjustments at birth remain largely unknown. This study demonstrates that despite appearing to have intact peripheral adrenergic pathways, preterm sheep have an impaired sympathetic response at birth consistent with the attenuated postnatal changes in cardiovascular function. The maturational effect of glucocorticoids on the sympathetic response at birth may be one mechanism by which maternal steroid administration improves cardiovascular homeostasis after birth and lessens the incidence of complications associated with hypotension and disorders of hemodynamic regulation.

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