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Postnatal Cardiovascular and Metabolic Responses to a Single Intramuscular Dose of Betamethasone in Fetal Sheep Born Prematurely by Cesarean Section

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ABSTRACT

Although the benefits of antenatal hormone treatment are well accepted, most studies have reported only pulmonary effects. There is evidence of beneficial cardiovascular and metabolic effects in studies using chronically catheterized animals; however because of the route of administration, the results are not directly applicable to clinical strategies. We previously demonstrated significant pulmonary effects in animals treated antenatally with a single, direct fetal, intramuscular injection of glucocorticoids. This study was performed to determine the effects of a single fetal injection of betamethasone (BETA) alone or in combination with thyroxine (T_4) on cardiovascular and metabolic responses after preterm birth. Hemodynamic and metabolic responses at birth were determined in fetuses (126-d gestation; term = 150 d) treated with ultrasound-guided intramuscular injections of 0.5 mg/kg BETA (n = 7), BETA plus 60 g/kg T_4 (n = 7), or saline (SAL, n = 9). After 48 h, lambs were delivered by cesarean section and studied for 3 h. BETA treatment increased mean arterial blood pressure [56 ± 6 (SEM) *versus* 42 ± 3 mm Hg], heart rate (152 ± 5 *versus* 123 ± 4 beats/min), and cardiac output (467 ± 17 *versus* 349 ± 36 mL/min/kg) *versus* SAL. Responses of BETA + T_4-treated animals were not different from animals treated with BETA alone. Glucose and FFA were similar among all groups. The increase in catecholamine levels normally seen at birth was significantly attenuated in both the BETA and BETA + T_4-treated animals. A single, intramuscular injection of glucocorticoids 48 h before delivery improves cardiovascular responses to preterm birth. This effect is not augmented by concomitant administration of T_4. (***Pediatr Res* 38: 709–715, 1995**)

Abbreviations

BETA, betamethasone
T_4, thyroxine
T_3, triiodothyronine
SAL, saline
TRH, thyrotropin-releasing hormone
ANOVA, analysis of variance
dP/dt, change in pressure per unit time

Multiple studies have documented improved outcomes of preterm human infants born to mothers treated antenatally with glucocorticoids. Most studies have focused primarily on pulmonary effects, although secondary outcome variables and retrospective metanalysis of clinical and other demographic data indicate beneficial effects in other organ systems (1, 2). Maternal corticosteroid treatment reduces nonrespiratory morbidities such as intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. The mechanism(s) for these varied clinical outcomes is uncertain.

In previous studies using chronically catheterized fetal sheep we demonstrated that antenatal corticosteroid infusion significantly improved cardiovascular responses at birth, as illustrated by increases in blood pressure, left ventricular contractility, and cardiac output (3). Infusion of both corticosteroids and TRH resulted in even greater improvement in postnatal blood pressure when compared with animals treated with corticosteroids alone or when compared with controls (4). Although these studies demonstrated significant effects, the use of chronically catheterized animals for drug administration is not directly applicable to development of treatment regimens which may be suited to clinical use. Catheterized animals generally receive continuous or multiple hormone treatments, and the effects of fetal surgery may alter the response of the fetus to hormone treatment (5). Recently, a single direct fetal injection of corticosteroids alone or in combination with thyroid hormones has been shown to improve ventilatory function in noncatheterized, prematurely delivered sheep (6–8). The direct fetal route of administration is attractive because, given

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the quality of imaging techniques clinically available, it is technically feasible to accomplish direct injection in the human as well. Before initiation of such treatments, however, it is necessary to fully evaluate the multiorgan system effects relative to studies using chronically catheterized models. Thus, our objective was to assess the effects of direct fetal hormone administration on postnatal cardiovascular and metabolic function. We evaluated BETA because of its demonstrated effects on pulmonary maturation. Thyroid hormones do not cross the placenta, so if the fetus is to benefit from the addition of thyroid hormone to antenatal glucocorticoids, it must either be given by intraamniotic injection, by fetal intramuscular injection, or indirectly by maternal administration of TRH. Maternal TRH administration induces only a modest effect on fetal thyroid levels. To evaluate the ability of thyroid hormone to augment the effects of glucocorticoids, we evaluated the effects of BETA alone and in combination with a near maximal dose of T_4. We compared our results with those previously reported in chronically catheterized animals.

METHODS

Animal model and delivery protocol. Pregnant ewes with singleton fetuses were obtained from our local supplier (Nebeker Ranch, Palmdale, CA). At 126-d gestation (term = 150 d) ewes were restrained without anesthesia for ultrasound imaging of the fetus (6–8). Using a real time ultrasound system (Ausonics) with a 5 MHz sector transducer, the fetal heart and chest were imaged and, using a 9-cm 20 gauge spinal needle, the fetus was injected in the shoulder with either SAL, 0.5 mg/kg BETA (Celestone Soluspan, Schering Pharmaceuticals) alone, or BETA plus 60 μg/kg T_4 (BETA + T_4). A body weight of 3 kg was used to estimate hormone doses in an injection volume of 2.5 mL of SAL.

At 128-d gestation, 48 h after fetal injection, the ewes were sedated with ketamine (15–20 mg/kg, intramuscularly) and given combined spinal-epidural anesthesia (10 mL of 2% lidocaine:0.5% bupivacaine, 1:1). The head and neck of the fetus were delivered through a midline abdominal incision and hysterotomy as described previously (3, 4, 9). Fetuses received an intramuscular injection of ketamine (10 mg/kg) and acepromazine (0.1 mg/kg). The anterior neck was infiltrated with 2% lidocaine, followed by tracheotomy and insertion of a 4.5-mm endotracheal tube. Lambs were delivered, dried, weighed, and treated with 100 mg/kg surfactant (Survanta®, provided by Ross Laboratories, Columbus, OH) via direct intratracheal instillation before the first breath. Lambs were mechanically ventilated with a time-cycled, pressure-limited infant ventilator set to deliver 100% O_2. Initial ventilator settings included a positive-end expiratory pressure of 3 cm H_2O, a rate of 40 breaths/min, and an inspiratory time of 0.7 s. Peak inspiratory pressure was initially set at 35 cm H_2O and adjusted to achieve arterial P_{CO_2} values of 4–5.5 kPa. Peak inspiratory pressure was limited to 40 cm H_2O to avoid pneumothorax.

The investigators delivering and managing the preterm lambs were blinded as to treatment group. All newborn lambs were managed as described previously in delivery protocols of chronically catheterized fetuses (3, 4, 9). Procedures included: insertion of an umbilical artery catheter for blood sampling and blood gas monitoring; administration of 10 mL/kg heparinized placental blood within 5 min of delivery to all animals; insertion of a left ventricular catheter via the right carotid artery during continuous measurement of left ventricular pressure, left ventricular dP/dt and the injection of microspheres; administration of 5% dextrose in water into the umbilical artery and left ventricular catheters at a total rate of 4.5 mL/kg/h throughout the study protocol. A suprapubic cystostomy catheter was also inserted within 10 min of delivery for continuous collection of urine. Local anesthesia was given before all procedures were carried out. The data describing effects on renal (10) and pulmonary function (7) are the subject of other reports. Total administered fluid volume, blood pressure and heart rate were monitored continuously.

Arterial blood samples (0.3 mL) for measurements of pH and blood gasses were obtained every 30 min, and/or 5 min after ventilator adjustments to permit careful monitoring of ventilatory status. Blood samples (6 mL) were collected from the umbilical cord after delivery of the lamb, and from the umbilical artery catheter at 20, 60, 120, and 180 min after delivery for measurements of catecholamines, glucose, FFA, T_4, and cortisol. Blood samples were replaced with an equal volume of washed, filtered maternal red blood cells. Body temperature was monitored continuously by rectal thermistor and maintained at 39 ± 1°C using a radiant warmer, heating pad, and heat lamps. Evaluation of postnatal adaptation continued until 3 h after birth, after which time the lambs were killed with an overdose of pentobarbital (100 mg/kg).

Cardiac output was measured at 30 and 180 min after birth using radiolabeled microspheres (10). Either ^{57}Co- or ^{43}Sr-labeled microspheres of known total radioactivity (DuPont NEN, Boston, MA) were mixed with 5 mL of maternal blood just before being injected over 15 s into the left ventricle. A reference sample was simultaneously withdrawn with a Harvard pump (Harvard Apparatus Co., South Natick, MA) from the descending aortic catheter at a rate of 5 mL/min for 2 min into a preweighed, heparinized syringe. The blood volume was determined by weight, and then radioactivity was quantified in a LKB Compugamma counter equipped with automatic pulse height correction.

Analytical techniques. Blood samples were placed immediately into chilled test tubes for determination of cortisol and T_4 (lithium heparin; 40 μg/mL blood) as well as catecholamines, glucose, and FFA (4 mM EGTA and 3 mM reduced glutathione/mL blood). Tubes were mixed and centrifuged immediately at 4°C. Plasma samples were separated and frozen (−20°C) for extraction within 1–2 wk. Plasma T_3 and T_4 levels were measured with commercially available RIA kits (ICN Pharmaceuticals, Costa Mesa, CA). Plasma catecholamine levels were determined by radioenzymatic assay sensitive to 10–20 pg/mL (3, 9). FFA were measured by a microcolorimetric assay and glucose by an automated analyzer (Yellow Springs Instrument Co., Yellow Springs, OH) as described previously (3, 9). Blood pH, P_{O_2}, and P_{CO_2} values were determined at 39°C on a Radiometer blood micro acid-base analyzer

system (BMS 3 MK2; Radiometer Co., Copenhagen, Denmark).

Data analysis. All values are expressed as the mean ± SEM. Differences over time and differences between treatment groups were assessed by two-way ANOVA for repeated measures where time was the within subjects factor and treatment was the between subjects factor. When individual time points were compared, differences were identified by *t* test. Statistical significance for all analyses was accepted at $p < 0.05$. These studies were conducted with the approval of the Institutional Committee for the Care and Use of Animals.

RESULTS

Umbilical cord blood pH, blood gases, and hematocrit are shown in Table 1. There were no significant differences among the three groups. Mean body weight and individual organ weights are shown in Table 2. As noted in previous studies of chronically catheterized animals treated with corticosteroids, there was a significant reduction in lung weight in the steroid treated animals (3, 4). In the present study, the lungs of both the BETA- and BETA + T_4-treated animals were significantly lighter than in animals treated with SAL alone. There were no other significant differences in organ weights among the groups.

Cardiovascular. Serial heart rate and blood pressure values are shown in Figure 1. Heart rate was significantly higher in the BETA-treated animals than in SAL controls, $p < 0.05$, ANOVA. This difference was apparent by 120 min of age and persisted through 180 min. Both mean arterial pressure and left ventricular pressure were significantly higher in the BETA-treated animals than in SAL controls, $p < 0.01$, ANOVA. In contrast, the heart rate and blood pressure of BETA + T_4-treated animals did not differ from the controls. Cardiac output, stroke volume, and calculated systemic vascular resistance are shown in Figure 2. Left ventricular output was significantly higher at 30 min of life in each of the groups than values previously reported for fetal left ventricular output (11). Unexpectedly, cardiac output was less at 30 min of life in animals treated with the combination BETA + T_4 compared with animals treated with SAL alone, but not the BETA alone animals. By 180 min, the BETA-treated animals had significantly higher cardiac output than the animals treated with SAL alone, but it was not significantly greater than the animals treated with BETA + T_4, $p < 0.001$. Left ventricular dP/dt and left ventricular end diastolic pressure are shown in Figure 3. Left ventricular dP/dt and stroke volume were significantly higher in the BETA-treated animals than either of the other two groups, $p < 0.01$. This improved contractility was evident despite the similarity in preload in all three groups as assessed by left ventricular end diastolic pressure and despite higher

Table 1. *Plasma values in umbilical cord blood from lambs treated with SAL, BETA, or BETA + T_4 48 h earlier*

	SAL	BETA	BETA + T_4
n	9	7	7
Umbilical cord blood			
pH	7.33 ± 0.02	7.36 ± 0.01	7.31 ± 0.01
Po_2 (kPa)	4.7 ± 0.4	5.3 ± 0.3	5.1 ± 0.4
Pco_2 (kPa)	5.6 ± 0.4	5.7 ± 0.3	6.3 ± 0.5
Hematocrit (%)	4.9 ± 0.1	5.2 ± 0.3	4.9 ± 0.1

Values are means ± SEM.

Table 2. *Body and organ weights of animals treated with SAL, BETA, or BETA + T_4 48 h earlier*

	SAL	BETA	BETA + T_4
n	9	7	7
Body weight (kg)	2.6 ± 0.1	2.6 ± 0.1	2.6 ± 0.1
Heart (g)	16.8 ± 1	17.1 ± 0.7	17.4 ± 1.2
Lung (g)	123 ± 8.1	84.0 ± 6.9*	94.5 ± 4.7*
Liver (g)	65.3 ± 8.2	81.3 ± 9.4	70.8 ± 6.3
Kidney weight (g)	16.7 ± 0.6	16.6 ± 0.5	16.9 ± 1.1
Adrenal (g)	0.30 ± 0.02	0.27 ± 0.02	0.29 ± 0.02

Values are means + SEM.
* Differs from corresponding saline value ($p < 0.05$).

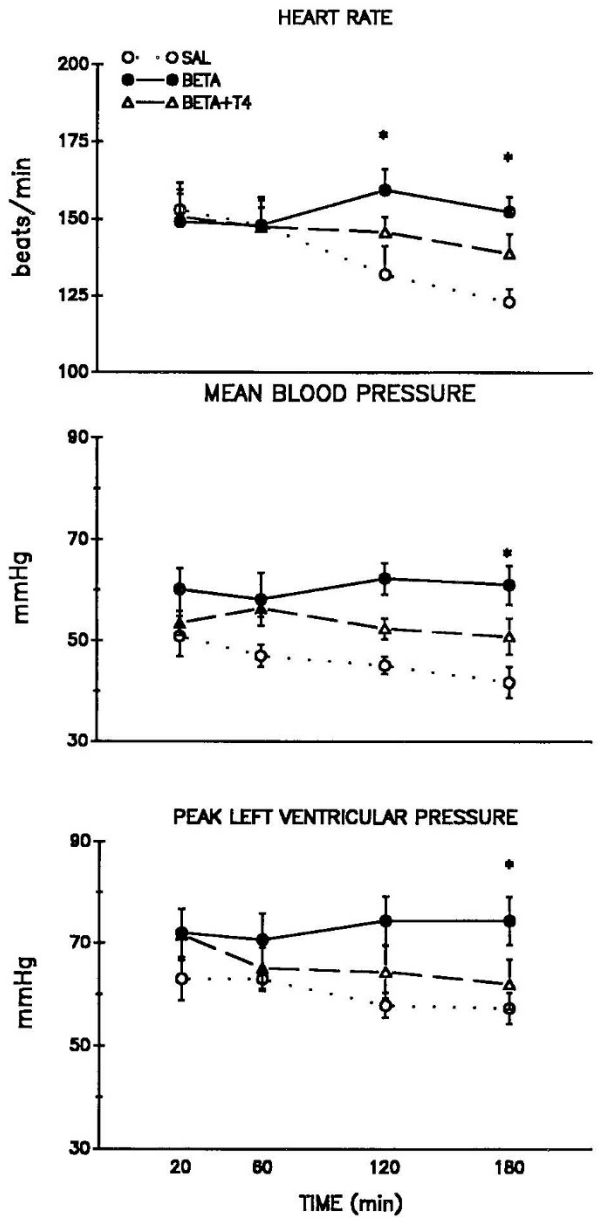

Figure 1. Serial heart rate, mean arterial blood pressure, and peak left ventricular (*LV*) pressure values in SAL-, BETA-, and BETA + T_4-treated animals. Time denotes number of minutes after birth. * denotes BETA significantly greater than SAL, by two-way ANOVA, $p < 0.05$ (±SEM).

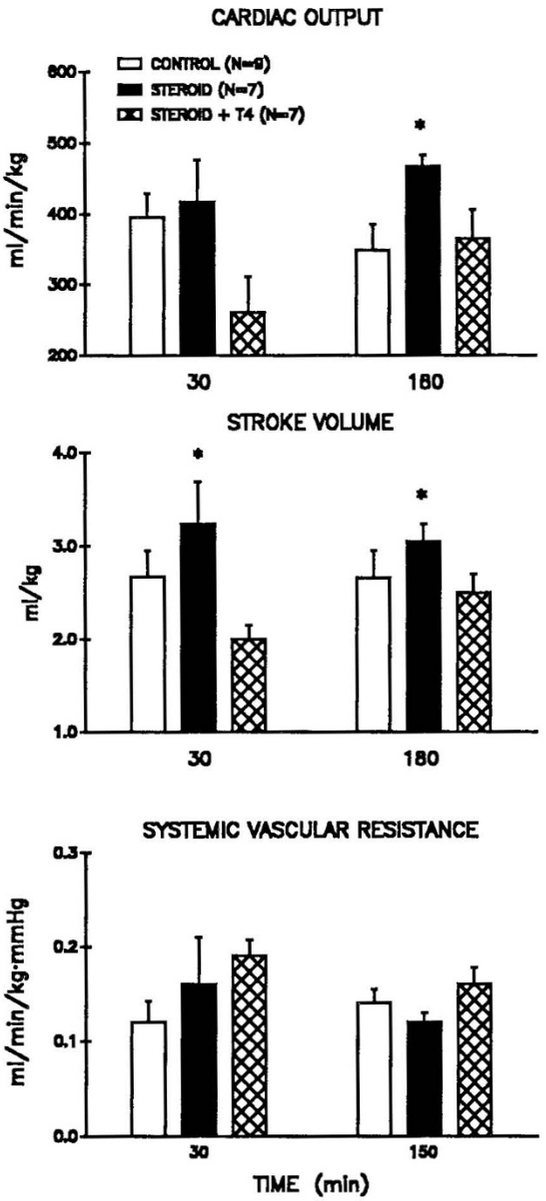

Figure 2. Cardiac output, stroke volume and calculated systemic vascular resistance at 30 and 150 min after birth in SAL-, BETA-, and BETA + T_4-treated animals. Cardiac output was determined by radiolabeled microspheres. * denotes BETA significantly greater than SAL, by two-way ANOVA, $p < 0.05$ (±SEM).

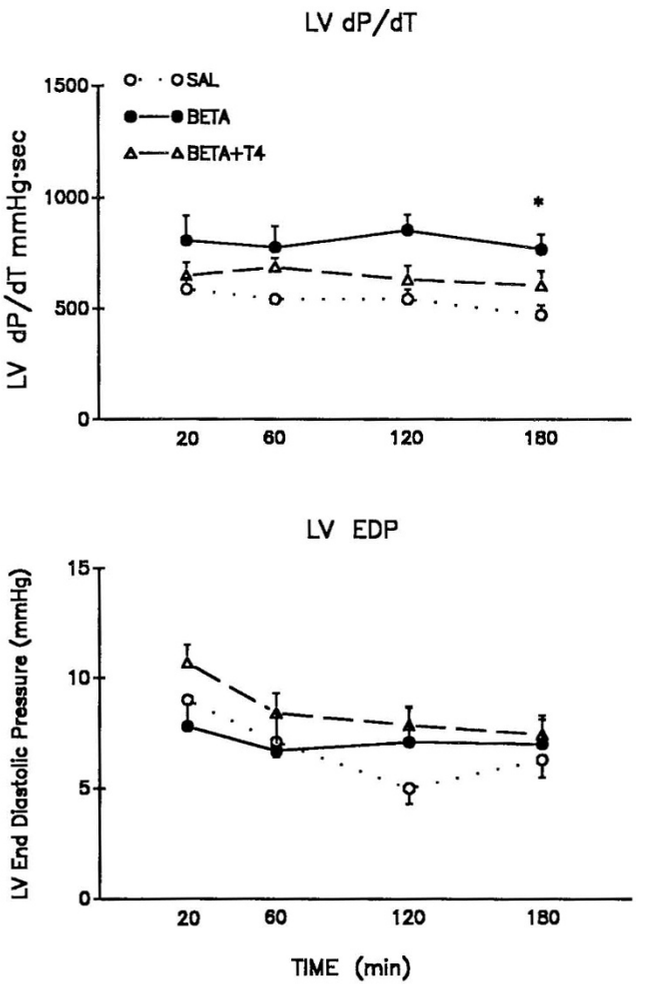

Figure 3. Left ventricular dP/dt and left ventricular end diastolic pressure (*EDP*) in SAL-, BETA-, and BETA + T_4-treated animals. Time denotes number of minutes after birth. * denotes BETA significantly greater than SAL, by two-way ANOVA, $p < 0.05$ (±SEM).

mean arterial pressures and calculated systemic vascular resistances in the BETA-treated animals at 30 min of age, $p < 0.05$. Calculated systemic vascular resistance was similar in all three groups at 180 min.

Metabolic. Plasma glucose and FFA levels after delivery are shown in Figure 4. Blood glucose levels did not change after birth, and there were no differences among the groups. There was a modest but significant overall increase in FFA after birth, 80 ± 5 μM/L before delivery *versus* 131 ± 13 μM/L at 180 min. However, there were no significant differences among the groups in postnatal FFA responses.

Endocrine. Circulating plasma catecholamine concentrations are shown in Figure 5. Both circulating norepinephrine and epinephrine levels increased significantly after delivery in SAL-treated lambs. By contrast in both the animals treated with BETA alone or BETA plus T_4, the increase in levels of both catecholamines was blunted. The plasma levels of T_3 and T_4 were measured in the umbilical cord samples and after birth at 30, 60, 120 and 180 min. The cord blood and levels at 120 min are shown in Table 3. The maximum increase in T_3 occurred at 120 min. As can be seen, the single injection of BETA was associated with a significant increase in T_3 concentration in cord blood and in the peak response at 120 min of life, $p < 0.05$. The plasma T_3 concentration at 120 min in the animals treated with BETA alone was significantly greater than that seen in the animals treated with BETA + T_4.

DISCUSSION

The present studies were carried out to assess the effects of direct fetal hormone administration on postnatal cardiovascular and metabolic function and to compare responses with those reported in chronically catheterized animals. We showed that a single fetal treatment with glucocorticoids results in significantly greater mean arterial pressure, cardiac output, and cardiac contractility than in SAL-treated control animals. Taken

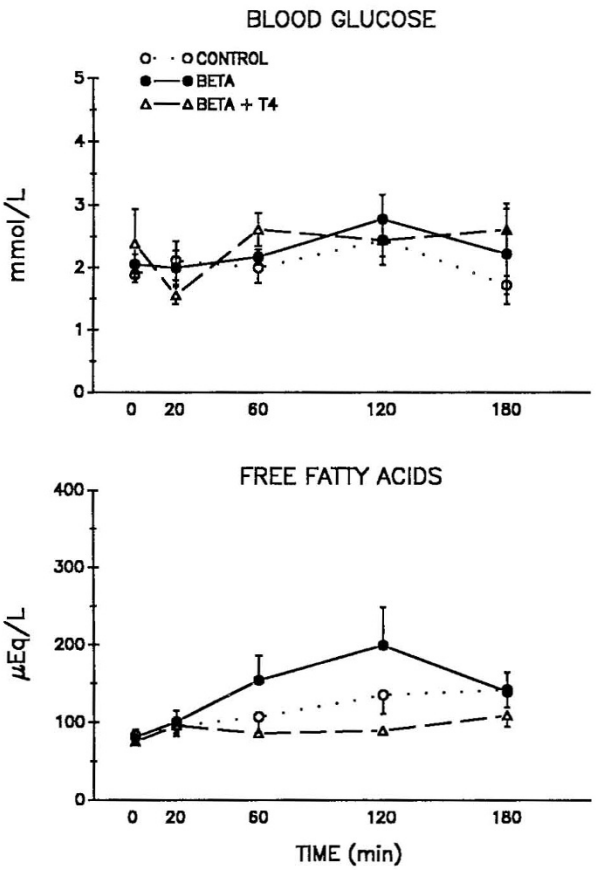

Figure 4. Serial plasma glucose (mmol/L) and FFA (μM/L) in SAL-, BETA-, and BETA + T_4-treated animals (±SEM). See text for details of treatment. Time denotes number of minutes after birth where time 0 indicates umbilical cord levels just before the time of cord cutting.

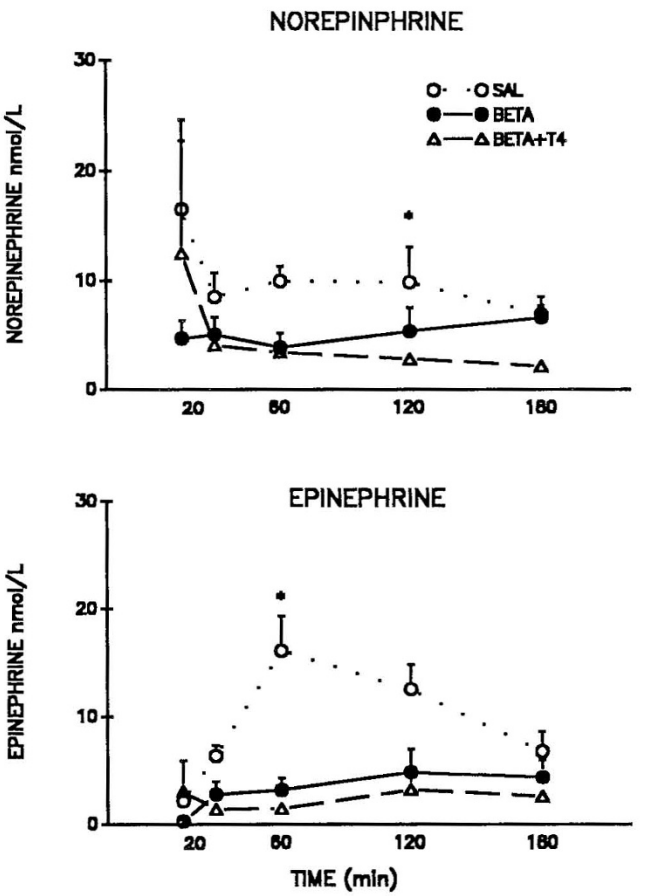

Figure 5. Serial plasma norepinephrine and epinephrine concentrations (pg/mL) in SAL-, BETA-, and BETA + T_4-treated animals. Time denotes number of minutes after birth where time 0 indicates umbilical cord levels just before the time of cord clamping. * denotes SAL significantly greater than BETA or BETA + T_4 by two-way ANOVA, $p < 0.05$ (±SEM).

Table 3. *Plasma T_3 and T_4 concentrations in cord blood and at 120 min in animals treated with SAL, BETA, or BETA + T_4 48 h earlier*

	T_3 (nmol/L)		T_4 (nmol/L)	
	Cord blood	120 min	Cord blood	120 min
SAL	1.3 ± 0.3	1.5 ± 0.2	103 ± 8	120 ± 9
BETA	3.0 ± 0.6*	4.3 ± 0.8*	109 ± 13	125 ± 9
BETA + T_4	1.9 ± 0.3*	2.3 ± 0.3*	108 ± 9	109 ± 5
	Cortisol (μg/dL)			
	Cord blood	60 min	120 min	180 min
SAL	1.1 ± 0.2	1.9 ± 0.4	1.8 ± 0.3	1.9 ± 0.3
BETA	0.9 ± 0.1	1.1 ± 0.3	1.5 ± 0.4	1.8 ± 0.4
BETA + T_4	1.6 ± 0.2	2.2 ± 0.3	2.0 ± 0.2	2.6 ± 0.3

Values are means ± SEM.
* Significantly > SAL, $p < 0.05$.

together with earlier studies in chronically catheterized animals and the results of clinical trials (3, 4, 12, 13), the present results add to the appreciation that significant augmentation in cardiovascular function at birth is also seen after fetal corticosteroid treatment.

A number of nonpulmonary neonatal morbidities are reduced after maternal steroid administration. These include intraventricular hemorrhage (1, 14–16), periventricular leukomalacia (16), necrotizing enterocolitis (17), and patent ductus arteriosus (12, 15–18). An important role for disordered blood pressure regulation and of hypotension in the etiology of intraventricular hemorrhage and periventricular leukomalacia has been established in both animal models (19) and humans (16, 20–24). Hemodynamic instability and hypotension, whether as a result of sepsis or asphyxia, are also important in the pathogenesis of necrotizing enterocolitis (25). The clinical relevance of the observations in the present study may be that corticosteroid induced improvements in cardiovascular function are involved in the reduction in incidence or severity of these complications in infants whose mothers received antenatal hormone treatment.

We chose to evaluate the additive effects of T_4 with BETA rather than T_3 because preliminary studies showed a greater improvement in lung compliance and lung volume with T_4 than T_3 when each was given in combination with corticosteroids by direct fetal injection (8). We evaluated T_4 at a dose of 60 μg/kg in combination with BETA. In fact, the daily production rate of T_4, 40–50 μg/kg/d, suggests this was a reasonable strategy to generate maximal effects. Unexpectedly, we found that administration of T_4 in combination with corticosteroids did not augment postnatal cardiovascular responses. Pulmonary function was neither augmented nor deleteriously affected. The mechanism(s) for the apparent inhibitory effect of the higher dose of T_4 on BETA-induced improvement in cardiovascular

function is not known. It is possible that a lower dose of T_4 would have been associated with more salutary cardiovascular effects than we observed. Further studies are needed to optimize the combination of corticosteroids, thyroid hormones, and other agents for fetal maturation.

In adult animals hyperthyroidism induces cardiac hypertrophy and increased cardiac contractility (26, 27). The effects of thyroid status on development of the cardiovascular system in fetal sheep is complex. Thyroidectomy of preterm fetal sheep significantly depresses the normal increases in blood pressure, cardiac output and oxygen consumption in animals born at term (11, 28). The latter effect is due in part to impairment of the ontogenetic increase in myocardial β-adrenergic receptors and β-receptor-stimulated adenyl cyclase (28). Thyroidectomy results in hypotension, obtunded blood pressure, and blunted catecholamine responses to induced hypoxia in chronically catheterized fetal sheep (29). The reductions in blood pressure and myocardial performance at birth after fetal thyroidectomy may be secondary to structural alterations or altered expression of myocardial isomyosin subtypes (30). Adrenergic mechanisms are also important in the increase in lung distensibility, lung stability, and surfactant flux seen after the combination of cortisol and TRH (31).

We evaluated alterations in growth by measuring body and organ weights. Studies in rats and rabbits have shown intrauterine growth retardation in corticosteroid-treated fetuses (32–34); similar effects have not been observed in sheep (3, 4) or humans (1). This adverse impact on intrauterine growth and significantly increased fetal mortality (34, 35) suggests that studies in small mammalian species are less relevant to the responses one sees in larger animals or humans. The greater reduction in lung wet weight noted after treatment with corticosteroids either alone or in combination with T_4 is consistent with the interpretation of enhanced lung fluid absorption due to corticosteroid-induced acceleration of this response. As noted by Barker *et al.* (36), the resorption of lung fluid does not normally occur until after 130 d of gestation. Resorption of fetal lung fluid is augmented by adrenergic mechanisms, and this response can be induced precociously in thyroidectomized fetal lambs treated with both glucocorticoids and thyroid hormone.

One of the important metabolic adaptations to postnatal life is a brisk increase in circulating glucose and FFA after birth (37, 38). Lipolysis with resultant increase in FFA and glycerol is vital to postnatal survival (38). The magnitude of this response is greater in mature newborn animals than in prematurely delivered sheep (39). We anticipated that antenatal hormone treatment of these preterm animals might augment this adaptive response (40, 41). As was seen for the cardiovascular effects, it is possible that a lower dose of T_4 may have augmented the FFA responses as had been anticipated. The results of the thyroid hormone assays demonstrate that antenatal BETA exposure augments fetal umbilical and postnatal circulating T_3 levels. The mechanism for this effect is presumed to be induction of the hepatic monodeiodinase activity responsible for T_4 to T_3 conversion (8, 42). The dose of T_4 we used in combination with BETA in the present study blunted both the prenatal and postnatal increase in T_3, presumably via suppression of thyroidal T_4 secretion. There was little effect of the antenatal T_4 injection on umbilical cord blood T_4 concentration or postnatal levels. As noted in previous studies using chronically catheterized animals infused with corticosteroids alone or in combination with TRH, antenatal exposure of the fetus to corticosteroids is also associated with a significant blunting of the usual exponential increase in circulating catecholamines (3, 4). Similar results were seen in the present studies where fetal hormone exposure was achieved with a single fetal intramuscular injection. The explanation for this effect is not known.

In summary, we showed that a single, direct fetal injection of BETA improved blood pressure, cardiac contractility, and cardiac output at birth. These effects were largely inhibited when the animals were also treated with a large dose of T_4. We believe that some form of direct fetal treatment will be part of clinically relevant approaches to improving fetal maturation in the future. Such an approach allows the use of agents which may not reach the fetus via the placental circulation or are contraindicated maternally. The present studies demonstrate the importance of prior testing to optimize dose and treatment combinations.

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