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Reversible Umbilical Cord Occlusion: Effects on Thermogenesis *In Utero*

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ABSTRACT. The initiation of thermogenesis at birth is an important adaptation for survival. We examined the sequential effects of cooling, increased oxygenation, and repeated episodes of umbilical cord occlusion on nonshivering thermogenesis in six fetal sheep at 139 to 145 d of gestation. The fetal sheep were cooled by circulating cold water through a coil placed around the trunk for 4 h. The fetal core temperature fell 2.47 ± 0.24°C in the first 60 min of cooling with minimal changes in plasma FFA and glycerol levels. After fetal arterial O_2 tension was increased above 6.65 kPa by ventilation, fetal temperature and thermogenic indices rose significantly in 60 min. After occlusion of the umbilical cord by a reversible occluder cuff, plasma FFA levels rapidly increased to 635 ± 69 μEq/L ($p < 0.005$) by 30 min, fetal temperature increased a further 0.96 ± 0.20°C ($p < 0.001$) and fetal O_2 consumption peaked at 25.3 ± 4.9 $mL \cdot min^{-1} \cdot kg^{-1}$. Release of cord occlusion caused a rapid fall in FFA to 149 ± 23 μEq/L ($p < 0.005$) and a fall in fetal core temperature of 0.90 ± 0.13°C ($p < 0.001$) in 30 min. After irreversibly snaring the umbilical cord, the plasma FFA rose to 611 ± 83 μEq/L ($p < 0.005$) and the fetal temperature rose 0.78 ± 0.09°C ($p < 0.02$). The effects on thermogenesis of interrupting and reestablishing placental flow are rapid and reversible and suggest the presence of placental inhibitors of brown adipose tissue thermogenesis. (*Pediatr Res* 30: 513–517, 1991)

Abbreviations

T_3, 3,5,3′ triiodothyronine

A rapid fall in environmental temperature accompanies the transition from intrauterine to extrauterine existence, and effective thermogenesis is essential to neonatal adaptation. Studies on temperature regulation have shown the importance of thermal homeostasis in reducing the mortality rate of low birth weight infants. The mortality in preterm infants subjected to cold stress is dependent upon the degree and duration of hypothermia (1, 2).

The demand for heat production is often maximal at the moment of birth, and the brown adipose tissue thermogenic response to chilling in newborn infants and precocial species such as the lamb is mediated by the sympathetic nervous system. Norepinephrine may increase oxygen consumption and heat production more than 3-fold (3, 4). The mammalian fetal environment is relatively thermostable, and the fetus does not appear to regulate its temperature independently of the mother (5). We have shown in previous studies of the fetal sheep that cooling the amniotic fluid by means of a coil placed around the fetal trunk fails to provoke nonshivering thermogenesis (6). However, shivering and appropriate cardiovascular (7) and endocrine responses including elevations of plasma catecholamines (8), thyrotropin (9), and cortisol (6) are stimulated by cooling *in utero* as early as 110 d gestation. Oxygenation of the cooled fetal sheep by ventilation *in utero* caused only a limited thermogenic response, whereas subsequent umbilical cord occlusion was followed by substantial nonshivering thermogenesis associated with increased oxygen consumption and heat production (10). One explanation of these findings was that the placenta produced factors that inhibited nonshivering thermogenesis *in utero*. The aim of this study was to further investigate this hypothesis.

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MATERIALS AND METHODS

Surgical preparation. Operations were performed on six pregnant Romney ewes at 139–145 d of gestation under halothane-O_2 anesthesia using aseptic techniques as previously described (11). Polyvinyl catheters were implanted into the fetal carotid artery, jugular vein, amniotic sac, and also into the maternal femoral artery and tarsal vein. Calibrated thermistors were placed in the fetal esophagus and maternal vena cava to record core body temperatures. Another thermal thermistor was placed near a fetal kidney to measure perirenal brown fat temperatures, because this is one of the major sites of brown adipose tissue in the lamb (12). A 5-m coil of plastic tubing was placed around the fetal thorax and neck. A loop of umbilical tape was placed loosely around the umbilical cord, and in addition a reversible cord occluder was placed around the umbilical cord. A tracheal cannula (6 mm outer diameter) was inserted and connected to a length of tubing (7 mm inner diameter; dead space 15 mL) to later ventilate the fetus (10). The breathing tube, thermistor leads, afferent and efferent arms of the cooling coil, snare, reversible cord occluder, and catheters were exteriorized through an incision in the maternal flank. After the operation the ewes were housed in a metabolic cage at a constant temperature of 16°C and 50% relative humidity and given free access to water, hay supplemented by alfalfa, corn, and sheep nuts. The animals were studied 24 h after surgery.

Experimental procedures. After suitable amplification, fetal arterial pressure, heart rate, tracheal pressure, and amniotic pressure were displayed on a polygraph. Fetal and maternal temperature measurements were made continuously using a five-channel, microprocessor-controlled, amplified transducer unit with a resolution of 0.01°C (11).

The effects of reversible cord occlusion. The following day, six fetal sheep were studied after a 30-min control period. Cooling was begun by passing cold water (14–19°C) through the coil at a rate of 160 to 290 mL/min, adjusted so that the fetal core temperature fell 2–3°C during the first hour of cooling (5). One h later, fluid was drained from the lungs and the tracheal tube connected to ventilate the lungs with O_2 from a closed rebreath-

ing circuit. This consisted of a respiratory pump (model 607; Harvard Apparatus Co., Inc., S. Natick, MA), a liter spirometer, one-way valving, and a CO_2 absorber. The ventilator settings were adjusted to maintain fetal arterial P_{CO_2} in the range 5.3–7.3 kPa (40–55 torr) and a P_{O_2} above 6.7 kPa (50 torr) throughout the rest of the experiment. After 1 h of ventilation, the reversible umbilical cord occluder was inflated by injecting a measured volume of saline. After 30 min of occlusion, the saline was withdrawn, thus reestablishing umbilical flow. Ventilation and cooling were then continued for an additional 30 min. To conclude the experiment, the snare around the umbilical cord was pulled tight, thus causing irreversible cord occlusion; responses were followed for an additional 1 h in isolation from the placenta.

Fetal carotid arterial blood samples (2.8 mL) were collected anaerobically every 15 min throughout the experiment and analyzed promptly for pH and blood gases. The plasma was then removed after centrifugation and stored at −20°C for later analysis.

After completion of the experiment, the ewe and fetus were killed with an overdose of barbiturate. The closed rebreathing circuit was checked for leaks. The location of the thermistors was verified, as was the complete occlusion of the umbilical cord. The fetus was weighed to the nearest gram. The thermistors were recalibrated to establish that their characteristics had not changed during implantation.

These studies were approved by the Animal Ethics Committee of the Auckland Medical School.

Analytical procedures. P_{O_2}, P_{CO_2}, and pH were measured at 39°C using microelectrodes (ABL330; Radiometer, Copenhagen, Denmark). Observed values were corrected to the body temperatures of the fetus (13). Plasma FFA were determined using the colorimetric method of Falholt *et al.* (14). Palmitic acid was used as the standard, and a sample size of 0.1 mL was used to increase sensitivity. Glycerol was analyzed after enzymatic conversion with glycerokinase by using the method of Pinter *et al.* (15). The within- and between-assay coefficients of variation were 2.2 and 4.1% for the glycerol assay and 9.0 and 14.1% for the FFA assay, respectively. The volume change in the spirometer with time was used as an index of O_2 uptake rate by the lungs. Slopes were averaged, the time to use 1 L was measured, and oxygen uptake was expressed as mL of O_2 standard temperature and pressure dry/min/kg of fetal weight. Before cord occlusion, pulmonary oxygen uptake included use by placental tissue as well as fetal tissue. After cord occlusion, pulmonary oxygen uptake became equal to the rate of oxygen consumption by the fetus alone.

Data analysis. Results are shown as mean ± SEM. Statistical comparisons were made by two-way analysis of variance with phase and time from the initiation of each intervention as repeated measures, and between the means at the start of each episode of the study and experimental values at the end of that episode using the paired *t* test. Repetitive measures to the control value were not examined.

RESULTS

Effects of reversible cord occlusion. Six fetuses with a gestation of 141 ± 1 d and weight of 4125 ± 708 g were studied.

Effects of cooling. After 60 min of cooling the fetal environment, the fall in fetal core temperature was 2.47 ± 0.24°C and the maternal temperature fell 0.08 ± 0.06°C (Fig. 1). The fetal maternal temperature gradient was thus reversed. The effects of cooling on fetal blood gases and pH are shown in Table 1. The fetuses became hypoxemic during cooling as previously reported (5). Plasma FFA and glycerol levels showed no significant response to 60 min of cooling. Plasma glucose rose from 0.62 ± 0.03 to 1.37 ± 0.09 mmol/L ($p < 0.001$) and plasma lactate rose from 3.3 ± 0.4 to 7.9 ± 0.4 mmol/L ($p < 0.001$).

Ventilation with oxygen. Effective ventilation with oxygen was typically achieved within 13 min, and the fetal arterial P_{O_2} was maintained above 6.65 kPa for the rest of the study (Table 1). The rate of cooling continued unchanged from that achieved during the preventilation phase, yet after 60 min of oxygenation the fetal core temperature had risen 0.92 ± 0.24°C ($p < 0.02$). The fetal plasma FFA and glycerol concentrations also rose from 78 ± 16 to 183 ± 29 μEq/L ($p < 0.01$) and from 204 ± 19 to 370 ± 41 mM/L ($p < 0.02$), respectively, from the values after 60 min of cooling (Fig. 2). The plasma glucose and lactate concentrations did not show any further changes.

Umbilical cord occlusion. After 30 min of occlusion of the umbilical cord, there was a rapid rise in fetal core temperature of 0.96 ± 0.20°C ($p < 0.001$) and plasma FFA and glycerol concentrations to 635 ± 69 μEq/L ($p < 0.005$) and 640 ± 51 mM/L ($p < 0.01$), respectively, from values at the end of the oxygenated period (Fig. 2). The oxygen consumption of the fetus peaked after occlusion at 25.3 ± 4.9 $mL \cdot min^{-1} \cdot kg^{-1}$. Plasma

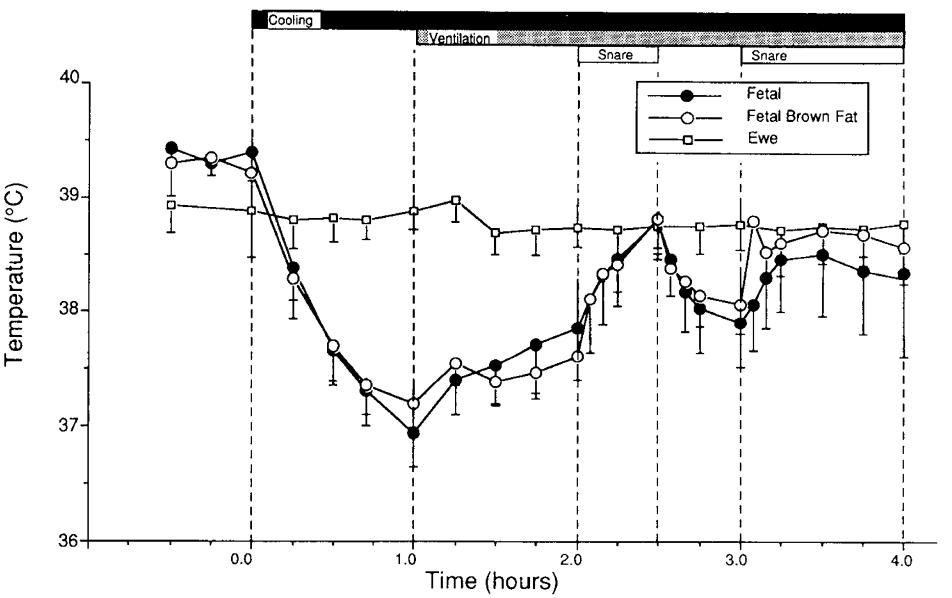

Fig. 1. Time course of responses of fetal core and brown fat temperatures and ewe temperatures during cooling, oxygenation, and two episodes of umbilical cord occlusion (*Snare*). Means and SEM for six fetal sheep are shown. ●, Fetal core temperature; ○, fetal brown fat temperature, □, ewe temperature.

Table 1. *Changes in fetal arterial blood gases and pH in response to cooling, ventilation with oxygen, and reversible and then irreversible umbilical cord occlusion**

	Time (min)	Pa_{O_2}	Pa_{CO_2}	pH
Control	−30	2.99 ± 0.16	7.55 ± 0.31	7.41 ± 0.01
	0	2.83 ± 0.09	7.38 ± 0.39	7.42 ± 0.01
Cooling	+30	2.27 ± 0.07	7.54 ± 0.23	7.37 ± 0.01
	+60	2.17 ± 0.07	7.29 ± 0.31	7.36 ± 0.01
Ventilation	+30	6.93 ± 0.72	8.83 ± 0.73	7.26 ± 0.04
	+60	7.14 ± 0.64	7.73 ± 0.35	7.33 ± 0.03
Snare cord	+15	7.34 ± 0.94	9.03 ± 0.55	7.30 ± 0.04
	+30	7.67 ± 1.26	8.05 ± 0.88	7.36 ± 0.04
Release snare	+15	7.78 ± 0.69	7.01 ± 0.45	7.37 ± 0.03
	+30	7.30 ± 1.05	7.46 ± 0.65	7.35 ± 0.03
Snare cord	+15	6.48 ± 0.52	8.06 ± 0.35	7.33 ± 0.02
	+30	6.69 ± 1.36	6.18 ± 0.45	7.44 ± 0.03
	+60	7.05 ± 1.26	5.61 ± 0.43	7.48 ± 0.03
	+90	7.22 ± 0.92	6.49 ± 0.59	7.43 ± 0.05

* $n = 6$, mean ± SEM. Pa_{O_2}, arterial O_2 tension; Pa_{CO_2}, arterial CO_2 tension.

glucose concentration was 1.73 ± 0.29 mmol/L, and lactate fell to 5.6 ± 0.6 mmol/L ($p < 0.05$) by 30 min.

Release of umbilical cord occlusion. Within 30 min of the reestablishment of umbilical cord circulation by the release of the umbilical cord occluder, the fetal core temperature fell 0.90 ± 0.13°C ($p < 0.001$) (Fig. 1). Plasma FFA concentration fell to 149 ± 23 μEq/L ($p < 0.005$), and plasma glycerol also showed a decline to 574 ± 114 mM/L (NS) (Fig. 2). The plasma glucose level was 1.70 ± 0.26 mmol/L, and lactate rose ($p < 0.04$) to 7.9 ± 1.1 mmol/L.

Irreversible umbilical cord occlusion. When the umbilical cord circulation was then occluded irreversibly by tightening the tape around the umbilical cord, thermogenic responses were again rapidly initiated. Within 30 min the fetal core temperature rose 0.78 ± 0.09°C ($p < 0.02$). There were no significant changes in maternal temperatures throughout the study (Fig. 1). The plasma FFA and glycerol concentration increased to 611 ± 83 μEq/L ($p < 0.005$) and 689 ± 109 mM/L, respectively, compared with the values after the release of cord occlusion (Fig. 2). These FFA and glycerol levels were 3- to 10-fold greater than mean control values and remained elevated for the remainder of the study. The oxygen consumption was 24.6 ± 4.7 $mL \cdot min^{-1} \cdot kg^{-1}$ 30 min after irreversible cord occlusion. The plasma glucose level was 1.53 ± 0.45 mmol/L and lactate fell to 6.2 ± 1.1 mmol/L ($p < 0.03$).

DISCUSSION

Nonshivering thermogenesis begins shortly after birth and is very well developed in the postnatal term lamb (4). Even preterm lambs delivered after glucocorticoid induction of premature parturition have the ability, although reduced, for nonshivering thermogenesis (16). In contrast, cooling the near-term fetal lamb *in utero* caused only very limited changes in FFA and glycerol levels in this and previous studies (6, 10, 17). Similarly, an infusion of norepinephrine in the fetal lamb caused only a minor increase in lipolysis (18) and oxygen consumption (from 8.2 to 10.2 mL/kg/min) (19), but no rise in fetal temperature (17). The remarkable capacity for thermogenesis of brown adipose tissue depends on the amount of uncoupling protein (thermogenin); this has been identified in the mitrochondria of the brown fat of human infants (20) and, in the fetal calf and lamb, is present by the beginning of the 3rd trimester (21).

An increase in oxygen delivery to brown adipose tissue is required for nonshivering thermogenesis, and an increased blood flow to brown fat occurs during fetal cooling (22). With the increased blood oxygen tension that followed ventilation with oxygen in the fetal lamb, the rise in plasma FFA and glycerol was modest in this as in our previous studies (10, 23). Our observations suggest that separation from the placenta is necessary for maximal nonshivering thermogenesis. Umbilical cord occlusion was the signal for a rapid increase in thermogenesis, whereas the release of cord occlusion was followed by an equally

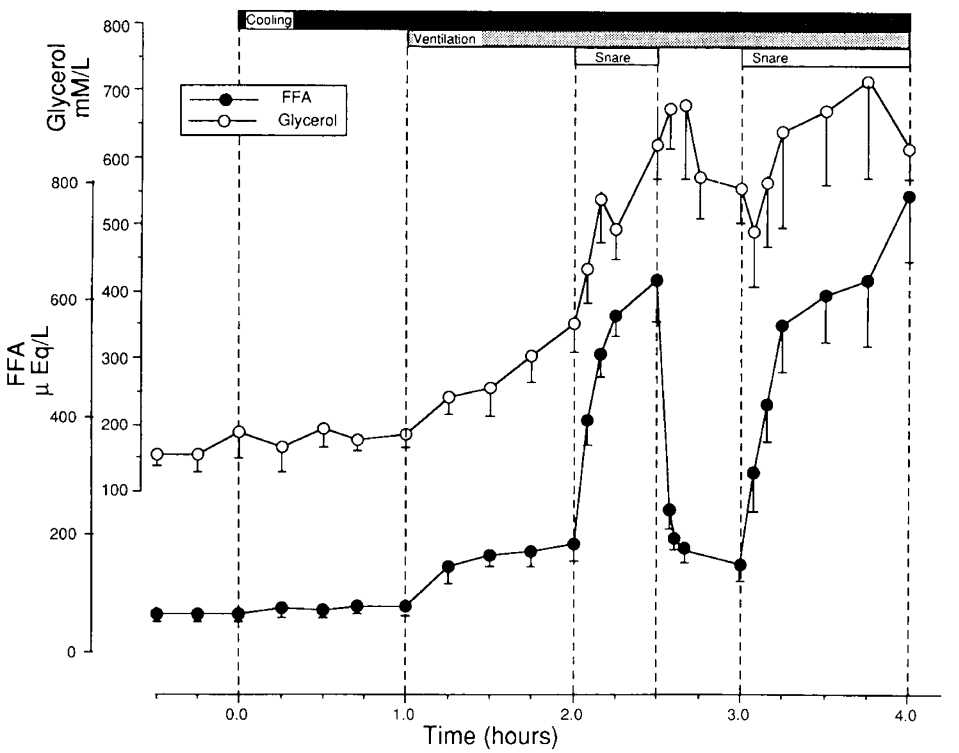

Fig. 2. Time course of responses of fetal plasma FFA and glycerol concentrations during cooling, ventilation with oxygen, and two episodes of umbilical cord occlusion (*Snare*). Means and SEM for six fetal sheep are shown. ●, FFA concentration; ○, glycerol concentration.

rapid fall in thermogenesis. Umbilical cord occlusion is not associated with a change in the metabolic clearance rate of glycerol (24) or FFA (Power GG, personal communication), so the increase in these lipolytic indices that we observed after cord occlusion was not due to kinetic changes.

Under basal conditions, 85% of the heat transfer from the fetus to the ewe occurs across the placenta (25). With the interruption of the placental circulation, the fetus is only able to lose heat through the uterus to the ewe and through the abdominal wall and then only if the temperature gradient is from fetus to ewe. In our study, as a result of passing cold water through a coil encircling the fetal thorax in the amniotic fluid, the fetal core temperature was below that of the ewe before umbilical cord occlusion, so the balance of heat transfer under these study conditions would be from the ewe to the fetus. Interruption of the placental circulation would stop this transfer of heat to the fetus; thus, the rapid rise seen in fetal temperature after umbilical cord occlusion must have been due to the initiation of brown adipose tissue thermogenesis.

In the present study, after cord occlusion the increase in fetal temperature was both rapid and of large amplitude; plasma FFA and glycerol increased 3- to 10-fold, and the fetal oxygen consumption peaked at 25.3 ± 4.9 mL/min^{-1}·kg^{-1}. All of these indices of brown adipose tissue heat production fell rapidly when umbilical cord occlusion was released.

There are several possible explanations for the effects of separation from the placental circulation that we observed.

The neonatal surge in plasma T_3 has been suggested as the signal for the initiation of nonshivering thermogenesis by Fisher and Klein (1980) (26), and circulating T_3 levels rise rapidly after cord snare in the lamb (10, 27). Thyroidectomy in midgestation resulted in the birth of profoundly hypothermic lambs that died (28). Thyroidectomy at 133 d gestation in fetal sheep was associated with reduced neonatal serum FFA levels and rectal temperatures (29). In contrast, acute thyroidectomy during delivery abolished the postnatal surge in plasma T_3 concentration, but there was no significant difference in oxygen consumption compared with controls (30). This may be due to the long half-life of thyroxine, which would allow intracellular conversion of thyroxine to T_3 to continue in the brown adipocyte. We have infused cooled, ventilated fetal lambs with a large dose of T_3 for 30 min, and this had no effect on the degree of nonshivering thermogenesis in the fetus (23). It appears that intracellular T_3 is an essential prerequisite for neonatal thermogenesis, but the circulating T_3 surge after delivery is not regulatory (29, 30).

Plasma catecholamine concentrations rise dramatically at birth in the human infant and lamb (31, 32). Catecholamines do not cross the placenta and in the fetal lamb increase after hypothermia (8), hypoxia (33), hemorrhage (34), labor (32), and umbilical cord cutting (35). The surge in catecholamine that occurs at birth is associated with a rise in plasma FFA levels. It has been suggested by Padbury *et al.* (35, 36) that this is the primary signal for the initiation of nonshivering thermogenesis. In previous studies (8, 23), the initial surge in plasma catecholamines after cooling without ventilation or cord snare was not accompanied by nonshivering thermogenesis. If brown adipose tissue responded *in utero* to the huge increases in circulating catecholamines that follow hypoxic stimuli (33) or labor (32) with nonshivering thermogenesis, the resulting increase in oxygen demand and heat production would jeopardize fetal survival.

We must therefore consider the possibility of a factor or factors secreted by the placenta that can inhibit nonshivering thermogenesis *in utero* in the presence of elevated circulating catecholamines. This placental inhibitor must be withdrawn for the initiation of maximal nonshivering thermogenesis and must therefore have a short half-life, inasmuch as nonshivering thermogenesis is rapidly initiated after umbilical cord occlusion and is equally rapidly suppressed when the cord occlusion is released. The presence of such inhibitor(s) would be of benefit to neonatal adaptation.

There are many possible placental inhibitors. For example, substances such as prostaglandin E_2 are antilipolytic (37) and are produced by the placenta (38). Another possible placental inhibitor is adenosine, which is an important regulator of metabolism in brown adipose tissue (39). Adenosine is found in perfusates of human placenta (40). Both fetal plasma prostaglandin E_2 (41) and adenosine (42) have been shown to fall after umbilical cord occlusion. The withdrawal of an inhibitor(s) at birth by separation from the placenta would allow the rapid initiation of nonshivering thermogenesis in the newborn in response to sympathetic stimulation.

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