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Hindlimb glucose and lactate metabolism during umbilical cord compression and acute hypoxemia in the late-gestation ovine fetus

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Abstract

The metabolic adaptation of the hindlimb in the fetus to a reversible period of adverse intrauterine conditions and, subsequently, to a further episode of acute hypoxemia has been examined. Sixteen sheep fetuses were chronically instrumented with vascular catheters and transit-time flow probes. In nine of these fetuses, umbilical blood flow was reversibly reduced by 30% from baseline for 3 days (umbilical cord compression), while the remaining fetuses acted as sham-operated, age-matched controls. Acute hypoxemia was subsequently induced in all fetuses by reducing maternal fractional inspired oxygen concentration for 1 h. Paired hindlimb arteriovenous blood samples were taken at appropriate intervals during cord compression and acute hypoxemia, and by using femoral blood flow and the Fick principle, substrate delivery, uptake, and output were calculated. Umbilical cord compression reduced blood oxygen content and delivery to the hindlimb and increased hindlimb oxygen extraction and blood glucose and lactate concentration in the fetus. However, hindlimb glucose and oxygen consumption were unaltered during umbilical cord compression. In contrast, hindlimb oxygen delivery and uptake were significantly reduced in all fetuses during subsequent acute hypoxemia, but glucose extraction, oxygen extraction, and hindlimb lactate output significantly increased in sham-operated control fetuses only. Preexposure of the fetus to a temporary period of adverse intrauterine conditions alters the metabolic response of the fetal hindlimb to subsequent acute stress. Additional data suggest that circulating blood lactate may be derived from sources other than the fetal hindlimb under these circumstances. The lack of hindlimb lactate output during acute hypoxemia in umbilical cord-compressed fetuses, despite a significant fall in oxygen delivery to and uptake by the hindlimb, suggests that the fetal hindlimb may not respire anaerobically after exposure to adverse intrauterine conditions.

hypoxia

THE MAJOR SUBSTRATES for oxidative metabolism in the fetus and thus the primary substrates for fetal growth have long been recognized as glucose, lactate, and amino acids (6). Significant reductions in the availability of any of these substrates or of oxygen itself precipitate a number of adaptive responses in the fetus that maintain the supply of oxygen and substrates to essential organs such as the brain and heart (24, 34). The nature of this fetal adaptation depends on the timing, duration, and severity of the nutrient deprivation. For oxygen, moderate reductions in delivery (40–50%) for up to 24 h, induced by restriction of

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either umbilical or uterine blood flow, are tolerated adequately by the fetus, as total oxygen consumption is maintained by an increase in the efficiency of oxygen extraction (8, 23). Indeed, only when oxygen delivery to the fetus is reduced by >50% does whole body oxygen consumption fall (23, 43). Therefore, in the short term, the fetus would appear to have a considerable margin of safety for fetal tissue oxygenation (32). However, in the longer term, this is not the case. Indeed, if oxygen delivery is reduced by a smaller amount (30-40%) but is extended beyond 24 h, the apparent margin of safety is lost, and consequently, fetal oxygen consumption becomes a linear function of oxygen delivery (3). Whole body oxygen consumption therefore falls (3), and fetal growth is restricted (2, 25).

Similarly, 5 days' global reduction in fetal energy supply produced by maternal fasting had little effect on whole body fetal oxygen or amino acid consumption (29). However, reductions in fetal energy supply for longer periods, secondary to maternal fasting for weeks, result in a slowing of fetal growth rate, which may then be subsequently restored on maternal refeeding (18), indicating a degree of metabolic adaptation in the fetus during the period of nutrient deprivation. For individual organs, metabolic adaptation to a global reduction in energy supply is more pronounced and results in elevated hepatic glucose output, reduced hepatic lactate uptake, (35) and an increase in amino acid catabolism, to supply gluconeogenic precursors such as alanine and glutamine (28, 31).

To date no study has investigated substrate metabolism in the fetal hindlimb during a prolonged period of adverse intrauterine conditions or, furthermore, whether any fetal metabolic adaptation to prolonged intrauterine compromise influences the fetal metabolic response to a subsequent acute challenge. Hence, the objectives of the present study were twofold: 1) to investigate the delivery, uptake, and/or output of oxygen and substrates (glucose and lactate) during 3 days of controlled compression of the umbilical cord (13) and 2) to examine the influence of 3 days of reversible compression of the umbilical cord on the metabolic response of the fetus during a subsequent acute hypoxemic challenge, induced 2-7 days after recovery from cord compression. The hindlimb was chosen to study regional fetal metabolism because the fetal hindlimb comprises mostly skeletal muscle, and its tissue composition (i.e., skin, muscle, and bone) is representative of nonvisceral tissue, which constitutes ~70% of the overall fetal weight.

METHODS

Animals and Surgery

Sixteen pregnant Welsh Mountain ewes of known gestational age were used in the study. All procedures were performed under the United Kingdom Animals (Scientific Procedures) Act of 1986 and fully conform to the American Physiological Society's "Guiding Principles for Research Involving Animals and Human Beings" (1). For 24 h before surgery, all food, but not water, was withdrawn from the animals. Surgery was conducted between 116 and 120 days gestational age (days GA; term is ~145 days GA). Anesthesia was induced with thiopentone sodium (20 mg/kg iv; Intraval sodium; Rhone Mérieux, Dublin, Ireland) and maintained with 1-2% halothane in 50:50 O₂-N₂O. In brief, fetal vascular (carotid and femoral arterial, jugular and femoral venous) and amniotic catheters were inserted, and transit-time flow transducers (Transonics, New York) were placed around the other femoral artery and one of the two umbilical arteries, close to the common umbilical artery, inside the fetal abdominal cavity. An inflatable occluder cuff (In Vivo Metrics) was positioned around the proximal end of the umbilical cord, as described previously in detail (13). Animals received antibiotics (0.20-0.25 mg/kg im; Depocillin; Mycofarm, Cambridge, UK) for 3 days postoperatively, and catheter patency was maintained by a continuous infusion of heparinized saline (25 IU heparin/ml at 0.1 ml/h in 0.9% NaCl) containing antibiotic (1 mg/

ml benzylpenicillin; Crystapen, Schering Plough, Animal Health Division, Welwyn Garden City, UK).

Experimental Procedure

Umbilical cord compression—No experiments were performed until at least 5 days after surgery. At 124 ± 0.5 days GA, the mean baseline value of unilateral umbilical blood flow was determined over a 24-h period in all fetuses. The animals were then divided randomly into two experimental groups. In nine fetuses the occluder cuff was inflated to reduce umbilical blood flow by $\sim 30\%$ from the predetermined baseline for 3 days [umbilical cord compressed (UCC); Fig. 1]. Compression of the umbilical cord was achieved by an automated servocontrolled system that inflated or deflated the occluder cuff according to the umbilical blood flow reading (13). After 3 days of compression, the occluder cuff was deflated, allowing return of umbilical blood flow to baseline. The duration of the umbilical cord compression was chosen at random. In the remaining seven fetuses, the occluder cuff remained deflated for the duration of the experimental procedure to provide sham-operated, age-matched controls. In two UCC fetuses, the venous catheter became blocked after compression, and therefore further hindlimb metabolic data were unavailable in these fetuses.

Induction of acute hypoxemia—At 2 ± 1 days after umbilical cord or sham compression, all fetuses were subjected to an episode of acute hypoxemia, induced by reducing maternal fractional inspired oxygen concentration. In brief, the protocol for acute fetal hypoxemia involved a 3-h experiment consisting of 1 h of normoxia, 1 h of hypoxemia, and 1 h of recovery. A large, transparent polythene bag was placed over the ewes' head into which air was passed at a rate of ~ 40 l/min for the first 1 h. After this normoxemic period, fetal hypoxemia was induced by changing the concentration of gases breathed by the ewe to 9% O_2 in N_2 with 1.5–2% CO_2 , which has been previously shown to reduce fetal carotid arterial PO_2 (PaO_2) to ~ 12 mmHg while maintaining arterial isocapnia (13, 15). After the 1-h period of hypoxemia, the ewe was returned to breathing air for the 1-h recovery period. At the end of all protocols, the ewes and fetuses were humanely euthanized using a lethal dose of pentobarbital sodium (200 mg/kg; Pentoject; Animal, York, UK), and the positions of implanted catheters and occluder and flow probes were confirmed.

Measurements and Data Collection

Measurements during umbilical cord compression and acute hypoxemia—

Umbilical and femoral blood flows were recorded on a T201 or T206 flow box (Transonics) at 8-s (during compression) or 1-s (during hypoxemia) intervals throughout the study using a data-acquisition system, as described previously (15). Maternal and fetal arterial blood samples (0.4 ml) were taken daily for monitoring of blood gases, percent saturation of oxygen in hemoglobin, hemoglobin concentration, and acid-base status using an ABL5 blood gas analyzer and OSM2 hemoximeter (Radiometer, Copenhagen, Denmark) corrected to $38^\circ C$ (maternal) and $39.5^\circ C$ (fetal). Maternal and fetal arterial blood glucose and lactate concentrations were measured using an automated analyzer (model 2300 Stat Plus Glucose/Lactate analyzer; Yellow Springs International, Farnborough, UK). Additional maternal and fetal arterial blood samples were taken at -1 h before umbilical cord compression and at $+1$ h and $+8$ h during umbilical cord compression for measurement of blood gases, glucose, and lactate concentrations.

Glucose and lactate metabolism—For calculation of metabolic indexes during umbilical cord compression, three paired hindlimb femoral arteriovenous blood samples (0.3 ml) were taken from each fetus over a 20-min period before umbilical cord compression (124 ± 1 days GA), and the average was calculated. This procedure was repeated during the

3rd day of umbilical cord compression (128 ± 1 days GA) and 3 days after deflation of the umbilical cord occluder (131 ± 1 days GA). For calculation of metabolic indexes during the acute hypoxemia protocol, values for paired fetal femoral arteriovenous samples at 15 and 45 min of normoxia, 15 and 45 min of hypoxemia, and 15 and 45 min of recovery were averaged for each epoch. In three control fetuses, blood samples were unable to be withdrawn during the acute hypoxemia experiment due to failure of catheter patency; therefore a further three control fetuses of similar instrumentation and gestational age were substituted for analysis during the acute hypoxemia experiment in which hindlimb metabolic data were not available during sham compression.

Fetal arterial blood oxygen content (Ca_{O_2}) and hindlimb oxygen delivery ($\text{O}_{2,\text{del}}$) were calculated according to Eqs. 1 and 2

$$\text{Ca}_{\text{O}_2} \text{ (mmol/l)} = \left(\frac{[\text{Hb}] \times \text{SatHb}}{100} \right) \times 0.62 \quad (1)$$

$$\text{O}_{2,\text{del}} \text{ (}\mu\text{mol/min)} = \text{Ca}_{\text{O}_2} \times \text{femoral blood flow (ml/min)} \quad (2)$$

where $[\text{Hb}]$ (g/dl) is the blood concentration of hemoglobin, SatHb (%) is the percent oxygen saturation of hemoglobin, and one molecule of Hb (mol wt 64,450) binds four molecules of oxygen. The contribution of oxygen dissolved in plasma is regarded as negligible (33).

Fetal hindlimb blood glucose or lactate deliveries were calculated, e.g., for glucose, according to Eq 3

$$\text{Glu}_{\text{del}} \text{ (}\mu\text{mol/min)} = [\text{Glu}_a] \times \text{femoral blood flow (ml/min)} \quad (3)$$

where $[\text{Glu}_a]$ is the blood glucose concentration (in $\mu\text{mol/ml}$) of the femoral artery.

Net hindlimb substrate (oxygen, glucose, and lactate) uptakes and/or outputs were calculated as the product of femoral blood flow and the arteriovenous concentration difference across the femoral vascular bed (Fick principle) according to Eq 4

$$\text{Substrate uptake/output (e.g., glucose)} = [\text{Glu}_a] - [\text{Glu}_v] \times \text{femoral blood flow (ml/min)} \quad (4)$$

where $[\text{Glu}_v]$ is the blood glucose concentration (in $\mu\text{mol/ml}$) of the femoral vein. The sensitivity of this methodology to determine significant uptakes/outputs of substrate was calculated according to Snedecor (40). For control fetuses, values of 1.40 and $-1.33 \mu\text{mol/min}$ for a significant uptake of glucose and output of lactate, respectively, were calculated. For UCC fetuses, equivalent values were 1.58 and $1.83 \mu\text{mol/min}$, respectively (40).

Glucose/oxygen and lactate/oxygen quotients were calculated as six and three times the ratio of glucose or lactate to oxygen uptake, respectively, as illustrated for glucose in Eq 5

$$\text{glucose/O}_2 \text{ quotient} = \frac{[\text{Glu}_a] - [\text{Glu}_v]}{[\text{O}_{2,a}] - [\text{O}_{2,v}]} \times 6 \quad (5)$$

where $\text{O}_{2,a}$ and $\text{O}_{2,v}$ are blood oxygen concentrations in the femoral artery and vein, respectively, and where the equivalent calculation for the lactate/oxygen quotient would assume the product to be 3.

The fractional extraction (%) of oxygen or glucose across the femoral vascular bed was calculated according to Eq 6

$$\text{fractional extraction of glucose (\%)} = \frac{[\text{Glu}_a] - [\text{Glu}_v]}{\text{Glu}_{\text{del}} (\mu\text{mol}/\text{min})} \times 100 \quad (6)$$

Statistical Analyses

Values for all variables are expressed as means $\pm$ SE unless otherwise stated. All measured variables were first analyzed for normality of distribution. Statistical analyses were conducted on parametric or log-transformed data using two-way ANOVA with repeated measures (Sigma-Stat; SPSS, Chicago, IL). Significant effects of time, group, or an interaction between time and group were isolated by the post hoc Student-Newman-Keuls test for unpaired data. For significance of a single mean value, for example, a significant uptake/output of substrate, statistical methods were conducted according to Snedecor (40). For all comparisons, statistical significance was accepted when $P < 0.05$.

RESULTS

Umbilical Cord Compression

Umbilical blood flow—Flow in a single umbilical artery during the baseline 24-h period (124 ± 0.5 days GA) was similar in sham-operated control and UCC fetuses (192 ± 26 vs. 195 ± 21 ml/min, respectively). In sham-operated control fetuses, umbilical blood flow remained unaltered from baseline throughout the experimental protocol (Fig. 1). In contrast, inflation of the umbilical cord occluder cuff at 125 ± 0.5 days GA, to reduce umbilical blood flow by $\sim 30\%$ from baseline in UCC fetuses, produced a controlled and sustained reduction in umbilical blood flow by $28 \pm 2\%$ to 140 ± 16 ml/min ($P < 0.0001$) for the 3 days of the challenge (Fig. 1). Umbilical blood flow returned to baseline values within 30 min after deflation of the occluder cuff in UCC fetuses and, for 20 h thereafter, was maintained at a level significantly greater than that measured during baseline (220 ± 22 ml/min, $P < 0.05$; Fig. 1).

Blood gases and acid-base status—Baseline maternal blood gas and acid-base status was similar in control and cord-compressed ewes and remained unchanged from baseline during the umbilical cord/sham compression protocol: control, arterial pH (pH_a) 7.50 ± 0.01 , arterial PCO_2 (PaCO_2) 33.3 ± 0.5 mmHg, PaO_2 98.3 ± 4.4 mmHg, %SatHb $91.6 \pm 3.4\%$, acid-base excess (ABE) 4.7 ± 0.9 meq/l; UCC, pH_a 7.48 ± 0.01 , PaCO_2 36.5 ± 1.3 mmHg, PaO_2 95.1 ± 2.6 mmHg, %SatHb $92.3 \pm 1.3\%$, ABE 3.9 ± 0.9 meq/l. In fetal sheep, baseline arterial blood gas and acid-base status was similar between sham-operated control and cord-compressed groups (Table 1). In sham-operated control fetuses, values remained similar to baseline throughout the experimental period with the exception of pH_a , which was significantly reduced on *days 3* and *4* of sham compression (Table 1). In contrast, compression of the umbilical cord produced fetal asphyxia, characterized by falls in pH_a , PaO_2 , and %SatHb and increments in PaCO_2 and Hb in UCC fetuses (Table 1). At 24 h after deflation of the occluder cuff, values for all variables, with the exception of pH_a , had returned to baseline levels in UCC fetuses (Table 1).

Fetal oxygenation and hindlimb oxygen handling—Before umbilical cord compression, fetal blood oxygen content (3.50 ± 0.17 vs. 3.25 ± 0.17 $\mu\text{mol}/\text{ml}$) and femoral blood flow to the hindlimb (Table 2) were similar in control and UCC fetuses, respectively. Consequently, the delivery (98.5 ± 10.6 vs. 95.2 ± 15.9 $\mu\text{mol}/\text{min}$), uptake (20.6 ± 2.5 vs. 16.8 ± 2.0 $\mu\text{mol}/\text{ml}$), and extraction (21.3 ± 2.3 vs. $19.6 \pm 2.0\%$) of oxygen by the hindlimb

were also similar in control and UCC fetuses, respectively. In control fetuses, blood oxygen content, delivery to, or uptake by, the hindlimb remained unchanged from baseline during sham umbilical cord compression. In contrast, in UCC fetuses, there were significant falls in blood oxygen content (to an average of $2.76 \pm 0.14 \mu\text{mol/ml}$, $P = 0.03$) and oxygen delivery to the hindlimb (to an average of $79.2 \pm 9.8 \mu\text{mol/min}$, $P = 0.03$) but no change in total hindlimb oxygen uptake ($19.4 \pm 3.6 \mu\text{mol/ml}$). Consequently, UCC fetuses exhibited a significant increment in oxygen extraction by the hindlimb (Fig. 2A).

Fetal blood glucose and hindlimb glucose handling—Maternal blood glucose concentration was similar between groups (control 2.29 ± 0.21 vs. UCC 2.46 ± 0.16 mM) and remained unchanged from baseline values over the experimental period. Baseline fetal blood glucose concentration, delivery to the hindlimb, and uptake and extraction by the hindlimb (28 ± 2.6 vs. $25.3 \pm 2.7\%$) were similar in control and UCC fetuses, respectively (Table 2). During umbilical cord compression, there was a significant increase in blood glucose concentration and a nonsignificant trend for increments in both glucose delivery to, and uptake by, the hindlimb in UCC relative to control fetuses (Table 2). Hindlimb glucose extraction was significantly lower in the recovery period after cord/sham compression relative to baseline in both control and UCC fetuses (Fig. 2B). The hindlimb glucose/oxygen quotient remained unchanged from baseline over the period of study in both control and UCC fetuses (Table 2).

Fetal blood lactate and hindlimb lactate handling—Maternal blood lactate concentration was similar in control and UCC ewes and remained unchanged from baseline throughout the experimental period (control 0.43 ± 0.07 vs. UCC 0.48 ± 0.18 mM). Baseline fetal blood lactate and lactate metabolism by the hindlimb were similar in control and UCC fetuses (Fig. 3). In contrast, umbilical cord compression led to a significant increase in fetal blood lactate (Fig. 3A) that was not associated with any concomitant change in hindlimb lactate metabolism (Fig. 3B). The baseline hindlimb lactate/oxygen quotient for both control (-0.05 ± 0.08) and UCC fetuses (-0.01 ± 0.17) remained unchanged throughout the study period.

Acute Hypoxemia

Effect on blood gases and acid-base status—In ewes, basal arterial blood gas and acid-base status were similar between groups (Table 3). During acute hypoxemia, maternal PaO_2 and SatHb fell, while arterial blood Hb concentration ($[\text{Hb}]_a$) increased (Table 3). The fall in SatHb was to a lesser extent in UCC relative to control ewes. During recovery, all maternal variables returned to basal values (Table 3). In fetuses, baseline pH_a , PaCO_2 , $[\text{Hb}]_a$, and ABE were similar, although both PaO_2 and SatHb were lower in UCC relative to sham-operated control fetuses (Table 4). Acute hypoxemia led to significant falls in pH_a , PaO_2 , %SatHb, and ABE and an increase in $[\text{Hb}]_a$ without any alteration to PaCO_2 in either group of fetuses (Table 4). While PaO_2 and SatHb returned to baseline levels during recovery, fetuses remained mildly acidemic (Table 4). In addition, all fetuses were transiently hypocarbic at 15 min after recovery from hypoxemia, and the decrease in $[\text{Hb}]_a$ after hypoxemia was exacerbated briefly in UCC fetuses (Table 4).

Fetal oxygenation and hindlimb oxygen handling—During the normoxic period, there were no significant differences in fetal arterial oxygen content (Table 5), femoral blood flow (control 36.4 ± 6.7 vs. UCC 27.2 ± 4.7 ml/min), or hindlimb oxygen delivery, uptake, or extraction (Table 5). After induction of hypoxemia, there were significant falls in arterial oxygen content, femoral blood flow, and hindlimb oxygen delivery and uptake in both groups of fetuses. However, there was a trend ($P = 0.07$) for a greater fall in femoral blood flow (Fig. 4) and greater increment in hindlimb oxygen extraction in control relative

to UCC fetuses (Fig. 2C). During the posthypoxemia period, all values returned toward baseline levels.

Fetal blood glucose and hindlimb glucose handling—Blood glucose concentrations, the glucose/oxygen quotient, and hindlimb delivery, uptake (Table 5), and extraction (Fig. 2D) were similar in control and UCC fetuses before hypoxemia. Acute hypoxemia did not affect hindlimb glucose delivery or uptake (Table 5) but led to significant increases in fetal blood glucose concentration and the hindlimb glucose/oxygen quotient in both groups of fetuses (Table 5). In control fetuses only, acute hypoxemia led to a significant increase in hindlimb glucose extraction (Fig. 2D). After hypoxemia all values returned to baseline levels.

Fetal blood lactate and hindlimb lactate handling—During the baseline period, any apparent differences in arterial blood lactate levels, between UCC and control fetuses, did not reach significance (Fig. 4). In addition, values for hindlimb lactate output (Fig. 4) and the lactate/oxygen quotient (Table 5) were similar between groups. Acute hypoxemia led to a progressive increase in blood lactate concentration in both groups of fetuses and a significant increase in hindlimb lactate output in control (an increment of $1.48 \pm 0.61 \mu\text{mol/min}$), but not UCC (an increment of $0.26 \pm 1.22 \mu\text{mol/min}$), fetuses (Fig. 4). There was no change to the fetal lactate/oxygen quotient during hypoxemia in either group of fetuses. During the recovery period all values returned toward baseline levels.

DISCUSSION

The results of the present study show that a 3-day period of adverse intrauterine conditions, induced by controlled compression of the umbilical cord, which successfully reduced umbilical blood flow by ~30% from baseline, reduced oxygen delivery to the fetal hindlimb by ~13% but did not change hindlimb oxygen consumption. Maintenance of fetal hindlimb oxygen consumption in the face of a reduction in delivery was enabled by an increase in hindlimb oxygen extraction. During cord compression, fetal blood glucose and lactate concentrations rose, which were accompanied by trends toward greater hindlimb glucose delivery and uptake, but no significant change to hindlimb lactate metabolism. During subsequent acute hypoxemia, fetal arterial oxygen content was reduced to ~1.78 (a reduction of 44%) and 1.67 (38%) mM, delivery by ~68 and 61%, and uptake by 52 and 43% in control and UCC fetuses, respectively. In response to hypoxemia, significant increases in hindlimb oxygen and glucose extraction and a significant increase in blood lactate concentration were observed in control, but not UCC, fetuses. Therefore, prior exposure to a reversible period of umbilical cord compression affected the fetal hindlimb metabolic adaptation to a subsequent episode of acute hypoxemia, of the type that may occur during labor and delivery (36).

Basal fetal substrate metabolism in both the whole body (5-7, 19) and in specific vascular beds such as the hindlimb (9, 10, 20, 31, 39, 42) has been well characterized. Values for basal hindlimb oxygen delivery and uptake and glucose uptake and consumption in relation to oxygen utilization in the present study are similar to values previously published for control fetuses during late gestation (9, 31, 39, 42). Fewer studies have extended these experimental techniques to investigation of fetal metabolic responses to short- and long-term adverse intrauterine conditions induced by reductions in uterine (8, 22, 37, 38) or umbilical (3, 23) blood flow. In the short-term i.e., <24 h, the fetus has a considerable buffer to reduced delivery of oxygen by increasing the efficiency of oxygen extraction from the blood. Indeed, while the delivery of oxygen may be reduced by up to 40-50% for durations between 5 min and 24 h, a concomitant increase in oxygen extraction from ~30% to 50-60% enables maintenance of tissue oxygen consumption (8, 11, 12, 23), so long as fetal acidemia

does not develop (38). This ability of the fetus to compensate metabolically for reduced delivery of oxygen has led to the concept of a margin of safety for fetal oxygenation (32). However, in longer-term studies in which the period of adverse intrauterine conditions has been extended beyond 24 h, an equivalent (40%) reduction in oxygen delivery to the fetus results in a strong correlation between total oxygen delivery to, and consumption by, the fetus (3), suggesting the breakdown of the oxygen margin of safety and that a longer-term reduction in the delivery of oxygen to the fetus leads to a downregulation of oxygen-consuming processes in the fetal body requiring oxygen consumption.

In the current study, a 30% reduction in umbilical blood flow in UCC fetuses only reduced oxygen delivery to the hindlimb by ~13% but, when coupled with the increase in hindlimb oxygen extraction that was observed, had no effect on the total oxygen consumption of hindlimb tissue. Thus, at first sight, the UCC fetus would appear to tolerate adequately a prolonged reduction in hindlimb oxygen delivery of <15%. However, on average, UCC fetuses are ~10% lighter than age-matched singleton control fetuses when weighed at post mortem, ~7 days after restoration of umbilical blood flow (16). This suggests a trend toward a downregulation of oxygen-consuming processes in the whole body, despite no measured changes in basal hindlimb oxygen consumption. The apparent reduction in body weight of UCC fetuses may relate to persisting effects of 3 days of cord compression on the placenta and placental capacity for oxygen transfer because fetal blood oxygen content remained between 10 and 20% below control values up to 7 days after ending the reduction in umbilical blood flow (16). In UCC fetuses, total placental weight is reduced by ~20%, due to a reduction in mean placentome weight and a significant shift in placentome distribution from the generally larger and greater weight of C/D type placentomes to predominantly A/B type (15). Taken together, the data indicate that a relatively mild and reversible reduction in umbilical blood flow has no effect on fetal oxygen consumption in the hindlimb per se, but a persistent reduction in blood oxygen content (<20%) as a result of cord compression precipitates fetal metabolic adaptation, which is manifest as a reduction in growth.

It is known that in the basal state, fetal blood lactate is a significant metabolic substrate for a number of tissues (6), but the fetal hindlimb, in particular, tends to show a net output of lactate relative to oxygen uptake (10, 39). The output of lactate from the hindlimb becomes more pronounced as the fetus becomes increasingly hypoxemic (9, 10). In the present study, while an inverse correlation may be drawn between femoral arterial oxygen content (which was reduced from 3.25 to 2.76 mM during the period of compression) and blood lactate concentration (which increases significantly during compression), there was no change in hindlimb lactate output. This is perhaps not surprising because in one study, during acute hypoxemic conditions, measured hindlimb lactate output was only provoked at arterial oxygen contents of <1.5 mM (10). Therefore, the increase in arterial blood lactate during cord compression must either be from 1) increased output from alternative organs in which the oxygen delivery during compression is compromised to a greater extent than the hindlimbs, and/or 2) decreased uptake in organs reliant on lactate as a significant metabolic substrate, and/or 3) altered placental handling of glucose and lactate. The first possibility is unlikely because the femoral bed offers a useful index of the peripheral vasoconstriction, and thus a reduction in oxygen and nutrient delivery, that occurs during episodes of fetal stress (9, 17). Although one study has shown decreased hepatic lactate uptake during acute umbilical cord compression (an ~50% reduction from baseline) that could potentially contribute toward greater circulating levels of lactate, no evidence exists to date that suggests that this response may be continued beyond 30 min or to a significantly lower, sustained reduction in umbilical blood flow, as occurred in the present study (35). It has been shown that the placenta, during periods of 24 h of adverse intrauterine conditions, acts as a major site of lactate clearance from the fetal circulation (22). While this appears to contradict the current data, it is unknown whether the placenta continues to clear fetal lactate

during periods of adverse intrauterine conditions lasting beyond 24 h. However, while placental weight is reduced by both uterine and umbilical blood flow reduction (16, 21, 26), fetoplacental glucose/lactate handling may be different between the two methodologies. Alternatively, because elevated glucose availability may fuel greater hindlimb lactate output (27), this may contribute to the greater circulating glucose concentrations and the trend toward greater hindlimb glucose uptake during cord compression.

To date, only two studies have examined fetal hindlimb substrate metabolism during an episode of acute hypoxemia (9, 10). In these studies the level of hypoxemia was severe (a blood oxygen content of ~ 1.4 mM) with hindlimb oxygen delivery being reduced by $\sim 70\%$. During severe hypoxemia, blood lactate increased to ~ 15 mM and specific output from the hindlimb doubled (10). The present study is the first to report changes in fetal regional metabolic responses to an episode of acute hypoxemia after a period of adverse intrauterine conditions. Indeed, after 2-7 days of almost full recovery of blood gas and metabolic status from a 3-day period of umbilical cord compression, the fetal hindlimb in UCC fetuses does not appear to respire anaerobically, despite a reduction in blood oxygen content to ~ 1.70 mM for a period of 60 min. This level of hypoxemia resulted in a significant increase in blood lactate concentration in both groups of fetuses, but in control fetuses only, it was also associated with a significant output of lactate from the hindlimb. In the present study, the measured output of lactate from the hindlimbs during moderate acute hypoxemia in control fetuses could only account for a maximum of 12-15% of the increase in fetal blood lactate concentration, indicating that a significant output of lactate from sources other than the hindlimbs must have occurred, as it did in UCC fetuses during the mild prolonged hypoxemia induced by umbilical cord compression. In contrast, during more severe hypoxemia, the hindlimbs may account for approximately one-half of the increase in blood lactate concentration, when calculated according to the data published by Boyle et al. (10). The reduced output of lactate from the hindlimb of UCC, relative to control, fetuses despite similar reductions in the delivery and uptake of oxygen could theoretically represent a beneficial metabolic adaptation to umbilical cord compression to prevent excessive lactate accumulation during further acute hypoxic stress (10). Indeed, an attenuation of myocardial lactate accumulation appears to underlie ischemic preconditioning in the adult pig heart (41). The weak lactacidemic response also has implications with regard to the peripheral handling and/or metabolic control of substrate and subsequent growth during late gestation and/or postnatal life in fetuses that have suffered a period of adverse intrauterine conditions.

The precise mechanism mediating this metabolic adaptation in fetuses after exposure to prolonged cord compression is not known although it may be expected to relate, in part, to altered expression and/or function of glucose transporter proteins in fetal skeletal muscle. Both glucose transporter proteins 1 and 4 (GLUT-1 and -4) are present in fetal skeletal muscle plasma membrane and cytosolic endosomal stores, respectively (4). In the fetus, both isoforms are sensitive to rising glucose concentration, but while GLUT-1 mediates basal glucose uptake, only GLUT-4 is sensitive to rising insulin concentration and controls insulin-mediated glucose uptake (4). One possibility may be that exposure to cord compression alters the developmental change in the relative densities of skeletal muscle GLUT-1 and GLUT-4, in favor of greater GLUT-4 numbers, because cord-compressed fetuses have persistently elevated cortisol concentrations (14) and cortisol upregulates GLUT-4 (30). Such a mechanism may underlie the trend for greater basal glucose uptake in UCC fetuses but unfortunately does not explain the fate of the glucose once internalized or why the glucose is not anaerobically metabolized to lactate under conditions of limited oxygen availability. In this regard, an effect of prior exposure to 3 days of mild hypoxemia on the metabolic pathways controlling muscular glycolytic flux and/or energy production is implicated (41).

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Fig. 1.

Change in umbilical blood flow during umbilical cord compression (UCC) or sham compression. Values are means $\pm$ SE of cardiovascular data (30 min average) for a baseline period (1 day before UCC), for the 3 days during UCC or sham compression (between dashed lines), and for 1 day of recovery after UCC or sham compression in control ($n = 7$; A) and UCC ($n = 9$; B) fetuses.

Fig. 2.

Change in fetal hindlimb oxygen or glucose extraction during umbilical cord/sham compression and subsequent acute hypoxemia. Values are means $\pm$ SE for control (open bars, $n = 7$) and UCC (solid bars, $n = 9$ or $n = 7$ during acute hypoxemia) fetuses. Paired fetal femoral arteriovenous blood samples were collected on 3 occasions over a 20-min period during baseline [124 ± 0.5 days gestational age (days GA)], after 3 days umbilical cord/sham compression (128 ± 0.5 days GA), and after 3 days (131 ± 1 days GA) recovery from umbilical cord/sham compression. During acute hypoxemia, paired fetal femoral arteriovenous blood samples were collected at 15 and 45 min of normoxia, 15 and 45 min of hypoxemia, and 15 and 45 min of recovery, and values during each epoch were averaged. Statistical differences: * $P < 0.05$ for significant extraction of substrate; † $P < 0.05$, baseline vs. umbilical cord/sham compression or hypoxemia and recovery.

Fig. 3. Fetal blood lactate (*A*) and fetal hindlimb lactate metabolism (*B*) during umbilical cord/sham compression. Values are means $\pm$ SE for control ($n = 7$) and UCC ($n = 9$) fetuses. Paired fetal femoral arteriovenous blood samples were collected on 3 occasions over a 20-min period during baseline (124 ± 0.5 days GA), after 3 days umbilical cord/sham compression (128 ± 0.5 days GA), and after 3 days (131 ± 1 days GA) recovery from umbilical cord/sham compression. Statistical differences: $\dagger P < 0.05$, baseline vs. umbilical cord/sham compression or hypoxemia and recovery; $\ddagger P < 0.05$, control vs. UCC fetuses.

Fig. 4.

Fetal femoral blood flow (*A*), blood lactate (*B*), and hindlimb lactate metabolism (*B*) during acute hypoxemia. Values are means $\pm$ SE for control ($n = 7$; open bars in *C*) and UCC ($n = 7$; solid bars in *C*) fetuses. For cardiovascular data, values are the minute means $\pm$ SE plotted as the absolute change from baseline. Paired fetal femoral arteriovenous blood samples were collected at 15 and 45 min of normoxia, 15 and 45 min of hypoxemia, and 15 and 45 min of recovery, and values during each epoch were averaged for the calculation of hindlimb lactate output. Statistical differences: * $P < 0.05$ for significant extraction of substrate; † $P < 0.05$, baseline vs. umbilical cord/sham compression or hypoxemia and recovery.

Table 1
Fetal arterial blood gas and acid-base status during umbilical cord compression

	Baseline		Umbilical Cord Compression				Recovery	
	-1 day	-1 h	+1 h	+8 h	+1 day	+2 day	+3 day	+4 day
pH_a								
Control	7.36±0.01	7.35±0.01	7.36±0.01	7.34±0.01	7.34±0.01	7.34±0.01	7.33±0.01 [*]	7.33±0.01 [*]
UCC	7.34±0.01	7.34±0.01	7.32±0.01 [†]	7.30±0.01 ^{†*}	7.31±0.01 ^{†*}	7.33±0.01	7.31±0.01 [*]	7.36±0.01 [†]
Paco₂, mmHg								
Control	49.2±1.5	50.2±0.6	48.2±1.0	50.2±1.3	52.2±0.5	51.3±0.9	53.0±1.1	52.8±1.0
UCC	53.8±1.6 [†]	54.0±1.4	56.7±1.5 [†]	59.0±1.1 ^{†*}	57.8±1.5 ^{†*}	55.8±0.9 [†]	57.1±1.3	54.5±1.7
PaO₂, mmHg								
Control	24.3±1.0	24.1±1.4	25.2±0.6	23.2±1.0	22.5±0.7	23.7±0.9	23.8±0.9	23.4±0.7
UCC	23.6±1.1	22.2±1.3	19.6±1.0 ^{†*}	18.8±0.4 ^{†*}	18.4±1.0 ^{†*}	19.8±0.9 ^{†*}	18.8±0.9 ^{†*}	21.2±1.2
SatHb, %								
Control	69.6±2.3	68.5±2.5	72.2±2.7	66.9±2.9	65.1±2.0	69.4±2.9	66.6±2.6	66.8±2.8
UCC	65.9±2.4	64.1±3.4	56.2±3.8 ^{†*}	53.6±1.9 ^{†*}	52.7±2.1 ^{†*}	57.5±2.9 ^{†*}	55.1±3.9 ^{†*}	60.0±2.5
[Hb]_{la}, g/dl								
Control	8.9±0.3	8.9±0.2	8.8±0.1	8.7±0.2	8.7±0.2	9.0±0.2	8.8±0.3	8.8±0.2
UCC	8.8±0.4	8.8±0.3	9.4±0.4	9.7±0.4 [*]	9.8±0.4 [*]	9.3±0.5	9.4±0.4	9.0±0.4
Base excess, meq/l								
Control	1.7±0.6	1.7±0.6	1.2±0.4	1.5±0.7	2.3±0.3	1.1±0.5	0.4±0.8	0.4±0.7
UCC	2.1±0.7	2.2±0.7	1.7±0.7	1.3±0.5	2.1±0.5	2.1±0.6	1.7±0.5	3.3±0.6

Values are means ± SE for control ($n = 7$) and umbilical cord compression (UCC) fetuses ($n = 9$). Fetal blood samples were collected for measurement of blood gases during a baseline period at -1 day and -1 h and subsequently at +1 h, +8 h, +1 day, +2 days, and +3 days during umbilical cord/sham compression and at +1 day of recovery after umbilical cord/sham compression. Fetal blood gas values were corrected to 39.5°C. pH_a, arterial pH; PaCO₂, arterial CO₂ partial pressure; PaO₂, arterial O₂ partial pressure; SatHb, percent oxygen saturation of hemoglobin; [Hb]_{la}, arterial blood concentration of hemoglobin; Base excess, acid-base excess. Statistical differences:

^{*} $P < 0.05$, baseline vs. UCC or recovery

[†] $P < 0.05$, control vs. UCC fetuses.

Table 2
Fetal glucose concentration and metabolism during umbilical cord/sham compression

	Baseline	Cord Compression	Recovery
Femoral blood flow, ml/min			
Control	28.4±3.5	34.4±3.7	33.3±3.4
UCC	24.0±2.7	26.3±3.2	32.1±2.5
Blood glucose, mmol/l			
Control	0.67±0.07	0.70±0.09	0.76±0.03
UCC	0.74±0.06	0.93±0.09 [†]	0.61±0.07
Glucose delivery, μmol/min			
Control	19.6±3.5	23.9±3.1	25.3±2.8
UCC	16.1±2.4	25.7±5.1	20.4±3.4
Glucose uptake, μmol/min			
Control	5.66±1.77 [*]	5.72±0.67 [*]	5.58±0.73 [*]
UCC	4.12±0.67 [*]	5.64±1.44 [*]	3.42±0.53 [*]
Glucose/oxygen quotient			
Control	1.83±0.26	2.11±0.33	2.23±0.44
UCC	2.11±0.55	2.02±0.39	1.57±0.29

Data are means ± SE for control ($n = 7$) and UCC fetuses ($n = 9$). Paired fetal femoral arteriovenous blood samples were collected on 3 occasions over a 20-min period during baseline [124 ± 0.5 days gestational age (days GA)], after 3 days umbilical cord/sham compression (128 ± 0.5 days GA), and after 3 days (131 ± 1 days GA) recovery from umbilical cord/sham compression. Statistical differences:

^{*} $P < 0.05$ for significant uptake, output, and/or extraction of substrate

[†] $P < 0.05$, baseline vs. during or after umbilical cord/sham compression.

Table 3
Maternal blood gas and acid-base status during acute hypoxemia

	Baseline		Hypoxemia			Recovery	
	N15	N45	H15	H45		R15	R45
pH _a							
Control	7.49±0.01	7.48±0.01	7.49±0.02	7.49±0.01		7.51±0.01	7.50±0.01
UCC	7.49±0.01	7.50±0.01	7.49±0.01	7.49±0.01		7.51±0.01	7.49±0.01
Paco ₂ , mmHg							
Control	35.3±0.7	35.8±1.3	35.5±1.1	36.7±1.1		32.8±0.5	34.1±0.7
UCC	37.0±2.0	35.5±1.9	38.2±1.4	38.7±1.2		34.4±1.0	36.2±1.4
PaO ₂ , mmHg							
Control	98.7±2.9	106.4±7.2	39.4±1.9 [*]	37.1±2.3 [*]		99.7±3.7	100.5±1.5
UCC	93.3±3.1	100.3±3.9	44.3±0.6 [*]	42.0±0.6 [*]		95.5±3.3	91.3±3.8
SatHb, %							
Control	90.4±1.2	90.4±1.2	59.5±3.5 [*]	55.1±3.2 [*]		91.0±0.9	91.1±1.3
UCC	92.4±1.5	92.7±1.2	69.0±1.9 ^{*,†}	66.4±2.6 ^{*,†}		92.6±1.6	92.2±1.3
[Hb] _{1a} , g/dl							
Control	8.2±0.6	7.8±0.5	9.2±0.5 [*]	9.7±0.6 [*]		8.5±0.7	8.5±0.6
UCC	8.6±0.5	8.1±0.3	9.1±0.5 [*]	9.1±0.5 [*]		8.1±0.5	8.0±0.5
ABE, meq/l							
Control	4.0±1.0	4.1±1.1	4.7±1.2	5.0±1.1		4.1±1.3	4.1±0.9
UCC	5.1±1.1	6.3±1.3	6.4±1.1	6.1±1.2		5.0±1.2	4.8±1.5

Values are means ± SE for control ($n = 7$) and UCC ($n = 7$) ewes at 15 (N15) and 45 min (N45) of normoxia (baseline), at 15 (H15) and 45 min (H45) of hypoxemia, and at 15 (R15) and 45 min (R45) of recovery. Maternal blood gas values were corrected to 38 °C. ABE, acid-base excess.

^{*} $P < 0.05$; baseline vs. hypoxemia.

[†] $P < 0.05$, control vs. UCC fetuses.

Table 4

Fetal blood gas and acid/base status during acute hypoxemia

	Baseline		Hypoxemia		Recovery	
	N15	N45	H15	H45	R15	R45
pH _a						
Control	7.33±0.01	7.33±0.01	7.30±0.02	7.26±0.01 [*]	7.23±0.02 [*]	7.27±0.02 [*]
UCC	7.33±0.01	7.33±0.01	7.31±0.01	7.27±0.01 [*]	7.27±0.03 [*]	7.28±0.02 [*]
Paco ₂ , mmHg						
Control	52.4±1.0	51.7±1.6	52.0±1.8	50.1±1.5	47.8±1.2 [*]	50.2±1.4
UCC	55.0±2.2	55.2±2.2	54.5±1.8	55.1±1.2	51.2±2.2 [*]	55.0±2.3
PaO ₂ , mmHg						
Control	24.7±0.8	23.8±0.7	12.7±0.2 [*]	12.5±0.2 [*]	26.2±2.1	22.7±1.5
UCC	18.8±1.4 [†]	18.6±1.6 [†]	12.2±0.3 [*]	12.0±0.4 [*]	19.2±1.6 [†]	17.4±0.8 [†]
SatHb, %						
Control	66.4±3.5	64.6±3.3	33.0±5.1 [*]	32.0±4.0 [*]	62.6±3.7	58.6±4.5
UCC	53.0±4.6 [†]	50.5±5.9 [†]	31.9±4.0 [*]	29.8±4.0 [*]	51.5±5.2	47.3±5.6
[Hb] _{1a} , g/dl						
Control	8.8±0.4	8.4±0.4	9.9±0.4 [*]	9.8±0.5 [*]	8.3±0.5	8.8±0.4
UCC	9.1±0.4	9.1±0.4	9.7±0.5 [*]	9.4±0.5 [*]	8.2±0.4 [*]	8.7±0.5
ABE, meq/l						
Control	1.5±0.9	1.0±0.6	-1.1±1.1	-5.0±1.4 [*]	-7.4±1.8 [*]	-3.8±1.6 [*]
UCC	1.6±0.8	1.6±0.7	0.0±1.0	-2.5±1.3 [*]	-4.0±1.5 [*]	-1.8±1.2 [*]

Values are means ± SE for control ($n = 7$) and UCC ($n = 7$) fetuses at 15 and 45 min of normoxia (baseline), at 15 and 45 min of hypoxemia, and at 15 and 45 min of recovery. Fetal blood gas values were corrected to 39.5 °C.

^{*} $P < 0.05$, baseline vs. hypoxemia or recovery.

[†] $P < 0.05$, control vs. UCC fetuses.

Table 5
Fetal metabolic data during subsequent acute hypoxemia

	Normoxia	Hypoxemia	Recovery
Arterial oxygen content, $\mu\text{mol/ml}$			
Control	3.11 ± 0.35	$1.78 \pm 0.32^{\dagger}$	2.85 ± 0.33
UCC	2.64 ± 0.25	$1.67 \pm 0.25^{\dagger}$	2.34 ± 0.32
Arterial oxygen delivery, $\mu\text{mol/min}$			
Control	105.5 ± 12.9	$38.1 \pm 12.8^{\dagger}$	94.1 ± 15.6
UCC	71.6 ± 18.6	$32.6 \pm 11.1^{\dagger}$	65.5 ± 18.7
Oxygen uptake, $\mu\text{mol/min}$			
Control	$20.6 \pm 2.3^*$	$9.6 \pm 2.3^{*\dagger}$	$18.8 \pm 2.2^*$
UCC	$14.3 \pm 2.8^*$	$8.7 \pm 2.3^{*\dagger}$	$14.7 \pm 3.8^*$
Blood glucose, mmol/l			
Control	0.80 ± 0.06	$1.19 \pm 0.13^{\dagger}$	$0.99 \pm 0.10^{\dagger}$
UCC	0.67 ± 0.10	$0.93 \pm 0.09^{\dagger}$	0.76 ± 0.10
Glucose delivery, $\mu\text{mol/min}$			
Control	22.6 ± 3.6	20.4 ± 5.4	28.6 ± 6.4
UCC	17.9 ± 4.8	17.8 ± 5.2	22.0 ± 5.3
Glucose uptake, $\mu\text{mol/min}$			
Control	$3.78 \pm 0.56^*$	$5.74 \pm 0.54^*$	$4.64 \pm 0.88^*$
UCC	$4.25 \pm 0.64^*$	$4.78 \pm 0.67^*$	$4.09 \pm 0.47^*$
Glucose/oxygen quotient			
Control	1.44 ± 0.40	$5.24 \pm 1.22^{\dagger}$	1.99 ± 0.75
UCC	2.17 ± 0.56	$4.91 \pm 1.10^{\dagger}$	1.74 ± 0.29
Lactate/oxygen quotient			
Control	-0.23 ± 0.08	-0.83 ± 0.09	-0.71 ± 0.46
UCC	-0.54 ± 0.17	-1.68 ± 0.61	-0.45 ± 0.40

Values are means $\pm$ SE for control ($n = 7$) and UCC ($n = 7$) fetuses. Paired fetal femoral arteriovenous blood samples were collected at 15 and 45 min of normoxia, 15 and 45 min of hypoxemia, and 15 and 45 min of recovery, and values during each epoch were averaged.

* $P < 0.05$ for significant uptake and/or output of substrate.

$^{\dagger} P < 0.05$, baseline vs. hypoxemia or recovery.