

## **PDF hosted at the Radboud Repository of the Radboud University Nijmegen**

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/21055>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

most of the preterm newborns <32 weeks. It remains to be determined whether increased tolerance of asphyxia or greater difficulty in recognition of severe complications in preterm newborns <32 weeks are factors contributing to these results.

Apgar scores are valuable predictors of newborn complications in the preterm newborns of both the asphyxia and control groups. However, as in the term newborn,<sup>5</sup> the Apgar score at 1 minute is a better predictor than the Apgar score at 5 minutes.

The results of this study indicate that intrapartum fetal asphyxia with metabolic acidosis is an important factor in the occurrence of severe complications in the central nervous system, respiratory system, and kidney in preterm newborns.

## REFERENCES

1. Gilstrap LC, Levano KJ, Burris J, Williams MI, Little BB. Diagnosis of birth asphyxia on the basis of fetal pH, Apgar score, and newborn cerebral dysfunction. *AM J OBSTET GYNECOL*. 1989;161:825-30.
2. Winkler CL, Hauth JC, Tucker MJ, Owen J, Brumfield CG. Neonatal complications at term as related to the degree of umbilical artery acidemia. *AM J OBSTET GYNECOL*. 1991;164:637-41.
3. Goldaber KG, Gilstrap LC, Levano KJ, Dax JS, McIntyre DD. Pathologic fetal acidemia. *Obstet Gynecol*. 1991;78:1103.
4. Goodwin TM, Belai I, Hernandez P, Durand M, Paul RH. Asphyxial complications in the term newborn with severe umbilical acidemia. *AM J OBSTET GYNECOL*. 1992;162:1506-12.
5. Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. *AM J OBSTET GYNECOL*. 1994;170:1081-7.

# Arterial oxygen saturation in relation to metabolic acidosis in fetal lambs

Roel Nijland, MD,<sup>a</sup> Henk W. Jongsma, PhD,<sup>a</sup> Jan G. Nijhuis, MD, PhD,<sup>a</sup>  
Paul P. van den Berg, MD,<sup>a</sup> and Berend Oeseburg, MD, PhD<sup>b</sup>

*Nijmegen, The Netherlands*

**OBJECTIVE:** We studied the relationship between preductal arterial oxygen saturation and metabolic acidosis in 18 chronically instrumented fetal lambs (gestational age 119 to 133 days) in two experimental designs. In the first group the onset of metabolic acidosis was determined. In the second group the progression of metabolic acidosis was studied as was the cardiovascular and hormonal changes resulting from hypoxemia.

**STUDY DESIGN:** In nine fetal lambs maternal fraction of inspired oxygen was lowered stepwise by increasing flows of nitrogen delivered into the trachea through a small indwelling catheter (group 1), and in nine fetal lambs maternal blood flow was reduced stepwise by means of a vascular occluder (group 2).

**RESULTS:** Baseline arterial oxygen saturation values ranged from 26% to 67% with normal pH and extracellular fluid base excess values in both groups 1 and 2. In both groups pH and extracellular fluid base excess started to decrease below 30% arterial oxygen saturation, with a progressive decrease below 20% arterial oxygen saturation to an end value for pH of 7.14. In some fetal lambs pH and extracellular fluid base excess decreased initially at 20% to 30% arterial oxygen saturation and then stabilized at the lower level. Fetal heart rate in group 1 increased during hypoxemia from 155 to 179 beats/min. In group 2 baseline fetal heart rate was 153 beats/min and fell with every step change in arterial oxygen saturation but subsequently increased to 172 beats/min by the end of the period of hypoxemia. Baseline values for epinephrine, norepinephrine, dopamine, cortisol, and mean arterial pressure were not related to baseline arterial oxygen saturation levels, and each of these variables was increased at the end of hypoxemia in group 2.

**CONCLUSION:** Preductal arterial oxygen saturation can reach values between 20% and 30% before anaerobic metabolism starts. During the progressive acidosis blood pressure was increased, which can be attributed to a strong rise in catecholamines. (*AM J OBSTET GYNECOL* 1995;172:810-9.)

**Key words:** Arterial oxygen saturation, hypoxemia, acidosis, fetal lamb

*From the Department of Obstetrics and Gynaecology<sup>a</sup> and the Department of Physiology,<sup>b</sup> Perinatal Research Group, University of Nijmegen.*

*Supported by Nellcor Inc., Pleasanton, California.*

*Received for publication April 26, 1994; revised July 27, 1994; accepted August 25, 1994.*

*Reprint requests: H.W. Jongsma, PhD, Department of Obstetrics and Gynaecology, University Hospital Nijmegen, 415 GYN, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands.*

*Copyright © 1995 by Mosby-Year Book, Inc.*

*0002-9378/95 \$3.00 + 0 6/1/60274*

Reduced oxygen supply is the primary cause of fetal asphyxia. If hypoxemia is prolonged, aerobic metabolism cannot be maintained and metabolic acidosis develops. During labor continuous fetal heart rate (FHR) monitoring is used to detect fetal hypoxemia. Specific FHR patterns can be recognized as a result of hypoxemia,<sup>1</sup> but the specificity is low.<sup>2</sup> With the development of fetal pulse oximetry, arterial oxygen saturation ( $\text{SaO}_2$ ) can be measured continuously during labor<sup>3</sup> and can give direct insight into fetal oxygenation. If pulse oximetry is to be used clinically as a monitoring technique, the relationship between  $\text{SaO}_2$  and metabolic acidosis should be known.

The first clinical measurements with fetal pulse oximetry suggest that  $\text{SaO}_2$  is linearly related to umbilical artery pH.<sup>4</sup> This is in contrast with experiments in unanesthetized fetal lambs. Studies with stepwise reduction of uterine blood flow<sup>1</sup> or induction of maternal hypoxemia<sup>5</sup> showed that  $\text{SaO}_2$  can be reduced substantially before metabolic acidosis occurs. Moreover, in fetal lamb studies in which oxygen consumption was determined, oxygen delivery could be reduced below 50% before anaerobic metabolism was manifested by an increase in lactic acid and a decrease in pH and base excess.<sup>6-9</sup> In most of these studies blood samples were only taken at the end of each hypoxemic period,<sup>5-9</sup> which does not give insight into the time of onset of the metabolic acidosis and its rate of progression.

We studied the relation between  $\text{SaO}_2$  and metabolic acidosis in fetal lambs as follows. First, we determined the onset of metabolic acidosis while fetal hypoxemia was induced by maternal hypoxemia. Then the hypothesis derived from the first experiments was tested in a second set of experiments in which fetal hypoxemia was induced by graded reduction of uterine blood flow, and the progression in metabolic acidosis was studied. In these latter experiments we also studied the cardiovascular and hormonal changes with hypoxemia.  $\text{SaO}_2$  was measured in arterial samples and simultaneously with pulse oximetry.

### Material and methods

**Surgery.** Eighteen ewes of the Dutch Texel breed were operated on between 119 and 133 days of gestation (term 147 days). Anesthesia was induced intravenously with 30 mg/kg pentobarbital with 0.5% atropine and was maintained with 2.0% ethrane in a 2:1 mixture of nitrous oxide and oxygen (ER 300 respirator, closed system ventilation, LKB Medical AB, Bromma, Sweden). The temperature of the ewe was kept constant by means of a thermostatic heating pad underneath the animal.

In group 1 (nine ewes) a tracheostomy of 1.5 cm<sup>2</sup> was made in the neck by partially removing one or two tracheal rings and suturing the skin to the tracheal wall; during the experiments this tracheostoma was used for

an indwelling catheter to change maternal fraction of inspired oxygen ( $\text{FIO}_2$ ). In group 2 (nine ewes) the abdomen was opened through a paramedian incision, after which the uterus was temporarily lifted out of the pelvis and covered with soaked gauze. The peritoneum was opened over the trifurcation of the aorta into the common internal iliac artery and the external iliac arteries. A flexible inflatable occluder (diameter 8 or 10 mm, Rhodes Medical Instruments, Woodland Hills, Calif.) was placed around the common internal iliac artery, and an electromagnetic blood flow sensor (diameter 3.5, 4, or 4.5 mm with slot cover, Skalar, Delft, The Netherlands) was placed around the internal iliac artery leading to the pregnant horn. In all ewes a pedal artery was catheterized.

The fetal lamb was approached by hysterotomy near the fetal head. A muscle of the forelimb was prepared, and a transmission sensor (Oxiband or prototype Dura Y-sensor, Nellcor, Pleasanton, Calif.) was placed in a stainless-steel support around the muscle, leaving 7 mm of space between light-emitting diodes and photodiode. The light-emitting diodes emit red and infrared light through the tissue, and from the cardiosynchronous alternating light intensities caused by the pulsating blood volume in the tissue  $\text{SaO}_2$  can be estimated.<sup>10</sup> A second sensor was placed around muscular tissue of the other forelimb or around a double layer of skin in the neck of the fetus. Three electrocardiogram electrodes were sutured subcutaneously on the sternum, right shoulder, and left side in the neck. Polyvinyl catheters (inner diameter 0.8 mm, outer diameter 1.6 mm) were inserted in the carotid artery, the jugular vein, and the amniotic cavity. The uterus was then closed and all electrodes and catheters were exteriorized through a skin incision in the ewe's flank and packed into a pouch on the ewe's back. Before the skin was closed 10<sup>6</sup> IU of penicillin was administered into the peritoneal cavity.

The animals were allowed to recover 4 days before experiments were started. On the day of operation and during the recovery period antibiotics were administered daily: streptomycin, 5 mg intramuscularly to the ewe; ampicillin, 125 mg intravenously to the fetus; and ampicillin, 125 mg into the amniotic cavity. Catheters were kept open by continuous infusion of heparinized saline solution (5 IU/ml at 1 ml/hr). Food and water before and after surgery were given according to the rules of the animal laboratory. The experiments were approved by the local ethical committee for animal research.

One arterial blood sample (0.4 ml) was taken each day during the recovery period to assess fetal condition.

### Experiments

**Group 1.** After a 1-hour baseline period fetal hypoxemia was induced by stepwise reduction of the maternal  $\text{FIO}_2$  by a tracheal catheter inserted in the tracheostoma



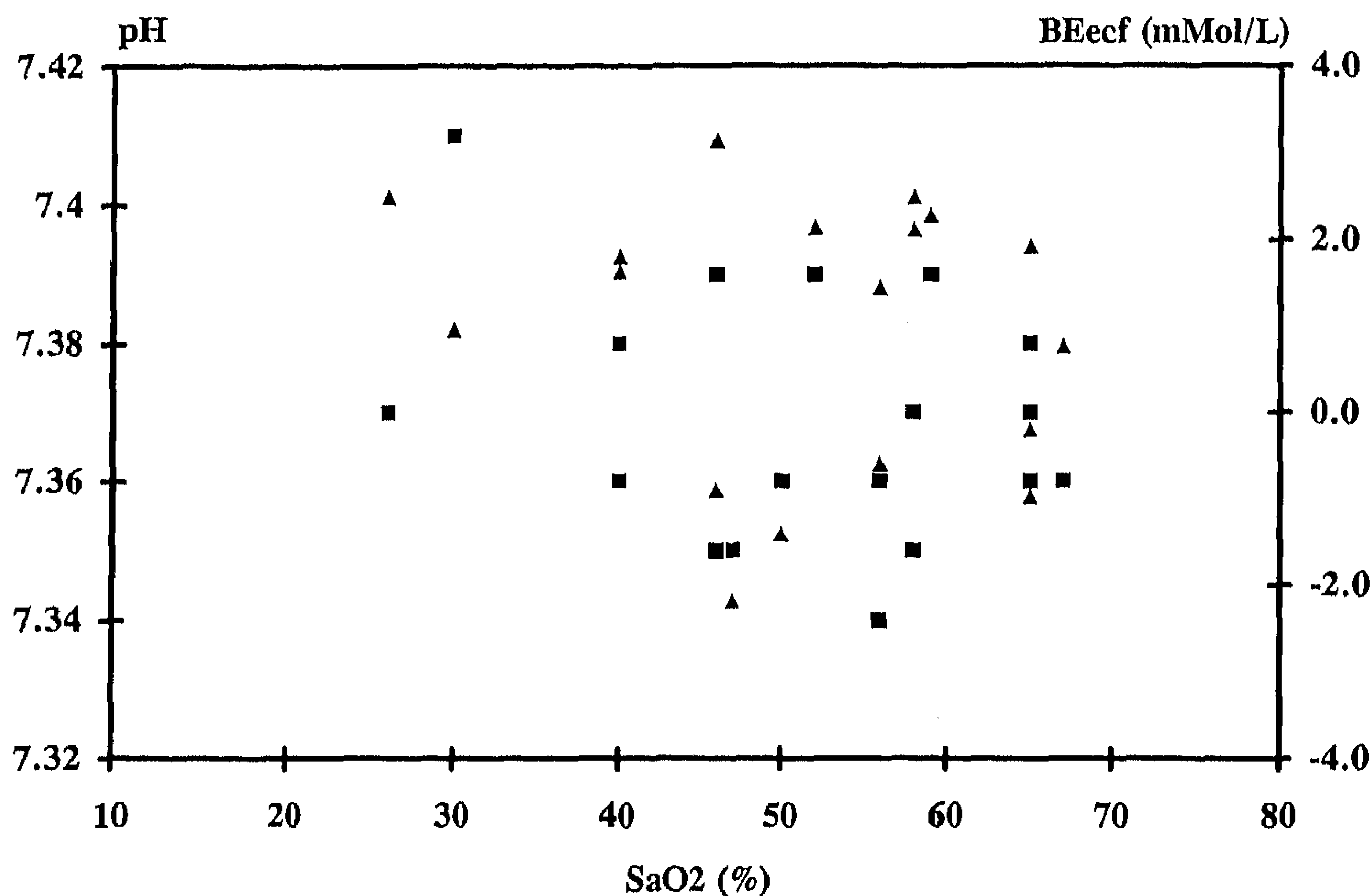


Fig. 1. Relationship between  $\text{SaO}_2$  and pH and extracellular fluid base excess ( $\text{BE}_{\text{ecf}}$ ) of first blood samples on day of experiment of total group of fetal lambs ( $n = 18$ ). ■, pH (Pearson correlation coefficient  $r = -0.29$ ,  $p > 0.10$ ); ▲, extracellular fluid base excess (Pearson correlation coefficient  $r = -0.16$ ,  $p > 0.10$ ).

from 20% to 10% in steps of 2.5%. Each level was maintained initially for 30 minutes but subsequently longer when pH and extracellular fluid base excess started to decrease. Arterial blood samples were taken from the fetus at 15-minute intervals during the whole experiment.

FHR and pulse oximetry were recorded continuously. Maternal arterial samples were taken in the baseline period, at the lowest point of hypoxia, and in the recovery period.

**Group 2.** After a 1-hour baseline period uteroplacental blood flow was reduced stepwise by occluding the common iliac artery to achieve fetal arterial  $\text{SaO}_2$  levels of 30% to 40% or  $<30\%$ . Each level was maintained for at least 1 hour. Fetal arterial blood samples for blood gases and pH (0.2 ml) were taken at 7.5-minute intervals and samples for  $\text{SaO}_2$  (0.2 ml) at 30-minute intervals and after each reduction in blood flow. When pulse oximetry indicated that  $\text{SaO}_2$  was out of the intended range, an additional sample for  $\text{SaO}_2$  was taken. If necessary, blood flow was further reduced until the intended  $\text{SaO}_2$  range was again achieved, and then this period was prolonged. In these instances each period lasted  $\geq 1$  hour. Such additional reductions had to be performed in three fetal lambs at the 30% to 40%  $\text{SaO}_2$  level. After the first hour of recovery samples were taken at 1-hour intervals until baseline values were reached again. At the start of the experiment and the end point of hypoxia, fetal arterial blood was collected for measurement of epinephrine, norepinephrine, do-

pamine, and cortisol levels (3 ml). Total blood loss was estimated to be within 10% of the total blood volume. Fetal arterial blood pressure and amniotic pressure were measured at the level of the ewe's back. These signals, FHR, and pulse oximetry saturation were recorded continuously.

**Data analysis.** The fetal blood samples were analyzed within 5 minutes to assess  $\text{SaO}_2$  (Instrumentation Laboratory 482, Lexington, Mass.), pH, and blood gases (Instrumentation Laboratory 1312). Results were corrected to  $39^\circ\text{C}$ . Then the oxygen content and the extracellular fluid base excess were calculated according to the formula used by the Instrumentation Laboratory blood gas analyzer. The extracellular fluid base excess is assumed not to be affected by a change in  $\text{Pco}_2$ .<sup>11</sup> All fetal lambs in group 1 showed a progressive decrease in pH and extracellular fluid base excess below a certain level of  $\text{SaO}_2$ . Before the onset of metabolic acidosis these variables showed a wide range at baseline (the variation in  $\text{SaO}_2$  could, for instance, fluctuate between 50% and 68%). Therefore a moving average was calculated for  $\text{SaO}_2$  and extracellular fluid base excess with three successive values.

Blood samples for fetal hormones were collected on ice. Catecholamines were measured by high-performance liquid chromatography with fluorometric detection<sup>12</sup> (interassay variation  $<12\%$ , intraassay variation  $<4\%$ ). Cortisol was measured by a standard radioimmunoassay.

The pulse oximetry sensors were connected to pro-

**Table I.** Mean values (SEM) of fetal blood variables and FHR during baseline period, end of hypoxic period, and recovery period of group 1 fetal lambs

	Baseline (n = 9)	End of hypoxia (n = 9)	Recovery	
			First hour (n = 9)	End point (n = 8)
SaO <sub>2</sub> (%)	47.9 (4.2)	17.4 (1.2)*		48.6 (3.7)
Oxygen content (mmol/L)	2.7 (0.3)	1.0 (0.1)*		2.8 (0.3)
PO <sub>2</sub> (mm Hg)	19.2 (1.2)	9.9 (0.5)*		19.6 (1.2)
PCO <sub>2</sub> (mm Hg)	43.6 (0.8)	38.9 (1.0)*		41.6 (1.1)†
pH	7.37 (0.01)	7.27 (0.01)*		7.37 (0.01)
Extracellular fluid base excess (mmol/L)	0.3 (0.5)	-8.8 (0.4)*		-1.3 (0.6)
Hemoglobin (mmol/L)	7.0 (0.2)	7.2 (0.2)		7.2 (0.2)
FHR (beats/min)	155 (6)	179 (5)‡	195 (4)*	165 (5)

\* $p < 0.001$ , compared with baseline value (Student paired  $t$  test).

† $p < 0.05$ , compared with baseline value (Student paired  $t$  test).

‡ $p < 0.01$ , compared with baseline value (Student paired  $t$  test).

tototype N-400 pulse oximeters (Nellcor). For group 1 the data of the pulse oximeter were not used in the current study. In group 2 SaO<sub>2</sub> values were obtained from the N-400 pulse oximeter. The median value of the SD of residuals around individual calibration lines was 3.7% (range 1.8% to 5.9%).<sup>13</sup>

Instantaneous FHR was measured from the fetal electrocardiogram. Arterial and amniotic pressures were measured with disposable transducers (TDN-R, neonatal use, Viggo Spectramed, Headfield, United Kingdom). Measurements of blood pressure (corrected for intraamniotic pressure) and FHR were averaged over the last 5 minutes in each period and during the nadir after the occlusion. The blood flow sensor was connected to an MDL 1401 electromagnetic flowmeter (Skalar). Maternal blood flow measurements were only used to verify the occlusion and were not further analyzed. All continuous signals were stored and calculated on a personal computer with the program Poly (Physiological Analysis Package, Inspektor Research System, Amsterdam).

**Statistics.** Blood gas values and cardiovascular variables were analyzed by Student paired  $t$  test and fetal hormones by Wilcoxon's signed-rank test. A Bonferroni correction was performed to obtain the proper  $p$  values, where more than one comparison was made. Blood gases and pH, SaO<sub>2</sub>, FHR, carotid blood pressure, and fetal hormone levels were compared between baseline, hypoxia, and recovery periods. Values are expressed as mean (SEM) for each group. For fetal hormone levels a logarithmic transformation was also carried out, and the relationship with the change in SaO<sub>2</sub> and pH was analyzed by the linear regression least-squares method.

## Results

**Baseline period.** During the recovery from surgery SaO<sub>2</sub> values for each fetus remained stable in a range similar to the value found later in the baseline period,

and pH was always  $\geq 7.34$ . SaO<sub>2</sub> showed intraindividual variations of between 4% and 18% of the respective mean values during the first hour of the baseline period.

In Fig. 1 the first blood sample values of the baseline periods are plotted for both groups 1 and 2 ( $n = 18$ ). SaO<sub>2</sub> varied from 26% to 67%. There was no correlation between SaO<sub>2</sub> and pH (Pearson correlation coefficient  $r = -0.29$ ,  $p > 0.10$ ) or between SaO<sub>2</sub> and extracellular fluid base excess ( $r = -0.16$ ,  $p > 0.10$ ).

**Group 1.** With stepwise reduction of the FIO<sub>2</sub> from 21% to 10%, maternal PCO<sub>2</sub> decreased from a mean of 104 mm Hg to 57 mm Hg at the lowest point. Fetal SaO<sub>2</sub> decreased to a mean lowest value of 17.4% (Table I). To investigate the relationship between SaO<sub>2</sub> and the onset of fetal acidosis, the change in the moving average in extracellular fluid base excess in a 10-minute interval was calculated and plotted against the moving average in SaO<sub>2</sub> (Fig. 2). When the moving average of SaO<sub>2</sub> reached 30%, the rate of change in extracellular fluid base excess was between -0.5 and 0.5 mmol/L per 10 minutes. Below an SaO<sub>2</sub> of 30% the changes in extracellular fluid base excess started to exceed -0.5 mmol/L per 10 minutes, with larger decreases in extracellular fluid base excess at lower SaO<sub>2</sub> values. This was true for all fetal lambs. At the end of the recovery period pH, extracellular fluid base excess, and the oxygen variables had returned to baseline values in all but one instance. This lamb died unexpectedly after the first hour of recovery although the pH had almost returned to the baseline level.

Maternal and fetal PCO<sub>2</sub> values showed small declines during hypoxia, probably because of maternal hyperventilation. Fetal hemoglobin concentration showed no significant change throughout the study.

FHR increased during the hypoxic period and was significantly higher at the end of this period. FHR increased further to a mean value of 195 beats/min during the first hour of recovery and returned slowly to baseline values by the end of the experiment. In one

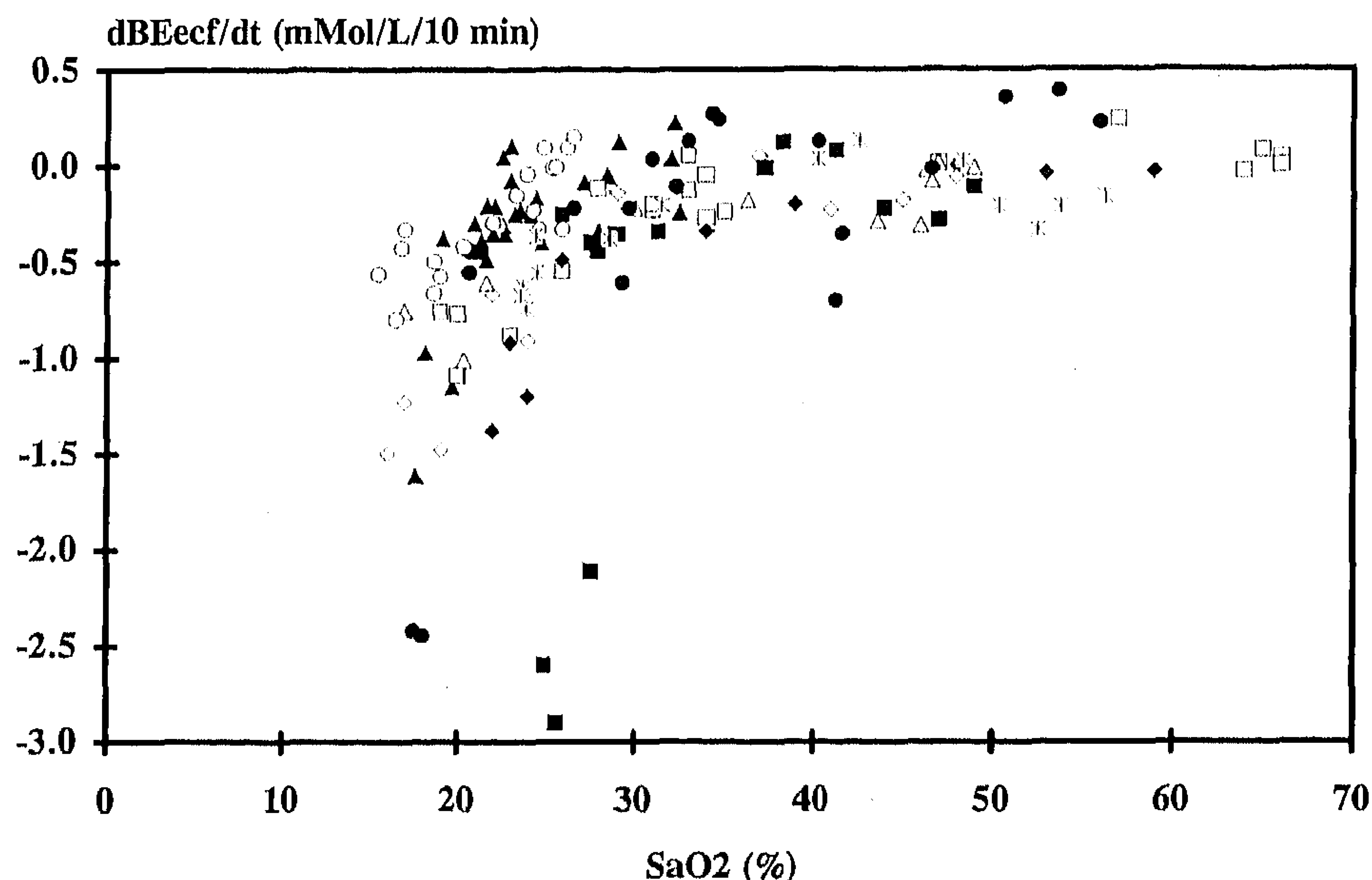


Fig. 2. Change in moving average of extracellular fluid base excess ( $dBE_{ecf}/dt$ ) in relation with moving average of  $SaO_2$  in nine fetal lambs, from start of experiment until moment of lowest extracellular fluid base excess. Each animal is represented by different symbol.  $\circ$ , Lamb died during recovery period.

**Table II.** Mean values and SEM of fetal blood variables, FHR, MAP, and time of period, during baseline period,  $SaO_2$  30% to 40%,  $SaO_2$  <30%, and recovery period, at end of each subsequent period of group 2 fetal lambs

	Baseline ( <i>n</i> = 9) (last 5 min)	$SaO_2$ 30%-40% ( <i>n</i> = 7)			$SaO_2$ <30% ( <i>n</i> = 9)			Recovery ( <i>n</i> = 9) (last 5 min)
		Nadir	Whole period	Last 5 min	Nadir	Whole period	Last 5 min	
$SaO_2$ (%)	53.6 (4.2)		35.6 (0.9)*		18.2 (1.5)*			47.8 (4.3)
Oxygen content (mmol/L)	3.3 (0.2)		2.3 (0.2)*		1.3 (0.1)*			2.9 (0.2)†
$PO_2$ (mm Hg)	21.4 (1.3)		17.7 (0.6)*		13.4 (0.6)*			21.4 (1.3)
$PCO_2$ (mm Hg)	47.2 (0.8)		49.4 (0.8)†		58.2 (2.0)*			46.9 (0.9)
pH	7.36 (0.01)		7.33 (0.01)†		7.14 (0.02)*			7.35 (0.01)
Extracellular fluid base excess (mmol/L)	1.5 (0.4)		0.5 (0.6)		-9.7 (0.6)*			0.4 (0.8)
Hemoglobin (mmol/L)	6.9 (0.4)		6.7 (0.5)		7.1 (0.4)			6.5 (0.3)
MAP (mm Hg)	44.4 (2.3)	45.3 (2.8)		49.1 (3.0)‡	52.1 (2.5)*		57.4 (2.8)*	42.5 (2.3)
FHR (beats/min)	153 (6)	120 (6)‡		159 (3)	123 (9)‡		172 (13)†	168 (8)
Time of period (min)	60 (0)		77 (7)			135 (21)		174 (38)

FHR and MAP are measured as mean around nadir and last 5 minutes of period.

\* $p < 0.001$ , compared with baseline value (Student paired *t* test).

† $p < 0.05$ , compared with baseline value (Student paired *t* test).

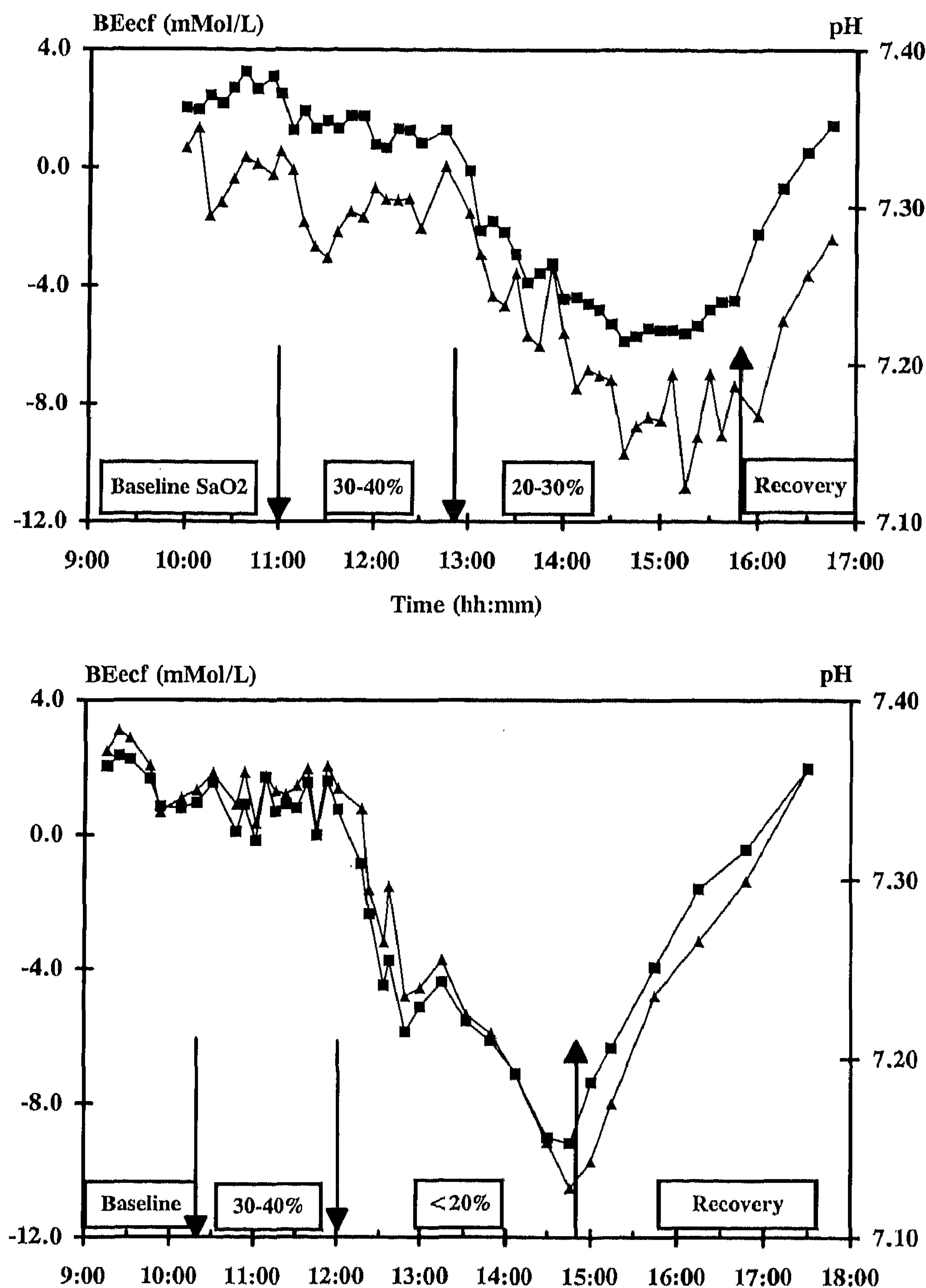
‡ $p < 0.01$ , compared with baseline value (Student paired *t* test).

fetal lamb FHR decreased below 100 beats/min when  $FI_{O_2}$  was lowered from 12.5% to 10%.

**Group 2.** Fetal blood gas variables, FHR, and mean arterial pressure (MAP) for these fetuses are summarized in Table II. Two fetal lambs started with baseline  $SaO_2$ s of 30% to 45%. In these two lambs the first reduction resulted in an  $SaO_2$  <30%. In the remaining fetuses  $SaO_2$ ,  $PO_2$ , and oxygen content were significantly reduced at a level of  $SaO_2$  of 30% to 40%.  $PCO_2$  rose and pH decreased immediately after the occlusion

but did not change further during this reduced level of 30% to 40%  $SaO_2$ . Extracellular fluid base excess decreased in a way similar to the pH but not statistically different (Fig. 3). The variable responses to the stepwise occlusions were not related to gestational age or weight of the fetus. FHR decreased in all animals, reaching a nadir within 1 to 3 minutes, but returned to baseline levels by the end of the  $SaO_2$  30% to 40% period. MAP increased significantly during this period from 44.4 to 49.1 mm Hg ( $p < 0.01$ ).





**Fig. 3.** Two examples of experiments in group 2 fetal lambs. *Upper figure*, Stabilization of pH and extracellular fluid base excess ( $BE_{ecf}$ ) at  $SaO_2$  level of 20% to 30%. *Lower figure*, Decrease of pH and extracellular fluid base excess below 25%. ↓, Stepwise reduction blood flow; ↑, stepwise rise of blood flow; ■ pH; ▲, extracellular fluid base excess.

With the second reduction of blood flow  $SaO_2$ ,  $PO_2$ , and oxygen content decreased further and  $PCO_2$  values increased. The effect on pH and extracellular fluid base excess was not identical in all fetal lambs. In two fetal lambs pH and extracellular fluid base excess decreased at an  $SaO_2$  level of 20% to 30% but showed a subsequent stabilization in pH and extracellular fluid base excess after 1.5 hours (Fig. 3, upper panel). In seven fetal

lambs pH and extracellular fluid base excess decreased constantly below an  $SaO_2$  of 25%; six of those fetal lambs had  $SaO_2$  values  $<20\%$  (Fig. 3, lower panel). MAP rose in all fetal lambs to a mean maximum value of 57.4 mm Hg ( $p < 0.001$ ) at the end of the hypoxic period. FHR decreased within 1 to 3 minutes after the increased occlusion but increased significantly by the end of the hypoxic period. After the occlusion was

**Table III.** Mean values and SEM of fetal hormones during baseline and at end point of hypoxia

	Baseline	End hypoxia
Dopamine (ng/ml)	0.10 (0.03)	0.85 (0.33)*
Norepinephrine (ng/ml)	0.87 (0.18)	7.81 (2.59)*
Epinephrine (ng/ml)	0.05 (0.01)	3.62 (2.83)*
Cortisol (ng/ml)	11.2 (1.8)	34.6 (5.5)*

\* $p < 0.01$ , compared with baseline values (Wilcoxon's signed-rank test).

released, all animals showed a period of tachycardia in which FHR rose significantly (compared with baseline) to a mean value of 189 beats/min (SEM = 9). In six fetal lambs FHR was still increased at the end of the experiment, although pH and extracellular fluid base excess had normalized. Fetal hemoglobin concentration showed no significant change throughout the study. All blood gas variables had returned to baseline values by the end of the hypoxic period except for oxygen content, which was still depressed.

Baseline levels for fetal catecholamines and cortisol showed wide ranges: dopamine 0.05 to 0.30 ng/ml, norepinephrine 0.37 to 1.83 ng/ml, epinephrine 0.01 to 0.12 ng/ml, and cortisol 7.0 to 24.0 ng/ml. There was no relationship between these values and baseline values for  $\text{SaO}_2$ , pH, extracellular fluid base excess, MAP, or FHR. In all fetal lambs fetal catecholamines and cortisol were increased at the end of the hypoxic period. The increase ranged from threefold to twentyfold for dopamine, from fivefold to nineteenfold for norepinephrine, from fifteenfold to 970-fold for epinephrine, and from threefold to fivefold for cortisol (Table III). There was no relationship between the changes in either catecholamines or cortisol and the change in  $\text{SaO}_2$  ( $p > 0.05$ ). The increases in catecholamines, but not in cortisol, were significantly related to the change in pH (Fig. 4).

All nine ewes showed normal values for pH,  $\text{PCO}_2$ , and  $\text{PO}_2$  during the baseline period. In three ewes blood samples were taken before, during, and after the experiment. No change in pH,  $\text{PCO}_2$ , or  $\text{PO}_2$  was seen.

### Comment

In this study we have determined the relationship between preductal  $\text{SaO}_2$  and metabolic variables as measured by pH and extracellular fluid base excess in fetal lambs at a premature age of between 0.81 and 0.90 of gestation. Baseline  $\text{SaO}_2$  values showed a wide range without significant correlation with pH or extracellular fluid base excess. This variation in  $\text{SaO}_2$  between individual fetuses has been observed previously in studies in fetal lambs<sup>4, 5</sup> and fetal baboons.<sup>14</sup> Some fetal lambs started the experiments with low  $\text{SaO}_2$  val-

ues that had been present from the first measurements on postoperative day 1 without any sign of acidosis. This indicates that these fetuses were not hypoxic in the sense that anaerobic metabolism was needed. Besides a large variation among different fetal lambs, the intraindividual variation in  $\text{SaO}_2$  was also substantial and ranged from 4% to 18% in the baseline period. Fetal arterial  $\text{SaO}_2$  values are on the steep part of the oxygen dissociation curve, and therefore even small variations in  $\text{PO}_2$  will lead to large variations in  $\text{SaO}_2$ . Such intraindividual variations in blood gases are probably attributable to uterine contractures, fetal movements, and maternal movements,<sup>15, 16</sup> which may lead to variations in  $\text{SaO}_2$  of 15% to 20% and variations in pH of 0.03.<sup>16</sup>

In all experiments in group 1, extracellular fluid base excess began to decrease at an  $\text{SaO}_2$  level  $< 30\%$ . As a result of the baseline variations, however, we had to calculate moving averages of  $\text{SaO}_2$  and extracellular fluid base excess to detect the starting point of acidosis. Reduction to an  $\text{SaO}_2$  level of 30% to 40% in group 2 resulted only in small and nonprogressive decreases in pH immediately after the initial partial occlusion. This indicates that above an  $\text{SaO}_2$  of 30% oxidative metabolism can be maintained, which can be explained by an increase of oxygen extraction and a decrease in oxygen consumption of nonvital organs.<sup>17</sup> An  $\text{SaO}_2$  level of 10% to 20% resulted in a progressive fall in pH and extracellular fluid base excess in all cases. An  $\text{SaO}_2$  level of 20% to 30% resulted in a progressive decrease in pH and extracellular fluid base excess in some fetuses and led to a stabilization at a somewhat lower level in others. Therefore some fetuses can compensate for oxygen saturations in the 20% to 30% range, whereas others deteriorate at this level.

This observation is similar to the findings of other studies. Paulick et al.<sup>4</sup> found the onset of metabolic acidosis at  $\text{SaO}_2$  levels of 15% to 20% (measured in the descending aorta) during stepwise reduction of uteroplacental blood flow. Postductal  $\text{SaO}_2$  is 5% to 6% lower than simultaneous preductal measurements.<sup>18</sup> An  $\text{SaO}_2$  level of around 30%, produced by reduction of the maternal blood flow and maintained for 24 hours, resulted in an initial decrease in pH with complete recovery by the end of the 24-hour period.<sup>19, 20</sup> With stepwise lowering of maternal  $\text{FIO}_2$  over several days Richardson et al.<sup>5</sup> showed that pH decreased when preductal  $\text{SaO}_2$  was close to 30%. Kitanaka et al.<sup>21</sup> induced long-term fetal hypoxemia (3 weeks) with a mean  $\text{SaO}_2$  around 45% and found no acidosis. If pulse oximetry becomes a monitoring technique to estimate the fetal  $\text{SaO}_2$  continuously, it should be considered that the human fetus may also have the ability to adapt metabolically to a reduced  $\text{SaO}_2$ .

Many investigators have measured fetal oxygen con-



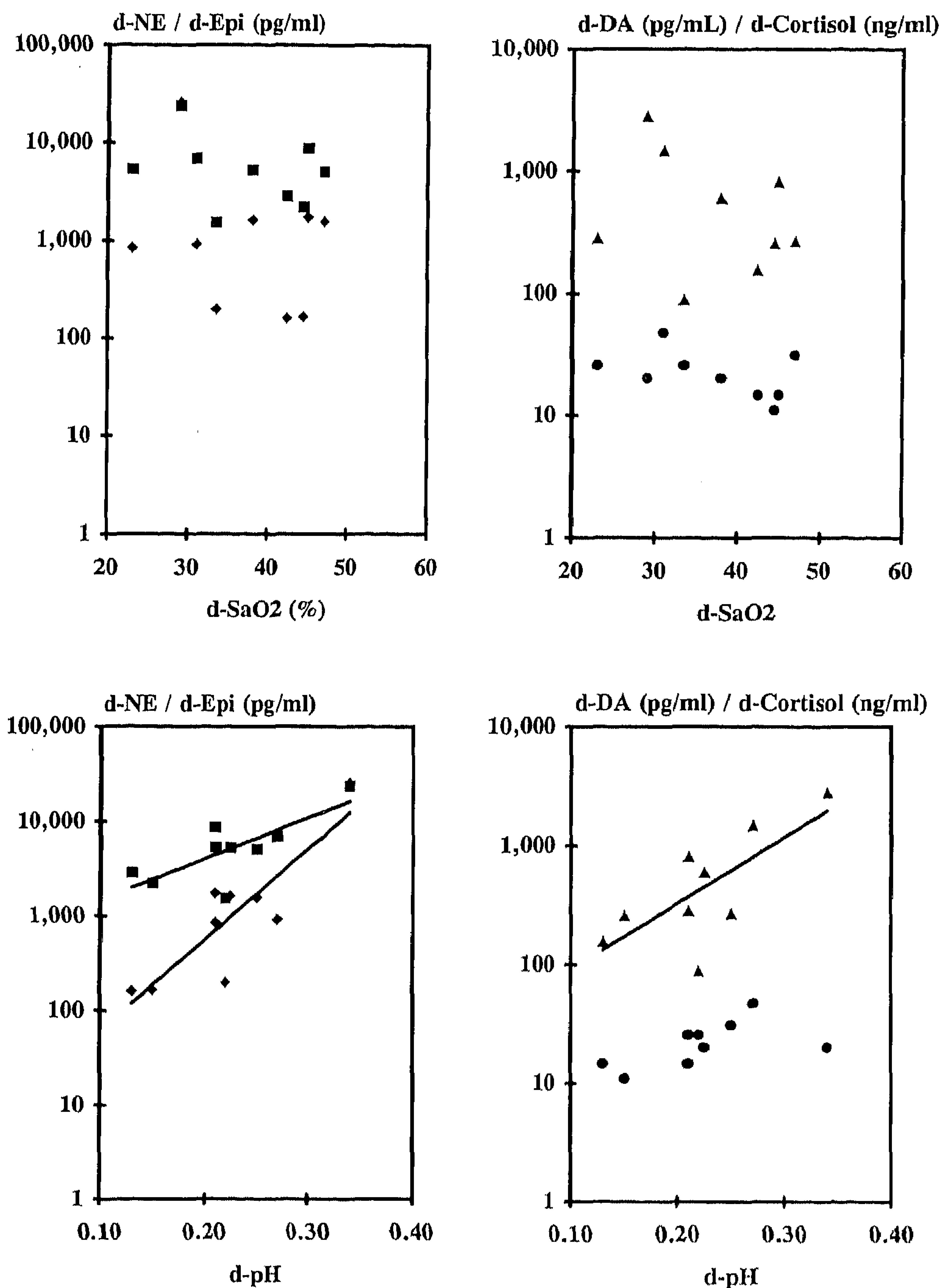


Fig. 4. Relation between difference (*d*) of beginning minus end hypoxic values for  $\text{SaO}_2$  and difference of end hypoxic minus beginning levels of catecholamines and cortisol (*upper figures*) and same for pH (*lower figures*). ■, Norepinephrine (NE); ♦, epinephrine (Epi); ▲, dopamine (DA); ●, cortisol. Relations and Pearson correlation coefficients (*r*) are  $\log d\text{-NE} = 4.34 \cdot d\text{-pH} + 2.74$ ,  $r = 0.76$ ,  $0.01 < p < 0.025$ ;  $\log d\text{-Epi} = 9.58 \cdot d\text{-pH} + 0.84$ ,  $r = 0.86$ ,  $p < 0.005$ ;  $\log d\text{-DA} = 5.57 \cdot d\text{-pH} + 1.40$ ,  $r = 0.72$ ,  $0.01 < p < 0.025$ .

sumption and have shown that oxygen delivery could be reduced to about 50% of control before oxygen consumption began to decrease.<sup>6-9</sup> With further reduction below 50% of baseline oxygen delivery, fetal oxygen consumption fell and metabolic acidosis developed.<sup>22</sup>

In contrast to the studies cited above, Jensen et al.<sup>23</sup> showed that acute severe reduction in uterine blood flow resulted in a linear relation between oxygen supply and oxygen consumption for the whole fetus and that graded reduction in uterine blood flow<sup>17</sup> resulted in a

linear relationship between oxygen supply and oxygen consumption for the lower carcass. When the fetal lungs were ventilated in utero, Askura et al.<sup>21</sup> also found a linear relation between  $PO_2$  and oxygen consumption. Moreover, when fetal skeletal muscle cells were studied at various levels of oxygenation in monolayer culture,<sup>25</sup> this linear relation was also found. In the study of Jensen et al.,<sup>23</sup> however, the reduction of blood flow resulted in an immediate  $SaO_2$  decrease below 20% with subsequent metabolic acidosis. These investigators did not look at the consequences of milder hypoxemia. In the study of Askura et al.<sup>21</sup> metabolic acidosis occurred only when oxygen content was  $<2$  mmol/L. Similar findings have been reported by Peeters et al.<sup>26</sup> An oxygen content of 2 mmol/L corresponds to an  $SaO_2$  of 20% to 33% if hemoglobin ranges from 6 to 10 mmol/L. At these levels of oxygenation oxygen consumption of vital organs such as heart and brain can be maintained because of redistribution of fetal blood flows.<sup>17, 26, 27</sup> An oxygen content  $<1$  mmol/L is associated with reduced cerebral blood flow and oxygen consumption and progressive acidosis<sup>28, 29</sup>; corresponding values for  $SaO_2$  if hemoglobin is between 6 and 10 mmol/L are  $<16\%$ .

In most previous studies the effect of acute hypoxemia on heart rate in the fetal lamb has been a transient bradycardia followed by a delayed return to baseline.<sup>27, 30</sup> In most of these studies the maternal  $FIO_2$  was lowered from 20% to 10% in one step, resulting in a rapid decrease in oxygen delivery to the fetus, activation of the fetal chemoreceptors, and reflex slowing of heart rate. Bradycardia was observed in only one fetus of group 1 when maternal  $FIO_2$  was lowered stepwise. This might have been related to failure of the gradual reduction of  $PO_2$  to evoke a chemoreceptor response. The rise in FHR during the hypoxemic period was probably the result of the increased fetal catecholamine levels. In group 2 all occlusions resulted in an initial fetal bradycardia with a nadir between 1 and 3 minutes, followed by a return to baseline FHR levels by the end of the  $SaO_2$  30% to 40% period, and tachycardia above baseline levels by the end of the  $SaO_2$   $<30\%$  period. When uteroplacental blood flow is reduced, both oxygen transport to the fetus and carbon dioxide transport from the fetus is restricted. Because both hypoxemia and hypercapnia result in fetal bradycardia,<sup>31, 32</sup> this may explain why stepwise partial occlusion resulted in a bradycardia whereas stepwise reduction of the  $FIO_2$  (when  $PCO_2$  decreased slightly) did not. A prolonged fetal tachycardia that could be abolished by  $\beta$ -adrenergic blockade has been described after 60 minutes of hypoxemia.<sup>33</sup> This indicates that the increase in FHR was the result of a prolonged increase in sympathetic activity.

Fetal mean arterial pressure showed a progressive gradual increase over the total hypoxemic period. This

finding has also been reported by others<sup>1, 8, 30</sup> and is held to be related to the rise in plasma catecholamines<sup>34</sup> and reflex vasoconstriction in the fetal carcass and several other vascular beds. In our experiments hypoxemia produced a marked increase in the plasma concentrations of catecholamines and, to a lesser extent, cortisol, as has also been observed by others.<sup>1, 33, 35</sup> This response is partly the result of direct effects of hypoxemia on the adrenal medulla and partly due to reflex stimulation.<sup>31</sup> During the baseline period there was no correlation between  $SaO_2$  and either catecholamine levels, cortisol, or MAP. Long-term hypoxemia without acidemia results in prolonged elevation of catecholamines.<sup>19, 21</sup> This reinforces the conclusion that our fetal lambs with low  $SaO_2$  values were not already hypoxemic at the beginning of the experiments. No correlation could be found between the decrease in  $SaO_2$  and the increases in catecholamines and cortisol, such as was reported by Jensen et al.<sup>36</sup> In that study hypoxemia and acidemia were closely interrelated. Paulick et al.<sup>1</sup> found that catecholamines started to increase exponentially when postductal  $SaO_2$  values reached 15% to 20%. In our study only the decrease in pH and the increases in catecholamines were linearly related. This suggests that it is not the decrease in  $SaO_2$  that is the determinant of the increase in catecholamines, but rather the degree of acidemia that is a consequence of the lack of oxygen.

In conclusion, oxygen delivery normally has a reserve in fetal lambs. Depending on the baseline level of oxygenation, oxygen delivery can be reduced substantially before oxidative metabolism is compromised and metabolic acidosis begins.  $SaO_2$  may decrease to 30% before a progressive decrease is seen in pH and extracellular fluid base excess. At an  $SaO_2$  of 20% to 30% a new balance of oxygen supply and oxygen consumption may develop. Below an  $SaO_2$  of 20% oxidative metabolism can no longer be maintained, and this will inevitably result in a progressive fall in pH and extracellular fluid base excess. If pulse oximetry is to become a monitoring technique during labor, it is important to know whether such a safety level also exists for the human fetus.

We thank Ineke Verbruggen, Jane Crevels, Jan Menssen, Theo Arts, and Biny Ringnalda for technical assistance; the Laboratory of Endocrinology and Reproduction for measurements of fetal hormones; and Professor C.B. Martin, Jr., for his critical comments during preparation of the manuscript.

#### REFERENCES

1. Parer JT, Livingston EG. What is fetal distress? *AM J OBSTET GYNECOL* 1990;162:1421-7.
2. Zuspan FP, Quilligan EJ, Iams JD, van Geijn HP. Predictors of intrapartum fetal distress: the role of electronic fetal monitoring. *AM J OBSTET GYNECOL* 1979;135:287-91.
3. McNamara H, Chung DC, Lilford R, Johnson N. Do fetal



- pulse oximetry readings at delivery correlate with cord blood oxygenation and acidemia? *Br J Obstet Gynaecol* 1992;99:735-8.
4. Paulick R, Kastendieck E, Weth B, Wernze H. Metabolische, kardiovaskuläre und sympathoadrenale Reaktionen des Feten auf eine progrediente Hypoxie-Tierexperimentelle Untersuchungen. *Z Geburtshilfe Perinatol* 1987;191:130-9.
5. Richardson BS, Carmichael L, Homan J, Patrick JE. Electrocardiac activity, electroocular activity, and breathing movements in fetal sheep with prolonged and graded hypoxemia. *AM J OBSTET GYNECOL* 1992;167:553-8.
6. Acheson GH, Dawes GS, Mott JC. Oxygen consumption and the arterial oxygen saturation in foetal and new-born lambs. *J Physiol* 1957;135:623-42.
7. Wilkening RB, Meschia G. Fetal oxygen uptake, oxygenation, and acid-base balance as a function of uterine blood flow. *Am J Physiol* 1983;244:H749-55.
8. Gu W, Jones CT, Parer JT. Metabolic and cardiovascular effects on fetal sheep of sustained reduction of uterine blood flow. *J Physiol* 1985;368:109-29.
9. Itskovitz J, LaGamma EF, Rudolph AM. The effect of reducing umbilical blood flow on fetal oxygenation. *AM J OBSTET GYNECOL* 1983;145:813-8.
10. Tremper KK, Barker SJ. Pulse oximetry. *Anesthesiology* 1989;70:98-108.
11. Siggaard-Andersen O. The acid-base status of the blood. 4th ed. Oxford: Alden & Mowbray, 1974:115-9.
12. van der Hoorn FAJ, Boomsma F, Man In 't Veld AJ, Schalekamp MADH. Determination of catecholamines in human plasma high-performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. *J Chromatogr* 1989;487:17-28.
13. Nijland R, Jongsma HW, Menssen JJM, Nijhuis JG, van den Berg PP, Oeseburg B. The accuracy of transmission pulse oximetry in fetal lambs. *J Physiol* 1994 [In press].
14. Daniel SS, James LS, MacCarter G, Morishima HO, Stark RI. Long-term acid-base measurements in the fetal and maternal baboon. *AM J OBSTET GYNECOL* 1992;166:707-12.
15. Jansen CAM, Krane EJ, Thomas AL, et al. Continuous variability of fetal  $PO_2$  in the chronically catheterized fetal sheep. *AM J OBSTET GYNECOL* 1979;134:776-83.
16. Harding R, Sigger JN, Wickham PJD. Fetal and maternal influences on arterial oxygen levels in the sheep fetus. *J Dev Physiol* 1983;5:267-76.
17. Jensen A, Berger R. Fetal circulatory responses to oxygen lack. *J Dev Physiol* 1991;16:181-207.
18. Nijland R, Jongsma HW, Crevels J, et al. The ductus arteriosus, pre- and postductal oxygen saturation measurements in fetal lambs. *Eur J Obstet Gynecol Reprod Biol* 1994;55:135-40.
19. Hooper SB, Coulter CL, Deayton JM, Harding R, Thornburn GD. Fetal endocrine responses to prolonged hypoxemia in sheep. *Am J Physiol* 1990;259:R703-8.
20. Bocking AD, White S, Gagnon R, Hansford H. Effect of prolonged hypoxemia on fetal heart rate accelerations and decelerations in sheep. *AM J OBSTET GYNECOL* 1989;161:722-7.
21. Kitanaka T, Alonso JG, Gilbert RD, Siu BL, Clemons GK, Longo LD. Fetal responses to long-term hypoxemia in sheep. *Am J Physiol* 1989;256:R1348-54.
22. Carter AM. Factors affecting gas transfer across the placenta and the oxygen supply to the fetus. *J Dev Physiol* 1989;12:305-22.
23. Jensen A, Hohman M, Künzel W. Dynamic changes in organ blood flow and oxygen consumption during acute asphyxia in fetal sheep. *J Dev Physiol* 1987;9:543-59.
24. Askura H, Ball KT, Power GG. Interdependence of arterial  $PO_2$  and  $O_2$  consumption in the sheep. *J Dev Physiol* 1990;13:205-13.
25. Braems G, Jensen A. Hypoxia reduces oxygen consumption of fetal skeletal muscle cells in monolayer culture. *J Dev Physiol* 1991;16:209-15.
26. Peeters LLH, Sheldon RE, Jones MD, Makowski EL, Meschia G. Blood flow to fetal organs as a function of arterial oxygen content. *AM J OBSTET GYNECOL* 1979;135:637-46.
27. Cohn HE, Sachs EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *AM J OBSTET GYNECOL* 1974;120:817-24.
28. Field DR, Parer JT, Auslender RA, Check DB, Baker W, Johnson J. Cerebral oxygen consumption during asphyxia in fetal sheep. *J Dev Physiol* 1990;14:131-7.
29. Richardson BS, Rurak D, Patrick JE, Homan J, Carmichael L. Cerebral oxidative metabolism during sustained hypoxemia in fetal sheep. *J Dev Physiol* 1989;11:37-43.
30. Giussani DA, Spencer JAD, Moore PJ, Bennet L, Hanson MA. Afferent and efferent components of the cardiovascular reflex responses to acute hypoxia in term fetal sheep. *J Physiol* 1993;461:431-49.
31. Hanson MA. The importance of baro- and chemoreflexes in the control of the fetal cardiovascular system. *J Dev Physiol* 1988;10:491-511.
32. Boekkooi PF, Baan J, Teitel D, Rudolph AM. Chemoreceptor responsiveness in fetal sheep. *Am J Physiol* 1992;263:H162-7.
33. Jones CT, Ritchie JWK. The effects of adrenergic blockade on fetal response to hypoxia. *J Dev Physiol* 1983;5:211-22.
34. Jones CT, Roebuck MM, Walker DW, Johnston BM. The role of the adrenal medulla and peripheral sympathetic nerves in the physiological responses of the fetal sheep to hypoxia. *J Dev Physiol* 1988;10:17-36.
35. Jones CT, Robinson RO. Plasma catecholamines in foetal and adult sheep. *J Physiol* 1975;248:15-33.
36. Jensen A, Künzel W, Kastendieck E. Fetal sympathetic activity, transcutaneous  $PO_2$ , and skin blood flow during repeated asphyxia in sheep. *J Dev Physiol* 1987;9:337-46.