The Effect of Halothane anaesthesia on the asphyxiated foetal lamb *in utero*

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In a previous study, we examined the effects of halothane on the normal foetal lamb in utero. The most significant finding was a 33 per cent fall in foetal mean arterial blood pressure (MABP). Cardiac output and placental blood flow were not affected. To determine if the asphyxiated foetus would respond similarly, the following study was performed. Seven pregnant ewes were surgically prepared two days prior to study with maternal and foetal indwelling arterial and venous cannulas. An inflatable occlusion loop was secured around the umbilical cord.

On the day of study, a tracheostomy was performed on each ewe. Microspheres were injected into the foetal circulation during the control period. The occlusion loop was inflated to produce foetal asphyxia and microspheres were again injected. The ewe was then anesthetized with halothane; and after 15 minutes, microspheres were injected into the asphyxiated foetus and halothane levels were measured.

The asphyxiated foetuses showed a significant rise in MABP, fall in heart rate and fall in cardiac output from control. Blood flow to the brain was significantly increased and flow to the placenta and gut decreased. Exposure of the asphyxiated foetus to halothane resulted in a fall of MABP to control but no significant change in cardiac output or brain blood flow. The mean halothane level in the foetus was $46.0 \text{ mg} \cdot \text{l}^{-1}$ or 0.32 vol%. Exposure of the asphyxiated foetus to halothane for 15 minutes does not produce significant further deterioration of the foetal lamb in utero.

Halothane is commonly used when general anaesthesia is required for obstetrical patients. Previous studies have shown that this agent, used in concentrations of 0.5–0.75 per cent, does not increase uterine bleeding¹ and is not depressant to the normal human fetus when exposure is short, i.e., less than 10 minutes.^{2,3} In previous animal experiments⁴ we documented the effects of halothane on mean arterial blood pressure (MABP), pulse rate, acid-base status and regional distribution of blood flow in the normal foetal lamb.⁵ We found that exposure for up to 96 minutes produced a significant fall in MABP (30 per cent) but no changes in any other parameters, including cardiac output. Halothane was well tolerated by the normal foetal lamb *in utero*.

We did consider, however, that the sharp decline in MABP might compromise the cardiovascular system of the asphyxiated foetus *in utero*. To determine if the asphyxiated foetus would tolerate exposure to halothane, the following study was performed.

Method

Seven pregnant ewes of 125–135 days gestation (term 150 days) were surgically prepared as follows: Under halothane-oxygen anaesthesia with tracheal intubation and controlled ventilation, a maternal groin incision was made for insertion of polyvinyl catheters into the femoral artery and vein. Through a midline abdominal incision the uterus was exposed and a small hysterotomy incision made. Polyvinyl catheters were placed in the foetal femoral artery and vein and the axillary artery, by extraction of the foetal limbs through the hysterotomy. An inflatable occlusion loop was secured around the umbilical cord 5–10 cm from the foetal abdominal wall. The occlusion of the foetal vessels

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was tested by inflation of the loop for ten seconds. Then all incisions were closed and the catheters tunneled subcutaneously to the maternal flank.

Each animal was allowed to recover for 24–48 hours. Stability of the animal model was assessed daily by analysis of maternal and foetal blood gases and acid–base status. No animal was included for study unless foetal and maternal blood gases were in the normal range.⁶ Just prior to a study, a tracheostomy was performed on the ewe, using local anaesthesia.

Each study began with a control period of 30 minutes with the ewe standing quietly in an experimental cart. The ewe breathed humidified oxygen at a flow rate of 12–15 l·min⁻¹ via the tracheostomy. Maternal and foetal MABP and pulse rate were recorded continuously via the femoral arterial catheters on an eight channel Hewlett-Packard recorder with digital readout (Model No. 7758C). Arterial blood gas samples were done at 15-minute intervals from the maternal femoral and foetal axillary arteries and analysed on a Corning Blood Gas Apparatus (Model 155-2). No studies were performed unless foetal arterial pH was greater than 7.35 and pO₂ was greater than 15 torr during the control period.

At the end of the control period, blood flow to foetal organs was measured by the injection of labelled microspheres. A suspension of plastic microspheres, 15 ± 0.5 microns in diameter labelled with either cerium¹⁴¹, chromium⁵¹ or strontium⁸⁵ (3M Company, Minneapolis), was diluted in 4 ml. of heparinized saline to yield an average injectate of 1.4×10^6 spheres.^{6,7} The 4 ml. dose was injected over 30 seconds into the foetal inferior vena cava, followed by 10 ml. of heparinized saline. Just prior to injection, withdrawal of blood from the axillary and femoral arteries was begun at a rate of 1.9 ml·min⁻¹ using a Harvard pump withdrawal system (Model 940). The withdrawal continued for 120 seconds after completion of the injection into the inferior vena cava. The two arterial blood samples were weighed and counted in a Searle Analytic Mark III gamma counter (Model No. 6880). These counts were used as reference samples to calculate blood flow to organs supplied above and below the ductus arteriosus according to the method of Rudolph and Heyman⁷ and as adapted to our model by one of the authors (W.A.T.) This calculation underestimates foetal

cardiac output by approximately ten per cent as there is no reference sample for pulmonary blood flow⁸.

After the control period, foetal asphyxia was produced by gradually inflating the umbilical cord occlusion loop until the foetal pH had declined to 7.10–7.15. The loop was maintained inflated for the remainder of the experiment.

When a stable state of foetal asphyxia was obtained the second microsphere injection was made using a different label. A constant inspired halothane concentration of 1.5 per cent was then added to the maternal breathing circuit using a semi-closed system, and maternal ventilation was controlled mechanically after five minutes. Inspired halothane concentrations were monitored on a Beckman LB2 infrared analyser. Maternal and foetal arterial halothane levels were measured at 5, 10, and 15 minutes. At 15 minutes, the third microsphere injection was made into the foetal circulation.

At the end of the experiment the ewe was killed with an injection of thiopental and saturated KCl. The foetus and placenta were removed and weighed. The foetus was dissected and all organs were weighed, labelled and ground separately. All specimens were then ashed over three days at 300°C. The ashed samples were placed in labelled counting vials. The counts obtained were then used to calculate blood flow to foetal organs during control, asphyxia and halothane anaesthesia to the asphyxiated foetus.^{7,8}

Two-way analysis of variance was used to determine whether there were significant differences during the whole study in the following parameters: maternal and foetal MABP, pulse rate, pO₂, pCO₂, pH and base excess. Unpaired tests were then used to determine specific inter-group differences. The regional blood flows for all foetal organs from the three microsphere injections were analysed in the same way. "P" values < 0.05 were considered significant.⁹

Results

During the three phases of the experiment (control, foetal asphyxia and foetal asphyxia with halothane anaesthesia) there were no significant changes in maternal MABP, pulse rate or PCO₂ (Table I). After the introduction of controlled ventilation with halothane anaesthesia there was a significant decrease in

TABLE I Maternal and foetal MABP and pulse rate during control period, production of foetal asphyxia and administration of halothane to the asphyxiated foetus

	Control 0	Asphyxia (Foetal)			Halothane and Asphyxia		
		30 min	60 min	90 min	5 min	10 min	15 min
Maternal MABP	92.3 ± 5.2	91.1 ± 6.0	90.8 ± 5.6	92.3 ± 6.2	86.6 ± 6.3	87.1 ± 6.8	86.3 ± 5.0
Pulse	106 ± 4	114 ± 6	107 ± 9	105 ± 7	121 ± 6	120 ± 6	116 ± 6
Foetal MABP	61.2 ± 1.0	67.1 ± 3.1*	74.0 ± 3.7*	73.4 ± 3.6*	70.6 ± 3.3*	63.6 ± 3.0	61.4 ± 3.9
Pulse	164 ± 7	122 ± 12*	115 ± 10*	106 ± 9*	152 ± 25	165 ± 15	177 ± 21

N = 7, Mean ± S.E.

*p < 0.05 = significantly different from control.

TABLE II Maternal and foetal blood gases and acid-base data during control period, production of foetal asphyxia and administration of halothane to the asphyxiated foetus

	Control	Foetal asphyxia			Halothane and Asphyxia		
	0	30 min	60 min	90 min	5 min	10 min	15 min
Maternal:							
pO ₂	250 ± 21	257 ± 24	193 ± 42	262 ± 29	364 ± 19*	344 ± 51*	344 ± 95*
pCO ₂	30 ± 2	29 ± 1	27 ± 2	27 ± 2	36 ± 2	37 ± 4	32 ± 2
(H ⁺) nanomole/ litre	32.4 ± 0.70	33.1 ± 0.70	33.1 ± 0.70	33.1 ± 0.70	39.8 ± 1.9*	41.7 ± 1.00*	35.5 ± 2.4
pH	7.49 ± 0.01	7.48 ± 0.01	7.48 ± 0.01	7.48 ± 0.01	7.40 ± 0.02*	7.38 ± 0.01*	7.45 ± 0.03
BE	1.2 ± 1.1	-4.3 ± 0.6	-1.3 ± 0.4	-0.5 ± 1.7	1.2 ± 1.3	-1.9 ± 1.89	1.1 ± 1.9
Foetal:							
pO ₂	24 ± 1.7	16 ± 2.0	20 ± 3.0	19 ± 1.8	22 ± 2.1	26 ± 4.2	26 ± 4.0
pCO ₂	41 ± 1.3	4 ± 3.3*	52 ± 3.0*	54 ± 2.7*	57 ± 3.5*	57 ± 1.8*	58 ± 2.0*
(H ⁺) nanomole/ litre	41.6 ± 2.1	48.9 ± 3.5*	64.5 ± 4.6*	72 ± 5.0*	81.2 ± 5.6*	81.2 ± 5.6*	81.2 ± 5.6*
pH	7.38 ± 0.02	7.31 ± 0.03*	7.19 ± 0.03*	7.14 ± 0.03*	7.09 ± 0.03*	7.09 ± 0.03*	7.09 ± 0.03*
BE	-0.5 ± 1.0	-4.0 ± 1.4	-7.9 ± 1.4*	-10.2 ± 1.0*	-12.2 ± 1.8*	-12.0 ± 1.5*	-12.01 ± 1.8*

N = 7, Mean ± S.E.

*p < 0.05 = significantly different from control values.

maternal pH during the initial ten minutes of halothane anaesthesia, but this returned to control values by 15 minutes. Maternal arterial pO₂ increased significantly with the institution of controlled ventilation (Table II).

Inflation of the umbilical occlusion loop produced foetal asphyxia in 90 ± 5 minutes (mean ± S.E.). At that time, foetal MABP has risen from a control value of 61.2 ± 1.0 torr to 73.4 ± 3.6 torr. Pulse rate decreased from 164 ± 7 to 106 ± 9

beats/minute. These changes were significantly different from control. Foetal pH fell from a control of 7.38 ± 0.02 to 7.14 ± 0.03; pCO₂ rose from 41 ± 1.3 to 54 ± 2.7 torr. These changes were also significantly different from control. There was no significant change in foetal pO₂ (Table II).

Foetal regional blood flows were also altered by asphyxia. Cerebral blood flow increased from 1.11 ± 0.18 to 3.00 ± 0.43 ml·gm⁻¹·min⁻¹ (Table III). Blood flows to the foetal kidneys, liver, gut,

TABLE III Foetal regional blood flows and calculated foetal cardiac output at control, during asphyxia and during asphyxia plus halothane anaesthesia

Organ system ml·g ⁻¹ ·min ⁻¹	Control	Asphyxia	Halothane and asphyxia
Heart	0.96 ±0.07	1.11 ±0.17	0.91 ±0.16
Brain	1.11 ±0.18	3.00* ±0.43	2.60* ±0.55
Kidney	2.44 ±0.09	1.44* ±0.38	1.23* ±0.24
Liver	0.82 ±0.05	0.22* ±0.10	0.24* ±0.08
Splanchnic bed†	4.12 ±0.80	0.43* ±0.55	2.07† ±0.41
Musculo-skeletal system	0.61 ±0.28	0.20* ±0.06	0.15* ±0.41
Skin	0.30 ±0.20	0.06 ±0.20	0.04 ±0.02
Placenta	0.96 ±0.11	0.30* ±0.02	0.36* ±0.07
Calculated foetal cardiac output ml·min ⁻¹	1063.8 ±102.0	616.1* ±122.0	538.2* ±73.0
Halothane blood Level, mg·l ⁻¹	0 0	0 0	46.0 ±3.1

N = 7, Mean ± S.E.

*p < 0.05 – significantly different from control.

†p < 0.05 – significant difference between asphyxia and asphyxia plus halothane.

‡ – includes stomach, small and large bowel, spleen, adrenals, genital organs.

placenta and musculo-skeletal system declined significantly from control but there were no significant changes in blood flow to the heart or skin. Calculated foetal cardiac output declined significantly from a control value of 1063 ± 102 to 616 ± 122 ml·min⁻¹ during foetal asphyxia.

The introduction of halothane anaesthesia produced the following changes: foetal MABP fell and pulse rate increased to pre-asphyxia levels. There was a further decrease in pH but the differences were not significant. There was no further significant change in foetal pCO₂.

Halothane anaesthesia did not significantly alter regional blood flows in the heart, brain or placenta from the asphyxiated state. Blood flow in the gut and liver increased, although not to control levels (Table III). Fifteen minutes of halothane anaesthesia did not significantly affect the cardiac output in the asphyxiated state.

Despite cord compression by the occlusion loop, halothane appeared in the foetal arterial blood rapidly, and by 15 minutes was 46.0 ± 3.1 mg·l⁻¹ or 0.32 vol%, as measured in the foetal axillary artery.

Discussion

The production of foetal asphyxia by umbilical cord compression was developed in our laboratory and has proven to be a reliable way of producing foetal distress.¹¹ It has considerable clinical relevance and has the advantage of producing foetal acidosis without the use of drugs or interference with maternal homeostasis. This model of foetal asphyxia has been shown previously to cause a marked increase in blood flow to the foetal brain.¹⁰

Our study demonstrated a shunting of blood from less vital structures such as the gut and musculo-skeletal system to preserve blood flow to the myocardium and increase cerebral flow despite a falling cardiac output. The increase in pCO₂ and decrease in pH likely facilitate the increase in cerebral blood flow by producing cerebral vasodilatation.

With the introduction of halothane anaesthesia the hypertensive response to asphyxia was reversed. Foetal MABP and pulse rate returned to control values. Cerebral blood flow remained elevated, however, suggesting that the foetus does possess some autoregulation of cerebral blood flow.

During 15 minutes of halothane anaesthesia to the asphyxiated foetus, foetal acid-base status did not significantly deteriorate. This may be due to the short exposure time and is in contrast to a similar study by Palahniuk *et al.*¹¹ which documented a further deterioration of the asphyxiated foetus when anaesthetized with halothane. In their study the ewe was initially anaesthetized with four per cent halothane in oxygen by mask until the ewe could be intubated. This necessitated a longer exposure to halothane than in our study and may have resulted in much higher halothane concentrations (arterial halothane levels were not measured).

In our study, supplemental oxygen was administered to the ewe through the tracheostomy during the control and asphyxia periods. In the study by Palahniuk *et al.*, the ewes breathed room air until the induction of anaesthesia. This may account, in part, for the higher foetal pO₂ in our study. The institu-

tion of controlled ventilation within five minutes of anaesthesia also guaranteed adequate oxygenation in the mother and may have been responsible for the maintenance of foetal oxygenation and acid-base status during exposure to halothane.

We did not measure foetal arterial oxygen contents. The production of acidosis would shift the oxygen saturation curve to the right and maintain pO_2 while content is decreased. In the study by Johnson *et al*, oxygen content was decreased during foetal acidosis.¹⁰ Therefore the maintenance of the pO_2 does not guarantee adequate oxygen supply to all tissues.

From our data we conclude that a short exposure of the asphyxiated foetal lamb to 1.5 per cent halothane in oxygen anaesthesia does not produce a significant fall in cerebral blood flow or cardiac output, despite a fall in MABP. Foetal acid-base status is not further affected by halothane, at least at levels of 0.32 vol% as measured in the foetal arterial circulation.

In this study of halothane anaesthesia in the normal foetal lamb, the foetal arterial blood levels of halothane were $64.3 \pm 11.8 \text{ mg} \cdot \text{l}^{-1}$ (0.36 vol%) after 16 minutes of anaesthesia.⁴ In the asphyxiated foetus, the arterial levels were $46.0 \pm 3.1 \text{ mg} \cdot \text{l}^{-1}$ (0.32 vol%). The level of 0.32 vol% has been shown by Gregory *et al*,¹² to be approximately 1 MAC for the foetus *in utero*. Even during asphyxia produced by cord compression, halothane crosses into the foetus and produces levels of approximately one MAC, although the concentration of halothane did not reach the levels obtained in the normal foetus.

We conclude that low levels of halothane anaesthesia in a stable maternal preparation do not cause further deterioration in the asphyxiated foetus if the duration of anaesthesia is less than 15 minutes.

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Résumé

Lors d'une étude antérieure, les auteurs avaient étudié les effets de l'halothane sur le fœtus de brebis in utero. La constatation la plus significative a été une chute de 33 pour cent de la pression artérielle moyenne. Le débit cardiaque et le débit placentaire n'ont pas été affectés. Pour déterminer si le fœtus asphyxié répondrait de façon similaire, l'étude suivante a été réalisée. Sept brebis gravides ont subi une préparation chirurgicale comprenant l'insertion de sondes maternelles et fœtales à demeure tant du côté artériel que veineux. Un lacet insufflable a été installé autour du cordon ombilical.

Le jour de l'étude on a trachéotomisé chacune des brebis. On a ensuite injecté des microsphères dans la circulation fœtale pendant la période de contrôle. Le lacet fut insufflé pour produire l'asphyxie fœtale et des microsphères ont été réinjectées. La brebis fut ensuite anesthésiée à l'halothane; après 15 minutes, on a injecté de nouveau des microsphères dans la circulation du fœtus asphyxié et on a mesuré la concentration de l'halothane dans le sang.

Les fœtus asphyxiés ont montré une élévation significative de la pression artérielle majeure, une chute de la fréquence et du débit cardiaque comparativement aux contrôles. Le débit sanguin cérébral a été augmenté de façon significative et les débits sanguins placentaire et intestinal diminués. L'exposition à l'halothane des fœtus asphyxiés a causé une baisse de la pression artérielle moyenne comparativement aux contrôles mais pas de changement significatif du débit cardiaque et du débit cérébral. La concentration sanguine de l'halothane dans le fœtus a été de $46.0 \text{ mg} \cdot \text{l}^{-1}$ ou 0.32 vol. pour cent.

L'exposition du fœtus en état d'asphyxie pendant 15 minutes ne produit pas de façon significative une détérioration plus marquée du fœtus de la brebis in utero.