Isoflurane potency and cardiovascular effects during short exposures in the foetal lamb

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Isoflurane is a relatively new volatile anaesthetic in clinical practice and increasing use for obstetrical patients might be expected. A previous study demonstrated that a 60–90 minute exposure of the foetus to isoflurane resulted in a significant fall in foetal cardiac output with development of foetal acidosis. To determine the cardiovascular effects of a shorter exposure of the foetal lamb to isoflurane and the potency (MAC) of isoflurane in the foetus, the following study was done.

Eleven pregnant ewes were surgically prepared by placing indwelling arterial and venous catheters into the mother and foetus. After a 48-hour recovery period, isoflurane, two per cent in oxygen, was administered to six ewes via a tracheostomy for 30 minutes. Foetal cardiac outputs and regional blood flows were measured by the microsphere method. In five ewes the concentration of isoflurane was varied and MAC determinations were done on both ewe and foetus. Arterial blood levels of isoflurane were used to determine foetal MAC.

Exposure to isoflurane resulted in a significant decrease in maternal and foetal mean arterial blood pressures and in foetal heart rate. Exposures up to 30 minutes did not result in foetal acidosis or a significant fall in cardiac output. Maternal and foetal MAC for isoflurane were determined to be 0.86 and 0.34 per cent respectively.

Key words

ANAESTHETICS, VOLATILE: isoflurane; POTENCY, ANAESTHETIC: MAC; PREGNANCY: foetus.

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Isoflurane is a relatively new volatile anaesthetic in clinical practice. It has several potential advantages over existing halogenated agents, such as lack of sensitization of the myocardium to catecholamines,¹ maintenance of cardiac output by decreasing total peripheral resistance and increasing heart rate,^{2,3} and minimal metabolism.⁴ Increasing exposure of parturients to isoflurane might therefore be expected.

A study by Biehl *et al.*⁵ demonstrated that isoflurane may be detrimental to the foetus. During a 90-minute exposure to isoflurane in pregnant sheep near term, progressive foetal acidosis developed by 48 minutes, and foetal cardiac index declined by 60 minutes. However, a shorter exposure time might be more clinically relevant, as, for example, for vaginal deliveries or Caesarean sections. We therefore felt it important to examine maternal and foetal events during a 30-minute anaesthetic with isoflurane.

We previously determined that foetal MAC (minimum alveolar concentration) for halothane in sheep is much lower than maternal MAC.⁶ To decide if this phenomenon also occurs with isoflurane, we determined the MAC for isoflurane in the foetal lamb.

Methods

Cardiovascular studies

Six pregnant sheep of 125–135 days gestation (term 145–150 days) were prepared as follows, using procedures we have previously described:⁵ under general anaesthesia with halothane in oxygen and controlled ventilation, polyvinyl catheters were inserted into a maternal femoral artery and vein and a foetal femoral artery and vein and an axillary

artery. All incisions were closed and the catheters tunnelled subcutaneously to the maternal flank and enclosed in a protective pocket. The sheep were allowed to recover for at least 48 hours.

On the day of the study, under brief general anaesthesia with isoflurane and oxygen, a tracheostomy was performed. Each animal was allowed to recover for at least one hour, while breathing humidified oxygen at a flow rate of 12 litres per minute through the tracheostomy tube.

Then, with the animal standing quietly in her cart, a control period of 30 minutes was established, to ensure stability of the preparation. Continuous recording of maternal and foetal blood pressure and heart rate was obtained by connecting the maternal and foetal femoral arterial lines to a Hewlett-Packard multichannel recorder. Normal saline (500 ml) was administered to the ewe during the control period. Arterial blood gases were determined from blood withdrawn from the maternal femoral and foetal axillary arterial catheters at 15-minute intervals. At the end of the control period, radioactive microspheres were injected into the foetal femoral vein, and blood continuously withdrawn from the foetal axillary and femoral arteries to serve as reference counts when calculating regional blood flows.⁷ Maternal and foetal blood samples were also obtained and stored on ice in glass syringes for determination of isoflurane concentrations by gas-liquid chromatography.⁸

The ewe was then administered isoflurane at an inspired concentration of two per cent in oxygen, through the tracheostomy. Ventilation was controlled after approximately five minutes to maintain maternal blood gases at control values. Maternal and foetal blood samples were withdrawn for blood gas analysis and for determination of isoflurane concentrations at 0, 5, 10, 15, 20, and 30 minutes. At 15 and 30 minutes labelled microspheres were again injected into the foetus, using a different microsphere for each injection.

At the end of the study the foetus and mother were killed by an intravenous injection of thiopentone and a saturated solution of KCl. The foetus and placenta were removed, the foetus dissected, and each organ system weighed, ground, and ashed. The radioactivity count of each ashed sample was determined and compared to the reference blood samples to calculate organ blood flow. The total

cardiac output was considered to be the sum of the individual organ flows.

Analysis of results for maternal and foetal blood pressure, pulse rate, blood gases, pH and foetal organ blood flows was by analysis of variance. Maternal and foetal isoflurane concentrations were compared by an unpaired "t" test. $P < 0.05$ was considered to be significant.

MAC Studies

Five pregnant ewes of the same gestation were prepared as described above, and also allowed to recover for at least 48 hours.

On the day of the study, a tracheostomy was performed on each animal under brief general anaesthesia with isoflurane and oxygen, and the animal was allowed to recover at least one hour, while breathing humidified oxygen through the tracheostomy tube.

Then each ewe was given a spinal anaesthetic at L₃₋₄ with tetracaine (10 mg) and placed on her right side. The maternal and foetal femoral arterial lines were connected to the Hewlett-Packard recorder for continuous recording of heart rate and blood pressure. The hysterotomy incision was re-opened, one of the non-cannulated foetal limbs withdrawn, and the incision closed around it. Baseline maternal and foetal blood gases and blood isoflurane concentrations were measured.

Two per cent isoflurane in oxygen was then administered through the tracheostomy tube, and after approximately five minutes ventilation was controlled to maintain maternal arterial blood gases at control values. At two-minute intervals 2 ml of blood was withdrawn into heparinized glass syringes from the maternal femoral and foetal axillary arterial lines and stored on ice to be analysed for isoflurane levels by gas-liquid chromatography. At the same time maternal end-tidal isoflurane concentrations were measured by a Beckman LB-2 analyser. The foetal foot web space was stimulated with a non-damaging clamp and observed for movement in response to the stimulus.

When "no movement" first occurred, the maternal inspired isoflurane concentration was reduced to 0.5 per cent. Blood sampling, end-tidal measurements of isoflurane, and foetal foot stimulation continued at two-minute intervals until movement

$$\frac{311}{273} \times \frac{700}{760} \times 22.4 \times \frac{\text{g}}{184.5} \times \text{blood gas coefficient}^* = \text{volume\% isoflurane}$$

temp
ambient
1 mole
MW

°kelvin
atm. pres
of gas
isoflurane

*Maternal 1.29

*Foetal 0.75

FIGURE 1 Formula for converting anaesthetic gas concentrations from $\text{mg} \cdot \text{L}^{-1}$ to volume %.

reappeared in response to the stimulus. The maternal inspired isoflurane concentration was increased once more to two per cent. All measurements were repeated at two-minute intervals until the "no movement" end point occurred again. This procedure was then repeated at least once more for each foetus.

The ear of the mother was stimulated in a similar fashion at two-minute intervals, along with simultaneous maternal arterial blood sampling and measurement of end-tidal isoflurane concentrations. The inspired concentration of isoflurane was adjusted between 0.5 and 2 per cent several times, as movement appeared and disappeared in response to the stimulus. At the end of the study the mother and foetus were killed with an injection of thiopentone and saturated KCl.

The isoflurane blood levels were determined by gas-liquid chromatography.⁹ MAC for both foetus and mother was estimated by averaging the isoflurane concentrations for each animal where the first "no movement" occurred and where the first "movement" occurred, the midpoint between the two values being MAC. For the foetuses, blood concentrations of isoflurane were used. For the mothers, MAC was determined both by using the blood concentrations and by using the end-tidal concentrations.

MAC is normally expressed as an alveolar or end-tidal concentration in volume per cent. This measurement is not possible in the foetus, so a "theoretical" end-tidal concentration was calculated from the measured blood concentrations, using the formula shown in Figure 1. For the mothers, the "theoretical" end-tidal concentrations of MAC for isoflurane were calculated from the measured blood

concentrations and then compared to the actual measured volume per cent MAC, as a check of the validity of the conversion formula used.

Results

Cardiovascular studies

Maternal mean arterial blood pressure decreased significantly from 87.5 ± 3.39 to 68.0 ± 6.77 mmHg after ten minutes of two per cent isoflurane, and thereafter remained stable. There were no significant changes in maternal pulse rate, or in maternal PO_2 , PCO_2 , pH, or base excess throughout the 30-minute study period (Table I, II).

Foetal mean arterial blood pressure fell significantly by ten minutes from 52.7 ± 1.54 to 42.5 ± 3.48 mmHg, and pulse rate fell from 152 ± 6.17 to 138 ± 6.84 beats per minute. There were no further significant changes in these variables. Foetal PO_2 , PCO_2 , pH and base excess did not change significantly (Tables I, II).

Analysis of the microsphere data revealed no significant change in total cardiac output at 15 or 30 minutes. A significant fall in regional blood flow to the kidney was demonstrated, but to all other organ systems, including the placenta, no significant change occurred (Table III).

The uptake of isoflurane by both the mother and foetus in $\text{mg} \cdot \text{L}^{-1}$ is shown in Table IV. Foetal blood concentrations of isoflurane are significantly different from maternal at every measurement, demonstrating that equilibration of mother and foetus had not occurred.

MAC studies

The mean foetal MAC for isoflurane was found to be

TABLE I Maternal and foetal mean arterial blood pressure (MABP) and pulse rate during 30 minutes of isoflurane anaesthesia ($F_I = 2.0\%$) ($N = 6$) (Mean $\pm$ SEM)

Time	Control	5 min	10 min	15 min	20 min	30 min
Maternal MABP (mmHg)	87.5 ± 3.39	82.3 ± 3.95	68.0* ± 6.77	60.8* ± 5.65	55.67* ± 6.52	58.27* ± 5.17
Pulse rate	111.0 ± 6.22	120.3 ± 6.84	112.0 ± 7.38	102.0 ± 6.00	100.0 ± 6.87	91.0 ± 6.08
Foetal MABP (mmHg)	52.7 ± 1.54	47.3 ± 3.17	42.5* ± 3.48	40.5* ± 3.03	38.3* ± 3.64	39.2* ± 3.35
Pulse rate	152.0 ± 6.17	151.0 ± 6.24	138.0* ± 6.84	142.0* ± 12.3	123.0* ± 4.07	122.0* ± 3.06

* $p < 0.05$ Significantly different from control values.
(Analysis of variance, then paired "t" with control).

TABLE II Maternal and foetal blood gas and acid-base status during 30 minutes of isoflurane anaesthesia ($F_I = 2.0\%$) ($N = 6$) (Mean $\pm$ SEM)

Time	Control	5 min	10 min	15 min	20 min	30 min
<i>Maternal</i>						
pO ₂ (mmHg)	214.0 ± 24.7	341.0 ± 34.1	338.0 ± 47.1	332.0 ± 44.4	313.0 ± 52.4	326.0 ± 53.8
pCO ₂ (mmHg)	34.0 ± 1.5	39.0 ± 4.3	36.0 ± 2.3	32.0 ± 2.6	32.0 ± 2.1	32.0 ± 2.8
BE	0.2 ± 1.8	-0.4 ± 1.0	1.7 ± 1.5	1.0 ± 1.3	2.0 ± 1.6	3.2 ± 2.0
pH	7.48 ± 0.03	7.40 ± 0.05	7.48 ± 0.03	7.51 ± 0.03	7.52 ± 0.04	7.53 ± 0.03
<i>Foetal</i>						
pO ₂ (mmHg)	22.2 ± 0.83	27.7 ± 1.62	27.0 ± 2.63	24.0 ± 2.63	24.0 ± 2.67	22.3 ± 1.67
pCO ₂ (mmHg)	44.3 ± 2.41	51.0 ± 4.00	47.8 ± 2.30	46.8 ± 1.66	46.0 ± 1.91	45.1 ± 1.19
BE	-0.6 ± 1.22	-0.1 ± 1.02	-0.4 ± 0.94	0.3 ± 1.22	0.3 ± 0.80	-0.6 ± 0.94
pH	7.34 ± 0.02	7.28 ± 0.02	7.30 ± 0.02	7.32 ± 0.02	7.34 ± 0.02	7.33 ± 0.02

No values significantly different from control.

$53 \pm 18.2 \text{ mg} \cdot \text{L}^{-1}$ (mean $\pm$ SD) and $0.86 \pm 16 \text{ vol}\%$. When converting the measured MAC from $\text{mg} \cdot \text{L}^{-1}$ to $\text{vol}\%$, the calculated "theoretical" end-tidal isoflurane concentration was $0.87 \text{ vol}\%$, very close to the actual measured concentration of $0.86 \text{ vol}\%$ (Figure 2).

The mean foetal MAC was found to be $36 \pm$

$6.3 \text{ mg} \cdot \text{L}^{-1}$, giving a calculated "theoretical" end-tidal concentration of $0.34 \text{ vol}\%$ (Figure 2).

Maternal and foetal blood/gas partition coefficients needed to be determined for these calculations, and were found to be 1.29 and 0.75 respectively. The maternal/foetal solubility ratio was 1.72 for isoflurane.

MAC FOR ISOFLURANE

FIGURE 2 Determination of maternal and foetal MAC for isoflurane in five pregnant ewes by correlation of withdrawal response to arterial and end-tidal concentrations of isoflurane. See text for details.

Discussion

In the previous study from our laboratory⁵ administration of two per cent isoflurane to the pregnant ewe for 90 minutes resulted in a significant

TABLE III Regional blood flows and cardiac output in the foetus during the administration of isoflurane anesthesia to the pregnant ewe (N = 6) (Mean $\pm$ SEM)

Organ flow (ml·g ⁻¹ ·min ⁻¹)	Control	Isoflurane 15 min	Isoflurane 30 min
Brain	1.64 ± 0.18	1.26 ± 0.12	1.29 ± 0.19
Heart	1.09 ± 0.04	1.02 ± 0.16	0.94 ± 0.12
Kidney	1.26 ± 0.06	0.88* ± 0.07	0.80* ± 0.06
Spleen	2.85 ± 0.55	2.88 ± 0.49	2.42 ± 0.32
Musculoskeletal	0.17 ± 0.01	0.16 ± 0.02	0.13 ± 0.01
Skin	0.15 ± 0.03	0.18 ± 0.07	0.21 ± 0.09
Placenta	1.26 ± 0.09	1.09 ± 0.09	1.01 ± 0.14
Calculated cardiac output	1163.0 ± 86.5	1073.0 ± 127.5	938.0 ± 103.4

*p < 0.05 Different from control (Analysis of variance, then paired "t").

decrease in foetal arterial pH by 48 minutes. Foetal cardiac index measured at 60 minutes was significantly lower than that of the nonanaesthetized foetus. The decrease in blood flow was greatest in the placenta and the splanchnic bed. The foetal arterial isoflurane concentrations at 48 and 60 minutes were 77.5 ± 7.9 mg·L⁻¹ and 85.7 ± 5.8 mg·L⁻¹. Using the MAC value obtained from this current study, these values correspond to 2.15 and 2.40 MAC respectively.

In both the previous study and this one, foetal MAC was reached after 8–10 minutes of exposure to isoflurane with an inspired concentration of two

TABLE IV Maternal and foetal isoflurane levels (mg·L⁻¹) F_I = 2.0% (Mean $\pm$ SEM) (N = 6)

Time	Control	5 min	10 min	15 min	20 min	30 min
Maternal 0 mg·L ⁻¹		49.2 ± 6.43	62.3 ± 6.8	73.5 ± 8.5	75.2 ± 7.13	84.7 ± 7.65
Foetal 0 mg·L ⁻¹		17.0* ± 4.5	27.7* ± 4.37	46.7* ± 7.15	49.0* ± 7.76	60.8* ± 7.37
FA/MA ratio		0.35	0.44	0.64	0.65	0.72

*p < 0.05. Foetal isoflurane levels significantly less than maternal (Unpaired "t" test).

per cent administered to the pregnant ewe. By 30 minutes foetal isoflurane concentrations were 1.7 MAC. At these concentrations foetal MABP and pulse rate were significantly lower than in the nonanaesthetized foetus but there was no significant difference demonstrated in foetal acid-base status or cardiac output. This suggests that exposure to two per cent isoflurane for less than 30 minutes does not depress the foetal myocardium, in contrast to exposures of 60 minutes or more. Except for the kidneys, regional blood flow remained unchanged during this shorter exposure to isoflurane. In particular placental blood flow was not decreased, once again in contrast to exposures of 60 minutes or more.

Maternal MAC for isoflurane was found to be 0.86 vol%, and calculated from blood concentrations to be 0.87 vol%. The close proximity of these two values supports the validity of the formula used to convert blood concentrations to a gaseous phase. Palahniuk *et al.*⁹ determined MAC in pregnant ewes for isoflurane to be 1.01 vol%, higher than our value. The reason for this difference is not known.

The blood/gas partition coefficients for isoflurane determined in our laboratory were somewhat lower, and the maternal/foetal solubility ratio somewhat higher than those reported by Gibbs *et al.*¹⁰ Their values for the blood/gas partition coefficient in the ewe were 1.51 ± 0.10 and in the foetus 1.35 ± 0.09 , giving a maternal/foetal ratio of 1.12. Several possibilities exist to explain these differences, including variations in blood lipid and protein levels and composition. For our calculations, values from our own laboratory were used.

As with halothane, foetal MAC for isoflurane was found to be less than half of maternal MAC. Low foetal MAC for potent inhalation agents is therefore not specific to halothane, but would appear to be a function of the foetal state. MAC for halothane has been demonstrated to rise rapidly after birth, roughly tripling by 12 hours of age (0.33 to 1.15 per cent).⁶ In humans MAC does not rise as rapidly after birth. Cameron *et al.*¹¹ demonstrated MAC to be $1.60\% \pm 0.01$ (SEM) in 0.1-month-old infants, and rose to $1.87\% \pm 0.12$ for 1–6-months-old children.

Palahniuk *et al.*⁹ demonstrated that MAC was lower in pregnant, as opposed to non-pregnant, ewes and suggested that progesterone may be responsible for decreasing MAC. Elevated proges-

terone levels and endorphin levels have been suggested as possible reasons for a decreased MAC in the foetus.^{6,11} Many changes occur between the foetal and extrauterine state, however, and which factor or factors are responsible for the rise in MAC after birth have not been elucidated.

Foetal cardiac output and organ blood flow in this animal model are not significantly decreased by exposure to isoflurane in concentrations that are less than 2 MAC. This supports the clinical impression that short exposure of the human foetus to potent inhalational agents does not adversely affect the newborn in his adaptation to extrauterine life.¹³ At Caesarean section induction–delivery intervals are usually ten minutes or less so isoflurane may be a rational choice for this procedure. Prolonged exposure of the foetus to isoflurane such as might occur with non-obstetric surgical procedures in the pregnant patient may result in foetal concentrations greater than 2 MAC and may not be safe. Surgery on the foetus *in utero* is now being contemplated for various congenital defects. This may also require prolonged exposure of the foetus to anaesthetic agents. Knowledge of foetal MAC and the effects of anaesthetic agents at multiples of MAC may be of importance in protecting the foetus during these surgical manipulations.

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Résumé

L'isoflurane est relativement nouveau comme agent anesthésique volatil. Son usage augmentera possiblement pour les procédures obstétricales. Une étude antérieure a démontré que à 90 minutes d'exposition du fœtus à l'isoflurane provoque une diminution significative du débit cardiaque fœtale ainsi qu'une acidose. Cette présente étude a été faite chez le fœtus de brebis afin de déterminer les effets cardiovasculaires d'une courte exposition à l'isoflurane; ainsi que sa puissance (MAC). Onze brebis gravides ont été préparées chirurgicalement en insérant des cathéters artériels et veineux chez la mère et le fœtus. Après 48 heures de stabilisation, de l'isoflurane deux pour cent avec l'oxygène a été administré pour 30 minutes à six brebis via une trachéostomie. Le débit cardiaque fœtal et les flots sanguins régionaux ont été mesurés par microsphères. Chez cinq brebis la concentration d'isoflurane était changée et la détermination du MAC a été faite tant pour la brebis mère que le fœtus. Le taux sanguin artériel d'isoflurane a été utilisé afin de déterminer le MAC fœtal. L'exposition à l'isoflurane a provoqué une diminution significative des pressions artérielles moyennes chez la mère et le fœtus ainsi que pour leurs fréquences cardiaques. Des expositions jusqu'à 30 minutes n'ont pas occasionné une acidose fœtale ou une diminution significative du débit cardiaque. Pour l'isoflurane le MAC fœtal était de 0.34 pour cent alors que pour la mère il était de 0.86 pour cent.