

## Laboratory Report

# *Anesthetic Solubility Coefficients for Maternal and Fetal Blood*

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Solubility coefficients for seven inhalation anesthetic agents were determined in maternal and fetal blood at 37 C. Halothane, isoflurane, diethyl ether, and nitrous oxide were significantly more soluble in maternal than in fetal blood, while methoxyflurane, fluroxene, and cyclopropane were significantly less soluble. Reasons for these differences cannot be accounted for by differences in the type or amount of hemoglobin present. (Key words: Solubility, anesthetic, fetal blood; Anesthetics, volatile, solubility; Anesthetics, gases, solubility; Anesthesia, obstetric, fetal gas solubilities.)

ANESTHETIC SOLUBILITY in blood is a major determinant of drug uptake and distribution. Theoretically, there are differences between fetal and adult blood that might affect anesthetic solubility. For example, hemoglobin concentration and configuration differ markedly,<sup>1,2</sup> lipid content is considerably less in fetal than in adult blood,<sup>3,4</sup> and there are minor differences in protein content.<sup>5</sup> We, therefore, determined blood-gas solubility coefficients for maternal and fetal blood for seven commonly used inhalation anesthetic agents at 37 C.

### Methods

Thirty-four paired samples of heparinized maternal venous and mixed-placental blood

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were collected immediately following delivery. Parturients received either pudendal block with lidocaine or nitrous oxide analgesia for delivery. In the laboratory, 111 determinations of anesthetic solubility were performed on paired blood specimens. A 2-ml sample from each specimen was exposed to 10 ml of a 2 per cent concentration (in oxygen) of halothane, isoflurane, diethyl ether, methoxyflurane or fluroxene. Because of their relatively low solubility in blood, 10 ml of 10 per cent cyclopropane or 100 per cent nitrous oxide were equilibrated with 10 ml of blood. Both maternal and fetal blood were equilibrated at 37 C by mechanical rotation for one hour. The gas phase was then analyzed for anesthetic content by gas chromatography using the method of Fink and Morikawa<sup>6</sup> and blood-gas partition coefficients calculated. The blood specimens then were centrifuged and hematocrits (packed cell volume) measured. With the exception of nitrous oxide, similar measurements and calculations were performed on the plasma from the same blood specimens. Anesthetic solubility in erythrocytes was calculated for each agent assuming a rectilinear relation using the measured values for plasma, whole blood, and hematocrit.

A Perkin-Elmer model 900 chromatograph with flame ionization detector was used in all analyses. Gas flow rates were: nitrogen 40 ml/min, hydrogen 40 ml/min, and compressed air 450 ml/min. The column used was a 5.5-m stainless steel tube packed with 3 per cent SE 30 on Chromosorb W, AW, DMCS (80/100 mesh). Injector temperature was kept at 45 C, column temperature 45 C, and manifold temperature 200 C. A precision gas-sampling valve was used for sampling gases. Results were analyzed using Student's *t* test.

TABLE I. Mean ( $\pm$  SD) Hemmerit Values and Blood-Gas Partition Coefficients from Paired Samples of Maternal (M) and Fetal (F) Blood at 37 C

	Concentration (Per Cent)	Number of Determinations	Hemmerit (Per Cent)		Plasma		Whole Blood		Erythrocytes	
			M	F	M	F	M	F	M	F
			Ratio F/M		Ratio F/M		Ratio F/M		Ratio F/M	
Halothane	2	39.3 $\pm$ 4.0	49.2* $\pm$ 4.6	2.32 $\pm$ .17	1.68* $\pm$ .12	2.53 $\pm$ .17	1.93* $\pm$ .10	2.85 $\pm$ .21	2.17* $\pm$ .19	0.76 0.76
Isoflurane	2	37.0 $\pm$ 4.7	47.8* $\pm$ 5.3	1.60 $\pm$ .08	1.46* $\pm$ .09	1.51 $\pm$ .10	1.35* $\pm$ .09	1.34 $\pm$ .09	1.221 $\pm$ .07	0.91 0.91
Diethyl ether	2	39.5 $\pm$ 3.6	57.0* $\pm$ 8.0	12.8 $\pm$ 0.8	12.21 $\pm$ 1.0	11.9 $\pm$ 0.9	11.21 $\pm$ 0.8	10.5 $\pm$ 1.4	10.3 $\pm$ 1.0	0.98 0.98
Nitrous oxide	100	—	—	—	—	.440 $\pm$ .008	.4381 $\pm$ .009	—	—	—
Methoxyflurane	2	39.5 $\pm$ 3.6	57.0* $\pm$ 8.0	9.9 $\pm$ 1.0	10.2 $\pm$ 1.1	12.3 $\pm$ 0.7	13.2* $\pm$ 1.0	16.0 $\pm$ 0.8	15.5 $\pm$ 0.6	0.97 0.97
Fluroxene	2	36.1 $\pm$ 1.2	45.1* $\pm$ 5.1	1.11 $\pm$ .06	1.20 $\pm$ .10	1.43 $\pm$ .04	1.57* $\pm$ .08	2.00 $\pm$ .04	2.05 $\pm$ .09	1.03 1.03
Cyclopropane	10	39.2 $\pm$ 4.1	56.2* $\pm$ 9.2	2.89 $\pm$ .027	.311 $\pm$ .026	.431 $\pm$ .023	.517* $\pm$ .039	.655 $\pm$ .035	.688 $\pm$ .033	1.05 1.05

\* P &lt; 0.05 compared with corresponding maternal values.

† P &lt; 0.01

## Results

Partition coefficients for maternal and fetal plasma, whole blood, and erythrocytes are shown in table 1. Halothane, isoflurane, diethyl ether and nitrous oxide were significantly less soluble ( $P < .01$ ) in fetal than in maternal whole blood; methoxyflurane, fluroxene and cyclopropane were significantly more soluble ( $P < .01$ ). With the exception of methoxyflurane, the same relationships also were observed for plasma and erythrocytes. Because of the large volumes of blood required, solubility coefficients for nitrous oxide in plasma and erythrocytes were not determined. The greatest difference between maternal and fetal solubilities was observed with halothane, and the least difference was seen with nitrous oxide. We quantitatively compared maternal and fetal solubilities by calculating the slope of solubility change from plasma to erythrocytes (0 to 100 per cent hematocrit). Solubility slope values ranged from  $-0.18$  per cent change per hematocrit unit for diethyl ether to  $+1.27$  per cent change per hematocrit unit for cyclopropane. No significant difference between slopes for maternal and fetal blood was observed for any anesthetic.

## Discussion

Our partition coefficient values for seven inhalation anesthetic agents in maternal blood are similar to previous findings in adults.<sup>7-9</sup> Comparable solubility data for fetal blood are not available. The observed differences in anesthetic solubility between maternal and fetal blood show no consistent relation to lipid,<sup>2,4</sup> protein,<sup>5</sup> or hemoglobin<sup>1</sup> contents known to be present in fetal blood. In addition to the quantitative hemoglobin differences, the structure of fetal hemoglobin is different from that of adult hemoglobin.<sup>2</sup> A difference in hemoglobin structure is of interest since Schoenborn<sup>10</sup> has shown that the binding of xenon, another anesthetic, to horse hemoglobin is influenced by the number and sequence of protein side-chain residues in hemoglobin. Our results show that while solubilities of most of the anesthetics studied increased with increasing hematocrit, the solubilities of diethyl ether

and isoflurane decreased. These observations are in general agreement with the results of others.<sup>11-13</sup> However, our findings are at variance with the report<sup>13</sup> that fluroxene solubility is unaffected by hematocrit, while methoxyflurane solubility is inversely related to erythrocyte content. No explanation for these discrepancies is apparent.

Since maternal and fetal partition coefficients differ at equal hemoglobin concentrations (plasma and packed erythrocytes), the quantity of hemoglobin is not the only factor causing the solubility differences. Also, since there was no significant fetal-maternal difference in solubility slope values from plasma to packed erythrocytes, the differing types of hemoglobin apparently are not responsible.

The observed differences in maternal-fetal blood-gas solubility coefficients may have important implications in obstetric anesthesia. For example, calculations of fetal uptake and distribution of anesthetic agents depend on solubility data. Our results indicate that considerable error would be induced by the use of maternal solubility coefficients where fetal values are desired. It is not known how long these differences in solubility persist beyond extruterine life, but if maintained, they would influence the uptake and distribution of anesthetic agents in newborns and infants. In addition, if the factors operative in affecting differences of anesthetic solubility in blood also influenced changes in other tissues (for example, an increased solubility in brain phospholipids), they would theoretically affect anesthetic requirement (MAC).<sup>14</sup> This speculation is interesting in light of the increase in halothane requirement during the first year of life.<sup>15</sup>

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## Renal Function

**HEMORRHAGIC HYPOTENSION AND RENAL FUNCTION** The effects of hemorrhagic hypotension on intrarenal blood flow and excretory function of the kidney were studied before and during mannitol and dextran infusion. Dogs were anesthetized with chloralose and barbiturates. Blood pressure, acid-base status, urine production and osmolality, clearance of PAH and creatinine, and total renal blood flow were determined. Cortical and medullary blood flow were estimated utilizing  $^{51}\text{Cr}$ -labeled erythrocytes and beta-sensitive needle detectors imbedded in the renal parenchyma. Following control measurements the dogs were bled 20 ml/kg. Determinations were repeated 20 and 90 minutes after the hemorrhage and again during the infusion of 15 per cent mannitol. In three experiments the initial hemorrhage was followed by a second sufficient to produce anuria (an additional 5-10 ml/kg). This period was followed by infusion of 15 per cent mannitol and 6 per cent dextran. The initial hemorrhage had minimal effects other

than a modest increase in urinary osmolality and slight decreases in blood pressure, urine volume, and base excess. Mannitol infusion had almost no effect except slight diuresis. Additional hemorrhage resulted in increased cortical vascular resistance, no change in medullary resistance, and more severe metabolic acidosis. Mannitol infusion again had almost no effect, but plasma expansion with dextran resulted in normalized acid-base status and a return of hemodynamic values towards normal. (Danielson, B. G., and others: *Kidney Function and Intrarenal Bloodflow Distribution after Bleeding and Infusions of Mannitol and Dextran, Acta Anaesthesiol Scand* 17:8-21, 1973.) **ABSTRACTER'S COMMENT:** Other investigators have found that mannitol partially reverses renal vasoconstriction secondary to hemorrhagic hypotension. What caused the discrepancy is not clear, but it may be related to different techniques for measuring renal blood flow.