

Placental Transmission of Nitrous Oxide

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Placental transmission of nitrous oxide was studied in 14 patients during elective cesarean section and in 26 patients during vaginal delivery. Duration of anesthesia varied between 2 and 19 minutes. Randomly-selected patients were hyper- or hypoventilated. Umbilical vein nitrous oxide levels ranged from 55 to 91 per cent of maternal values (average 79 per cent). The fetal-maternal nitrous oxide concentration ratio showed no correlation with incidence of uterine contractions, duration of anesthesia (after the first two minutes), or maternal pH (7.32-7.59) or P_{aCO_2} (14-41 torr). Umbilical artery nitrous oxide levels ranged from 34 to 90 per cent of the umbilical vein levels. The umbilical artery-vein nitrous oxide concentration ratio increased progressively with increasing durations of anesthesia. The data demonstrate rapid transmission of nitrous oxide across the human placenta as well as rapid uptake by the fetus. (Key words: Nitrous oxide; Placental transmission; Fetal uptake.)

IN STUDIES of the transfer of nitrous oxide across the human placenta^{1,2} using the Van Slyke manometric method (modification of Orcutt and Waters),³ nitrous oxide levels in fetal blood were found to be 50 to 65 per cent of the maternal values. This large maternal-fetal gradient was attributed to delayed establishment of equilibrium across the placenta, possibly related to uterine artery constriction owing to maternal hyperventilation.⁴ We felt it worthwhile to reinvestigate the placental transmission of nitrous oxide in conjunction with simultaneous measurements of pH and carbon dioxide tension.

Method

Forty healthy parturients with unremarkable prenatal courses were included in our study; 14 underwent elective repeat cesarean

section (Group I), and 26 had vaginal delivery, ten by forceps and 16 spontaneously (Group II). The women in Group I were anesthetized with 150-250 mg thiopental (Pentothal) followed by nitrous oxide-oxygen via endotracheal tube and 0.1 per cent succinylcholine (Succostrin) by intravenous infusion. The women in Group II received nitrous oxide-oxygen by mask plus local anesthesia. The nitrous oxide-oxygen mixtures were administered in a semiclosed system with circle absorber, using a total flow of 10 l/min during the first two minutes and 5 l/min thereafter. In 12 cases, the concentration of nitrous oxide was 70 per cent; in 22 cases, 60 per cent; in six cases, 50 per cent. Time from nitrous oxide administration to delivery of the infant ranged from 2 to 19 minutes. Twenty randomly-selected patients were hyperventilated manually (increase in rate and volume) and six were hypoventilated manually (decrease in rate). At the time of parturition, blood was drawn from the maternal brachial artery and from the umbilical vein and artery of a cord segment doubly clamped prior to the infant's first breath.

All samples were collected anaerobically in heparinized glass syringes or glass vacuum tubes. For pH and P_{CO_2} determinations, bloods were placed in ice and analyzed within ten minutes at 37 C, using Radiometer electrodes and a Radiometer readout (Model 27). Base deficit values were calculated from the nomogram of Siggaard-Anderson *et al.*⁵ For the nitrous oxide determination, 2 ml of blood, introduced into a vacuum tube, were heated in a water bath at 37 C and equilibrated with air to atmospheric pressure. The nitrous oxide concentration in the overlying gas phase was determined in 2 ml-samples by gas chromatography, using a Perkin-Elmer 154-C Vapor Fractometer. Blood nitrous oxide standards were established by tonometry of non-anesthetized patients' blood with known concentrations of nitrous oxide and oxygen. Blood-gas solubility coefficients used for calculation were

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TABLE 1. Mean Maternal Nitrous Oxide Levels (vol per cent) in Relation to Concentration of N₂O Inflow and Duration of Administration.*

Time (min)	Concentration of N ₂ O Inflow		
	70%	60%	50%
2-4	19.2 (3)	19.8 (4)	17.7 (2)
5-9	29.3 (3)	25.5 (11)	18.6 (4)
10-14	30.3 (3)	26.4 (6)	—
15-19	30.2 (3)	25.8 (1)	—

* Numbers in parentheses denote number of cases in each group.

TABLE 2. Umbilical Vein Blood Nitrous Oxide Concentration—Expressed as Ratio of Maternal Level—in Relation to Duration of N₂O Administration.

Time (min)	Number of Cases	Fetal-Maternal N ₂ O Concentration Ratio	
		Mean ± SE.	Range
2	3	0.64	0.62-0.68
3-4	6	0.83 ± 0.02	0.75-0.89
5-9	18	0.78 ± 0.02	0.55-0.89
10-14	9	0.80 ± 0.02	0.62-0.91
15-19	4	0.81	0.72-0.86

0.46 for maternal bloods (hematocrit 30-36 per cent) and 0.47 for fetal bloods (hematocrit 46-54 per cent).^{6,7} The clinical condition of each neonate was evaluated by recording the time to sustained respiration (TSR) and the Apgar scores one and five minutes after birth. The data are expressed as the mean ± standard error of the mean, and the coefficient of correlation⁸ was used for the statistical analyses.

Results

Maternal nitrous oxide levels ranged from 15.8 vol per cent following two minutes of administration of a 50 per cent nitrous oxide mixture to 32.1 vol per cent following 15 minutes of administration of a 70 per cent mixture. After four minutes of anesthesia the further increases in nitrous oxide levels were small (table 1).

Nitrous oxide levels in umbilical vein blood ranged from 11.2 to 28.8 vol per cent and

varied between 55 and 91 per cent of the maternal values (average 79 per cent). The low fetal-maternal value of 55 per cent occurred in a case of cord compression in which the infant was delivered by forceps after six minutes of administration of a 70 per cent mixture. The high value of 91 per cent was found in an uneventful cesarean section following 12 minutes of administration of a 60 per cent mixture. The correlation coefficient between nitrous oxide concentrations in maternal arterial and umbilical vein bloods was 0.812 ± 0.094 ($P < 0.01$) in cesarean deliveries and 0.785 ± 0.076 ($P < 0.01$) in vaginal deliveries. There was no correlation between the fetal-maternal nitrous oxide concentration ratio and a) duration of anesthesia (after the first two minutes) (table 2) or b) maternal pH (7.32 to 7.59) (normal 7.44 to 7.46)^{9,10} or PaCO₂ (14 to 41 torr) (normal 30 to 35 torr)^{9,11} (figs. 1 and 2).

Nitrous oxide levels in umbilical artery blood, determined in 32 cases, ranged from 6.0 to 20.1 vol per cent (table 3), representing 34 to 90 per cent of the umbilical vein blood levels and 23 to 78 per cent of the maternal arterial blood levels. The nitrous oxide concentration ratios for umbilical artery-umbilical vein bloods increased progressively with increasing durations of anesthesia.

Four of the 40 neonates had one-minute Apgar scores of 6 or less, associated with pro-

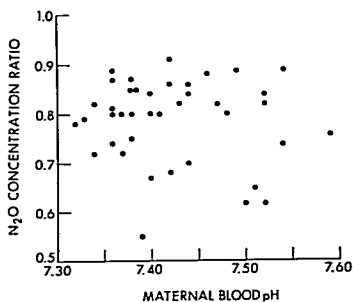


FIG. 1. Fetal-maternal nitrous oxide concentration ratios in 40 patients plotted against maternal arterial blood pH values. No correlation was demonstrable.

longation of the time to sustained respiration beyond 60 seconds. Pertinent data are shown in table 4. Severe fetal acidosis was noted in three infants and a high fetal nitrous oxide level with normal acid-base values in one. All five-minute Apgar scores were 9 or 10.

Discussion

The data demonstrate rapid transmission of nitrous oxide across the human placenta, unrelated to the presence or absence of uterine contractions (vaginal delivery vs. elective cesarean section), maternal carbon dioxide tension, or pH. Nevertheless, equilibration across the placenta is not as rapid as saturation of other vessel-rich organs because of the non-homogeneity of the blood in the intervillous spaces and the uptake of anesthetic agent by the uteroplacental tissues. Thus, after 10 to 14 minutes of nitrous oxide administration, the fetal-maternal concentration ratio was only 0.8, whereas richly-perfused organs such as brain or heart have almost complete saturation.¹² Decreases from the normal rate of placental transfer may be found during cord compression, which occurs to some extent in approximately a third of vaginal deliveries.¹³ This complication was diagnosed by fetal heart-rate pattern and confirmed at delivery in our infant with the lowest maternal-fetal nitrous oxide gradient.

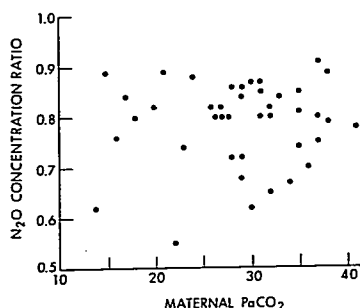


FIG. 2. Fetal-maternal nitrous oxide concentration ratios in 40 patients plotted against maternal arterial blood carbon dioxide tensions. No correlation was demonstrable.

TABLE 3. Umbilical Artery Blood Nitrous Oxide Concentration—Expressed as Ratio of Umbilical Vein Blood N_2O Concentration—in Relation to Duration of N_2O Administration.

Time (min)	Number of Cases	Umbilical Artery—Umbilical Vein N_2O Concentration Ratio	
		Mean \pm SE.	Range
2-4	8	0.57 \pm 0.05	0.34-0.72
5-9	14	0.72 \pm 0.02	0.53-0.84
10-14	7	0.79 \pm 0.03	0.67-0.89
15-19	3	0.87	0.84-0.90

Placental transfer of nitrous oxide is, thus, comparable to that observed with other inhalation agents.¹⁴⁻¹⁶ The reason or reasons for the previously-reported wide maternal-fetal nitrous oxide gradients are not apparent, since details of the cord blood sampling techniques were not given. The Van Slyke method, *per se*, was shown to be reliable in a recent study of cesarean deliveries following prolonged anesthesia (24-43 minutes) which revealed a mean fetal-maternal nitrous oxide concentration ratio of 87 per cent.¹⁷

Our results also show that fetal uptake of nitrous oxide occurs rapidly, with 87 per cent equilibration within 15-19 minutes (table 3). This value is in good agreement with the data of the aforementioned study,¹⁷ which reported a nitrous oxide concentration ratio for umbilical artery-umbilical vein of 89 per cent over a time interval of 24 to 43 minutes (average 36 minutes). Therefore, the increased incidence of neonatal depression and prolonged time to sustained respiration associated with nitrous oxide administration exceeding 15 to 17 minutes at cesarean section¹⁷⁻¹⁹ may represent fetal narcosis resulting from the anesthetic partial pressure in the brain. In addition, diffusion hypoxia may play a role, considering the low arterial oxygen tension and small functional residual capacity of the infant at birth. Studies of the nitrous oxide concentrations in expired air of seven newborns delivered by cesarean section following 4 to 25 minutes of administration of 66.6 per cent nitrous oxide to the mother revealed values of 10 to 15 per cent in the two cases with the longest durations of anesthesia.²⁰ The resultant decrease in inspired oxygen (to 19 and 18

TABLE 4. Pertinent Data of Four Neonates Born with Low One-minute Apgar Scores (6-4)

Delivery	Duration of Anesthesia (min)	Time to Sustained Respiration (sec)	Umbilical Artery Blood			Umbilical Vein Blood N ₂ O (vol %)	Ratio Umbilical Artery-Umbilical Vein	Maternal Arterial Blood N ₂ O (vol %)	Ratio Vein-Maternal Artery
			pH	Base Deficit (mEq/l)	N ₂ O (vol %)				
Forceps	6	90	7.20	12.5*	11.1	16.2	0.69	29.2	0.55
Spontaneous	9	75	7.12	13.5	16.2	23.8	0.68	29.6	0.80
Cesarean	12	180	7.28	5.5	19.8	23.4	0.85	30.0	0.78
Forceps	13	90	7.09	16.5	—	18.7	—	25.9	0.72

* Case of cord compression. Reason for severe acidosis in other two cases undiagnosed.

per cent in room air) may be significant, particularly when associated with respiratory irregularity or respiratory obstruction²¹ following birth.

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