The Pulmonary Exchange of Nitrous Oxide and Halothane in Infants and Children

Ernest Salanitre, M.D., and Herbert Rackow, M.D.†*

During the uptake of anesthetic concentrations of N_2O and halothane, the F_E/F_I ratio of each gas was found to rise faster in infants and children than in adults. The ratio F_E/F_I for N_2O was unity for infants 0–6 months of age, and 0.98 for children 1–5 years, after 25 minutes of breathing a constant N_2O concentration of 60 per cent. At the end of 60 minutes of breathing ¾ per cent halothane the children's group had a F_E/F_I ratio of 0.81. The reasons for the more rapid rise of alveolar concentrations in infants and children seem to be related, in part, to physiologic differences which are most pronounced in infancy: increased cardiac output, greater alveolar ventilation and a proportionately larger compartment of well-perfused tissues relative to body mass.

THE PULMONARY EXCHANGE of anesthetic agents in the infant and child has not been described. This information could be of major clinical importance, particularly for infants. Cardiac arrest during anesthesia has been reported to occur in one in 719 anesthetized infants less than a year of age,[1] and one in 1,000 less than six months old.[2] The present study was designed to obtain basic data in this area of pharmacokinetics.

Material and Methods

Twenty-three patients, two days to five years old, were studied. All were in good condition, and required anesthesia for various surgical procedures, none of which involved the heart or lungs. Measurements were made during the course of operation. Some studies were abandoned because of the necessity for modifying anesthetic management to meet changing patient requirements. For this, and other reasons, the data of only 12 subjects are presented.

Preanesthetic medication was given according to the wishes of the anesthesiologist, who was not part of the study team. In general, the infants received only a belladonna drug; the older children were given, in addition, secobarbital or a narcotic or both. General anesthesia was induced by either of two methods:

1. Halothane, up to 2 per cent, in oxygen was given by mask in a semiclosed circle absorption system. Endotracheal intubation was done with an uncuffed, snug-fitting tube after administration of intravenous or intramuscular succinylcholine. Anesthesia was then continued with ¾ per cent halothane in oxygen, using a Frumin nonrebreathing valve and a volume-limited, time-cycled pediatric Frumin respirator.

2. Cyclopropane + oxygen was given by mask in a closed circle absorption system. After endotracheal intubation, with or without succinylcholine, the patient was kept unconscious with intravenous sodium pentothal and ventilated with 100 per cent O_2, using the same respirator as for the other method.

During a short, variable control period, the inspiratory tidal volume was adjusted to give a constant end-tidal CO_2 concentration of about 5 per cent. At the end of the control period, in all patients, the inspired gas mixture was changed abruptly to ¾ per cent halothane + 60 per cent nitrous oxide + balance oxygen. This permitted the measurement of

* Associate Professor of Clinical Anesthesiology.
† Associate Professor of Anesthesiology.
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nitrous oxide equilibration in seven patients anesthetized with method 1, and the measurement of nitrous oxide and halothane equilibration in five patients anesthetized with method 2. During the study period, some patients required changes in tidal volume to keep $P_{E_{CO_2}}$ at a satisfactory level. These studies were rejected.

Gas mixtures were obtained from a standard anesthesia machine and kettle-type vaporizer. Inspired nitrous oxide and halothane concentrations were monitored periodically throughout the study and, for the most part, remained remarkably constant. Two studies, however, were rejected because inspired gas concentrations fluctuated during the study period.

Samples of end-tidal air were taken from the endotracheal tube, by means of a needle and fine-bore tubing, with an automatically cycled single-stroke diaphragm pump, and injected into the serially-arranged analyzers. The sample, ¾ ml, represented 4 per cent of the tidal volume of the smallest infant in the series. Breath-by-breath analysis of N_2O and CO_2 was done with Beckman LB-1 infrared analyzers. Halothane was determined at minute intervals by gas chromatography, using a Perkin-Elmer Vapor Fractometer, model 154 DG, with a polypropylene glycol column and hydrogen flame ionization detector. The outputs of the infrared analyzers were recorded on an Offner dynograph; the ionization detector signal was recorded on a Texas Rectiriter.

The measured end-tidal N_2O and CO_2 values were corrected because of:

(a) The effects of crossover and collision broadening on the infrared analysis of N_2O and CO_2 in a mixture of the two gases. An overall correction of the experimental values was applied by constructing appropriate calibration curves obtained with precise mixtures of the gases involved. These mixtures were prepared in a dry, mercury "O"-ring spirometer.* The presence of 5 per cent CO_2 in gas mixtures containing 40–60 per cent N_2O in oxygen caused a detectable but insignificant increase in the N_2O signal when the nitrous oxide analyzer case was charged with CO_2—this was ignored. On the other hand, the presence of 40–60 per cent N_2O resulted in a measurable increase of the CO_2 values, when the CO_2 analyzer case was charged with N_2O. The experimental CO_2 determinations, therefore, were corrected by an amount indicated by the calibration curves.

(b) The effect of water vapor on the infrared analysis of N_2O. When mixtures of nitrous oxide in oxygen were saturated with water vapor at 25 C, the nitrous oxide measurement was increased by 1 per cent absolute over the entire range of 40–60 per cent nitrous oxide. This was the range of N_2O measured in our studies. The experimental N_2O values accordingly were lowered by 1 per cent absolute.

Two physiologic factors which theoretically affect end-tidal gas measurements were ignored: the R.Q. effect and the dilution of the dry inspired gases by pulmonary water vapor. These effects, opposite but not necessarily equal, were not satisfactorily quantitated. The reasons for ignoring them have been considered elsewhere.[3]

The end-tidal N_2O and halothane values, $F_{E_{N_2O}}$ and $F_{E_{halothane}}$, were used to calculate the respective F_E/F_I ratios, and these were plotted against time, on an arithmetic scale, to construct nitrous oxide and halothane equilibration curves for each patient. The 12 nitrous oxide curves were divided into two groups according to the patients' ages: 0–6 months and 1–5 years. A composite curve for each group was calculated and then compared with composite nitrous oxide curves for adults reported in other studies.[4, 5] The subjects of the five halothane studies were children 1–5 years of age. A composite equilibration curve for this group was also calculated and compared with similar adult curves constructed from data obtained from the literature.[6, 7]

In eight subjects, exhaled air was collected during the end of the control period and the beginning of uptake. Tracings from a nine-liter Collins spirometer were recorded on a direct-writing kymograph. Corrections were made for the ¾ ml end-tidal sample taken after every breath.

* Designed by A. S. J. Lee, Director, Medical Instrumentation Laboratory, Fort Lee, New Jersey.

TABLE 1.

Subject	Age	Weight (kg)	Hemoglobin (grams per cent)	$F_E/F_{I_{N_2O}}$ (per cent) Minutes 2	4	6	8	10	12	14	16	18	20	25
1	2 days	2.5	22.0	90.7	93.5	95.1	96.4	97.2	97.7	98.6	99.1	99.6	99.9	100.2
2	4 days	4.0	16.3	81.5	86.2	89.3	91.8	93.7	95.0	96.6	98.0	98.8	99.7	100.5
3	3 mo	6.6	12.3	90.5	92.5	94.4	95.7	96.3	97.1	97.4	97.8	98.1	98.3	99.2
4	3 mo	5.3	12.3	89.1	93.1	95.1	97.0	98.0	98.8	99.1	100.0	100.3	100.6	100.9
5	4 mo	6.0	10.0	87.0	91.6	94.2	96.0	96.5	97.0	97.3	97.6	97.8	98.0	98.5
6	6 mo	6.0	10.4	88.0	92.8	95.0	96.5	97.3	98.0	98.4	99.0	99.7	100.0	100.5
7	1 yr	8.8	11.3	85.4	91.5	94.0	95.3	96.4	97.2	97.7	98.0	98.9	99.7	100.7
8	2 yr	11.3	12.7	80.0	86.0	89.0	90.7	92.5	94.0	95.0	96.0	96.8	97.5	98.5
9	4 yr	16.4	11.9	86.0	91.3	93.7	95.3	96.4	97.1	97.4	97.7	97.9	98.0	98.5
10	4 yr	14.8	12.1	87.5	93.6	95.5	96.4	96.9	97.0	97.2	97.5	97.8	98.0	98.5
11	5 yr	15.8	12.3	82.0	86.7	89.1	90.7	92.2	93.2	94.0	95.2	95.8	96.2	96.9
12	5 yr	17.2	11.6	88.5	92.4	94.3	95.5	96.5	97.4	98.0	98.5	98.6	99.2	99.5

TABLE 2.

Subject	$F_E/F_{I_{Halothane}}$ (per cent) Minutes 5	10	15	20	25	30	35	40	45	50	60
7	54.5	65.5	71.5	76.0	79.0	80.5	81.5	82.0	82.5	83.0	83.5
8	49.0	62.5	69.5	74.5	78.0	80.5	81.5	82.5	83.0	83.5	84.0
9	50.5	61.0	67.5	71.5	73.5	75.0	76.0	77.0	77.5	78.0	78.5
10	36.0	47.0	56.0	63.0	68.0	71.0	74.0	76.0	77.0	78.0	79.0
11	53.5	61.0	66.0	69.5	72.0	74.5	76.0	78.0	79.5	81.0	83.0

Results

Tables 1 and 2 summarize the data and some of the physiologic characteristics of the patients. Figure 1 shows composite N_2O equilibration curves for infants 0–6 months of age, children 1–5 years, and for two adult studies. The four curves are similar in shape and contour, but show an inverse relationship between age group and rapidity of approach of exhaled to inhaled N_2O concentrations. The infant group reached apparent equilibrium in about 25 minutes, while the older children were measurably short of this point at that time. The adult groups had attained 96–97 per cent of equilibrium at 60 minutes.

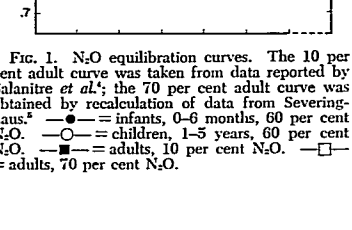

FIG. 1. N_2O equilibration curves. The 10 per cent adult curve was taken from data reported by Salanitre *et al.*[4]; the 70 per cent adult curve was obtained by recalculation of data from Severinghaus.[5] —●— = infants, 0–6 months, 60 per cent N_2O. —○— = children, 1–5 years, 60 per cent N_2O. —■— = adults, 10 per cent N_2O. —□— = adults, 70 per cent N_2O.

The more rapid approach to equilibrium by the younger age group is more obvious for halothane (fig. 2). At the end of an hour of breathing a constant concentration, the 1–5-year-old group had reached 80 per cent of equilibrium, the adult groups about 65 per cent.

Figure 3 shows equilibrium curves for N_2O and halothane in a 2-year-old child (subject 8). Also shown are the measured exhaled tidal volumes obtained during the end of the con-

trol period when the patient was breathing 100 per cent oxygen and during the initial part of uptake when inspired gases were halothane, nitrous oxide and oxygen. The exhaled tidal volumes fell from an average of 71 ml during the last three minutes of control to a low of 61 ml during the second minute of uptake and returned to 68 ml by the sixth minute. During this period no measurable change in CO_2 end-tidal concentration occurred.

Discussion

The data presented show that the approach of expired (F_E) to inspired (F_I) concentration of N_2O or halothane is more rapid in the infant than in the adult, when either gas is breathed at a constant inspired tension. The fact that this difference was demonstrated for two gases of different blood and tissue solubilities and widely separated ranges of anesthetic concentration suggests that physiologic differences between infant and adult played a role.

It must be emphasized that N_2O studies in pediatric and adult groups were not performed under identical conditions. Both adult groups breathed spontaneously, but in one group the inspired N_2O concentration was 10 per cent,[4] while in the other it was 70–75 per cent.[5] In the present study the children breathed 60 per cent N_2O and the lungs were ventilated mechanically. A part of the observed difference in the results must be due to the different study conditions.

The pulmonary absorption (or excretion) of soluble gases into (or from) pulmonary blood is the basis of a volume difference between inspiratory and expiratory volumes.[8] This difference occurs with spontaneous respiration and with any type of mechanical ventilation.[9] If the absorbed (or excreted) gas is not bound, but merely dissolved, the volume absorbed (or excreted) is a function of gas concentration and solubility, according to the gas laws and Henry's law of solubility.

Spontaneous respiration may be considered an expiratory volume-limited type of ventilation in which arterial CO_2 is kept constant by variations in inspired volume. Thus, if CO_2 production is constant, exhaled CO_2 concentration is unchanged and exhaled volume also remains constant. The two adult studies were done with this kind of ventilation and the absorption of anesthetic gas resulted in an increase of inspired volume. In the infants and children, on the other hand, respiration was

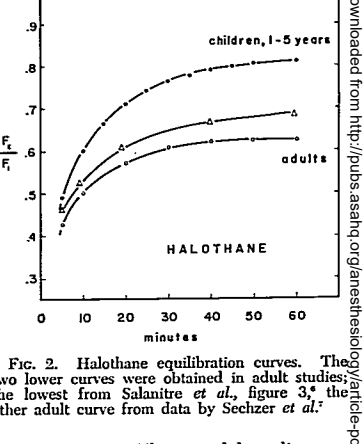

FIG. 2. Halothane equilibration curves. They two lower curves were obtained in adult studies; the lowest from Salanitre *et al.*, figure 3,[6] the other adult curve from data by Seehzer *et al.*[7]

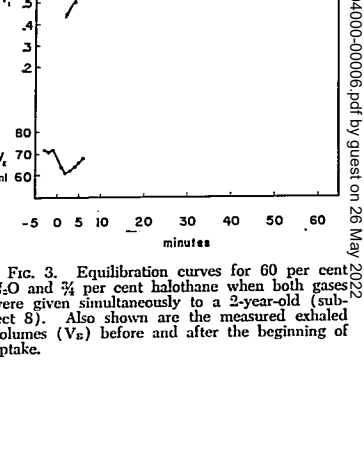

FIG. 3. Equilibration curves for 60 per cent N_2O and ¾ per cent halothane when both gases were given simultaneously to a 2-year-old (subject 8). Also shown are the measured exhaled volumes (V_E) before and after the beginning of uptake.

inspiratory-limited and the absorbed anesthetic gas caused a decrease in exhaled volume. The added ventilation might have been expected to increase the adult N_2O equilibration rates, yet figure 3 shown they were slower than those of infants and children. This would suggest that under the same conditions of ventilation adult and infant N_2O equilibration rates would be even more widely different.

The inspired N_2O concentrations were different for all groups compared. High concentrations of N_2O result in greater absorption,[10] and a larger difference between inspired and exhaled tidal volumes, than low concentrations. The 60 per cent N_2O concentration used in the infants and children could be expected to result in a faster rise of $F_{E_{N_2O}}$ when compared with the 10 per cent breathed by one adult group, but the opposite when compared with the 70–75 per cent N_2O breathed by the other adult group. The fact that the pediatric groups equilibrated more rapidly compared with *both* adult groups supports the contention that a real difference exists between children and adults.

Epstein *et al.*[11] showed that when dogs were ventilated with 0.5 per cent halothane and either 10 or 70 per cent N_2O the concentration effect due to the higher N_2O tension resulted in *average* increases of 6 per cent in N_2O uptake and 12 per cent in halothane uptake during the first five minutes of uptake. This effect decreased with time and could be expected to be negligible as $F_E/F_{I_{N_2O}}$ reached unity. The results of our study show that the $F_E/F_{I_{halothane}}$ in children was more than 12 per cent greater than $F_E/F_{I_{halothane}}$ in adults at the end of one hour, long after the concentration effect of N_2O could be a factor.

The absorption of halothane also must have contributed to the more rapid rise of $F_{E_{N_2O}}$. This effect must be small because of the low concentration of halothane and its modest solubility. The maximum volume of halothane absorbed from a concentration of ¾ per cent halothane is approximately equal to the volume of N_2O absorbed from a concentration of 1.6 per cent N_2O. Therefore, the combined absorption effect of 60 per cent N_2O and ¾ per cent halothane, balance O_2, would not be greater than that of 61.6 per cent N_2O, balance O_2.

Other factors which could have influenced the findings were: (a) reflexes arising out of the surgical manipulations; (b) changes in body temperature; (c) infusion of intravenous fluids during the study period. None of these variables could be rigidly controlled. Body temperature was maintained, for the most part, at about 98 F, but temporary variations ranged from 96 to 99.5 F. No large changes in blood pressure took place, but in the two youngest infants blood pressure measurements were not always reliable.

The reasons for the more rapid rise in $F_{E_{N_2O}}$ seen in the pediatric groups are undoubtedly many. One can only speculate, however, regarding the influences of those physiologic features which distinguish the infant from the adult. Decreased blood solubility of either gas in the infant, because of different blood composition, could increase uptake rates. During the first months of life, the infant undergoes large changes in hemoglobin levels. Kety[12] showed that the solubility of N_2O varied by 3 per cent as the hematocrit increased from 0.29 to 0.52. This change in blood solubility, although small, could be important during the period of physiologic anemia, when lowered hemoglobin results in decreased N_2O solubility, which, in turn, allows alveolar concentration to be higher from the beginning of uptake. This was not demonstrable in our small series. As a matter of fact, the 2-day-old and 4-day-old infants, who had hemoglobin values of 22 and 16 grams per cent, respectively, showed much the same equilibrium curves as the older infants in that group. These older infants had a range of hemoglobin values of 10 to 12 grams per cent. In the case of halothane, hematocrit changes could be expected to have a more pronounced effect on blood solubility, given the high solubility of the gas in hemoglobin and lipid, 6.7 and 126, respectively, compared with 0.70 in water.[13] It is unlikely that this factor played a large role, since none of the children in the halothane group had hemoglobin values lower than 11.3, or greater than 12.7, grams per cent.

A different relationship between the lung volumes of the infant, compared with the adult, could also affect uptake. A smaller functional residual capacity/tidal volume (FRC/TV) ratio

would decrease lung washout time and cause alveolar concentrations to rise more rapidly. The available data, however, seem to indicate that the FRC/TV ratio is either the same[14] or larger[15] in the infant than it is in the adult, and one could expect, if anything, a delay in rise of alveolar concentration.

It is our feeling that the experimental findings are related to physiologic differences between child and adult, and which are most pronounced when comparing the newborn with the adult. There is evidence that the newborn has a higher cardiac output, more alveolar ventilation, and a proportionately larger percentage of highly perfused tissue relative to body weight than the adult. Both cardiac output and alveolar ventilation are approximately twice adult values.[16, 17] The amount of highly perfused visceral tissue in the newborn has been calculated to be about 19 per cent of the body mass,[18] compared with 7 per cent in the adult.[19]

Theoretically, if ventilation is kept constant, a higher cardiac output will delay rise in alveolar gas tension during early uptake. However, since its overall effect is to increase total body uptake of gas per unit time, body saturation must be achieved at an earlier time. The F_E/F_I ratio must reflect the more rapid body saturation by its quicker arrival at unity. Kety showed this effect in figure 2 of his theoretical analysis of inert gas exchange.[20]

When cardiac output is kept constant, increased ventilation tends to keep alveolar gas concentrations higher *throughout* the uptake period, and also hastens body saturation.

Higher cardiac output in children should have resulted in lower F_E/F_I values during early uptake. This was not seen in our studies. We believe the reason for this is related to the opposing effect of increased ventilation on alveolar gas concentration and the influence of a proportionately larger compartment of highly perfused tissue.

A larger well-perfused compartment will receive a greater percentage of cardiac output and its venous outflow will contribute a greater percentage to mixed venous blood. Since venous blood from well-perfused tissue has a faster rise of gas tension than venous blood from less well-perfused tissue, its relative increase must increase gas tension of mixed venous blood and thus reduce the gradient between pulmonary venous blood and alveoli. The reduced gradient tends to keep alveolar gas tension higher.

In five subjects, the F_E/F_I nitrous oxide ratios were greater than unity by the twenty-fifth minute of uptake. This could be merely an indication of instrument error. However, known corrections, such as crossover and collision broadening, had been applied. An alternate conclusion could be that the measured F_E value required suitable correction for physiologic reasons. This would imply that true body saturation might not have occurred even if F_E/F_I were unity. Some support for this contention may be seen in table 1. None of the values for any one subject reached plateau levels, indicating that equilibrium probably had not been reached by the end of the study. This is not surprising when one considers that the probable half-time of adipose tissue uptake of N_2O in the adult is about 70 minutes.[21] One must explain, however, the apparent absurdity of breathing out a higher gas concentration than is breathed in. There is a firm physiologic basis for this phenomenon. Canfield and Rahn[22] have pointed out that any difference in volume of CO_2 excreted and volume of O_2 absorbed must be accompanied by changes in alveolar concentration of N_2. If the respiratory exchange ratio (R) is less than one the alveolar concentration of N_2 is higher than inspired. The opposite is true when $R > 1$. The ratio R may change $P_{A_{N_2}}$ not only as a result of CO_2 produced and O_2 consumed, but also because local ventilation–perfusion alterations in one area are not balanced by opposite alterations in another area. West[23] found that even in normal man regional pulmonary differences in ventilation and perfusion resulted in R values ranging from 0.65 to 2.0 in various parts of the lung. Due to the nonlinearity of the hemoglobin–oxygen dissociation curve, areas with low R values are not exactly compensated for by areas with high R values. As a result, there is an overall concentrating effect of alveolar N_2, which must reach higher concentrations than that of inspired air. This concentrating effect applies to all alveolar gases. When equilibration is close, it may be seen as an F_E/F_I ratio greater than unity. This is seen with N_2O in the present study.

and also was reported in previous work on the uptake of ethylene.[3]

Alterations of ventilation–perfusion relationships of different magnitudes, resulting from the fact that all the infants and children were mechanically ventilated while all the adults breathed spontaneously, could not be excluded as a factor.

In the early phase of uptake of 60 per cent N_2O, a small concentrating effect on $P_{A_{CO_2}}$ must have occurred. The inverse of this phenomenon in adults during excretion of 79 per cent N_2O has been reported.[9] At that time, a sensitive analytical technique was used, since the total change in CO_2 tension was only a few mm Hg. In the present study, the sensitivity of the detector was not large enough to measure changes of this magnitude with accuracy.

The interrelationships of the factors discussed are complex, but must be considered by the practicing anesthesiologist. Changes in cardiac output and ventilation during the anesthetic state are not rare. The faster response of the child to these changes results in more rapid fluctuations of anesthetic levels and a greater sensitivity to overpressure and to hyperventilation.

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