Delayed Approach of Arterial to Alveolar Nitrous Oxide Partial Pressures in Dog and in Man

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Simultaneous measurement of arterial (P_a) and end-tidal (P_{ET}) nitrous oxide partial pressures in dog and in man revealed differences of 10–20 per cent [$1 - (P_a/P_{ET}) = 0.1$ to 0.2] following a half minute of ventilation with nitrous oxide. These differences decreased to 5 to 10 per cent by 4 minutes and to less than 2 per cent after 32 minutes. The differences were increased by onset of anesthesia and were reduced by raising the alveolar nitrous oxide concentration. The results suggest that the end-tidal partial pressure of a gas is less representative of the arterial partial pressure when uptake of that gas is great.

In 1945, Kety published his now classic work on the determination of cerebral blood flow in man.[1] He administered a known inspired concentration of nitrous oxide and measured both arterial and internal jugular nitrous oxide concentrations. He also determined the blood/gas partition coefficient for nitrous oxide.[2] These data may be used to determined the partial pressure produced by a given arterial concentration of nitrous oxide. They suggest that after 15 minutes of breathing a constant concentration of nitrous oxide, the arterial nitrous oxide partial pressure was still less than 80 per cent of that inspired. This difference between inspired and arterial partial pressure cannot be explained on the basis of currently available figures for uptake of nitrous oxide, and probably represents a true end-tidal * (P_{ET}) to arterial (P_a) difference.

We have recently determined cerebral blood flow with a modified Kety technique.[3] Modifications were first, to monitor the end-tidal concentration of nitrous oxide and hold it constant from the first moments of measurement, and second, to determine arterial and jugular venous nitrous oxide contents by infrared analysis. We found the P_a/P_{ET} ratio for nitrous oxide to be 0.80 to 0.85 in the first minute. The ratio increased to 0.91 after 2 minutes, and to 0.96 after 32 minutes. Thus, the nitrous oxide partial pressure in arterial blood was 15–20 per cent less than alveolar at first, 9 per cent less after 2 minutes, and 4 per cent less after 32 minutes. However, because the number of arterial samples obtained was small and the blood/gas partition coefficients not known for each subject, the figures were taken as qualitative rather than quantitative estimates of the delayed approach of P_a to P_{ET}. To obtain a more quantitative description, we undertook the following study.

Methods

The study was divided into two parts. In the first, 5 dogs were anesthetized with pentobarbital (30 mg./kg. intravenously), their traches intubated, then placed on intermittent positive pressure with room air. Esophageal temperature was monitored with a Yellow

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*Alveolar partial pressure (P_A) will be considered synonomous with P_{ET} throughout this paper.

Springs telethermometer. A cannula was introduced into the femoral artery and threaded into the abdominal aorta. Another cannula was inserted into the femoral vein and threaded into the right ventricle, exact placement being confirmed by the ventricular pulse wave. The dogs were then given 12,000 units of heparin intravenously so that we could withdraw samples without diluting them by heparin in the syringe. The inspired gas mixture was then suddenly changed to approximately 20 per cent nitrous oxide, 60 per cent nitrogen and 20 per cent oxygen. Nitrous oxide concentration in the end-tidal gas was measured with an infrared analyzer and held at approximately 16 per cent. Known concentrations of nitrous oxide were produced from the pure gas by dilution (with oxygen or air) from calibrated syringes. These concentrations were then used to produce calibration curves for the infrared analyzer. Tanks of nitrous oxide in oxygen or nitrous oxide in air at appropriate concentrations were used to recalibrate these curves intermittently. Calibrating gases were humidified approximately at the partial pressure in the end-tidal samples. Samples of arterial and central venous (right ventricle) blood were drawn 0 (blank specimen) ½, 1, 1½, 2, 4, 8, 16, and 32 minutes after the desired end-tidal nitrous oxide concentration had been reached. Samples were analyzed for nitrous oxide by a modification of the Severinghaus technique.[3] Each blood sample was drawn through a 3-way stopcock into a 2 ml. syringe whose tip was uppermost. An initial 1 ml. of blood was drawn and ejected preceding the drawing of each sample. This replaced the dead space in the catheter, 3-way, and syringe with blood containing nitrous oxide. The stopcock was again turned to the catheter and the syringe filled with blood to approximately 2½ ml. Syringe and stopcock were detached from the catheter and the blood in excess of 2 ml. ejected. The stopcock was turned to trap the remaining blood and the open portion was cleared of blood by blowing through it. A 10 ml. syringe, whose plunger had been lubricated with mineral oil, was attached to the stopcock and the 2 ml. aliquot of blood injected into it. The stopcock was then turned to trap the blood injected into the 10 ml. syringe, and the 2 ml. syringe detached. Blood in the open portion of the stopcock was flushed out with air. Eight milliliters of air were added to the 10 ml. syringe and the mixture of blood and air was agitated for 25 minutes. The 8 ml. of gas were then injected through the sample cell of the infrared nitrous oxide analyzer, which had been re-calibrated to accomodate the (far) lower concentrations of nitrous oxide in the tonometered gas sample. From this, the nitrous oxide content of the gas sample was calculated. The nitrous oxide content in the blood remaining in the syringe was calculated from the partition coefficient for nitrous oxide in blood at room temperature. The blood/gas partition coefficient for each dog was determined at room temperature and at 37° C. using the Scholander technique described by Saidman *et al.*[4] These two points were plotted on semilogarithmic graph paper and connected by a straight line. Partition coefficients for temperatures other than 37° C. and room temperature were obtained from this graph. From these data, the total nitrous oxide content of the sample was determined for room temperature. The content at body temperature was determined from the gas laws, and the partial pressure this content exerts calculated.

After 32 minutes of breathing nitrous oxide, nitrogen, and oxygen, the dogs breathed 100 per cent oxygen for 45 to 60 minutes. An arterial sample was then taken for determination of *p*H and carbon dioxide partial pressure (Pa_{CO_2}). A simultaneous end-tidal gas sample was obtained and analyzed for carbon dioxide partial pressure ($P_{A_{CO_2}}$) with the carbon dioxide (Severinghaus) electrode. Nitrous oxide in oxygen was then administered to obtain and maintain an end-tidal concentration of approximately 16 per cent. Arterial and central venous blood samples were obtained at the time intervals taken in the first study, analyzed for nitrous oxide content, and the partial pressure calculated.

Following this, the animal again breathed pure oxygen for a period of 45 to 60 minutes. A second blood sample was taken at this time and analyzed for Pa_{CO_2}, and *p*H. A simultaneous end-tidal sample was obtained and analyzed for carbon dioxide. Nitrous oxide was then administered to produce an end-tidal concentration of approximately 77 per cent.

TABLE 1. Ratio of Arterial (P_a) to End-tidal (P_{ET}) Nitrous Oxide Partial Pressure for 5 Dogs

$O_2 + N_2 + 16\%$ N_2O			$O_2 + 16\%$ N_2O			$O_2 + 77\%$ N_2O		
Time	P_a/P_{ET}	S.D.	Time	P_a/P_{ET}	S.D.	Time	P_a/P_{ET}	S.D.
0.5	0.83	0.03	0.5	0.83	0.05	0.5	0.87	0.10
1.17	0.87	0.07	1.0	0.87	0.06	1.17	0.94	0.05
1.83	0.87	0.07	1.5	0.93	0.05	1.67	0.96	0.04
2.33	0.91	0.03	2.17	0.91	0.07	2.17	0.97	0.04
4.0	0.92	0.05	4.0	0.92	0.05	3.83	0.95	0.03
8.17	0.93	0.06	8.17	0.95	0.04	8.33	0.98	0.03
16.67	0.96	0.05	16.17	0.96	0.05	16.33	0.96	0.02
33	0.98	0.04	32	0.98	0.02	32	0.98	0.03

Time is minutes following a stable end-tidal nitrous oxide partial pressure.

Blood samples were again taken, at the same time intervals and analyzed for nitrous oxide.

In the second part of the study, 5 healthy human volunteers were prepared in the following manner. Under local anesthesia, a catheter was inserted into a brachial artery. The supine awake subject breathed 100 per cent oxygen for 15 minutes from an anesthetic circle absorption system. A control (blank) blood sample was drawn. Nitrous oxide was then added to the gas mixture, so as to obtain rapidly, and maintain an end-tidal concentration of approximately 18 per cent. Arterial blood samples were drawn ½, 1, 1½, 2, 4, 8, 16 and 32 minutes after this alveolar concentration was achieved. The samples were treated as in the dog experiments with the following difference. The subjects had not received heparin, so it was necessary to rapidly transfer the blood from the 2 ml. to the 10 ml. syringe. The dead space of the 10 ml. syringe was filled with heparin. Nitrous oxide blood/gas partition coefficients at room temperature and at 37° C. were determined with a Scholander apparatus for each subject. Fifteen to 20 minutes after the introduction of nitrous oxide an arterial blood specimen was drawn and P_{CO_2}, *p*H, and P_{O_2} determined.

Following the 32 minute sample period, the nitrous oxide was eliminated from the anesthetic circuit with 10 liters/minute inflows of oxygen. Anesthesia was induced with 100–150 mg. of thiopental intravenously, and continued with halothane and oxygen at a total inflow of 4–5 liters/minute. Anesthesia was deepened to permit tracheal intubation without benefit of succinylcholine. Following intubation, the subject was mechanically ventilated with intermittent positive pressure to hold depth and rate of respiration constant throughout the remainder of the study. Anesthesia was maintained thereafter with less than 0.8 per cent halothane in the inflowing mixture (4 liters/minute or greater). Approximately 45 minutes after the first sample period, nitrous oxide was again introduced to obtain rapidly, and maintain an end-tidal concentration of approximately 18 per cent. Arterial blood samples were taken for nitrous oxide analysis at the same intervals as before. Between 15 and 20 minutes following the outset of ventilation with nitrous oxide, an arterial blood sample was taken for *p*H, P_{CO_2}, and P_{O_2} analysis. Following the 32-minute sample, the inspired gas mixture was changed to oxygen plus halothane for 45 minutes. Nitrous oxide was then re-introduced so as to obtain rapidly, and maintain an end-tidal concentration of approximately 72 per cent. Arterial blood samples were taken and analyzed as before. Between 15 and 20 minutes following the onset of ventilation with nitrous oxide, an arterial sample was taken for P_{CO_2}, P_{O_2}, and *p*H analysis.

Results

Table 1 gives the ratio of arterial (P_a) to end-tidal ($P_A = P_{ET}$) partial pressures of nitrous oxide for three experiments in the 5 dogs. The deviation of P_a/P_{ET} from 1, is an index of the magnitude of the delay in the approach of arterial to alveolar values. Thus, at one half minute in the first experiment (O_2 20 per cent, N_2O 20 per cent, N_2 60 per

TABLE 2. Ratio of Nitrous Oxide Partial Pressures of Central Venous (P_V) to Arterial (P_a) Blood for 5 Dogs

$O_2 + N_2 + 16\% N_2O$			$O_2 + 16\% N_2O$			$O_2 + 77\% N_2O$		
Time	P_V/P_a	S.D.	Time	P_V/P_a	S.D.	Time	P_V/P_a	S.D.
0.58	0.30	0.05	0.56	0.26	0.08	0.55	0.29	0.07
1.13	0.41	0.05	1.25	0.43	0.03	1.02	0.44	0.09
1.75	0.56	0.05	1.52	0.48	0.07	1.59	0.50	0.08
2.33	0.68	0.07	2.5	0.61	0.10	2.12	0.55	0.07
4.17	0.72	0.04	4.17	0.70	0.12	4.50	0.63	0.09
8.17	0.80	0.07	8.0	0.78	0.08	8.33	0.77	0.04
16.67	0.90	0.08	16.33	0.81	0.08	16.17	0.87	0.07
33	0.91	0.05	32	0 89	0.03	32	0.88	0.04

Time is minutes following a stable end-tidal nitrous oxide partial pressure.

cent) where the ratio was 0.83, the arterial partial pressure was 17 per cent less than the end-tidal partial pressure of nitrous oxide. This rose fairly rapidly, so that by 33 minutes there was little or no difference between end-tidal and arterial values. A ratio of 0.98 or a 2 per cent difference was obtained at this time. A similar set of figures were obtained in the experiment with oxygen as background gas. No statistically significant difference was found between the ratios for this as opposed to the first study. The ratio was 0.83 initially, and rose in 32 minutes to 0.98. However, in the third experiment where nitrous oxide was given in high concentrations, the ratios for the same point in time were higher than those ratios obtained when nitrous oxide was given in low concentrations. Paired analysis showed this difference to be significant ($P < 0.01$) for the first 8 minutes.

The ratio of venous to arterial partial pressures of nitrous oxide in 3 dog studies were not

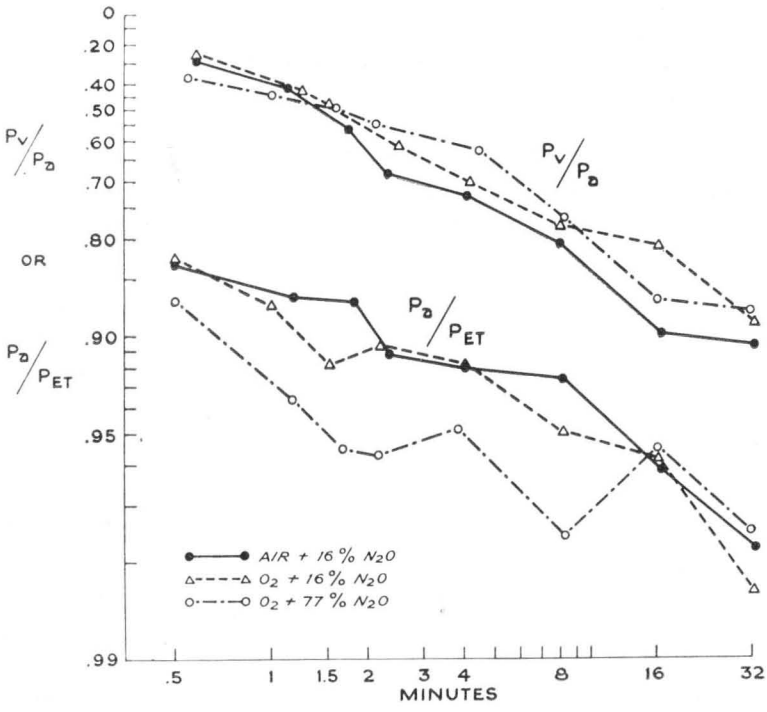

FIG. 1. Time course of the nitrous oxide P_V/P_a ratios (upper 3 graphs) and P_a/P_{ET} ratios (lower 3 graphs). P_V is the partial pressure of nitrous oxide in the central venous blood, P_a that in arterial blood, and P_{ET} that in end-tidal air (see tables 1 and 2). The time at which a predetermined P_{ET} was reached (and held constant thereafter) is zero time; that is, actual ventilation with nitrous oxide began some 20 to 40 seconds prior to zero time. $1 - P_a/P_{ET}$ is representative of the fractional arterial-to-end-tidal difference. Thus, at 0.5 minutes this would be $1 - 0.85$ or 0.15, or 15 per cent. Similarly $1 - P_V/P_a$ represents the fractional venous-to-arterial difference. The rise in P_a/P_{ET} is proportionate (parallel) to the rise in P_V/P_a. This and all the subsequent charts are plotted on log-log coordinates.

TABLE 3. Blood Gas Values for 5 Dogs

	Between First and Second Study	Between Second and Third Study
$P_{A_{CO_2}}$	26.4 ±2.9 S.D.	25.7 ±2.2 S.D.
Pa_{CO_2}	32.7 ±3.2	32.2 ±2.0
*p*H	7.435± .046	7.445± .016
Base excess	−1.6 ±1.1	−1.9 ±1.1

significantly different (table 2). If the arterial to end-tidal difference is related to anesthetic uptake then P_a/P_{ET} and P_V/P_a should rise at the same proportionate rate. Summaries of the data from the first 2 tables are plotted in figure 1, and show that the changes in these ratios are parallel (proportionate). Table 3 gives the arterial blood values for the 5 dogs.

The P_a/P_{ET} values for men (table 4) paralleled those for the dogs. However, the rate at which the P_a/P_{ET} value approached unity was significantly more rapid ($P < 0.01$) in the awake subjects than in the same subjects under anesthesia (first versus second study). The rate at which the P_a/P_{ET} value approached unity was also significantly greater ($P < 0.01$) at higher nitrous oxide concentrations (72 per cent versus 18 per cent) in the same anesthetized subjects (third versus second study). Figure 2 summarizes the P_a/P_{ET} values obtained in man. Table 5 gives the arterial blood values obtained during each study.

Discussion

Our study shows that there is a difference between the partial pressure of nitrous oxide in end-tidal gas and in arterial blood. This difference is greatest when the gas is first breathed. One half minute after the end-tidal nitrous oxide concentration is stable, it is 13–17 per cent in dogs and 16 to 23 per cent in man. The difference is less than 2–4 per cent after 8 to 16 minutes. Both in dogs and in man, increasing the end-tidal nitrous oxide concentration decreases the difference. In dogs, altering the background gas from oxygen to nitrogen and oxygen does not affect it; in man the difference is increased by anesthesia.

Although these differences have not been previously described for nitrous oxide, they have been observed for at least 4 other gases, including both oxygen and carbon dioxide.[5] The arterial to end-tidal partial pressure difference for carbon dioxide is increased by anesthesia,[6–9] the same as our finding for nitrous oxide. For nitrous oxide, of course, the difference is in the opposite direction. The carbon dioxide difference is also increased by an elevation of the partial pressure of oxygen,[10] but we did not observe this for nitrous oxide in anesthetized dogs. The work of Isbister, Schofield, and Torrance may also be interpreted to show an alveolar to arterial partial pressure difference for xenon.[11] Anesthesia appeared to increase this difference, whereas mechanically augmented ventilation reduced it. Lastly, there is Holaday's finding of an enormous difference for methoxyflurane (end-tidal 50–100 per cent greater than arterial) maintained for the duration of anesthesia.[12]

Several factors may explain these end-tidal to arterial differences: (1) a diffusion barrier;

TABLE 4. Ratio of Arterial to End-tidal Nitrous Oxide Partial Pressures in 5 Human Subjects

Awake			Anesthetized					
O_2 + 18% N_2O			O_2 + 18% N_2O			O_2 + 72% N_2O		
Time	P_a/P_{ET}	S.D.	Time	P_a/P_{ET}	S.D.	Time	P_a/P_{ET}	S.D.
0.48	0.84	0.06	0.50	0.77	0.06	0.52	0.84	0.04
0.93	0.91	0.06	0.95	0.86	0.04	1.03	0.88	0.03
1.68	0.92	0.06	1.55	0.89	0.03	1.70	0.91	0.04
2.15	0.93	0.04	2.08	0.88	0.02	2.17	0.94	0.03
4.02	0.95	0.03	3.98	0.91	0.01	4.12	0.96	0.04
8.23	0.98	0.02	8.05	0.97	0.03	8.28	1.00	0.02

Time is minutes following a stable end-tidal nitrous oxide partial pressure.

(2) contamination of the end-tidal sample with inspired gas dissolved in the walls of the airway; (3) ventilation of unperfused or hypoperfused alveoli; (4) shunting of blood through the lungs; (5) inadequate sampling of the true alveolar nitrous oxide concentration; and (6) diffusion of nitrous oxide into the walls of the pulmonary vein wall or heart or into the walls of the arteries between the heart and point of sampling.

The first possibility, diffusion, is unlikely except in pathological states. No significant barrier to diffusion can be demonstrated or calculated for carbon dioxide or nitrous oxide in normal lungs.[13, 14]

The second possibility, contamination of the end-tidal sample by inspired gas dissolved in the lining of the tracheobronchial tree, has been suggested for gases such as ether or acetone that have high tissue/gas partition coefficients.[15, 16] This would also apply to methoxyflurane.[17] However, gases such as nitrous oxide,[2] or xenon (DeBon, F. L. and Featherstone, R. M.: Unpublished observations) have a limited solubility (tissue/gas partition coefficient less than 0.5). The quantity of these gases dissolved in the lining of the conducting airways could not be sufficient to appreciably contaminate the end-tidal sample. For example, the lining of the purely conducting airways has a surface area of approximately 6,300 square cm.[18] Gases probably penetrate less than 0.01 cm. in the 1 to 2 seconds of inspiration.[13] Thus, the total tissue volume of solution would be 63 ml. ($6{,}300 \times 0.01$). With a tissue/gas partition coefficient of 0.5, this represents an effective volume of 31.5 ml. (63×0.5) which might contaminate the end-tidal gas with inspired concentration. The human subjects had alveolar tidal volumes of approximately

TABLE 5. Blood Gas Values for 5 Human Subjects Ventilated With Oxygen Plus Various Concentrations of Nitrous Oxide

	Awake	Anesthetized	
	O_2+18% N_2O	O_2+18% N_2O	O_2+72% N_2O
P_{aO_2}	382 ±13	374 ±21	95 ±15
P_{aCO_2}	37.9 ± 2.4	34.3 ± 6.2	34.3 ± 5.5
pH	7.46± 0.02	7.49± 0.06	7.48± 0.06
Base excess	+3.2 ± 0.5	+3.2 ± 1.0	+2.4 ± 1.3

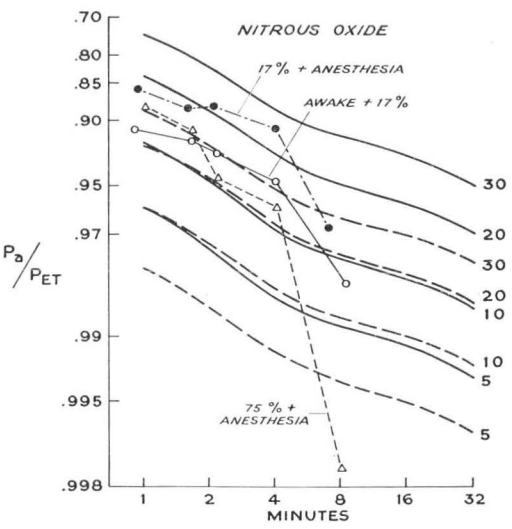

FIG. 2. Change in P_a/P_{ET} nitrous oxide ratios with time for 3 circumstances. The dashed lines (5, 10, 20, 30) are the ratios predicted when 5, 10, 20, and 30 per cent of ventilation is directed to unperfused alveoli. Total alveolar ventilation is assumed to remain constant. The solid lines (5, 10, 20, 30) are the predicted values for 5, 10, 20, and 30 per cent right-to-left vascular shunts. Summary plots of the P_a/P_{ET} ratios obtained in man (table 4) under the circumstances noted on the graph are also shown (O, ●, △).

500 ml. and thus the 31.5 ml. would represent 6.3 per cent contamination (31.5/500). When the 17 per cent end-tidal nitrous oxide concentration was studied, the inspired nitrous oxide concentration at ½ to 1 minute was about 50 per cent greater than end-tidal concentration (P inspired/$P_{ET} = 1.5$). Thus, at these times, the 6.3 per cent contamination would produce at most, a 3 per cent end-tidal to arterial difference. In the 4-minute sample, the inspired was 20 per cent greater than the end-tidal concentration, hence 6.3 per cent contamination would produce only a 1.2 per cent difference. These figures are far less than those actually found. The possibility of contamination is even more remote for the studies at 72 per cent end-tidal nitrous oxide, since even at one half minute, the inspired was less than 10 per cent greater than end-tidal concentration (concentration effect[19, 20]).

Ventilation of unperfused alveoli is a more likely cause of the differences found. The effect of various proportions of ventilation being directed to unperfused alveoli may be

predicted from a previous examination of uptake at a constant arterial concentration.[21] Equation 4 in that work gives:

$$F_{INS} = \frac{F_A\dot{V}_A + \dot{V}_U}{\dot{V}_A + \dot{V}_U} \quad (1)$$

where F_{INS} is the fractional inspired concentration, F_A is the fractional alveolar concentration, $\dot{V}_A$ is alveolar ventilation and, $\dot{V}_U$ is anesthetic gas uptake. When a fraction (F_W) of the inspired ventilation is directed to unperfused alveoli, but $\dot{V}_A$ is held constant (*i.e.*, ventilation is increased by the amount of the wasted ventilation) then the fractional end-tidal anesthetic concentration (F_{ET}) may be obtained by:

$$F_{ET} = (1 - F_W)F_A + F_WF_{INS}. \quad (2)$$

Since the end-tidal anesthetic partial pressure (P_{ET}) equals F_{ET} times the barometric pressure (BP) we may obtain the ratio of arterial anesthetic partial pressure (P_a) to P_{ET} by:

$$\frac{P_a}{P_{ET}} = \frac{P_a}{BP \cdot F_{ET}} = \frac{(V_A + V_U)P_a}{BP[F_AV_A + V_U(F_A - F_AF_W + F_W)]}. \quad (3)$$

Using previously predicted and verified[22] uptake figures for a constant alveolar concentration of nitrous oxide we have produced the graphs shown in figure 2 for a 17 per cent alveolar concentration. These suggest that to explain our findings, approximately 30 per cent of the alveoli would have to be ventilated but not perfused. This disagrees with estimates of alveolar dead space in awake and in anesthetized man,[8, 9] and hence, ventilation of underperfused alveoli cannot wholly explain our findings. That other factors probably operate to produce the differences is also suggested by our study with 72–77 per cent end-tidal nitrous oxide. In this study, as predicted by the concentration effect, the end-tidal and inspired concentrations rapidly approached each other. Since the difference between the two was negligible contamination of end-tidal with inspired gas could not appreciably alter the end-tidal concentration. The predicted effect of altering the alveolar concentration, on the end-tidal to arterial difference produced by various sized alveolar dead spaces, is illustrated in figure 3. At an alveolar concentration of 72 per cent (dashed lines) the difference is negligible even if 30 per cent of the ventilated alveoli are unperfused. Since at 72 per cent alveolar concentrations the effect of alveolar dead space is negligible, the difference between the experimental results obtained with this concentration and those obtained with 17 per cent nitrous oxide may be attributed to ventilation of unperfused alveoli. By comparing the data for the second and third experiments in dogs and in man we estimate that this factor accounts for about 30 to 40 per cent of the end-tidal to arterial difference. The graphs in figure 2 suggest that 10 to 20 per cent ventilation of unperfused alveoli would account for 30 to 40 per cent of the difference found. In agreement with this is the finding that the end-tidal partial pressure of carbon dioxide in the dogs was 20 per cent less than arterial partial pressure.

Ventilation of unperfused alveoli will not produce the same end-tidal to arterial differences for all anesthetics. As anesthetic solubility increases so does the difference between inspired and alveolar concentrations. The greater the difference between inspired and alveolar concentrations, the greater is the impact of contamination of alveolar gas with inspired (dead space) gas. This is illustrated in figure 4 for halothane, and figure 5 for ether. The graphs (dashed lines) were derived from equation 3. The greater the anesthetic solubility in blood, the greater is the effect of ventilation of unperfused alveoli. For example, at 4 minutes, with 20 per cent ventilation of unperfused alveoli, the partial pressure of ether in arterial blood is 44 per cent of that in end-tidal gas; partial pressure of halothane is 75 per cent of that in end-tidal gas; while partial pressure of nitrous oxide is almost 97 per cent of the end-tidal concentration (fig. 2). This may explain the large end-tidal to arterial difference seen by Holaday with the very soluble anesthetic, methoxyflurane.[12]

Perfusion of unventilated alveoli (shunting) also contributes to the end-tidal to arterial differences. The effect of diverting a fraction

(F_{Q_1}) of the cardiac output ($\dot{Q}$) through a shunt may be predicted from equation 4.[21]

$$\frac{P_a}{P_{ET}} = \frac{P_a}{BP \cdot F_{ET}} = \frac{P_{a\lambda}\dot{Q}F_{Q_2}}{BP(F_{Q_2}\dot{V}_T + F_{Q_1}\dot{V}_U)}$$

$$= \frac{F_{Q_2}\dot{V}_T}{F_{Q_2}\dot{V}_T + F_{Q_1}\dot{V}_U} \quad (4)$$

where λ is the blood/gas partition coefficient, F_{Q_2} is the fraction of the cardiac output passing normally ventilated alveoli and $\dot{V}_T$ is the volume of anesthetic carried per minute by arterial blood. The continuous graphs in figure 2 were obtained from this equation. As seen in that figure, our results in man may be entirely explained by about a 15 per cent shunt. However, we estimate from the arterial P_{O_2} figures that although a shunt of 10 per cent might exist, a more reasonable estimate would be between 5 and 8 per cent.[5] Actually, the predicted graphs obtained for shunting assume perfusion through collapsed alveoli. If perfusion occurred through unventilated but gas-filled alveoli the effect of such "shunting" would be greater than predicted because the gas space would buffer the increase in nitrous oxide partial pressure. If these alveoli were initially filled with oxygen, such a "shunt" could not be determined from Pa_{O_2} values. Shunting and ventilation of unperfused alveoli probably account for 70 to 90 per cent of the end-tidal to arterial difference we have found.

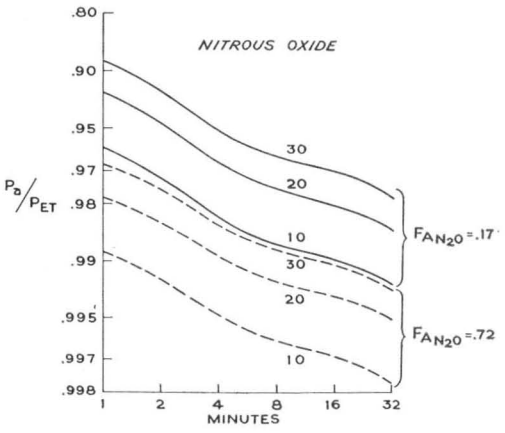

FIG. 3. Comparison of the time course of P_a/P_{ET} for nitrous oxide with ventilation of unperfused alveoli when the alveolar concentration is 17 per cent (solid lines) versus 72 per cent (dashed lines). The numbers 10, 20, and 30 indicate the percentage of alveoli that are ventilated but unperfused.

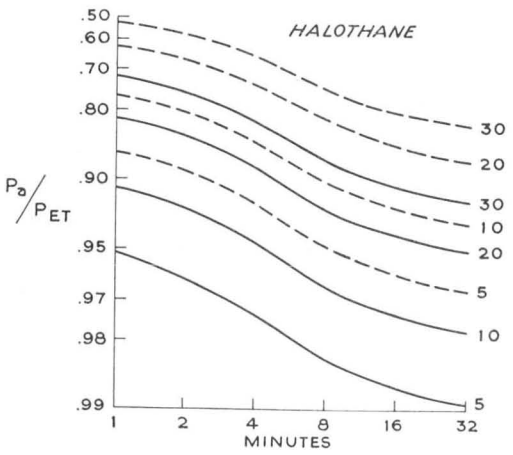

FIG. 4. Effect on the P_a/P_{ET} ratio of changes in ventilation/perfusion ratios for halothane. The dashed lines are the predicted graphs for 5, 10, 20, and 30 per cent ventilation of unperfused alveoli. The continuous lines are the P_a/P_{ET} ratios produced by 5, 10, 20, and 30 per cent left-to-right vascular shunts. Compare these graphs to those seen in figure 2.

As may be seen in equation 4, the effect of a given sized shunt is determined by the amount of anesthetic taken up by the tissues relative to the amount carried to them. It is not affected by total uptake, or by alveolar concentration. Since tissue uptake relative to total uptake is similar for all anesthetics, the effect of a given shunt does not vary appreciably from one anesthetic to another (figs. 2, 4, and 5). For example, with a 20 per cent shunt, at 4 minutes the P_a/P_{ET} ratio predicted for nitrous oxide is 0.916, for halothane is 0.889, and for ether is 0.929. Although shunting may be of great importance as a cause of the differences seen using nitrous oxide, it is of relatively little importance for ether, where the effect of ventilation of unperfused alveoli would be enormous.

The remaining explanations for the end-tidal to arterial differences are unlikely. Inadequate sampling of the concentration of nitrous oxide in the alveoli would probably reduce the apparent difference found. Consider that as inspiration occurs, the alveolar (and arterial) nitrous oxide concentration rises, reaching a peak near the end of inspiration. Uptake of

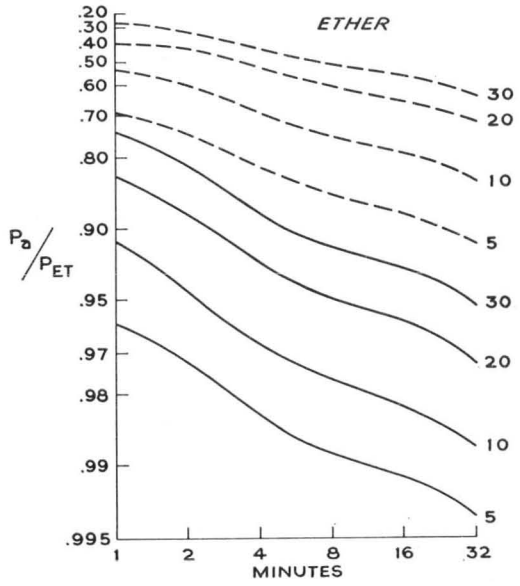

FIG. 5. Effects of changes in ventilation/perfusion ratios for ether. Compare these graphs with those in figures 4 and 2.

nitrous oxide opposes this rise and causes the alveolar concentration to fall as inspiration ceases and exhalation begins. The alveolar concentration is lowest immediately before or at the start of the succeeding inspiration. Since our end-tidal samples were taken from gas leaving the lungs towards the end of expiration, and since there were no long end-expiratory pauses, our recorded end-tidal nitrous oxide concentrations were, if anything, below the mean alveolar concentrations. Furthermore, at high alveolar concentrations, uptake does not effect the alveolar concentration (concentration effect). Thus, inadequate end-tidal sampling cannot explain any appreciable difference at 72–77 per cent nitrous oxide in the alveoli.

Absorption of nitrous oxide by the walls of the pulmonary veins, the heart, and the aorta also may be dismissed as unlikely. The surface area available for absorption is too small to account for the differences.

The finding of an end-tidal to arterial nitrous oxide partial pressure difference has several implications. Any study which depends on end-tidal samples as a measure of arterial partial pressure will be somewhat inaccurate. The degree of inaccuracy will be a function of the inspired to end-tidal difference and hence will be greater with the more soluble gases. The inaccuracy will be greatest with any one gas during the first few breaths of that gas when uptake is greatest. Thus, measurement of pulmonary capillary blood flow by the inert gas uptake technique[16, 23, 24, 25] will underestimate flow. Similarly, studies of rate of rise of end-tidal anesthetic concentration will not directly define the rate of rise of arterial anesthetic partial pressure.

In the steady state, the end-tidal to arterial difference may be eliminated or reduced by any technique that eliminates the inspired to end-tidal difference. For example, assume that a particular arterial anesthetic partial pressure is sought. The end-tidal partial pressure is held far in excess of this (2 to 4 times) for a period of 15 to 45 minutes. This reduces or eliminates anesthetic uptake at the lower partial pressure sought. With elimination of uptake the inspired to end-tidal difference is zero and hence, the end-tidal anesthetic partial pressure is representative of that in arterial blood. The inspired to end-tidal difference is also reduced by hyperventilation.[20, 21, 22] This technique may be adequate for the less soluble anesthetics, but is not sufficient for an anesthetic such as methoxyflurane.

Summary

We have found an end-tidal to arterial nitrous oxide partial pressure difference in dogs and in man. The difference is about 15 per cent of the end-tidal partial pressure at first, decreases to 10 per cent by 1–2 minutes, and to 4 per cent or less by 16 to 32 minutes. These results may be explained either by ventilation of unperfused alveoli or by perfusion of unventilated alveoli (shunting), although neither explanation alone appears to account for the magnitude of the changes seen.

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HEPARIN THERAPY Administration of heparin may result in fresh bleeding in a recent surgical wound. But heparin does not prevent embolism after thrombosis has occurred. In fact, it may cause an adherent clot to become free-floating. Both phenomena, bleeding and embolism, may be caused by clot lysis while the laying down of new fibrin is inhibited by heparin. This thesis was proved by incisions in the venae cavae of dogs. Simultaneous administration of aminocaproic acid and heparin prevents clot lysis, hemorrhage and embolism. *(LeVeen, H., and others: Prevention of Wound Hemorrhage and Embolism during Heparin Therapy, Arch. Surg. 91: 817 (Nov.) 1965.)*