Effects of Hyperventilation on the Rate of Cerebral Anesthetic Equilibration

Calculations Using a Mathematical Model

Edwin S. Munson, M.D., and Donald L. Bowers †*

The effects of hyperventilation, increase in V_A and decrease in cerebral blood flow (CBF), on the rate of cerebral anesthetic equilibration have been studied using a mathematical model. Increase in V_A increases the alveolar (arterial) anesthetic partial pressure. The degree to which increase in arterial partial pressure will rise is proportional to the anesthetic solubility in blood. A simultaneous effect of hyperventilation is the reduction of Pa_{CO_2} and CBF. It is predicted that with anesthetic agents of high solubility in blood, the effect of increased ventilation partially compensates for the effect of a decreased cerebral circulation on the attainment of the cerebral partial pressure of anesthetic. With anesthetic agents relatively insoluble in blood, the effect of ventilation is reduced so that achievement of cerebral anesthetic equilibrium may be unchanged or even prolonged.

THE RATE of the rise of the partial pressure of an anesthetic gas in the brain is influenced largely by cerebral blood flow (CBF), alveolar ventilation (V_A), cardiac output and anesthetic solubility in blood and brain. The technique of hyperventilation is generally considered one method by which induction of anesthesia can be accomplished more rapidly.[1] Hyperventilation at a constant inspired anesthetic concentration increases the rate at which the alveolar, and hence arterial anesthetic partial pressure, approaches the inspired partial pressure (concentration). The degree to which an increase in V_A will elevate the arterial anesthetic partial pressure is proportional to the solubility of the anesthetic in blood.[2] An increase in the arterial partial pressure of anesthetic will hasten the rate at which the cerebral partial pressure of anesthetic approaches the inspired partial pressure. However, the rise of the cerebral anesthetic partial pressure during hyperventilation is opposed by a concomitant reduction in CBF as a result of a decrease in arterial partial pressure of carbon dioxide (Pa_{CO_2}). Kety [3] calculated that a reduction in CBF would slow the attainment of anesthetic partial pressure in brain (depth of anesthesia), and that an increased CBF (with 5 per cent CO_2 inhalation) would result in the more rapid attainment of cerebral anesthetic partial pressure and therefore, the onset of "anesthesia." [4]

This concept is supported by experimental studies in both man and dog. Alexander *et al.*[5] measured cerebral uptake of ^{85}Kr in patients anesthetized with halothane. They demonstrated an inverse relationship between CBF and the time for 50 per cent whole brain equilibration of ^{85}Kr and suggested that achievement of cerebral anesthetic equilibration during hyperventilation might be prolonged as a result of a diminished CBF. Guy *et al.*[6] studied the effects of an altered Pa_{CO_2} on the rate of cerebral depression in dogs anesthetized at constant volume ventilation. The rate of cerebral depression as judged by electroencephalographic tracings was less rapid when end-tidal P_{CO_2} was maintained at half of normal (19.6 ± 4.5 mm. of mercury).

The dual effects of hyperventilation on the achievement of cerebral anesthetic equilibrium have not hitherto been evaluated. Previous studies of cerebral uptake of anesthetic have considered alterations of V_A and CBF individually. This study attempts to evaluate and

* Assistant Professor of Anesthesiology, University of Virginia School of Medicine.
† Senior Scientist, Research Laboratories for the Engineering Sciences, University of Virginia, Charlottesville, Virginia 22903.
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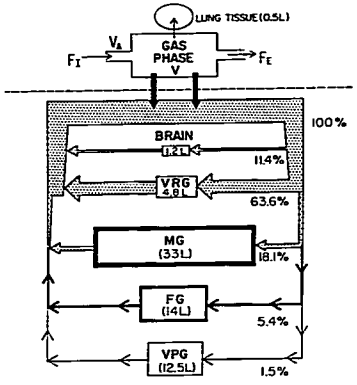

FIG. 1. The mathematical model is shown in the form of an analog.

predict the combined effects of hyperventilation on the rate of rise of the cerebral partial pressure of anesthetic using a mathematical model.

Method

Calculations of anesthetic uptake and distribution were made using a mathematical model patterned after that of Severinghaus [5] and of Eger.[6] A schematic diagram of the model is shown in figure 1. Anesthetic input into the gas phase is maintained at a constant inspired partial pressure. Functional residual capacity of the lung is taken to be 2.7 liters. Parenchymal lung tissue and arterial blood within the pulmonary capillaries are assumed to be in equilibrium with the gas (alveolar) phase at all times. The volume of blood within the lung is taken to be 1 liter. The remainder of the blood volume is divided in proportion to the distribution of the cardiac output to various tissues. Total cardiac output is taken to be 5 liters per minute. The body is divided into five compartments and grouped according to blood flow per unit of tissue and/or by solvent characteristics of tissues. The first compartment is the brain. The second is the vessel-rich group (VRG) which includes the heart, hepatoportal system, kidneys and endocrine glands. The third is the muscle group (MG). The fourth is the fat group (FG), and the fifth is the vessel-poor group (VPG) which includes relatively avascular structures such as bone.

The equations used to determine the arterial partial pressure (F_E) and cerebral partial pressure (F_B) for any of the several anesthetic agents are as follows. The first equation represents the rise of the anesthetic partial pressure within the lung.

$$\frac{1}{V_A}\frac{dq}{dt} = F_I - F_E$$

where F_I and F_E equal inspired and expired partial pressures, respectively. The model assumes that expired, alveolar, and arterial partial pressures are in equilibrium at all times. V_A equals anesthetic input into the system and F_I is arbitrarily taken as 1.0. At equilibrium, F_E is equal to the anesthetic uptake by the lung (q_L) which includes the FRC (V) and lung tissue (V_L).

$$F_E = \frac{q_L}{V + \lambda_1 V_L}$$

Differences in anesthetic solubility within blood and tissues are accounted for by using appropriate tissue/gas (λ) partition coefficients. Similarly, the rate of cerebral uptake (q_B) is proportional to CBF (Q_B) and equals the arterial-brain difference.

$$\frac{1}{\lambda_2 Q_B}\frac{dq_B}{dt} = F_E - F_B$$

At equilibrium brain partial pressure (F_B) equals brain uptake (q_B) per brain volume (V_B).

$$F_B = \frac{q_B}{\lambda_2 V_B}$$

Equations representing uptake in the other four body compartments are similar to the equations for the brain. Total body uptake is calculated as the sum of anesthetic uptake within each compartment.

$$\frac{dq}{dt} = \frac{dq_L}{dt} + \frac{dq_B}{dt} + \ldots$$

A program to solve this system of equations was written for the Burroughs 5500 digital

TABLE 1. Effects of Hyperventilation on the Rate of Cerebral Anesthetic Equilibration

	V_A (L./min.)	$Paco_2$ (mm. Hg)	CBF (ml./100 g./min.)	T_{95} Per Cent (min.)					
				M(13)	E(12.9)	H(2.3)	F(1.37)	N(0.16)	C(0.11)
A	4	40	44*	33.6	18.8	28.6	14.5	9.2	9.0
B	8	40	44*	11.8	6.7	13.0	7.5	6.9	6.2
C	8	20	25	16.4	9.2	20.4	12.1	12.0	10.7

V_A = alveolar ventilation; $Paco_2$ = arterial carbon dioxide partial pressure; CBF = cerebral blood flow.
* CBF for halothane was assumed to be 52 ml./100 g./min. (see text); T_{95} per cent = time for 95 per cent brain equilibration with arterial blood. M = methoxyflurane, E = ether, H = halothane, F = fluroxene, N = nitrous oxide and C = cyclopropane. Figures in ( ) refer to blood/gas partition coefficients.

computer.* Arterial and cerebral anesthetic partial pressures were plotted on the CalComp plotter.

Methoxyflurane (Penthrane), ether, halothane (Fluothane), fluroxene (Fluoromar), nitrous oxide and cyclopropane were selected for study. The solubility characteristics of these agents in human blood and tissues have been described.[8-11] Arterial and cerebral partial pressures were calculated at V_A 4 liters per minute and 8 liters per minute with CBF normal, and with CBF reduced approximately to half of normal. CBF for halothane was taken to be 52 ml./100 g./minute as reported by Wollman *et al.*[12] CBF for cyclopropane and for methoxyflurane was assumed to be equal to normal unanesthetized values and was taken to be 44 ml./100 g./minute as determined by Wollman *et al.*[12] and Lassen and Munck.[13] Calculations for all agents at a reduced CBF assumed a value of 25 ml./100 g./minute as suggested by the work of Wollman *et al.*[12] and of Reivich.[14] The small fraction of the cardiac output that remained after the reduction of CBF was arbitrarily assigned to the VRG within the model.

Results and Discussion

Calculations for all agents are shown in table 1. Results are expressed as the time required for 95 per cent cerebral anesthetic equilibration with arterial blood. The figures were plotted by the computer-plotter and show the data for methoxyflurane, halothane and cyclopropane. Figure 2 shows the rate of rise of the arterial partial pressure plotted as a fraction of the inspired partial pressure, for each agent. Arterial curves for normal and reduced CBF are the same (curve b) since tissue/blood partition coefficients for brain and VRG are similar. The effect of increased ventilation on uptake of methoxyflurane is apparent. The high solubility of methoxyflurane in blood results in the removal of a relatively large proportion of anesthetic from alveolar gas. As a result, there is a relatively greater reduction in the alveolar anesthetic partial pressure (curve a). Increase in anesthetic input by an increase in ventilation (V_A 8L/M) offsets the effect of uptake, resulting in a marked increase in alveolar partial pressure (curve b). The effect of increased ventilation on uptake is less pro-

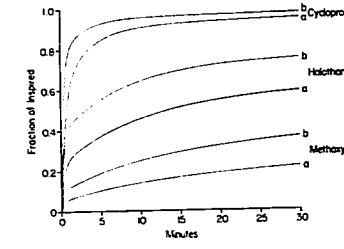

FIG. 2. The rate of rise of the alveolar (arterial) anesthetic partial pressure is plotted as a fraction of the inspired partial pressure for each agent. Curves represent arterial partial pressure when V_A is 4 liters/minute with CBF normal (a), V_A 8 liters/minute with CBF normal (b), and V_A 8 liters/minute with CBF reduced to half of normal (c). Curves b and c (not shown) are identical since tissue/blood partition coefficients for brain and VRG are similar.

* Computer-Science Center, University of Virginia.

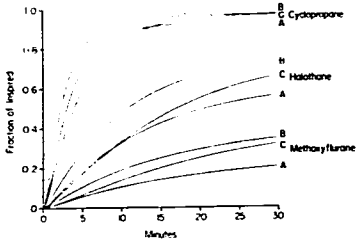

FIG. 3. The rate of rise of the cerebral anesthetic partial pressure is plotted as a fraction of the inspired partial pressure for each agent. The shapes and positions of these curves are similar to the corresponding arterial curves in figure 2. Curves represent cerebral anesthetic partial pressure when V_A is 4 liters/minute with CBF normal (A), V_A 8 liters/minute with CBF normal (B), V_A 8 liters/minute with CBF reduced to half of normal (C). The effect of increased ventilation on opposing the effect of a decreased CBF is most effective with methoxyflurane and least effective with cyclopropane. Note that the rate of rise of cyclopropane curve C lags behind and crosses curve A at 14 minutes.

nounced with cyclopropane. Cyclopropane is relatively insoluble in blood so that anesthetic removal, *i.e.*, uptake by arterial blood is small relative to the total amount of gas present on the alveoli. Therefore, the alveolar (arterial) partial pressure rapidly approaches the inspired partial pressure (curve a). Further increase in anesthetic input by ventilation has little effect on producing a further rise in the alveolar partial pressure (curve b). The effect of ventilation on the alveolar partial pressure of an anesthetic of moderate solubility such as halothane lies between that of cyclopropane and methoxyflurane.

Figure 3 shows the rate of rise of the cerebral anesthetic partial pressure plotted as a fraction of the inspired partial pressure. Curves A and B represent partial pressure in brain when V_A is 4 and 8 liters per minute respectively with CBF normal. The shapes and relative positions of these curves are similar to their corresponding alveolar (arterial) curves in figure 2. Curves C represent the cerebral anesthetic partial pressure when V_A is 8 liters per minute and CBF is reduced to approximately half of normal.

Cerebral equilibration with the arterial partial pressure of methoxyflurane is 95 per cent complete at 33.6 minutes (Curve A, bottom). This represents an absolute partial pressure of 22 per cent of the inspired partial pressure of methoxyflurane. This same partial pressure would be attained on Curve B at 11.8 minutes, and on Curve C at 16.4 minutes. The difference between B and C, *i.e.*, the effect of a reduced CBF, is small, amounting to 14 per cent (16.4–11.8/33.6).

Cerebral equilibrium with halothane occurs in 28.6 minutes (Curve A, middle). This same cerebral partial pressure of halothane (59 per cent of the inspired partial pressure) would be attained on Curve B at 13.0 minutes and on Curve C at 20.4 minutes. The difference between B and C with halothane is greater than with methoxyflurane, amounting to 26 per cent.

Cerebral anesthetic equilibrium with cyclopropane occurs at 9.0 minutes (Curve A, top). The same cerebral partial pressure (90 per cent of the inspired partial pressure) occurs at six minutes on Curve B. The achievement of this same cerebral partial pressure on Curve C occurs, not in less time than on Curve A as with halothane and methoxyflurane, but is actually prolonged to a time greater than on Curve A. The difference between B and C in this instance is greater than with the agents of greater solubility in blood, amounting to 50 per cent.

The interval required for the achievement of specific cerebral anesthetic partial pressures was arbitrarily chosen as 95 per cent equilibration of brain with arterial blood. The reduction in this interval during hyperventilation is related primarily to anesthetic solubility in blood and ranges from 50 per cent with methoxyflurane to 112 per cent with cyclopropane. The effect of an increased V_A on counter-balancing the effect of a decreased CBF in the achievement of cerebral equilibrium is most prominent with the agents of greatest solubility in blood. Increased V_A is unable to compensate for decreased CBF with the agents of least solubility and as a result equilibrium may be prolonged beyond control values of time (table 1). The height to which the alveolar partial pressure can rise

during hyperventilation determines the extent to which the arterial anesthetic partial pressure can counter-balance the reduction of CBF in the final achievement of a cerebral anesthetic partial pressure.

These predictions of altered pharmacodynamics during hyperventilation have obvious clinical implications during induction as well as recovery from anesthesia. Alterations in ventilation in the direction of *hypoventilation* should also produce changes in the rate of achievement of a cerebral anesthetic partial pressure. The most soluble anesthetic agents would be expected to show the greatest delay in cerebral equilibration since variations in ventilation have the greatest effect on the alveolar anesthetic partial pressure (fig. 2). The combination of an increased V_A and a normal (or greater than normal) CBF would be expected to produce the most rapid achievement of cerebral anesthetic partial pressure (see figure 3, B).

The design of the mathematical model is based on general assumptions.[15] The use of a theoretical model in the calculation of altered uptake oversimplifies the effects of anesthetic agents on multiple organ and compartmental systems. However, we believe that the use of this model system to separate the effects of ventilation and circulation on the rate of cerebral equilibrium is justified.

Conclusions

The effects of hyperventilation on the rate of cerebral anesthetic equilibration have been studied using a mathematical model. It is predicted that achievement of a cerebral anesthetic partial pressure during hyperventilation at a constant inspired anesthetic partial pressure would occur more rapidly with anesthetic agents having the greatest solubility in blood. The rate of rise of the cerebral anesthetic partial pressure with an anesthetic insoluble in blood would be unchanged or even prolonged during hyperventilation.

A more rapid attainment of cerebral anesthetic equilibration could be produced with any anesthetic, regardless of solubility, by the combination of hyperventilation and the maintenance of a normal or greater than normal CBF such as could be produced by rebreathing or inhalation of CO_2.

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