P_{aCO_2} for Optimum Washout of Inhalational Anesthetics from the Brain. A Model Study

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SUWA, K., MATSUSHITA, F., OHTAKE, K. and YAMAMURA, H. *P_{aCO_2} for Optimum Washout of Inhalational Anesthetics from the Brain. A Model Study.* Tohoku J. exp. Med., 1979, 129 (4), 319-326 — A hypothesis was established that, during emergence of inhalational anesthesia, hyperventilation and accompanying hypocapnia beyond a certain limit may actually disturb rather than enhance the washout of inhalational anesthetics from the brain because of a decreased cerebral blood flow. Two mathematical models were constructed and the washout of nitrous oxide, halothane and methoxyflurane were studied. In model 1, the whole body consisted of a single compartment, and blood flow to this compartment was assumed to change proportionally with the P_{aCO_2} . In model 2, the body was divided into two compartments, brain and the rest of the body. It was assumed that the blood flow to the brain compartment varies proportionally with the P_{aCO_2} , while that to the rest of the body remains constant. The analysis indicated that there indeed existed the P_{aCO_2} values at which the washout of anesthetics from the brain can be maximally achieved. In model 1, they were 49.0, 22.1 and 9.7 mmHg for nitrous oxide, halothane, and methoxyflurane, respectively. In model 2, these P_{aCO_2} values varied with time. While the hypothesis was proven to be valid, we conclude that it is of limited clinical significance. For halothane and methoxyflurane, these theoretically optimum P_{aCO_2} values are sufficiently low. For nitrous oxide, the variation of P_{aCO_2} makes little difference clinically, because its washout is fast enough regardless of P_{aCO_2} . ——— inhalational anesthetics; anesthetic washout; P_{aCO_2} ; cerebral blood flow; model

Hyperventilation during emergence is considered usually to increase the washout of inhalational anesthetics through the lung. Hypocapnia, which accompanies hyperventilation, reduces the cerebral blood flow (CBF) (Kety and Schmidt 1948; Wollman et al. 1964, 1965), and this reduction in CBF should delay the removal of the anesthetics from the brain (Munson and Bowers 1967). Combining these two factors, it is conceivable that hyperventilation, even though it is applied clinically with the intention of rapid recovery from inhalational anesthesia,

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may in fact delay the anesthetic washout, and that there is an optimum Pa_{CO_2} which achieves rapid recovery.

Using mathematical models, this study was made to check the hypotheses, whether or not such an optimum Pa_{CO_2} level exists, and whether or not it is within the clinically significant range so that we may have to keep it in mind in the daily anesthesia practice.

MODELS

Two models were constructed. In model 1, the whole body except the lung consisted of a single compartment, which is perfused by the entire cardiac output. This cardiac output was assumed to decrease proportionally with the reduction of Pa_{CO_2} . In model 2, the whole body consisted of two compartments, the brain and the rest of the body. The CBF was assumed to change linearly with Pa_{CO_2} , while the blood flow through the rest of the body was assumed to remain constant regardless of Pa_{CO_2} .

The models were linear, which means that two parameters, i.e., ventilation and blood flow, remained constant during the course of anesthetic washout. The venous blood draining its respective compartment was considered in partial pressure equilibrium with regard to the anesthetic.

Model 1

The washout of anesthetic x through the lung at time t ($\dot{V}x(t)$) may be written using a concept of alveolar ventilation equation,

$$Pax(t) = \frac{0.863 \dot{V}x(t)}{\dot{V}_A} \quad (1)$$

where $Pax(t)$ is the partial pressure of gas x in the arterial blood at time t (considered equal to that in the alveolar air). $\dot{V}_A$ is the alveolar ventilation. Ignoring the time required for the blood to flow from the body to the lung, $\dot{V}x(t)$ can be written as,

$$\dot{V}x(t) = abl, x \{P\bar{v}x(t) - Pax(t)\} \dot{Q} \quad (2)$$

where abl, x is the solubility of that anesthetic in blood, and $P\bar{v}x(t)$ is the venous blood partial pressure of the anesthetic at time t . The washout of the anesthetic causes the reduction of the tissue partial pressure of the anesthetic, which is equal to $P\bar{v}x(t)$.

$$\dot{V}x(t) = -abl, x \cdot V \cdot \frac{dP\bar{v}x(t)}{dt} \quad (3)$$

where abl, x is the solubility of the anesthetic in the tissue, and V is the amount of the body tissue.

Solving these three equations for $P\bar{v}x(t)$, we obtain,

$$P\bar{v}x(t) = P\bar{v}x(o) \cdot \exp(-t/T) \quad (4)$$

where $P\bar{v}x(o)$ is the value of $P\bar{v}x(t)$ at time zero, and T is the time-constant as shown below,

$$T = \frac{abl, x}{abl, x} \cdot \frac{V}{\dot{Q}} \left(1 + 0.863 abl, x \frac{\dot{Q}}{\dot{V}_A} \right) \quad (5)$$

Model 2

A similar set of equations are written using the same principle applied in model 1.

$$\dot{V}x = \frac{1}{0.863} \dot{V}_A Pax(t) \quad (6)$$

$$\dot{V}x = abl, x \{P\bar{v}x(t) - Pax(t)\} (\dot{Q}_{br} + \dot{Q}_{bt}) \quad (7)$$

$$\dot{V}br, x(t) = abl, x \{P\bar{v}br, x(t) - Pax(t)\} \dot{Q}_{br} \quad (8)$$

$$\dot{V}bt, x(t) = abl, x(Pbt, x(t) - Pax(t)) \dot{Q}bt \quad (9)$$

$$\dot{V}br, x(t) = -abr, xVbr(dPbr, x(t)/dt) \quad (10)$$

$$\dot{V}bt, x(t) = -abt, xVbt(dPbt, x(t)/dt) \quad (11)$$

$$\dot{V}x(t) = \dot{V}br(t) + \dot{V}bt(t) \quad (12)$$

$$P\bar{v}x(t) = \{\dot{Q}br/(\dot{Q}br + \dot{Q}bt)\} Pbr, x(t) + \{\dot{Q}bt/(\dot{Q}br + \dot{Q}bt)\} Pbt, x(t) \quad (13)$$

In these equations, suffix br indicates "brain", and bt indicates "the rest of the body." Equations 6 and 7 are similar to equations 1 and 2, equations 8 and 9 are Fick's principle applied to the brain and to the rest of the body, and equations 10 and 11 are similar to equation 3, applied to the brain and to the rest of the body, respectively. Equation 12 is self-explanatory. Equation 13 is the mixing equation, indicating that the partial pressure of the mixed venous blood is the mean of these two venous blood, weighted by the blood flow.

Equations 6 through 13 were solved for $Pbr, x(t)$, which gives a solution of the following pattern,

$$Pbr, x(t) = E \exp(p \cdot t) + F \exp(q \cdot t) \quad (14)$$

where E , F , p and q are independent of time.

NUMERICAL SOLUTIONS

Three agents, nitrous oxide, halothane and methoxyflurane, were chosen considering their blood solubilities. Solubilities of these agents to the blood and to the brain were assumed as those shown in Table 1 (Eger, II, 1974). vbl and vbt was assumed to be equal to each other.

The blood flow in model 1 ($\dot{Q}$) and the Pa_{CO_2} were related by the following equation,

$$\dot{Q} = 0.125 Pa_{CO_2} \text{ l/min/mmHg} \quad (15)$$

In model 2, $\dot{Q}bt$ was fixed at 4 liters/min, while $\dot{Q}br$ and the Pa_{CO_2} were assumed to relate,

$$\dot{Q}br = 0.025 Pa_{CO_2} \quad (16)$$

The following values were assumed for, V , Vbr , and Vbt ; V was 50 liters, Vbr 1.5 liters and Vbt 48.5 liters. CO_2 output was assumed to be 185.4 ml/min, which reduces the alveolar ventilation equation for CO_2 to the following,

$$Pa_{CO_2} = \frac{160}{\dot{V}_A} \quad (17)$$

TABLE 1. *Solubilities of anesthetics applied in this study.*
(ml of anesthetic/ml of blood or tissue/mmHg)

	Nitrous oxide	Halothane	Methoxyflurane
abr	6.555×10^{-4}	6.960×10^{-3}	2.684×10^{-2}
abl	6.184×10^{-4}	3.026×10^{-3}	1.578×10^{-2}

RESULTS

Model 1

Equation 4 is a single exponential function, and the speed of reduction of $Pbr, x(t)$ is solely dependent on the time-constant, which, in turn, is dependent on abl , x and Pa_{CO_2} . Using equations 15 and 17, and the numerical values given, the time-constant can be written as,

$$T = 400 (1/P_{aCO_2} + 0.0006742 \alpha bl, x P_{aCO_2})$$

The graphical expression of this equation is shown in Fig. 1. For each anesthetic agent, the time-constant achieves a minimum value at a certain P_{aCO_2} value below which the time-constant starts to rise again. These P_{aCO_2} values are 48.97 mmHg for nitrous oxide, 22.13 mmHg for halothane and 9.69 mmHg for methoxyflurane. The values of time-constant at these P_{aCO_2} 's are 16.3, 36.1 and 82.5 min respectively.

Fig. 1. Relationship between P_{aCO_2} and time-constant for three agents in model 1. Arrows indicate the P_{aCO_2} value where the time constant achieves a minimum value.

Model 2

In this model, the speed of anesthetic washout from the brain cannot be expressed so explicitly as in model 1. Starting from the same $P_{br}, x(t)$ value at time zero ($P_{br}, x(o)$), $P_{br}, x(t)$ values were actually calculated at various times and P_{aCO_2} values. The ratio of $P_{br}, x(t)$ to $P_{br}, x(o)$ is graphically presented in Figs. 2, 3 and 4. The P_{aCO_2} values at which the fastest anesthetic washout from the brain vary with time. For all three agents, an optimum washout can be achieved with relatively high P_{aCO_2} at the beginning, but as the time proceeds, the optimum P_{aCO_2} moves down to a lower level.

DISCUSSION

Our initial hypothesis was that hyperventilation during emergence may interfere with the anesthetic washout from the brain rather than enhance it, because hypocapnia decreases the cerebral blood flow, one of the important determinants for the anesthetic washout from the brain. Using two models, this hypothesis has been proven to be valid, but only superficially. While this con-

Fig. 2. A reduction in brain nitrous oxide as a fraction of the initial value is shown as a function of the Pa_{CO_2} . The time is shown as a third parameter. Note that the Pa_{CO_2} of optimum washout is relatively large initially, then it moves down to a lower level gradually.

Fig. 3. A reduction of brain halothane plotted similarly to Fig. 2.

Fig. 4. A reduction of brain methoxyflurane plotted similarly to Fig. 2.

Fig. 5. A reduction in brain halothane as a fraction of the initial value is shown as a function of time. The P_{aCO_2} is shown as a third parameter. Note that Figs. 3 and 5 are essentially the same, only plotted differently.

cept may be important, its clinical significance is dubious. For halothane and methoxyflurane, the P_{aCO_2} values, below which the washout from the brain starts to slow down, are under 25 mmHg. In other words, down to 25 mmHg, the lower the P_{aCO_2} , the better the anesthetic washout. Extreme hyperventilation, which achieves a P_{aCO_2} of well below 20 mmHg, should not be used anyway, unless specifically indicated. Clinical significance of the result of this model study may be even more dubious, when we take into account a more realistic relationship between P_{aCO_2} and the CBF. In this model, we assumed a linear relationship between P_{aCO_2} and the CBF all the way down to P_{aCO_2} of zero. In fact, however, the CBF levels off and tends to remain constant below 20 mmHg. Therefore, in the extreme low level of P_{aCO_2} , the anesthetic washout is unlikely to be disturbed so much as these models indicate.

For nitrous oxide, the P_{aCO_2} values at which the fastest washout can be achieved are relatively high in both models. Between 10 and 60 mmHg of P_{aCO_2} in model 1, and between 10 and 40 mmHg in model 2, however, the time-constant (T) or $(Pbr, N20(t)/Pbr, N20(o))$ varies only little with the change in P_{aCO_2} . The contribution of ventilation factor to the washout of this agent is very small. Furthermore, the washout of nitrous oxide from the brain is so fast that a little difference in speed makes no difference clinically.

We may turn this logic around, however, to suggest that more than modest degree of hyperventilation is unlikely to enhance much the washout of anesthetic from the brain. Use of excessive hyperventilation to achieve rapid recovery from inhalational anesthesia is discouraged.

An optimum washout can be achieved if we maintain a normal or high P_{aCO_2} and a large alveolar ventilation at the same time. It should be pointed out that neither a mechanical dead space nor a circle system without a CO_2 absorber can be used for this purpose. These methods maintain large minute ventilation, but not large alveolar ventilation. In other words, patients inhale their own expired CO_2 and keep their P_{aCO_2} high, at the expense of re-inhaling their own expired anesthetic agents. The only way of achieving a large alveolar ventilation and normal P_{aCO_2} is to add exogenous carbon dioxide to the inspired gas.

It is interesting to note that in model 2, normocapnia and slight hypocapnia achieve a better washout at the early phase, but at the later phase of washout intermediate to severe hypocapnia achieves a faster reduction in the brain anesthetics. This is clearly shown for halothane in Fig. 5, but a similar conclusion can be drawn for other two anesthetics using Figs. 2 and 4. Our interpretation of these findings is as follows. The anesthetic washout from the brain depends on the product of the CBF and the tissue-to-arterial difference of anesthetic ($Pbr - Pa$). In the early phase of washout, the tissue to arterial difference is small because we started from equilibrated state. The washout depends, therefore, solely on the CBF, which is large when P_{aCO_2} is high. In the later phase, $Pa, x(t)$ goes down and the tissue-to-arterial difference widens, especially when ventilation is large and P_{aCO_2} is low. This wide tissue-to-arterial difference overcomes the effect of a decreased

CBF. The washout is better even though the CBF is low.

We conclude that, within the range of clinically applicable ventilation, hyperventilation ensures a better washout of halothane and methoxyflurane from the brain.

References

- 1) Eger, E.I., II (1974) *Anesthetic Uptake and Action*, 1st Ed. Baltimore. Williams and Wilkins, p. 82.
 - 2) Kety, S.S. & Schmidt, C.F. (1948) The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young man. *J. clin. Invest.*, **27**, 500-510.
 - 3) Munson, E.S. & Bowers, D.L. (1967) Effects of hyperventilation on the rate of cerebral anesthetic equilibration: calculation using a mathematical model. *Anesthesiology*, **28**, 377-381.
 - 4) Wollman, H., Alexander, S.C., Cohen, P.J., Chase, P.E., Melman, E. & Behar, M.G. (1964) Cerebral circulation of man during halothane anesthesia: effects of hypocarbia and of d-tubocurarine. *Anesthesiology*, **25**, 180-184.
 - 5) Wollman, H., Alexander, S.C., Cohen, P.J., Smith, T.C., Chase, P.E. & Van der Molen, R.A. (1965) Cerebral circulation during general anesthesia and hyperventilation in man: thiopental induction to nitrous oxide and d-tubocurarine. *Anesthesiology*, **26**, 329-334.
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