**Krypton**⁸⁵ and Nitrous Oxide Uptake of the Human Brain During Anesthesia

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The production of anesthesia with an inhalational agent depends on the achievement of an anesthetic concentration of the agent in the brain. Likewise, the speed of induction of or recovery from anesthesia is intimately related to the rate of uptake or loss of the anesthetic agent by the brain. Therefore, measurement of the rate of brain uptake of anesthetic gases is of considerable importance. However, the kinetics of inert gas exchange in the brain of man have not been well studied.

Ideally, the measurement of the rate of brain uptake of an anesthetic agent should begin with the induction of anesthesia. However, during induction alterations of cerebral blood flow (CBF) can occur, either through an effect of the anesthetic agent itself or through secondary effects such as respiratory depression and breath-holding.¹ ² ³ As an alternative it was decided to measure brain inert gas uptake after anesthesia was established and CBF had become stable. This measurement involves the inhalation of an inert gas in subanesthetic concentrations (15 per cent N₂O, or traces of Kr⁸⁵) during anesthesia produced by another agent.

**Methods**

Brain Kr⁸⁵ uptake was studied in 13 normal male volunteers whose age ranged from 21–41 years. No premedication was administered. They were anesthetized with halothane in oxygen. Halothane was vaporized by means of a calibrated Fluotec vaporizer and the inhaled concentration was maintained at 1.2 per cent. The trachea was intubated following an intravenous dose of 60–80 mg. of succinylcholine and respiration was controlled with a Bird respirator in a nonrebreathing system using a Frumin valve. Ventilation was kept constant at about 12 liters/minute in each subject and arterial P<sub>CO₂</sub> was controlled by varying the inhaled CO₂ concentration with a gas ratiometer.⁴ The studies were conducted during hypocarbia (P<sub>ACO₂</sub> = 23 mm. of mercury), normocarbia (P<sub>ACO₂</sub> = 37 mm. of mercury) and hypercarbia (P<sub>ACO₂</sub> = 50 mm. of mercury). Each subject was studied during two of these three conditions. Twelve measurements were made during hypocarbia, six during normocarbia, and six during hypercarbia. Six of twelve measurements made during hypocarbia were made without any other drugs being administered. In all other instances 40–60 mg. of d-tubocurare were given intravenously in divided doses. When measurements were made a steady state had been present for at least 10 minutes, as indicated by end-tidal CO₂ and halothane concentrations, which were monitored with appropriate infrared analyzers. Arterial P<sub>CO₂</sub> was determined in a CO₂ electrode and minute ventilation (V<sub>E</sub>) was measured with a Wright anemometer. CBF was measured with Kr⁸⁵ by a modification of the inert gas method of Lassen and Munck.⁵ Pierce et al. have also made measurements of CBF in subjects during thiopental anesthesia using N₂O as the inert gas; suitable data were available in five subjects from that study (subjects 5, 6, 11–13).² Arterial and jugular venous concentrations of Kr⁸⁵ and N₂O were measured for periods of up to 28 minutes in these two investigations. These data have been used to calculate brain uptake of these gases at various levels of CBF in the manner outlined below.
TABLE 1. Brain Kr\textsuperscript{85} Uptake During Halothane Anesthesia

<table>
<thead>
<tr>
<th>Situation</th>
<th>No. of Meas.</th>
<th>( V_E ) (L/min.)</th>
<th>( P_{\text{a}, CO_2} ) (mm Hg)</th>
<th>( CBF ) (ml/100 g/min.)</th>
<th>( T_{50 \text{ per cent}} ) (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>S.E.</td>
<td>Mean</td>
<td>S.E.</td>
</tr>
<tr>
<td>Hypocarbia</td>
<td>12</td>
<td>12.0</td>
<td>0.5</td>
<td>23.4</td>
<td>0.9</td>
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<td>Normocarbia</td>
<td>6</td>
<td>13.1</td>
<td>0.9</td>
<td>37.3</td>
<td>0.8</td>
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<tr>
<td>Hypercarbia</td>
<td>6</td>
<td>11.5</td>
<td>0.5</td>
<td>51.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

\( V_E \) = volume expired/minute; \( P_{\text{a}, CO_2} \) = arterial \( P_{CO_2} \); \( CBF \) = cerebral blood flow; \( T_{50 \text{ per cent}} \) = time for brain saturation to reach 50 per cent of final value.

\( C_B L = CBF \int_0^t (A-V) \, dt \)  \hspace{1cm} (1)

where \( C_B L \) represents cerebral blood flow in milliliters/100 g brain/minute and \( C_B L \) is the volume of gas accumulated to time \( t \) in 100 g brain.

At any time, \( t \):

\[ \text{Percentage brain saturation} = \frac{C_B L}{C_K} \times 100 \text{ per cent} \] \hspace{1cm} (2)

where \( C_K \) represents brain inert gas concentration at infinite time. Therefore, at any time, \( t \):

\[ \text{Percentage saturation} = \frac{\text{CBF} \int_0^t (A-V) \, dt}{\text{CBF} \int_0^t (A-V) \, dt} \] \hspace{1cm} (3)

where

\[ \int_0^t (A-V) \, dt = \int_0^{t_f} (A-V) \, dt + \int_{t_f}^t (A-V) \, dt \] \hspace{1cm} (4)

\( t_f \) represents the time at which the final measurements of arterial and venous concentrations are made. CBF, being constant, disappears from the equation; \( \int_0^t (A-V) \, dt \) and \( \int_{t_f}^t (A-V) \, dt \) are calculated from the measured arterial and venous gas concentrations. The calculation of the integral \( \int_0^t (A-V) \, dt \) makes use of the fact that after sufficient time* the arterial-jugular venous differences of both Kr\textsuperscript{85} and N\textsubscript{2}O decrease in a predictable exponential manner with time, such that:

\[ (A-V)_t = K (A-V)_i \] \hspace{1cm} (5)

where \( (A-V) \) represents the arterial-venous difference at any time, \( t \), \( K \) is a constant, and \( \alpha \) is the rate constant.\textsuperscript{2,7} Integration of equation 5 from \( t_f \) to infinity yields:

\[ \int_0^\infty (A-V) \, dt = \frac{(A-V)_i}{\alpha} \] \hspace{1cm} (6)

The value of \( \alpha \) may be obtained from a semilogarithmic plot of the \( A-V \) differences as a function of time and \( (A-V)_i \) is measured. Thus, percentage saturation at any time \( t \):

\[ = \frac{\int_0^t (A-V) \, dt}{\int_0^{t_f} (A-V) \, dt + \frac{(A-V)_i}{\alpha}} \times 100 \text{ per cent} \] \hspace{1cm} (7)

Equation (7) has been used to perform the calculation of brain inert gas saturations in this study.

\textbf{Results}

Table 1 summarizes the pertinent respiratory and circulatory data obtained in the study of brain Kr\textsuperscript{85} uptake. \( V_E \) did not differ significantly among the three conditions imposed during this study \( (P > 0.5) \). Arterial \( P_{CO_2} \) was maintained at the desired levels by controlling the inhaled CO\textsubscript{2} concentration. As CBF increased, the time required for 50 per cent equilibration of the brain, \( T_{50 \text{ per cent}} \) fell.

In Figure 1 the results of the calculations of Kr\textsuperscript{85} uptake by the brain are shown as well as the arterial and jugular venous concentrations. In the nonbreathing system employed, arterial Kr\textsuperscript{85} concentration reached its final value about seven minutes after inhalation was begun and jugular venous concentration lagged behind the arterial value. At all three levels of CBF the jugular venous concentrations con-
continued to rise and arterio-venous equilibrium was not obtained during the period of study. Furthermore, brain Kr$^{85}$ concentration approached its final value considerably more slowly than did the jugular venous concentration. For example, after ten minutes of Kr$^{85}$ inhalation during normocarbia, the brain reached only 83.7 per cent of its final concentration while the jugular venous blood had attained 94.9 per cent of its final concentration.

The observed values of $T_{50\%}$ plotted as a function of CBF, are shown in figure 2. This relationship appeared to be hyperbolic and a log-log plot yielded a straight line. A linear regression could therefore be calculated for $\log T_{50\%}$ as a function of $\log$ CBF. This line is defined by the expression: $\log T_{50\%} = 1.78 - 0.73 \log$ CBF. The linearity of this relationship is statistically significant ($P < 0.001$) and the slope of the line is significantly different from zero ($P < 0.01$).

The curve representing this relationship of $T_{50\%}$ to CBF at a mean $V_E$ of 12.2 liters/minute is depicted in figure 2.

Table 2 summarizes the information on the uptake of N$_2$O obtained from an analysis of the data collected by Pierce et al. in the study of CBF during thiopental anesthesia. In that investigation, arterial $P_{CO_2}$ was controlled by varying ventilation, and consequently $V_E$ was lower during normocarbia (4.7 liters/minute) than during hypocarbia (14.9 liters/minute) ($P < 0.001$).

Figure 3 illustrates the arterial N$_2$O values obtained in that investigation. The concentrations continued to rise slowly after 15 minutes during both normocarbia and hypocarbia. During normocarbia, the mean increase in arterial N$_2$O concentration from 15-25 minute.
Table 2. Brain N₂O Uptake During Thiopental Anesthesia

<table>
<thead>
<tr>
<th>Situation</th>
<th>No. of Means</th>
<th>$V_E$ (L/min.)</th>
<th>$P_{con}$ (mm. Hg)</th>
<th>CBF (mL/100 g./min.)</th>
<th>Observed $T_{50%\text{per cent}}$ (min.)</th>
<th>Predicted $K_{ra}$ $T_{50%\text{per cent}}$ (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>S.E.</td>
<td>Mean</td>
<td>S.E.</td>
<td>Mean</td>
</tr>
<tr>
<td>Hypocarbia</td>
<td>5</td>
<td>14.9</td>
<td>1.7</td>
<td>16.6</td>
<td>0.5</td>
<td>14.1</td>
</tr>
<tr>
<td>Normocarbia</td>
<td>5</td>
<td>4.7</td>
<td>0.9</td>
<td>40.9</td>
<td>0.9</td>
<td>25.0</td>
</tr>
</tbody>
</table>

Predicted $K_{ra}$ $T_{50\%\text{per cent}}$ during hypocarbia was obtained by extrapolation of $K_{ra}$ data to a CBF of 14.1 mL/100 g./minute (fig. 2).

$V_E$ during thiopental anesthesia with normocarbia was much lower than during the study of brain $K_{ra}$ uptake (table 1); therefore, predicted $K_{ra}$ $T_{50\%\text{per cent}}$ is not compared with observed $N₂O$ $T_{50\%\text{per cent}}$ during this phase. (See table 1 for abbreviations.)

utes was 0.3 volume per cent ($SE_m$ 0.03, $P < 0.01$); during hypocarbia the mean increase was smaller (0.1 volume per cent, $SE_m$ 0.02) but statistically significant ($P < 0.05$). The decreased $V_E$ during normocarbia is reflected in the lower N₂O concentrations obtained during this stage. Despite the rise in CBF of 10.9 mL/100 g./minute during normocarbia ($P$ of difference < 0.001), $T_{50\%\text{per cent}}$ did not change significantly ($P > 0.25$). The value of $T_{50\%\text{per cent}}$ obtained for N₂O during hypocarbia is compared with the value extrapolated from the equation relating $T_{50\%\text{per cent}}$ for Kr$^{85}$ to the rate of cerebral blood flow (fig. 2) and good agreement is noted.

Discussion

The rate of inert gas uptake by the brain is influenced by many factors, the most important of which are cardiac output, the rate of cerebral blood flow, alveolar ventilation and the solubility of the gas in blood and brain. This discussion will deal in detail with the latter three factors.

Cerebral Blood Flow. The uptake of such dissimilar agents as xenon and chloroform has been demonstrated to be essentially a flow-limited process in the dog brain. Further, several investigators have demonstrated that inert gas uptake is not diffusion-limited. The present calculations of Kr$^{85}$ uptake by the human brain at three levels of CBF at a constant ventilation extend these observations of the flow dependence of inert gas uptake by the brain. As CBF decreases below a normal value of about 44 mL/100 g./minute, the rate of brain equilibration decreases sharply. An elevated CBF increases the rate of approach to brain equilibrium; however, since the relation of CBF to the rate of brain saturation is hyperbolic, an increase in CBF changes the rate of brain equilibration less than an equal decrease in flow rate.

As shown in figure 1, complete brain Kr$^{85}$ equilibration is never achieved during the experimental periods of this study at any level of cerebral perfusion observed, and brain saturation lags behind venous saturation at all times. Even in those subjects with the highest blood flow, brain Kr$^{85}$ saturation reaches only 91 per cent after 14 minutes of inhalation, while jugular venous blood is 98 per cent equilibrated. This slow saturation of the brain and its lag behind the jugular venous blood is at variance with earlier experimental work which indicated a more rapid saturation of the brain with an inert gas. However, there is reason to believe that mean whole brain saturation should follow the pattern found in this investigation. Jones and also Pittenger and his co-workers found evidence that the cerebral circulation was at least a two-compartment system. Later, Kety and his associates elegantly demonstrated that brain flow is heterogeneous and varies greatly from one region to another. Although there is a wide range of flow rates throughout the brain, in general one may assume two compartments, grey matter with the highest rate of flow and white matter, the more slowly perfused compartment. Therefore, the difference between whole brain and venous saturation (fig. 1) is accounted for by the early equilibration of the rapidly perfused areas of the brain; the failure of the
whole brain to attain complete equilibrium even at a very high level of CBF after 14 minutes of Kr\textsuperscript{85} inhalation may be explained by the incomplete saturation of slowly perfused areas.

**Alveolar Ventilation.** The lack of change in $T_{50\%}$ for $N_2O$ between hypocarbia and normocarbia illustrates the interaction of alveolar ventilation and CBF on brain $N_2O$ uptake. During normocarbia CBF increased 75 per cent and this would tend to increase the rate of brain $N_2O$ uptake. It should be noted, however, that $V_B$ in the normocarbic phase was decreased approximately 70 per cent from the level imposed on the hypocarbic subjects. As Kety has shown this decrease in $V_B$ would be expected to slow the rate of rise of arterial $N_2O$ content.\textsuperscript{6} The arterial uptake of $N_2O$ was indeed slower during normocarbia (fig. 3). The slowed arterial uptake would tend to depress the rate of brain $N_2O$ equilibration. Thus during normocarbia the expected increase in brain $N_2O$ uptake with a more rapid CBF has been offset by the decrease in alveolar ventilation. A fall in cardiac output during hypocarbia would also produce a slower rise in arterial $N_2O$ concentration similar to the pattern seen in figure 3.\textsuperscript{6} Although the increased positive pressure ventilation used by Pierce et al. to produce hypocarbia may have reduced cardiac output, no data on this parameter are available.

**Blood and Brain Solubility.** Although the brain/blood coefficients of $N_2O$ and Kr\textsuperscript{85} are similar (1.0 and 1.1 respectively), $N_2O$ is approximately 10 times more soluble in blood than is Kr\textsuperscript{85}.\textsuperscript{13,15} In order to evaluate the effect of blood solubility on the brain uptake of these two gases, comparisons must be made under conditions of comparable pulmonary ventilation and CBF. $V_B$ in the hypoxic phase of Pierce’s study is comparable to the level of $V_B$ imposed in the present study. The value of $T_{50\%}$ for $N_2O$ at a CBF of 14.1 ml./100 g./minute (hypocarbia) is 7.9 minutes while the extrapolated value of $T_{50\%}$ for Kr\textsuperscript{85} at a similar level of CBF is 8.7 minutes. Thus, the rate of brain uptake of these two gases seems similar despite the difference in their blood solubility.

**Clinical Implications.** The fact that both brain blood flow and alveolar ventilation affect cerebral gas equilibration has clinical import. An anesthetist may attempt to hasten brain gas uptake or elimination by increasing pulmonary ventilation since arterial equilibration is enhanced by a rise in alveolar ventilation. Under usual clinical conditions, however, an increase in ventilation decreases arterial $P_{CO_2}$ and hence cerebral blood flow is lowered. This diminished brain blood flow could completely negate or even reverse the desirable effects produced by increased pulmonary ventilation. However, hyperventilation can be used to produce a rapid alteration of brain inert gas concentrations if approximately 4 per
cent CO₂ is maintained in the inspired anesthetic mixture to prevent a reduction in arterial P<sub>co₂</sub> and a fall in CBF. This inspired CO₂ concentration might be maintained either by direct addition to the inspired gases or indirectly by removing the CO₂ absorber from the anesthetic circuit in a semiclosed system with the appropriate flow rates. Under these conditions, the production of pulmonary hyperventilation while preventing a reduction in CBF would permit a rapid, efficient change in brain inert gas content. Such a method would be particularly advantageous during the administration of the more soluble anesthetics such as halothane, diethyl ether, trichloroethylene or chloroform, if the possible elevation of arterial P<sub>co₂</sub> was shown not to be otherwise harmful.

Summary

A method of calculating whole brain inert gas uptake during periods of stable cerebral blood flow (CBF) has been developed. This method has been used to calculate brain Kr<sup>85</sup> uptake at three levels of CBF in 13 human subjects during halothane anesthesia at constant pulmonary ventilation. In addition, brain N<sub>2</sub>O uptake has been calculated in 5 humans during thiopental anesthesia at two levels of CBF. The rate of whole brain Kr<sup>85</sup> uptake was shown to vary in a hyperbolic manner with CBF. In addition, alveolar ventilation was demonstrated to be an important determinant of the rate of brain inert gas uptake. At comparable levels of alveolar ventilation and CBF, the rate at which brain N<sub>2</sub>O uptake proceeded did not differ markedly from the rate of brain Kr<sup>85</sup> saturation. Whole brain Kr<sup>85</sup> saturation lagged behind jugular venous saturation at all times. Complete whole brain Kr<sup>85</sup> equilibration was never achieved during the experimental periods of this study even at high levels of CBF.

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References