Cerebral Blood Flow Determined by Saturation and Desaturation with Krypton: An Evaluation of the Validity of the Inert Gas Method of Kety and Schmidt

By Niels A. Lassen and Axel Klee

In the original inert gas method of Kety and Schmidt the saturation of the brain with the inert gas, N₂O, is followed for 10 minutes. In a group of subjects we have studied both the saturation and the desaturation of the brain with krypton as the inert gas. The results give an experimental demonstration of a relatively small systematic error inherent in the method apparently due to differences of the uptake rate of inert gas in the various cerebral tissues. The error is discussed with particular emphasis on the use of extrapolation to infinity for the purpose of counteracting it.

Methods
Eleven male subjects aged 23 to 83 years were studied using the inert gas method of Kety and Schmidt in the modification described by Lassen and Munck. Each study lasted 20 minutes. For the first 10 minutes (saturation period) the patient breathed in a closed circuit of about 60 liters of atmospheric air containing about 0.1 mc/liter of krypton. For the following 10 minutes (desaturation period) the patient breathed in an open circuit which permitted inspiring atmospheric air containing no krypton and expiring to the ambient atmosphere. Care was taken to adjust resistance to respiration in both circuits to ensure similar breathing conditions throughout the experiment.

Needles were placed in one internal jugular vein and one femoral artery and remained in position while 18 samples of 3 ml each were taken from each vessel. Samples for oxygen saturation analysis were taken from both vein and artery during the first 10 minutes and also during the latter part of the study in order to check the constancy of the cerebral blood flow. Assuming the cerebral metabolic rate of oxygen is stable, constancy of the arteriovenous oxygen difference also points to a constant cerebral blood flow. Only studies with essentially constant (A-V)o₂ are reported in this paper.

Calculations
The cerebral blood flow (CBF) was calculated according to the equation of Kety and Schmidt as expressed for its use during desaturation also:

\[ CBF = 100 \lambda \frac{C_v(t_f) - C_v(t_i)}{\int_{t_i}^{t_f} (C_a - C_v) \, dt} \text{ ml/100 g/min} \]  

where CBF is the cerebral blood flow in ml per 100 g of brain per minute.

\( \lambda \) is the brain: blood partition coefficient for Krypton, \( \lambda = 1.09 \) for normal hematocrit values, and this value has been used throughout in the present series.

\( C_v \) and \( C_a \) are the venous and arterial Krypton concentrations in arbitrary units.

\( t_i \) and \( t_f \) are the initial and final times in minutes of each period of the study. They equal 0 to 10 minutes for the saturation period and 10 to 20 minutes during the desaturation period.

No correction for the mean circulation time through the brain was used.

Results
The arterial and cerebral venous concentrations of Krypton in three of the subjects are
given in figure 1. These cases have been selected to give a wide range of calculated CBF, the values for flow for the 10-minute saturation period being 22.1, 57.2, and 92.3 ml/100 g/min for cases 1, 9, and 11, respectively. The corresponding values obtained during desaturation were 31.7, 62.5, and 88.7, respectively.

For the material as a whole the calculated values for CBF during saturation and desaturation are given in table 1. The desaturation value exceeded the saturation value in 9 of the 11 cases and statistical analysis showed that this difference was significant (P < 0.01). Expressed as a percentage of the saturation value (fig. 2), this difference averaged +8.5% for the 8 cases with blood flow values near the normal range (cases 3 to 10).

For the two studies with very low blood flows (cases 1 and 2), both obtained in patients aged about 80 years and with marked dementia, the percentage deviation was large (+40%). For the study with very high blood flow (case 11), the percentage deviation was small (−3.9%).

**Discussion**

Kety and Schmidt compared the results of their method to those of a bubble flow meter in a series of simultaneous observations in
TABLE 1
Cerebral Blood Flow During Saturation and Desaturation With Krypton81

<table>
<thead>
<tr>
<th>Case</th>
<th>$Cv(0) - Cv(10)$</th>
<th>$Cv - Cm$</th>
<th>CBF *</th>
<th>$Cv(10) - Cv(20)$</th>
<th>$Cv - Cm$</th>
<th>CBF</th>
<th>CBF_{est} - CBF_{desat} in % of CBF_{est}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.49</td>
<td>80.4</td>
<td>22.1</td>
<td>-12.32</td>
<td>-44.6</td>
<td>31.7</td>
<td>43.4</td>
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<tr>
<td>2</td>
<td>14.65</td>
<td>68.9</td>
<td>25.9</td>
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<td>-40.7</td>
<td>36.6</td>
<td>37.4</td>
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<tr>
<td>3</td>
<td>16.21</td>
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<td>45.1</td>
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<td>-36.7</td>
<td>46.1</td>
<td>2.2</td>
</tr>
<tr>
<td>4</td>
<td>17.26</td>
<td>40.3</td>
<td>49.0</td>
<td>-16.05</td>
<td>-33.7</td>
<td>54.5</td>
<td>11.2</td>
</tr>
<tr>
<td>5</td>
<td>15.71</td>
<td>36.0</td>
<td>50.0</td>
<td>-14.60</td>
<td>-29.6</td>
<td>56.4</td>
<td>12.8</td>
</tr>
<tr>
<td>6</td>
<td>18.76</td>
<td>42.4</td>
<td>50.6</td>
<td>-17.80</td>
<td>-35.9</td>
<td>56.8</td>
<td>12.2</td>
</tr>
<tr>
<td>7</td>
<td>17.40</td>
<td>39.6</td>
<td>50.9</td>
<td>-16.25</td>
<td>-35.3</td>
<td>53.5</td>
<td>5.1</td>
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<tr>
<td>8</td>
<td>17.41</td>
<td>33.5</td>
<td>57.2</td>
<td>-16.38</td>
<td>-31.7</td>
<td>56.9</td>
<td>-0.5</td>
</tr>
<tr>
<td>9</td>
<td>16.67</td>
<td>33.2</td>
<td>57.2</td>
<td>-15.78</td>
<td>-26.8</td>
<td>62.5</td>
<td>9.3</td>
</tr>
<tr>
<td>10</td>
<td>19.57</td>
<td>36.4</td>
<td>57.2</td>
<td>-16.95</td>
<td>-27.1</td>
<td>72.6</td>
<td>16.1</td>
</tr>
<tr>
<td>11</td>
<td>18.20</td>
<td>23.2</td>
<td>92.3</td>
<td>-17.40</td>
<td>-23.1</td>
<td>88.7</td>
<td>-3.9</td>
</tr>
</tbody>
</table>

* CBF = cerebral blood flow in ml/100 g/min.

monkeys. Observations over a wide flow range (between 17 to 76 ml/100 g * min) showed good agreement, because the standard deviation of the differences between the two sets of observations was only 6 ml/100 g * min. This result therefore confirmed the finding in dogs of nearly the same N₂O concentration in brain tissue and mixed cerebral venous blood after 10 minutes of inhalation. If, in disease, some areas of the brain are perfused minimally, or not at all, then they do not influence the observed mixed cerebral venous curve measurably and hence such areas are totally or largely excluded from the result. This has been expressed by Kety by saying that the unit of reference is 100 g of perfused cerebral tissue. But apart from this condition of focal cerebral ischemia there would seem little doubt that the observations in animals can be taken to reflect the condition in man, i.e., the Kety-Schmidt technique does in fact give a measure of the cerebral perfusion rate. This conclusion is amply supported by many observations on the effects of various procedures or drugs, e.g., CO₂ on the cerebral circulation, the results of which are in excellent agreement with observations in animals using different methods for measuring the cerebral blood flow.

The evidence summarized here does, however, not exclude the possibility that the inert gas method is subject to some degree of systematic error. That this is actually the case is demonstrated by the present studies as will be discussed in the next section.

ERROR OF Employing A 10-Minute SATURATION PERIOD

The classical technique of Kety and Schmidt involves the indirect estimation of the average inert gas concentration in the brain after a saturation period of 10 minutes (equation 1). However, if 10 minutes sufficed to equilibrate the brain completely, then a desaturation study after 10 minutes of saturation should give the same result as the saturation study. The experiments here reported show that this is not always the case. The statistically significant difference between the two sets of calculated CBF values indicates that a systematic error is made by assuming $C_{\text{brain}} = \lambda C_{\text{blood}}$ after only 10 minutes. The experiments also showed that the difference between the values for saturation and desaturation flows tended to be larger at low calculated flows. This suggests that the error mentioned increases at low flow levels.

The systematic error introduced by saturating for only 10 minutes demonstrates experimentally a fundamental uncertainty of the "indirect Fick" method of Kety and Schmidt. It can be avoided by extending the saturation period to infinity, but this is obviously im-

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FIGURE 3
Decrease of calculated cerebral blood flow calculated with progressively longer duration of saturation and also extrapolated to infinity, in a subject studied in the steady state.

Possible. It is not enough to saturate until the venous concentration reaches the arterial level, i.e., until no measurable concentration difference can be observed. At this time when \( C_{\text{ven}} = C_{\text{artery}} \), there may still remain unsaturated regions in the brain and a very slow uptake rate will not result in a measurable extraction of inert gas from the blood flowing through the brain.

**EXTRAPOLATION TO INFINITY**

Using krypton-85 as the inert tracer gas and extending the observation period to 15 minutes, Lassen and Munck\(^2\) introduced an extrapolation procedure in order to avoid the error mentioned above. The extrapolation is based on the experimental finding, after six to eight minutes of Kr\(^{85}\) inhalation, of an almost constant arterial concentration and of a cerebral venous concentration curve that approaches the arterial level in a fashion that can be approximated by a simple mono-exponential function. Using this procedure, the calculated “infinity” value of cerebral blood flow is always somewhat lower than the value obtained at 10 minutes (fig. 3).

The validity of this extrapolation procedure cannot be verified by simply extending the observation period because of the experimental errors involved in assessing accurately small arteriovenous inert gas concentration differences. The “half-time” of the exponential function is usually about five to six minutes in agreement with extracranially recorded Kr\(^{85}\) clearance curves (see below). Similar mono-exponential extrapolation procedures are used in a number of other indicator dilution techniques where the theoretically necessary condition of an infinitely long observation period is likewise impossible to satisfy. It is used, for example, in the Stewart-Hamilton indicator dilution method for determining cardiac output and in this situation the many comparisons with other methods have supported the general, if not absolute, validity of the mono-exponential extrapolation procedure.

By employing the extrapolation procedure it is possible, from the extrapolated “infinity” value, to calculate the degree of saturation of the brain as a whole at any time \( \frac{C_{\text{brain}}(t)}{C_{\text{brain}}(\infty)} \) during the experiment. As also pointed out by Alexander et al.\(^6\) the following equation is applicable:

\[
\frac{C_{\text{brain}}(t)}{C_{\text{brain}}(\infty)} = \int_{0}^{t} Ca(\tau) - Cv(\tau) d\tau / \int_{0}^{\infty} Ca(\tau) - Cv(\tau) d\tau \quad (2)
\]

Applying an extrapolating exponential function with a “half-time” of five minutes and calculating the degree of saturation of the brain from equation 2, the error of the Kety-Schmidt technique is graphically illustrated (fig. 4) because the degree of saturation of the brain is clearly lower than that of the cerebral venous blood at all times during saturation, and vice versa during desaturation. In a large series of krypton-85 saturation studies published elsewhere both “10-minute” CBF values and those extrapolated to “infinity” were
FIGURE 4

Curve with crosses is the calculated average degree of saturation of the brain tissue as described in the text.

reported. On this basis it appears that using a ten-minute saturation period at a normal flow level overestimates CBF by about 10% when the Kety-Schmidt equation \(^1\) is applied. A relatively greater error is found at lower flow levels as seen in figure 5 in which are plotted all the observations in the study mentioned.

COMMENTS

Theoretically the best method for measuring cerebral blood flow in man is the “direct Fick” method as first employed by Lewis et al. \(^8\) In this method the amount of the tracer taken up in the brain is assessed by employing a radioactive tracer, krypton \(^7\), and an external detector. The arteriovenous concentration difference of the tracer is measured as in the classical Kety-Schmidt technique. However, the difficulties involved in estimating accurately the total uptake of isotope (in \(\mu\)C) in the whole brain (excluding isotope taken up elsewhere) are great. In the studies of Lewis et al. the “direct Fick” CBF values were systematically higher than the “indirect Fick” ten-minute CBF values in the same studies, probably indicating that the cerebral uptake of Krypton \(^7\) had been overestimated.

Owing to the difficulties mentioned, the techniques based on the direct Fick principle will probably be the method of choice only for estimation of total cerebral blood flow in situations where fairly rapid changes of this parameter compromise the steady-state condition required by the indirect method.

Recently an inert gas injection method for measurement of cerebral blood flow in man has been described. \(^9\) Employing a brief intracarotid injection of krypton \(^8\) dissolved in saline, together with external recording of the concentration changes in a region of the brain, the blood flow of the region can be calculated. It is noteworthy that this “brief intra-arterial inert gas injection” method is fundamentally very closely related to Kety’s “prolonged inert gas inhalation” method. In both procedures the crucial factor is the relative size of the area that gives the mean transit time of the gas through the brain. \(^10\)

Both methods are unable to include nonperfused cerebral areas and both methods require extrapolation to infinity to describe the total area. The two methods have been compared in a series of studies and they give almost identical results over relatively wide flow range. \(^10\)

Being fundamentally similar to the Kety-Schmidt technique and involving intracarotid injection, this new method is not a substitute for the older method as applied to measurement of total cerebral blood flow in man. The value of the injection method is
that it makes regional observations of the perfusion rate of the brain possible.

Several modifications of the Kety-Schmidt technique may be used to minimize the error due to the lack of equilibrium after 10 minutes. The several modifications include choice of inert gas, duration of study, considerations regarding analytical accuracy of the inert gas determinations in blood, and the number of samples analyzed.

It is advantageous to use an inert gas of relatively low solubility in blood and tissues in order to render the arterial concentration almost constant after the first few minutes. Nitrous oxide inspired at a constant concentration ("open system") results, as mentioned, in a gradually rising curve even after 10 minutes of inhalation. Krypton, being less soluble, gives a more constant arterial concentration as would also hydrogen gas. This latter gas can be accurately analyzed by the use of a platinum electrode and, if no systematic analytical error results from differences of oxygen saturation between the arterial and venous samples, then hydrogen might be a very useful tracer gas.

The duration of the study should be about 15 minutes in subjects in whom a normal flow level is expected, but a period of 25 to 30 minutes is preferable at low flow level. A desaturation technique as recently described by McHenry with krypton requires an initial saturation period of about 30 minutes. This procedure has distinct advantages; no mouthpiece or mask encumbers the subject during the flow study, and extrapolation to infinity is more accurate.

The importance of attaining highest possible accuracy in analyses of inert gas is obvious. It is also clear that if extrapolation is to be used then multiple samples are necessary. Moreover, multiple samples increase accuracy. Regarding the sampling technique it should also be mentioned that bilateral sampling of internal jugular blood increases the precision of the individual observation.

Although extrapolation to infinity is theoretically preferable, this procedure may be too inaccurate or even impossible due to the actual shape of the curves obtained. If such is the case then the use of the original equation at 10 or 15 minutes produces probably, as discussed above, an overestimation of flow by approximately 10 to 5%. This overestimation increases somewhat at low flows but it is very unlikely that this discrepancy, if taken into account when evaluating data, will lead to erroneous conclusions.

The conclusion reached in the present study can be formulated as an answer to the question raised by Sapirstein and Ogden regarding the validity of the Kety-Schmidt method. As applied to the human brain the method is essentially valid but it cannot be applied to other tissues without knowledge of the rate of saturation and of tissue inhomogeneity involved. Thus, it cannot be considered a reliable method for the study of the blood flow in the lower extremities as attempted by Shepherd and Warren. Here very marked overestimation of blood flow is bound to occur, and changes in calculated average blood flow may not necessarily parallel changes in true average blood flow. The criticism by Sapirstein and Ogden was based precisely on their attempted use of the principle for the study of leg blood flow and here the point raised is certainly valid. This has been expressed by Kety as follows: "The inert gas method is not necessarily applicable to measurements for which it was not designed" (personal communication).

Summary

Cerebral blood flow was studied in 11 subjects using the krypton method during a 10-minute saturation period followed by a 10-minute desaturation period. The calculated cerebral blood flow averaged 8.5% higher during desaturation than during saturation for the eight cases with blood flow values in the normal range. At higher flow (one case) the deviation was less pronounced, while at lower flows (two cases) the percentage difference increased. It is suggested that this systematic difference is due to the failure, at 10 minutes, of reaching equilibrium between
average tissue and mixed venous blood in the human brain.

The studies disclose a systematic error inherent in the Kety-Schmidt technique. According to observations in the literature this error is, however, not of such magnitude that it affects seriously the method as applied to the brain. Employing an inert gas saturation period of 10 minutes, an overestimation of the flow by about 10% probably occurs in normal subjects, while at subnormal flow levels the magnitude of this error increases somewhat. The error mentioned may be counteracted by prolonging the saturation period to 15 or 20 minutes and by extrapolation of the curves to infinity.

References


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