Human Cerebral Blood Flow Measured by Two Inert Gas Techniques

COMPARISON OF THE KETY-SCHMIDT METHOD AND THE INTRA-ARTERIAL INJECTION METHOD

By N. A. Lassen and K. Høedt-Rasmussen

Abstract

Two inert gas methods for measurement of tissue blood flow were compared. The two methods are (1) Kety and Schmidt's inert gas saturation method, in which the tissue saturation is followed by detecting the concentration of the tracer in the venous blood leaving the organ and (2) the intra-arterial radioactive inert gas injection method where the tissue washout is measured by detecting the residue inside the tissue by an external scintillation detector.

Theoretical considerations show a close relation between the two methods when carried to the time of full saturation or desaturation of the tissue or when stopped before full saturation.

Experimental studies of cerebral blood flow in nine human subjects using Kr86 revealed a close correlation between the two methods without any systematic difference between the two sets of data.

The Kety-Schmidt outflow detection method is the method of choice for studying over-all tissue perfusion and metabolism. The residue detection method is best suited for measuring flow through circumscribed regions inside an organ and for resolving the flow curve to yield estimates of flow and relative weight of various tissue components.

Additional Key Words: Kr85 tissue Kr85 clearance indicator transit times external counting theoretical analysis

In 1945 Kety and Schmidt introduced the use of an inert gas as a tracer for measurement of organ blood flow (1). The method they described is based on inhalation of the gas, e.g. nitrous oxide or Kr85, and on following the rate of tissue uptake by analysis of multiple arterial and venous blood samples. It provides measurements of the average blood flow and metabolism per 100 g of tissue in the brain, myocardium or kidney. Since the essential feature of the method and its modifications is detecting the uptake of the tracer by measurements on the venous outflow, we will call it the outflow detection method.

The possibility of introducing a radioactive inert gas directly to the organ by intra-arterial injection was described in 1961 by Lassen and Ingvar (2) as a means of measuring the blood flow in a small region of the cerebral cortex. In this approach the washout of the residue of tracer from the tissue is followed by an external radiation detector. The principle has since been applied to other organs, but its main field of application has been measurement of regional cerebral blood flow. A detailed description of the approach used in clinical studies in man has recently been published by Høedt-Rasmussen et al. (3). The flow values are obtained in units of milliliters per 100 g per min. As the essential feature of this method consists of following the washout of the residual radioactivity, we will call it the residue detection method.

It is the purpose of the present paper to
compare the two methods. As will be shown, they are theoretically closely related. Experimental evidence supporting this concept will be given on the basis of data obtained by applying both methods to the human brain.

**Theoretical Considerations**

The following description of the theory of blood flow measurement by the two methods is based on the application of elementary stochastic theory to the transit of the indicator molecules through the tissue. This subject has recently been reviewed by Zierler (4), and the reader is referred to his paper for formal proofs of the theorems given in the introductory paragraph.

**The Frequency Function of Indicator Transit Times**

Let \( h(t) \) (or just \( h \)) be the function describing the distribution of transit times in a given segment of the circulation and for a given indicator. The indicator is assumed to be introduced instantaneously as a bolus at the upstream end of the segment and to mix uniformly with the blood here. \( h(t) \) is then defined at the outflow site so that the fraction of all transit times that lies between \( t \) and \( t + dt \) is given by \( h(t) \cdot dt \). Hence we have \( \int_0^\infty h \cdot dt = 1 \) and \( \int_0^\infty h \cdot t \cdot dt = t \), where \( t \) is the mean transit time through the segment. The integral \( \int_0^t h \cdot dt \) is denoted by \( H(t) \) (or just \( H \)) and hence \( \lim H(t) = 1 \) for \( t \rightarrow \infty \).

By integration by parts it is seen that \( \int_0^\infty (1 - H) \cdot dt = l \). As shown by Meier and Zierler (5), \( l \) is the ratio of the equilibrium volume of distribution of the indicator through the segment \( V \), and the total blood flow through the segment \( F \):

\[
I = V/F. \tag{1}
\]

Dividing both numerator and denominator on the right hand side of (1) by the weight of the segment \( W \) and defining \( \lambda = V/W \) and \( f = F/W \), one obtains

\[
I = \lambda/f. \tag{2}
\]

Let it be specified that the vascular segment under consideration is an organ or part of an organ. Then \( h(t) \) is the distribution of indicator transit times through that organ or organ part, \( \lambda \) is the equilibrium volume of distribution per gram of tissue, i.e. it is the tissue:blood partition coefficient, and \( f \) is the tissue blood flow in ml/g \cdot min.

The amount of indicator, \( dq \), leaving the segment between \( t \) and \( t + dt \) must equal the total flow in that time, \( F \cdot dt \), multiplied by the indicator concentration in the outflow, \( C(t) \), i.e. \( dq = F \cdot C(t) \cdot dt \). Let the total amount of indicator be denoted by \( q_0 \). One can then calculate that fraction of the total amount that leaves in the small time interval to be:

\[
\frac{dq}{q_0} = \frac{F}{q_0} \cdot C(t) \cdot dt. \tag{3}
\]

If two segments, 1 and 2, are put in series, then the frequency function of the combined system, \( h_{1+2} \), is the convolution integral of \( h_1 \) on \( h_2 \):

\[
h_{1+2} = \int_0^t h_1(t - \tau)h_2(\tau)\,d\tau,
\]

which is written as \( h_{1+2} = h_1 \ast h_2 \).

It follows from the theory of the convolution of this type of function that the mean transit times bear the following simple relation:

\[
l_{1+2} = l_1 + l_2. \tag{5}
\]

**Outflow Detection Method**

Inhalation of an inert gas at a constant concentration results in a rising arterial concentration which approaches asymptotically to the equilibrium concentration, \( C_e \) (Fig. 1). The time course of the arterial curve \( C_a(t) \) (or just \( C_a \)) may therefore be described as the convolution of \( C_a \) by a frequency function, \( h_a(t) \):

\[
C_a = C_e \ast h_a = C_e \ast H_a. \tag{6}
\]

Equation 6 defines \( h_a \): it is that frequency function which convoluted by \( C_e \) generates \( C_a \). \( h_a \) is thus the frequency function of the indicator transits from the mouth to the artery at the point of inflow to the organ as influenced by the recirculation of tracer to the lung via mixed venous blood.

Let \( h_j \) denote the frequency function of the gas molecules through the organ. Then \( C_v \), the venous concentration, is given by

\[
C_v = C_a \ast h_j = C_e \ast h_i \ast h_j
\]

\[
= C_e \ast h_{i+1} = C_e \ast H_{i+1}. \tag{7}
\]

A function \( R(t) \) may then be defined by

\[
R(t) = C_v \int_0^t (C_a - C_v) \cdot dt. \tag{8}
\]

The significance of this definition is clear from the classical expression derived by Kety and Schmidt (6) on the basis of integrating the fun-
damental differential equation (the Fick principle).

Inserting equations 6 and 7 in 8 yields

\[ R(t) = H_k + \int_0^t (H_k - H_k + j) \, dt, \quad (9) \]

i.e. \( \lim_{t \to -} R(t) = l/(l_i + l_j) = l/l_i = f/l_i \). \( (10) \)

This result (equations 8 and 10) was obtained in a slightly different manner by Kety (6): The ratio of the blood flow per gram of tissue and the partition coefficient is given by the ratio of the height of the venous curve at complete saturation and the area between the arterial and venous saturation curves (see also Fig. 1).

\[ R'(t) = (q_{\text{max}} - q_0 \cdot H_k + q_0 \cdot H_k + j) \int_0^t q_0 (H_k - H_k + j) \, dt. \quad (15) \]

But since \( q_{\text{max}} = q_0 \) and \( H_k = 1 \) for \( t > t_{\text{max}} \), this equation becomes

\[ R'(t) = H_k + \int_0^t (H_k + H_k + j) \, dt. \quad (18) \]

\[ \lim_{t \to -} R'(t) = l/(l_i + l_j) = l/l_i = f/l_i. \quad (17) \]

This result and the method used to derive it are almost the same as those given by Zierler (7). They were repeated here to obtain the relation expressed in equation 16, which will be discussed below. By combining equations 14 and 17 it is seen that the ratio of the blood flow per gram of tissue and the partition coefficient is given by the ratio of the height and the total area under the curve from zero to infinity, i.e. until complete washout of all residual counts has occurred (Fig. 1).

COMPARISON OF THE TWO METHODS

The main result of the above analysis may be expressed in the following way. A brief intrarterial injection of a radioactive inert gas combined with external counting of the residue in the organ constitutes fundamentally the same observation as one can obtain by prolonged inhalation of the same gas at a constant concentration combined with arterial and venous sampling. Both techniques essentially represent an estimation of the mean transit time, \( l_\text{a} \), of the indicator gas through the tissue (compare equations 10 and 17). Both require extrapolation to infinity and both require that the partition coefficient, \( \lambda \), be known in order to calculate the blood flow.

This fundamental similarity does not, however, imply that the two methods are necessarily identical in practice. Consider, as we shall below, the application of both methods to the study of cerebral circulation in man using \( \text{Kr}^{85} \).
as the indicator gas. An obvious difference may here lie in the difference in brain areas under study. With jugular venous sampling one gets an estimate of the blood flow in the tissues drained to that vein, i.e., some kind of “average” brain mostly representing the ipsilateral hemisphere. With external counting, more circumscribed regions may be observed, and here geometrical and efficiency factors influence the exact delineation of the region. Corresponding to these differences of area there may also be differences in λ.

The necessity for extrapolation to infinity in order to calculate the total area represents the main difficulty of both methods. A very important aspect of the outflow detection method was the realization by Kety and Schmidt that when applied to the human brain only a relatively minor error was committed by employing equation 8 for \( t = 10 \text{ min} \) for calculating the cerebral blood flow (6). This approximation was important, since with nitrous oxide as the inert gas, extrapolation to infinity is practically impossible because of the slightly rising arterial curve and of analytical errors. Using Kr\(^{85}\), Lassen and Munck introduced extrapolation to infinity on the basis of a more horizontal arterial curve, a somewhat higher experimental accuracy, more blood samples and a 14- to 16-min experimental period (8, 9). Even so, extrapolation adds a considerable amount of random error to the procedure. With the residue clearance method, extrapolation is easier to perform; nevertheless, it adds some uncertainty, as even a very small amount of indicator recirculation to the counting field would reduce the accuracy (3).

For this reason it is of interest to note that the two types of studies are also closely similar when the blood flow is calculated without making use of extrapolation, e.g., to a time of 10 min in the case of the human brain. This is seen from the similarity of \( R(t) \) and \( R'(t) \) shown in equations 9 and 16 and by noting that \( H_k \) and \( H_0 \) both are of arterial inflow frequency functions. In fact, since \( H_k \) closely represents an instantaneous “step function” of concentration from 0 to 1, the two equations 9 and 16 would have been identical if the inert gas inhalation in the outflow detection study had resulted in an instantaneous rise of the arterial concentration to its equilibrium value. And, this particular shape of the arterial curve would not alter any of the arguments on which Kety and Schmidt based their choice of an experimental duration of 10 min as an appropriate duration of inert gas inhalation for obtaining a fair degree of saturation of the brain.

The conclusion reached here is that one may omit extrapolation with both methods, thereby committing the same type of error which in both cases is related to inhomogeneity of blood flow in the tissue. For both methods we may thus write

\[
T = \lambda \left[ \frac{\text{Height}}{\text{Area}} \right] \text{ml/g} \cdot \text{min} \quad (18)
\]

where Height is the difference in amplitude, i.e., \( C_0(t) - C_0(0) = C_0(t) \) for the outflow detection method and \( q_{\text{res}} - q(t) \) for the residue detection method, and where Area is the area between the curves respectively under the curve, and \( t \) an appropriately chosen clearance time (Fig. 1). The approximation to the true blood flow value, inherent in using equation 18, has been discussed in relation to the human brain by Lassen and Klee, who estimated that it results in an overestimation of about 10% for normal levels of cerebral blood flow and for \( t = 10 \text{ min} \), and in relatively larger errors at subnormal blood flow levels (10). However, the point made here is that practically the same overestimation is made by omitting extrapolation in both methods.

**Experimental Studies**

The outflow detection method used was the Kr\(^{85}\) modification of the Kety-Schmidt technique (8). The tracer gas was mixed with atmospheric air and administered via a mouthpiece for 14 min. During this time 14 samples were taken from a peripheral artery and from the internal jugular vein. The samples were drawn continuously over the 1-min collection period, with an automatic sample collector to draw the blood. The ratio of tissue blood flow and partition coefficient, \( f/\lambda \), was calculated according to equation 18 using a time, \( t \), of 10 min. The venous concentration at that time, \( C_0(10) \), was calculated as the arithmetic mean of the concentrations of the tenth and eleventh samples, to reduce random analytical errors.

The residue detection method used was the intra-arterial inert gas injection method of Høedt-Rasmussen et al. (3). About 2 mc of Kr\(^{85}\) dissolved in 0.9% NaCl was injected into the internal carotid artery of the same side as the jugular vein punctured in the outflow detection method. The uptake and subsequent clearance of Kr\(^{85}\) in the injected hemisphere were measured by a NaI(Tl) scintillation crystal 2 inches in diameter. The crystal was collimated so that almost all of the hemisphere was “seen” by it. Pulse height discrimination was used to ensure that mainly the primary gamma radiation was detected. The output from the preamplifier and discriminator was fed to a “digital ratemeter” (Societa Elelettronica Lombardica, Italy), thus obtaining a record of the actual number of impulses in time periods that could be made to vary between 1 sec and 1 min. The clearance curve was recorded for 15 min.
Experimental curves in case 8 (Table 1). Upper graph shows the result of the outflow detection method of Kety and Schmidt. The area $A_{10}$ was obtained as the sum of the arteriovenous differences. Lower graph shows the result of the intra-arterial injection method using a digital rate meter to record the Kr$^{85}$ gamma radioactivity remaining in the brain. In this subject the isotope recirculation was estimated experimentally by injecting the same dose of Kr$^{85}$ intravenously. $H_{10}$ is the actual amplitude at 10 min of desaturation. It would have been more correct to have subtracted the recirculating counts at 10 min (about 1%). This small error is fairly constant and has not been corrected for on the graph, since it is included in the computer program that was used for calculating the result (3). (One may note that the true recirculation does not quite take the form shown here after a brief intravenous injection.)

The ratio $f/\lambda$ was calculated using equation 18 and a duration ($t$) of 10 min. Care was taken to correct all counting rates for coincidence loss and to subtract the small amount of recirculating radioactivity (3).

Before, during, and after both types of studies the arterial $P_{CO_2}$ was checked using a glass electrode covered with teflon film. Experiments with more than 2 mm Hg variation during a blood flow determination were discarded.

Circulation Research, Vol. XIX, October 1966
The nine subjects studied were selected from the neurology department among patients in whom cerebral perfusion studies are made in conjunction with cerebral angiographic studies. Both studies were performed on the same day, usually with an interval of about 1 hour. The patients were selected to include some with and some without signs of diffuse degenerative cerebral disorders as manifested by severe dementia. In this way it was hoped to include subjects with normal as well as with markedly reduced cerebral circulation in the series, so that the methods could be compared over a fairly wide range of values.

The results obtained are shown in Table 1, which also gives the Paco₂ values measured during the study. Since this parameter so markedly influences the cerebral circulation, we attempted to correct for the small variations in Paco₂ noted during the two experiments. A correction of 3% per mm Hg was used for correcting both values to the average Paco₂ (11). As is evident from Table 1 and from Figure 2, a close and highly significant correlation was found with no tendency to a systematic difference between the results of the two methods.

Discussion

The theoretical analysis showing the close relation between the two techniques may at first sight come as somewhat of a surprise. One can, perhaps, "explain" it by stating that in the outflow method one integrates the frequency function by using a prolonged almost step-function-like input. In the residue method the tracer is supplied as a bolus. But here the integration is accomplished by the tissue itself, since it is readily seen that the (negative) slope of the washout curve must have the same shape as the frequency function.

The result shows clearly that the two methods are based on the same sets of assumptions, both when extrapolation to infinity is used and when the data are calculated to a finite experimental duration. Hence the Kety-Schmidt approach (6) and Zierler's frequency function concept (7) are in reality one and the same method despite the difference in conceptual background used by the authors.

The experimental results as such cannot be taken as a confirmation of the theory but as evidence of the similarity of the tissues used for measurements in the two methods. It is thus appropriate to interpret the good agreement found as indicating that the imperfections of both methods are not very great when applied to the human brain; they lack sources of error such as extracerebral contamination of internal jugular blood in the outflow detection method, variations caused by the somewhat slowly rising arterial curve in the outflow detection method, an inert gas transit through the brain which is too rapid.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Cerebral Blood Flow Determined by Kr⁺⁵ with the Outflow Detection Method (Kety-Schmidt) and the Residue Detection Method (Intra-arterial Injection and External Counting)</th>
</tr>
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<tbody>
<tr>
<td>Case</td>
<td>Sex</td>
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<td>8</td>
<td>♂</td>
</tr>
<tr>
<td>9</td>
<td>♂</td>
</tr>
</tbody>
</table>

*Side of carotid and jugular puncture.

Equation: 

\[ \frac{f/\lambda}{1 + \Delta \cdot 0.03} \]

Where \( \Delta \) = mean Paco₂ meaured, i.e., the correction is 3% per mm Hg of deviation from the mean Paco₂ value.
to satisfy the condition of $q_{\text{max}} = q_0$ in the residue detection method, a change in blood flow related to the injection of saline in the residue detection method, and variations in the Kr$^{85}$ recirculation in the residue detection method.

The present studies were designed to compare the results obtained after 10 min and not to test the accuracy of the extrapolation procedure. This would have required continuation of the studies for a somewhat longer time (e.g., 20 min) and a higher degree of stability of the arterial Kr$^{85}$ concentration than in the present outflow studies. It cannot be doubted, however, that such studies would not show quite as good a correlation because the non-cerebral factors mentioned above would tend to increase the errors.

The virtual identity of the type of information obtainable with both methods—that of observing the mean transit time, $t$, of the indicator gas would suggest that one might use either of the two methods interchangeably. This appears to be so. As summarized in a recent study of the cerebral blood flow in man by Ingvar et al. (12), the methods have practically the same normal values: by outflow detection $\text{CBF} = 50.4 \text{ ml/100 g \cdot min (SD = 4.9, n = 11)}$ when calculated to 10 min of Kr$^{85}$ saturation; by residue detection after Xenon-133 injection the corresponding value was $\text{CBF} = 49.8 \text{ ml/100 g \cdot min (SD = 4.1, n = 7)}$. Also when using extrapolation to infinity on the same studies, one obtains very similar values, with an outflow-CBF of $43.0 \text{ ml/100 g \cdot min (SD = 3.7, n = 11)}$ and a residue-CBF of $44.7 \text{ ml/100 g \cdot min (SD = 4.5, n = 7)}$. The same type of results was obtained in a study of the cerebral circulation in patients with Down's syndrome, in which the two methods were used in two different series of subjects with almost the same average value and standard deviation in both series (Lassen and others, unpublished observations).

In most cases one may assume that an intrarterial cannulation and injection carry a greater risk of complications than the venous sampling procedure. Moreover, since tissue metabolism is measurable only at the outflow, for total blood flow measurements the outflow method is usually preferable to the residue method, despite the advantages of the latter. However, two other aspects of the residue detection method have prompted its current use in clinical investigations: (1) blood flow in circumscribed regions of the injected organ can be measured and (2) flow and weight of the two major tissue components can be estimated (3). These flow and weight estimates are based on a compartmental analysis which differs fundamentally from the stochastic approach employed in the present study. In our opinion, the two types of analyses supplement one another (3). The purpose of this study
is, therefore, not to advocate the exclusive use of 10- or 15-min studies of cerebral blood flow in the residue detection method, but to stress the theoretical and experimental evidence indicating that such values are basically the same as those obtained in 10- or 15-min clearance studies with the venous outflow detection method of Kety and Schmidt.

References
Human Cerebral Blood Flow Measured by Two Inert Gas Techniques: Comparison of the Kety-Schmidt Method and the Intra-Arterial Injection Method

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Circ Res. 1966;19:681-688
doi: 10.1161/01.RES.19.4.681

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