Estimation of Error Limits for Cerebral Blood Flow Values Obtained From Xenon-133 Clearance Curves

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I provide the theoretical basis for an error calculus for measurements of cerebral blood flow using a freely diffusible tracer substance such as xenon-133. The use of the error calculus is exemplified by a study of the effect on the error margins in measurements of gray matter blood flow from flow level, relative weight of the gray matter compartment, and use of the earliest parts of the clearance curves. The clinical value of the error calculus is illustrated by its ability to separate different sources of measurement error. As a consequence, it is possible to optimize the method for blood flow calculation from the clearance curves, depending on the type of cerebral blood flow measurement. I show that if a true picture of the regional gray matter blood flow distribution is sought, the earliest part of the clearance curves should be used. This does, however, increase the error in the estimate of the average cerebral blood flow value. (Stroke 1989;20:205-210)

Knowledge of the error limits for cerebral blood flow (CBF) values measured by xenon-133 clearance is necessary for the interpretation of their significance. Usually the performance of a CBF measurement system is characterized by its “normal values,” the mean and standard deviation of CBF measurements for a group of resting normal volunteers. The standard deviation of these normal CBF values contains biologic variability in brain activity due to, for example, variations in wakefulness or anxiety, and due to the measurement error, which is a function of errors in the recorded xenon-133 input and clearance curves and of the method of curve analysis. Analysis of simulated, noise-contaminated clearance curves have been used to compare the variability of the CBF results that is caused by different methods of CBF analysis. However, the value of that approach is limited by the fact that the results reflect properties of the specific algorithms for CBF analysis rather than the general properties of all CBF methods based on measurements of the clearance of a freely diffusible tracer substance.

I introduce a method for error calculus that is founded upon the basic relations between the input and the clearance of a freely diffusible tracer substance as described by the Fick equation and its solution for xenon-133 given by Kety. The error calculus enables a comparison of the influence on the measurement error of different factors in the recording and analysis of xenon-133 clearance curves. Thus, it becomes possible to optimize the method for gray matter blood flow analysis depending on whether the main object of the regional CBF measurement is a correct measurement of the flow pattern or of the mean flow level.

Methods

From the principle of conservation of matter (the Fick principle), it follows that the change in the quantity, \( Q_t \), of a tracer substance in a given tissue volume, \( V \), is the amount transported into the tissue minus the amount cleared from the tissue. If the tracer substance is transported by the blood flow, \( F \), we get

\[
\frac{dQ_t}{dt} = F \times (C_a - C_v)
\]

(1)

where \( C_a \) and \( C_v \) are the concentrations of the tracer in the arterial and the venous blood, respectively. When there is a diffusion equilibrium between the concentration of the tracer in the tissue, \( C_t \), and \( C_v \), then

\[
C_t = C_v \times \lambda
\]

(2)

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where λ is the tissue/blood partition coefficient. Division of Equation 1 by V and insertion of Equation 2 gives

$$\frac{dC}{dt} = f \cdot C_a - K \cdot C_t$$  \hspace{1cm} (3)

where regional flow $f = F/V$ and clearance constant $K = f/λ$.

When CBF is measured by extracerebral recording of xenon-133 clearance, the clearance curve, $H$, usually consists of a sum of subcurves, $H_i$, with different $K_i$ due to different $f_i$ and/or different $λ_i$. The xenon-133 input is measured separately, usually by recording the concentration of the tracer in end-tidal air (Figure 1A and B) or in the lungs. The input function, $U$, recorded this way is usually considered to be closely proportional to the arterial input to the brain ($C_a = α \cdot U$, where $α$ is a proportionality constant). Insertion of this formula into Equation 3 gives

$$H' = \frac{dH}{dt} = α \cdot U \cdot \sum f_i \cdot w_i - \sum K_i \cdot H_i$$  \hspace{1cm} (4)

where $w_i$ is the relative weight of each tissue compartment. Equation 4 can be written alternatively as

$$H' = P \cdot U - K_m \cdot H$$  \hspace{1cm} (5)

where

$$P = \sum f_i = α \cdot \sum f_i \cdot w_i = α \cdot f$$  \hspace{1cm} (6)

and

$$K_m = \sum K_i \cdot H_i / H.$$  \hspace{1cm} (7)

$K_m$ is generally time-dependent due to time dependence of $H/H$. Equation 4 has the well-known solution

$$H = \sum_{i=1}^{n} \int_{t_i}^{t} U \cdot e^{-K_i (t - t_i)} dt$$  \hspace{1cm} (8)

where $n$ is the number of different tissue compartments.

When a time segment, $t_1 - t_2$, of the clearance curve (Figure 1C) is used to calculate CBF, then $H$ becomes $A = \int_{t_1}^{t_2} H \cdot dt$ (A is the area under the clearance curve), $H'$ becomes $I = \int_{t_1}^{t_2} dH$ (I is the increase of xenon-133 in the tissue), $P \cdot U$ becomes $D = \int_{t_1}^{t_2} U \cdot d\tau$ (D is the amount of xenon-133 delivered into the tissue), and $K_m$ becomes $K_{m_1} = \sum K_i \cdot A_i / A$ ($K_{m_1}$ is the average clearance constant for a given time segment and is generally time-dependent).

Since all the formulas above are valid for each time point within any selected time segment, they are also valid for the entire time segment. Thus, when CBF is determined from a time segment Equation 5 becomes

$$\int_{t_1}^{t_2} H' \cdot d\tau = P \cdot U \cdot d\tau - K_m \cdot \int_{t_1}^{t_2} H \cdot d\tau$$

or

$$I = D - K_{m_1} \cdot A.$$  \hspace{1cm} (9)

Equation 9 is an alternative formulation of the Fick principle; the increase in the quantity of xenon-133 in the tissue is equal to the amount delivered into the tissue minus the amount that is cleared from the tissue.
When Equation 9 is written as \( K_m = D/A - I/A = D/A - (H(t_2) - H(t_1))/A \) or

\[
K_m = D/A + H(t_1)/A - H(t_2)/A
\]  

(10)

it becomes obvious (see Figure 1C) that it is also a more general form of the height/area formula for the calculation of mean CBF.  \(^6\)

When CBF is calculated using bicompartamental analysis, the clearance curve is divided into a high-flow compartment (with clearance \( K_1 \) and area \( A_1 \)) and a low-flow compartment (with clearance \( K_2 \) and area \( A_2 \)) (Figure 1D). The relation between \( K_1 \), \( K_2 \), and \( K_m \) is given by Equation 7 as applied to a time segment as shown in Figure 1D.

\[
K_m \times A = K_1 \times A_1 + K_2 \times A_2.
\]  

(11)

For small variations in the parameters, differentiation of Equation 10 gives \( \Delta K_m = \Delta(D-I)/A + (D-I) \times \Delta(A/A) = \Delta D/A - \Delta I/A - \Delta A \times K_m/A \). Division by \( K_m \), insertion of Equation 9, and rearrangement gives

\[
\frac{\Delta K_m}{K_m} = \frac{\Delta D}{D(1 + \frac{1}{K_m \times A})} - \frac{\Delta I}{K_m \times A} - \frac{\Delta A}{A}.
\]  

(12)

Equation 12 describes the relation between \( \Delta K_m/K_m \) and the nonstatistical (bias) errors in the recording of 1) the xenon-133 input, \( D \); 2) the tracer increase, \( I \); and 3) the total amount, \( A \), of the tracer substance in the tissue during a given time segment; the three error terms are independent. For statistical (nonbias) independent error terms, Equation 12 becomes

\[
\frac{(\Delta K_m)^2}{K_m^2} = \frac{(\Delta D)^2}{(D)^2}(1 + \frac{1}{K_m \times A})^2 + \frac{(\Delta I)^2}{(K_m \times A)^2} + \frac{(\Delta A)^2}{(A)^2}.
\]  

(13)

Equations 12 and 13 are also valid for the subvolumes of the clearance curve, which are found by bicompartamental CBF analysis.

Thus, the statistical error in \( K_1 \) can be calculated by inserting the relevant parameters into Equation 13:

\[
\frac{(\Delta K_1)^2}{(K_1)^2} = \frac{(\Delta D)^2}{(D)^2}(1 + \frac{I_1}{K_1 \times A_1})^2 + \frac{(\Delta I_1)^2}{(K_1 \times A_1)^2} + \frac{(\Delta A_1)^2}{(A_1)^2}.
\]  

(14)

where \( I_1 \) is the xenon-133 increase in the high-flow compartment during the given time segment; \( \Delta I_1 \) is the error in the determination of \( I_1 \). When the high-flow compartment is considered to be the cerebral gray matter, \( \Delta K_1/K_1 \) can alternatively be written as \( \Delta f_p/f_p \), where \( f_p \) is the gray matter blood flow.

When the error margins of a \( f_p \) value from a CBF measurement with xenon-133 are calculated from Equation 14, the errors in the recording of the input and the clearance of xenon-133 must be considered separately.

**Error in Input Function**

When the input of xenon-133 is measured by recording its concentration in end-tidal air, a close proportionality between the concentration of the tracer in respiratory air and the arterial input to the brain is assumed \(^1\), \(^2\); the validity of this assumption is affected by factors such as the depth and regularity of respiration and a laminar and/or turbulent flow pattern of the blood that carries the tracer to the brain. Both irregular respiration and turbulent blood flow cause statistical errors in the input function, \( \Delta D/D \). The error due to irregular respiration can be estimated from a simultaneous end-tidal \( P_{CO_2} \) recording, but to measure the effect of turbulent blood flow, intra-arterial blood sampling is necessary. Since the error due to irregular respiration generally is considerably larger than the statistical radiation error in the recording of the input function, \( \Delta D/D \) can be assumed to be independent of time. Recording of the concentration of xenon-133 in the lungs by means of an external detector is less affected by respiratory irregularities, but it is influenced by the concentration of xenon-133 in the bronchial air and extrapulmonary tissue. \(^7\) The effect of these errors on individual CBF measurements cannot be determined entirely with noninvasive methods. Thus, the magnitude of \( \Delta D/D \) is generally unknown.

**Errors in Recording of Clearance Curve**

The errors in recording of the clearance curve due to statistical variations in the emission of gamma quanta from xenon-133 can be expected to have a Poisson distribution. Thus, the minimal standard error (SE) of a recorded clearance curve is \( \sqrt{c(t)} \), where \( c(t) \) is the number of recorded gamma quanta.

This fact is used to estimate \( \Delta A_1 \) and \( \Delta I_1 \). \( \Delta A_1 \) is the statistical error in the estimated area of the high-flow component. Since in bicompartamental flow analysis \( A_1 = A - A_2 \), it follows that the bias error is \( \Delta A_1 = \Delta A - \Delta A_2 \) and that the statistical error is \( \Delta A_1 = \sqrt{(\Delta A)^2 + (\Delta A_2)^2} \). If the estimation of the low-flow component is exact (separation error \( \Delta A_2 = 0 \)), then the statistical error in \( A_1 \) is

\[
(\Delta A_1)_{\text{min}} = \Delta A = \sqrt{A}.
\]  

(15)

Equation 15 gives the minimal possible statistical error in the estimation of \( A_1 \) that can be achieved with any method of biexponential analysis. In analogy with the minimal possible statistical error in the estimation of \( \Delta A_1 \), the minimal possible statistical error in the estimation of \( \Delta I_1 \) is \( \Delta I_1 \). The increase error can be estimated as the average error in determining the curve height during a given time interval: \( \Delta I_1 = \sqrt{\langle (\Delta H)^2 \rangle} / (t_2 - t_1) \). Thus, the minimal statistical increase error is

\[
(\Delta I_1)_{\text{min}} = \Delta A/(t_2 - t_1) = \sqrt{A/(t_2 - t_1)}.
\]  

(16)

To evaluate the dependence of the statistical \( f_p \) error on the different flow parameters, \( \Delta f_p/f_p \) was calculated from Equations 14, 15, and 16 and simulated parameter values. Also, \( \Delta D/D \) and the clear-
ance curve errors (ΔΑ, and ΔI) were calculated separately. The simulated parameter values were obtained from clearance curves that had a gray matter compartment comprising 11 high-flow components with a Gaussian distribution (standard deviation of 0.2, see Reference 5), a mean value of f_g, and a compartment weight of w_g. The low-flow component was given the values K_2=0.1 min^{-1} and w_2=1-w_g. The partition coefficients were λ_1=0.8 and λ_2=1.5. The clearance curves were generated according to Equation 8. To study the effect of a prolongation of the input of the tracer substance, the clearance curves were generated from both intravenous (Figure 1A) and 1-minute inhalation (Figure 1B) input functions taken from two consecutive xenon-133 CBF studies conducted at rest in a patient with no known respiratory disease. The start fit time (SFT) of the time segment of the clearance curves that was used to calculate CBF was varied between 0 and 3 minutes. The end fit time (EFT) was 11.0 minutes. AD/D (bolus error, BE) was varied between 0% and 15%, except when the effect of f_g and w_g on the flow error was studied; BE was then given a value of 10%. Except when their effect on the flow error was studied, f_g and w_g were given the values 75 ml/100 g/min and 0.5, respectively. The peak count rate of the clearance curves was kept at 300 cps, that is, 1500 counts for a 5-second interval.

All the error values I present are SE as percent of the value of the relevant parameter.

Results

Figure 2, A and B shows the relation between the f_g error and SFT. It is obvious that the f_g error is strongly influenced by the choice of the first time point on the clearance curve (SFT) that is included in the time segment used for calculating CBF. Except for the case of 0% error in the recording of the tracer input, the f_g error is high (equal to BE) at a SFT of 0 (whole-curve analysis), decreases to a minimum at SFT of approximately 2 minutes, and increases again for later SFT values.

Figure 2, C and D shows the relation between the f_g error and w_g. It is an expected finding that the f_g error increases at low values of w_g. It is, perhaps, less expected that this effect is strongly increased at high SFT values. Note the independence of the f_g error and changes in w_g when SFT=0, except for very low (<0.1) w_g values.

Figure 3 shows the relation between the f_g error and f_g values. The f_g error (Figure 3, A and B), as expected, increases for low f_g values, approaching the CBF of the white matter. This is mainly due to increasing sensitivity to errors in the tracer input (Figure 3, C and D), but also to errors in the clearance curve (Figure 3, E and F). There is a f_g error minimum at a f_g value of approximately 15–30 ml/100 g/min, except when SFT=0. The f_g error level for SFT=0 appears to be independent of f_g for values above approximately 30 ml/100 g/min. For SFT values of 1–3 minutes, there is an increasing sensitivity to errors in the tracer input (Figure 3, C and D) with higher f_g values (above approximately
20 ml/100 g/min). A similar $f_g$ error increase with higher $f_g$ values is seen in the sensitivity to errors in the tracer clearance (Figure 3, E and F).

The duration of the tracer input appears to have little effect on the $f_g$ error. The main difference between the intravenous input function in Figure 1A and the 1-minute inhalation input function in Figure 1B is the longer duration of the tracer input in the latter. The effect of prolonged input duration appears mainly to be a higher $f_g$ error for SFT values later than approximately 2 minutes (Figure 2, A and B), especially for $f_g$ values of greater than approximately 100 ml/100 g/min (Figure 3, A and B). There is no noticeable effect of the longer input duration on the relation between the $f_g$ error and $w_g$ (Figure 2, C and D).

**Discussion**

The object of my study is to evolve a comprehensive theory for those methods of CBF measurement that are based on the Fick principle and the use of freely diffusible tracer substances; this theoretical basis is then used for an error analysis. The error margins of the measured CBF values are shown to be the combined effect of the errors in the measurements of the tracer kinetics and of the limitations of the Fick principle. I do not account for recording errors due to radiation from the airways or to temporal misalignment between the input and clearance curves.

The kind of information that is available from the error analysis is exemplified by a calculation of
The error values do not include errors in the bicompartmental separation but illustrate the minimal error that can be achieved with any method for CBF analysis under the given conditions. The separation error is not included in the error calculus since it depends on the specific method used for separating the two flow compartments.8-10 I show that the separation error affects only the clearance and not the input part of the f_g error; the separation error is independent of the other clearance errors. The main factors that influence the bicompartmental separation error are the difference between the high- and low-flow components, the EFT, and the curve height for the low-flow component.5 Thus, the separation error can be expected to influence the f_g error mainly at low f_g levels and when both the input and the clearance errors are low (at a SFT of approximately 1–3 minutes).

The clinical value of the error calculus is illustrated by its ability to separate different sources of measurement error. As a consequence of this possibility of studying the error factors separately, it is possible to optimize the method for calculating CBF from the clearance curve, depending on the type of CBF measurement. Thus, for CBF measurements in which a correct global f_g value and a low error margin are of primary importance, the optimal SFT of the clearance curve segment, which is used for CBF calculation, appears to be approximately 2 minutes (Figure 2, A and B), provided there is a low bicompartmental separation error. An earlier SFT increases the error due to increasing influence from incorrect assessment of the tracer input, and a later SFT increases the error due to decreasing amount of tracer in the gray matter. When, on the other hand, the regional distribution of f_g is more important, a SFT of 0 minutes (whole-curve analysis) appears to be optimal. The influence on the f_g error of D/D is then independent of f_g or w_g, except for extremely low f_g values (Figure 2, C and D and Figure 3, C–F).

The influence from statistical errors in the clearance curve on the f_g error is minimal for a SFT of 0 minutes (Figure 3, E and F), which is in agreement with the reports on whole-curve analysis methods for CBF calculation.3,4 My results, however, indicate that for errors in the tracer input of more than approximately 5%, the f_g error is higher for a SFT of 0 minutes (whole-curve analysis) than for a SFT of 1–2 minutes (Figure 2, A and B), at least when the bicompartmental separation error is low.

The f_g error appears to be insensitive to the duration of tracer input for a SFT of up to approximately 2 minutes. For SFT values of >2 minutes, a longer tracer input duration increases the f_g error. This finding is in principal agreement with the similar sensitivity for high-flow components in intravenous and inhalation CBF measurements found in earlier studies.1,11 Thus, it may be argued that although the two methods appear to be of equal value in the study of low CBF values, the intravenous method may be preferable in studies of psychophysiological activation in normal subjects when high f_g values and a prolongation of the tracer input duration (i.e., due to verbal activity) are expected.

In conclusion, the method presented here for calculating the CBF measurement errors enables an objective evaluation of how they are caused. Thus, it may become a valuable tool for creating regional CBF measurements with an optimal selection of the xenon-133 administration technique (intravenous or inhalation), recording time, and analysis parameter settings (SFT), depending on the conditions and aims of the study.

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