Some Experimental Errors in Calculating Regional Cerebral Blood Flow From the Intracarotid $^{133}\text{Xe}$ Clearance Curve

A QUANTITATIVE EVALUATION EMPLOYING A DIGITAL MODEL

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Abstract:
A digital model study has been developed for quantitative assessment of experimental errors in the analysis of $^{133}\text{Xe}$ clearance curve from the brain. A small computer synthesized a model of the clearance curve, varying combinations of fast and slow components. The curves were convoluted with Poisson random digits to simulate statistical fluctuations. Identical curves were overlapped with varying intervals to study the influence of remaining activity.

The height over area method to ten minutes was confirmed to overestimate CBF by 10% to 15% with a slow component of 20 ml/100 gm per minute, and the overestimation was increased with a lower slow flow component. The initial slope value was shown to have a close relationship with the fast flow component when the latter was less than 100 ml/100 gm per minute. Errors due to statistical fluctuations were determined only by the initial height ($H_0$ cps), as the percent standard deviation was $\Delta H_0/H_0$ in the height over area method and $2\Delta H_0/H_0\log H_0$ in the initial slope method, where $\Delta H_0 = \sqrt{H_0}$. Remaining activity caused errors of 1% to 3% in the initial slope method with an injection interval of 15 minutes. The influence of remaining activity can be eliminated with an injection interval of more than 25 to 30 minutes in the initial slope method and more than 40 minutes in the height over area method.

Additional Key Words
- computer simulation
- initial slope method
- remaining activity
- statistical fluctuation
- background correction

Introduction
This communication discusses some experimental errors in the analysis of $^{133}\text{Xe}$ clearance curve from the brain: discrepancies among the various methods for curve analysis, errors due to statistical fluctuations on the curves, and errors caused by remaining activity from previous measurements. In clinical studies, an evaluation of these errors is becoming increasingly important with the widespread use of a gamma camera or a multidetector device. A digital model study has been developed for the quantitative assessment of these problems.

Methods

COMPUTER
A small computer was used (JEC-7, JEOL, Japan) with a core memory of 8 k 20-bit words, memory cycle time of 1 $\mu$s, a 32 k word magnetic drum and a magnetic tape. All computed results were printed out by an IBM typewriter. Programs were written using FORTRAN IV except for a Poisson random digit generating subroutine, which was made using the assembler.

THE CONSTRUCTION OF A CLEARANCE CURVE MODEL
A measured $^{133}\text{Xe}$ clearance curve from the brain is built up of many monoexponential decay curves. However, the curves tend to merge into two main components, fast and slow, which are thought to largely represent the gray and the white matter respectively. To simplify the computerized construction of simulated curves, we have made two assumptions. First, that the brain consists of only two uniformly perfused components, fast and slow, and second, that the indicator diffuses into the brain instantaneously.

The computer was fed with arbitrary values for the flow in fast and slow flow components, and a $^{133}\text{Xe}$ clearance curve model was constructed as defined by the biexponential equation:

$$C(t) = H \cdot \frac{W_g \cdot f_g}{F_r} \cdot \exp\left(-\frac{f_g}{\lambda_g} t\right) + \frac{(1-W_g) \cdot f_w}{F_r} \cdot \exp\left(-\frac{f_w}{\lambda_w} t\right)$$

where $H$ is the height at zero time, $\lambda_g$ and $\lambda_w$ are the partition coefficients of $^{133}\text{Xe}$ between tissue and blood (0.8 and 1.5, respectively), $f_g$ and $f_w$ are the fast and slow flow components, and $W_g$ is the relative weight of the fast component. $F_r$ is a mean flow of the fast and the slow, given by the bicompartamental analysis method:

$$F_r = W_g \cdot f_g + (1-W_g) \cdot f_w$$

The $F_r$ is used as the reference standard in the following analysis. Figure 1 shows a diagram of the curve model.
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the present study, C(t) is used in the discontinuous form giving a value every second for 15 minutes:

\[ [C(i)] (i = 0, 1, 2, \ldots, 900) \]  

(3)

THE CALCULATION OF THE FLOW VALUES

From the synthesized clearance curve a flow value was obtained by the height over area method and the initial slope method.

Height Over Area Method

Employing Zierler's equation, cerebral blood flow (CBF) can be calculated from the \(^{133}\)Xe clearance curve:

\[ F_h = 100 \cdot \frac{H_0}{A_0} \text{ ml/100 gm per minute} \]  

(4)

where \(H_0\) is a height of the clearance curve at zero time, \(A_0\) is an area from zero time to infinity, and \(\lambda\) is the mean partition coefficient of \(\lambda_g\) and \(\lambda_w\). In practical use, the calculation of formula (4) is impossible without approximation because the area \(A_0\) needs an infinite measurement. Generally the measurement is limited to 10 to 15 minutes, and the following formula is used:

\[ F_h = 100 \cdot \frac{H_{10}}{A_{10}} \text{ ml/100 gm per minute} \]  

(5)

where \(H_{10}\) is the height at ten minutes after the clearance and \(A_{10}\) is the area from zero time to ten minutes. Formula (5) is used in the present study.

Initial Slope Method

The initial slope value is an index of CBF rather than a true flow value. It is widely used in human CBF investigation because of the short period of measurement. The following formula is commonly used:

\[ F_i = 100 \cdot \frac{\lambda_g \cdot (-D)}{A} \text{ ml/100 gm per minute} \]  

(6)

where \(\lambda_g\) is the partition coefficient of the gray matter and \(D\) is the slope of the first two minutes of the logarithmically displayed clearance curve. In the present study, \(\lambda_g\) was the conventional value of 0.87, and \(D\) was obtained by eliminating the fluctuations using the least-squares method.

ESTIMATION OF DIFFERENCES AMONG THE METHODS FOR CURVE ANALYSIS

The relationship between the reference standard (\(F_r\)) and the height over area flow (\(F_h\)) or between \(F_r\) and the initial slope value (\(F_i\)) was examined with various combinations of the fast and slow components of the curve model. The fast component (\(f_g\)) was varied from 20 to 180 ml/100 gm per minute with an interval of 10 ml/100 gm per minute, and the slow component (\(f_w\)) from 10 to 40 ml/100 gm per minute with an interval of 5 ml/100 gm per minute. The relative weight (\(W_g\)) was fixed at 0.5. Percent difference was defined as follows:

\[ \delta_h = \frac{F_h - F_r}{F_r} \times 100\% \]  

(7a)

\[ \delta_i = \frac{F_i - F_r}{F_r} \times 100\% \]  

(7b)

EVALUATION OF ERRORS DUE TO STATISTICAL FLUCTUATIONS

To simulate statistical fluctuations, the curve model was convoluted by Poisson random digits. This means that each point of formula (3) was taken as the mean of a Poisson distribution of random numbers. With this procedure it is easy to arbitrarily change the relative size of fluctuations by varying \(H\) in formula (1), as shown in figure 2.

The influence of the statistical fluctuations was evaluated for various values of the initial height (\(H\)) of this model. For each value of \(H\), the computer created 1,500 curve models changing the scatter of the Poisson random digits. The standard deviations of \(F_h\) and \(F_i\) of these 1,500 curve models were calculated at each of the values of the initial height (\(H\)) from 50 to 10,000 counts per second (cps).

EFFECT OF REMAINING ACTIVITY

The \(^{133}\)Xe clearance curve will be influenced by the remaining activity from previous measurements. This is a problem frequently encountered in clinical studies. To evaluate the magnitude of the problem, we made a compound model by overlapping two identical curves, as shown in figure 3. The compound model is described by the formula:

\[ C(t) = C_1 (t + T) + C_2 (t) \]  

(8)

where \(C_1\) and \(C_2\) are the identical clearance curves, \(t\) is time and \(T\) the injection time interval. The \(F_i\) and \(F_h\) were calculated from the model of formula (8) and compared to flow values from the single model not influenced by the remaining activity. The background just before each injection was used as background during the clearance measurement.

Results

Figures 4 and 5 show the differences between the methods in relation to the fast and the slow flow components. The height over area flow (\(F_h\)) was systematically higher than the reference standard (\(F_r\)). In the range more than 30 ml/100 gm per minute of \(F_h\), the \(\delta_h\) showed a constant but slightly increasing value for the same slow component (\(f_w\)). When the \(f_w\) is 20 ml/100 gm per minute, which is the normal in man, the height over area method underestimated flow by 10% to 15%. In the initial slope method, no constant relationship between the \(\delta_i\) and the \(F_i\) was revealed. When \(f_w\) decreased, the overestimation of...
the flow value became more extensive than in the height over area method. For the values of \( f_g \) up to 100 ml/100 gm per minute, the \( \delta_i \) increased with increasing \( F_i \); and in this range, \( F_i \) was determined almost exclusively by the fast component (\( f_g \)).

The errors due to statistical fluctuations are shown in figure 6. The curves represent percent standard deviations of \( F_h \) and \( F_i \) obtained as the initial height was varied. The curves were derived for values of \( f_g = 80 \) and \( f_w = 20 \) ml/100 gm per minute, giving a reference standard flow of 50 ml/100 gm per minute. Identical results were obtained when \( f_g \) and \( f_w \) were varied, so that the absolute flow values had no influence on statistical errors. In the height over area method the standard deviation was 3% at 1,000 cps of the initial height and 10% at 100 cps, and below this range it increased in an accelerated fashion. In the initial slope method the error was reduced to one-third or one-fourth of the height over area method.

The influence of remaining activity is shown in figure 7 for three representative reference standards, 30 ml/100 gm per minute (\( f_g = 45 \), \( f_w = 15 \)), 50 ml/100 gm per minute (\( f_g = 80 \), \( f_w = 20 \)), and 70 ml/100 gm per minute (\( f_g = 110 \), \( f_w = 30 \)), with variable injection interval (\( r \)). Both the initial slope value and the height over area flow were increased by the preceding clearance and clearance of remaining activity.
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50
100
flow by height over area method (Fh)

FIGURE 4

Difference between the height over area flow (Fh) and the reference standard (Fr). With models in various combinations of fg and fw, Fh was calculated by formula (5), and Fr was given by formula (2). Percent difference of 100 • (Fh—Fr)/Fr is shown on the ordinate, Fh on the abscissa, with curve parameters fg and fw.

remaining activity. The increments were reduced when the interval was prolonged and when the model flow was increased. With a 15-minute injection interval, remaining activity caused an overestimation of flow which was 1% to 3% with the initial slope method and 3% to 10% with the height over area method. The injection interval with which the influence of remaining activity can be neglected (less than 1%) is more than 25 to 30 minutes for the initial slope method and more than 40 minutes for the height over area method.

Discussion

THE 133Xe CLEARANCE CURVE MODEL

Modeling techniques have been used by previous investigators in nuclear medicine. The main advantage of this method is that the data studied are entirely well defined, so that the analysis can concentrate solely on methodology. An obvious risk is that the synthetic data may represent an oversimplification of nature.

When CBF is measured by the 133Xe intracarotid injection method in normal man, the clearance curve is found to be bicompartamental. This allowed for the construction of clearance curves for two components in the present study. It should be mentioned, though, that Reivich et al. in an autoradiographical study in cats found many different flow values in the brain with a bimodal distribution around the well-known fast and slow components. Furthermore, in human brain disease, the 133Xe clearance curve seems to be monoexponential or on the contrary consists of more than two components.

In the present study, some assumptions were made to simplify the calculations. The clearance curve was assumed to be bicompartamental. The partition coefficients used in the present study were those found by Veall and Mallett assuming a hemoglobin value of 15 gm/100 ml. The relative weight of the gray matter of 0.5 simplified the calculations. However, these values are not essential to the modeling.

DISCREPANCY AMONG THE METHODS

The discrepancies among the three established
methods for $^{133}$Xe clearance curve analysis have been dealt with by several investigators based on practical experiments. The present study has confirmed these earlier observations, and offered a more precise quantification in relation to effects of fast and slow flow components.

The overestimation of the ten-minute height over area method has been accurately calculated by Lassen and Ingvar and others as 10% to 15% in normal man. However, as shown in figure 4, we found this overestimation to become slightly decreased as the fast flow component was decreased below 50 ml/100 gm per minute. The overestimation was also observed to be more marked when the slow flow component declined. In the initial slope method, as theoretically expected, a close relationship was recognized between the fi and the fg. As shown in figure 5, the lines of the parameter fg under 100 ml/100 gm per minute are nearly perpendicular to the abscissa. This means that the initial slope value is determined only by the fast flow component. In the same range of fg, the methodological error $\delta$ is monotonically increasing, so that a change of the fast flow component caused a greater change of the initial slope value. These findings confirm that the initial slope method is suitable to evaluate the change of the fast component.

**Statistical Fluctuations**

The problem of statistical fluctuations is inevitable when measuring radioactivity. As seen in figure 6, statistical fluctuations influence the height over area method more than the initial slope method. This is readily understood, as in the height over area method the fluctuations directly influence the initial height in formula (5). In the initial slope method the fluctuations are eliminated by the use of the least-squares method.

Statistical fluctuations follow the Poisson distribution and thus the standard deviation ($\Delta N$) of a measured amount of radioactivity (N) is given by the formula:

$$\Delta N = \sqrt{N}$$

(9)

Based on this relation we have tried to evaluate quantitatively the errors caused by the statistical fluctuations. In the following formula, $\Delta$ represents the statistical difference of each variable.

To estimate the influence of statistical fluctuations on the height over area flow, formula (5) was differentiated:

$$\Delta Fh = 100 \cdot \frac{A_i}{A_{10}} \cdot \frac{\Delta (H_0 - H_{10})}{(H_0 - H_{10})} \cdot \frac{\Delta A_{10}}{A_{10}}$$

(10)

From formulas (5) and (10),

$$\frac{\Delta Fh}{Fh} = \frac{\Delta (H_0 - H_{10})}{H_0 - H_{10}} \cdot \frac{\Delta A_{10}}{A_{10}}$$

(11)

was obtained. Considering,

$$H_0 >> H_{10}, \frac{\Delta H_0}{H_0} >> \frac{\Delta A_{10}}{A_{10}}$$

(12)

The relation $\frac{\Delta H_0}{H_0} >> \frac{\Delta A_{10}}{A_{10}}$ is introduced as follows: It is obvious by equation (9) that the relative deviation $\frac{\Delta N}{N}$ is decreased as radioactivity N is increased. Practically measured $A_{10}$ shows $10^2$-$10^3$ times amount as $H_0$. Consequently, the relative contribution of $A_{10}$ to $\frac{\Delta Fh}{Fh}$ is considerably smaller than the contribution of $H_0$.

Formula (11) can approximately be written:

$$\frac{\Delta Fh}{Fh} \approx \frac{\Delta H_0}{H_0}$$

(13)

Formula (13) means that the statistical error of $Fh$ is independent of flow and only dependent on the initial height $H_0$, and its relative size is proportional to that of $H_0$. Formula (13) agrees well with figure 6.
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With the initial slope method it was difficult to develop a theoretical expression of statistical errors, but we were able to derive an empirical formula from the data. The simulation result showed that the statistical error was independent of the flow value and that its ratio to that of the height over area flow was approximately \(2/\log H_0\). Consequently, the empirical formula was obtained as:

\[
\frac{\Delta F_i}{F_i} \approx \frac{2}{\log H_0} \frac{\Delta H_o}{H_o}, \quad (14)
\]

According to the above description the statistical errors of the flow values are determined only by the magnitude of the initial height of the clearance curve. These results are particularly relevant to CBF studies in man employing a gamma camera or a multidetector device. In this situation it may become difficult to obtain enough count rates for each clearance curve. According to formulas (13) and (14) the statistical errors will then become a problem that must be dealt with.

REMAINING ACTIVITY

The effect of remaining activity on the result of a CBF measurement is dependent on the way the background is handled in the calculation. Remaining activity from the previous measurement will cause a slightly decreasing background during subsequent \(^{133}\text{Xe}\) clearance measurements. For practical reasons, the background can be assumed to be constant and equal to the value just before the \(^{133}\text{Xe}\) injection. This caused an overestimation of flow. In the present study we found this overestimation to be higher with lower flow and shorter injection interval. The minimal injection time interval with which the influence of the remaining activity can be neglected (less than 1%) is 25 minutes for a flow of 70 ml/100 gm per minute and 40 minutes for 30 ml/100 gm per minute with the height over area method. With the initial slope method it is somewhat shorter, 25 minutes and 30 minutes, respectively.

As for correction of remaining activity, extrapolation from the tail part of the previous clearance curve is undoubtedly the best method. In practical use, however, we encountered several problems with this method. It needs prolonged recording before each \(^{133}\text{Xe}\) injection, which requires too much memory for on-line computer analysis. And the curve sometimes includes artifacts caused by a head or a body movement which easily spoils the extrapolation. A diagram similar to figure 7 may be used for correction, since the injection time interval and the flow value of the previous measurement are known.

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