Cerebral Blood Flow Studies in Man Using Recirculation Corrected Height/Area (H/A) Computations for Intravenous Injection of 133Xenon

RICHARD NAMON, O. M. REINMUTH, M.D.,* and ROSS SCHWELM

SUMMARY Our height/area (recirculation-corrected) non-invasive cerebral blood flow method compares well with $k_v$ values and $k_{average}$ as determined from $k_1$, $k_p$, and $p_0$ by Obrist computations. The height/area method provides regional flow measurements with less variability than $k_v$ due to low regional head counts, head motion and end-tidal gas sample variations.

Derivation of the mathematical model is for a single flow compartment and suited for tomographic measurements such as PET. Collimated detector data using our computation provides a good approximation of flow even for multiple compartments. Our approach permits a lower counting rate by either a smaller isotope dose or better detector collimation than multicompartment curve fitting methods.

ETHICAL AND PRACTICAL considerations prevent widespread clinical use of the intracarotid regional cerebral blood flow method (rCBF). It requires either puncture or cannulation of the internal carotid artery; in practice its use is limited to situations where it can be combined with indicated arteriographic procedures.

Computations of intracarotid rCBF have been made using three methods:

a) Multicompartment curve fitting (curve stripping).

b) Height-over-area.

c) Initial slope.

These three methods yield essentially the same type of information either when compared altogether or separately. From the published data it appears that $F_0$ (flow in gray matter), $F_{H/A}$ (height/area or stochastic flow), and $F_t$ (flow by initial slope) computations are not independent. That is, high “fast” flows and sharp initial slopes are accompanied by fast “mean” flows. Where probe detector collimation allows several fast compartments to be sensed simultaneously, the term “fast” flow is not specific or singular.

Because the inhalation and intravenous injection methods were strongly influenced by the intracarotid method, Veal and Mallet and subsequently Obrist et al., derive “fast flow” information from the head curves by multicompartmental analysis. Various attempted improvements have been inevitable since compartmental analysis requires the most perfect of data to work well. Risberg et al adopted the initial slope method in place of the Obrist $k_v$ as a measure of flow index. There the curve is reconstructed from Obrist values without arterial recirculation and the slope between the second the third minute is used as a flow index.

Height-over-area computations are inherently simple and are less sensitive to “noise”. We have applied this approach to non-invasive rCBF mindful that Zierler showed a non-bolus arterial input of isotope requires additional computation to determine a meaningful H/A.

Methods

To study regional cerebral blood flow we built our own data acquisition system. The system consists of sub-systems as follows:

1) A lead helmet is mounted on a hydraulic stand with adjustable height. There are 32 holes available for placement of the 16 NaI detectors (¼ in × ½ in). One detector is dedicated to end-tidal gas sampling. Each hole provides axial adjustment and the helmet can be turned to accommodate fixed head rotation. The 70° collimated probes are set approximately ½ cm from the scalp.

2) Data from all probes are counted and transferred at one second intervals by a data storage and transfer system. A 5 kev lower-discriminator level was commonly employed.

3) A digital tape recorder was used for permanent raw data recording with analysis on a UNIVAC 1100 Computer.

4) An end-tidal gas sampling system for 133Xe concentration and CO₂ measurements was designed for optimal end-tidal timing.

The subject breathes through a face mask with a unidirectional flow valve assembly that holds the head in place. There is a metal tube to withdraw gas samples by the mask (fig. 1). A thermistor (less than 0.1 second time constant) monitors exhalation gas temperature. On observing maximal end-tidal temperature an operator triggers a vacuum-actuated withdrawal of 10cc in 0.1 second through the radio-isotope counting chamber and CO₂ analyzer head (Beckman LB-1 Gas Analyzer). In this way continuous end-tidal CO₂ is displayed and 133Xe concentration is recorded by the blood flow data system. Expired radioactive gas is trapped in a Xenon Gas Trap.
A Bicor Model 680 hair blower pumps room air through the helmet from the vertex to minimize the effect of facemask leaks.

In addition to modifying the Obrist 2-compartment computer program to accept our tape data input, we added two features for Obrist computations:

1) A visual presentation of the entire observed and fitted curves.

2) A number approximating the expected standard deviation for a curve fit due to the statistical nature of detected isotope radiation which is:

\[
\text{Total Counts for Fitted Curve Portion or TC} \quad \text{Number of Data Points or DP}
\]

for comparison with the measure of the curve

\[
\text{Sum of Square Differences or SSQ.}
\]

The visual presentation allows inspection of the head curve for motion artifacts and indicates how well the fitted curve follows the head curve prior to the beginning of the curve fit. The SSQ is compared to the expected statistical variation, TC/DP. The curve fit is considered unreliable if SSQ is more than 2.5 times higher than TC/DP. While this may not be a sufficiently stringent curve fitting criterion by itself, it relates SSQ to a fitting parameter for various count rates.

Originally, we used inhalation for \(^{183}\text{Xe}\) administration. However we found that reasonable arterial concentrations of \(\text{Xe}\) can be reached by I.V. infusion in saline (fig. 2). A rapid intravenous bolus results in a head curve more similar to that produced by carotid injection. As suggested by Austin,\(^{12}\) the \(^{183}\text{Xe}\) injection is made into a vein distal to a tourniquet which is then rapidly released. The usual injection is 6 to 9 mc in 4 ml saline.

Subject groups were: 1) normals (mean age 31 years), and 2) stroke patients (mean age 60 years) at least 30 days post-ictus. All subjects gave their informed consent for these studies. Normals had no history of cerebral vascular disease or symptoms. Stroke patients were selected from the Neurology Service of Jackson Memorial Hospital and the Miami V.A. Hospital. All had some degree of dementia but were not aphasic.

Hyperventilation, when performed, was started 2.5 minutes prior to isotope injection. End-tidal \(\text{CO}_2\) was followed and instructions given to the subject concerning respiratory rate: this held the \(\text{CO}_2\) range within \(\pm\) 0.1% during the CBF determination. With 5% \(\text{CO}_2\), inhalation was started 3.5 minutes prior to injection of

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**Figure 1.** End tidal respiration sampling system.

**Figure 2.** End-tidal \(^{133}\text{Xenon concentration resulting from equal isotope doses via inhalation and intravenous injection routes versus time.}**
the isotope and the CO₂ analyzer was used as a monitor.

We used a Height/Area (H/A) computation that takes into account the arterial curve (using end-tidal samples) which is as follows:

\[
k = \frac{\text{Area Total Head Curve}}{\text{Area Total Arterial Curve}} \times \left( \frac{\text{Air Curve Area}}{\text{Area Head Curve From Zero to Analysis Point}} \right)
\]

where k is (mean flow)/(mean partition coefficient) [see Appendix I for the derivation].

Areas were determined by summation of detector counts over the appropriate time intervals. The peak was determined by fitting 18 six-second time interval points with the Obrist two compartment program. This large number of data points provides a reliable value of the peak not obtainable by simply lumping together several data points. We chose the total head curve area to be from 133Xe injection time (zero) to 10.5 minutes after that. Using the slope of the curve from 9.5 to 10.5 minutes, we estimated the total head curve area to determine mean flow and the ratio of:

\[
\frac{\text{Area Total Head Curve}}{\text{Area Total Arterial Curve}}
\]

All data were analyzed using the Obrist and our H/A computations. To test basic concepts a mean flow was calculated from the Obrist constants k₁ and k₂ (fast and slow flow components) and p₁ and p₂ (parameters used to obtain best fit of calculated curve to observed curve for a given k₁ and k₂ combination) as follows:

\[
k_{\text{ave}} = \frac{k_{1}k_{2}(p_{1} + p_{2})}{k_{2}p_{1} + k_{1}p_{2}}.
\]

In addition to individual detector analysis, all counts from the 15 probes were pooled together to give a total head curve. This provided a curve representing essentially an average head curve with high count rates; it was less affected by head motion than individual probes since a head motion away from one detector generally was compensated by head motion towards another.

**Results**

Data of the average total head curve (sum of counts all head detectors) were analyzed for 19 subjects (15 normals and 12 CVD patients).

Normals age ranged from 18 to 49 years (Mean = 31 yrs) with 8 males (Mean = 34 yrs) and 7 females (Mean = 26 yrs). Normals were broken into two groups of ages 18-24 yr and 27-49 yr (table I).

Plotting individual data as k₁ vs Age and H/Α₁₀.₅ vs Age showed a best fit of data by the equations:

\[
k_{1} = .73 + \frac{5.52}{\text{Age}}, \quad \text{and} \quad \frac{H}{\text{Α}}_{10.5} = .29 + \frac{3.67}{\text{Age}}.
\]

For these two plots the statistical significance was not great, \( r = 0.31 \) and 0.61 respectively, where

\[
y_{1} \text{ is the ith data point, } \bar{Y} \text{ is the mean of all } Y \text{'s and } \bar{Y} \text{ represents the } Y \text{ value predicted from } X, \text{ and } n \text{ is the number of data points. The theoretical minimum values for great age are 0.73 for } k_{1} \text{ and 0.29 for } H/\text{Α}_{10.5}. \text{ Both data confirm that cerebral blood flow decreases with age.}
\]

The relation between \( k_{1} \) and mean flow using only Obrist calculation parameters for normal and CVD subjects is given in figure 3. The data show that \( k_{1} \) and \( k_{\text{ave}} \) are related in normal and CVD subjects (\( r = .82 \)). The residual variance is 0.016. The slope of the line is 0.34 or \( k_{\text{ave}} = 0.34k_{1} \). For the majority of measurements \( k_{1} \) is 2.95 \( k_{\text{ave}} \), and generally \( k_{1} \) reflects the mean flow with higher mean flows having higher \( k_{1} \) values.

To compare computations for \( k_{\text{ave}} \) (from Obrist \( k_{1}, k_{2}, p_{1}, p_{2} \) and the recirculation corrected \( H/\text{Α} \) (H/A with tail of head curve added on)), data were plotted for all subjects (fig. 4). The straight line relation (\( r = .96 \), residual variance of 0.0048) demonstrates a close correlation exists between the absolute values for mean flow by both methods; \( H/\text{Α} \) is 0.84 \( k_{\text{ave}} \). Data covers a flow range of over 3.5 to 1 and a large range of 133Xe arterial curves from 27 subjects.

A comparison of the ratio \( \int_{0}^{\infty} \text{Head Counts dt} / \int_{0}^{\infty} \text{Arterial Curve dt} \) for \( H/\text{Α} \) with that determined by Obrist computations \( \int_{0}^{\infty} \text{Head dt} / \int_{0}^{\infty} \text{Air dt} = \frac{p_{1}}{k_{1}} + \frac{p_{2}}{k_{2}} \), gave:

\[
\int_{0}^{\infty} \text{Head dt} / \int_{0}^{\infty} \text{Air dt} = 1.05 \left( \frac{p_{1}}{k_{1}} + \frac{p_{2}}{k_{2}} \right).
\]

The relation was linear (\( r = .98 \) with a residual error of 0.56 for the normal subjects (fig. 5). The integral ratio being higher than \( p/k \) could result from overestimation of head curve area due to scattered radiation from the air passages and/or error in the curve tail area computation.

Subject data for \( k_{1} \) and recirculation corrected \( H/\text{Α}_{10.5} \) were compared in three ways: \( k_{1} \) vs \( H/\text{Α}_{10.5} \) in Normals, \( k_{1} \) vs \( H/\text{Α}_{10.5} \) in CVD patients, and \( k_{1} \) vs \( H/\text{Α}_{10.5} \) in Normals and CVD patients (where the mean ratio of \( H/\text{Α}_{10.5} \) was 0.45, 0.41, and 0.45 respectively). Using the linear equation \( Y = A + BX \), correlation coefficients were 0.83, 0.78, and 0.83 with residual variances of 0.0014, 0.0013, and 0.0021 respectively. The data for all subjects are shown in figure 6.

Recirculation corrected \( H/\text{Α}_{10.5} \) was compared to mean flows in normal subjects. There is a striking linear relation between \( k_{\text{ave}} \) (by Obrist values of \( k_{1}, k_{2}, p_{1}, p_{2} \) and \( H/\text{Α} \)) and the recirculation corrected \( H/\text{Α} \). (\( r = 0.94 \) with residual error of 0.00025). This relation is seen in the comparison of \( H/\text{Α}_{10.5} \) with \( H/\text{Α} \) for the same group yielding \( r = \ldots \)
The effect of respiratory rate on the end-tidal air curve is seen in figures 7a and 8a. A young, somewhat apprehensive normal female subject was studied with normal ventilation, hyperventilation and 5% CO₂ inhalation. The duration of arterial recirculation is considerably shorter for hyperventilation (0.7 minute for the control and approximately 0.4 minute for hyperventilation). Head curves (fig. 7b and 8b) are related to the shape of the end-tidal respiration curve. The head curve during hyperventilation (fig. 8b) rises to a peak more quickly and falls more quickly than for the control. Without considering the end-tidal ¹³³Xe concentration curve, one would conclude higher flow existed during hyperventilation: both Obrist and H/A₁₀.₆ computations show decreased flow (see table 2). The 5% CO₂ inhalation data demonstrate that k₁ and H/A₁₀.₆ show increased flow. Percent changes are given in table 2.

Mean flow parameters (k₁ and H/A₁₀.₆) for homologous regional detectors are given in table 3 for the fifteen normal subjects. In addition, paired data for the homologous detectors were analyzed to determine left/right ratios. Figure 9 indicates probe locations. Higher flows are seen on the left side from frontal through mid-central regions. The error ratios or detector pairs F and G indicate no statistically significant differences between left and right for the Obrist k₁ computations even though the mean ratios indicate a higher flow on the right side. The deviation ratio of k₁ L/R is essentially the same from frontal to occipital; for the H/A₁₀.₆ computations it is greatest in frontal to midtemporal and significantly less in the occipital regions. Generally occipital probes detect less isotope and, therefore, have lower count rates; this may account for k₁ variability in that region.

To establish the effect of count rate on the computations, normal subjects with lower head count rates were compared with those having approximately 2.5 times higher count rates. The higher count rate group would be expected to have 37% less statistical "noise." Left versus right side k₁ values by the Obrist computation were compared for lower counts and higher counts (fig. 10a and b). A much stronger relationship between right and left side k₁ values is seen with higher detector count rates (r of 0.78 for higher versus 0.39

### Table 1  The Effect of Age on CBF Values in Normals

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Age range</th>
<th>Mean age</th>
<th>k₁ ± s.e.</th>
<th>H/A₁₀.₆ ± s.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>18-24 yrs.</td>
<td>22.4 yrs.</td>
<td>0.99 ± 0.07</td>
<td>0.46 ± 0.02</td>
</tr>
<tr>
<td>8</td>
<td>27-49 yrs.</td>
<td>37.9 yrs.</td>
<td>0.87 ± 0.03</td>
<td>0.38 ± 0.02</td>
</tr>
</tbody>
</table>

0.95 with a residual variance of 0.00047. Such dual relationships are anticipated since H/A∞ is related to kₐ𝑣ₑ (fig. 4).

The mean flow parameters (k₁ and H/A₁₀.₆) for homologous regional detectors were given in table 3 for the fifteen normal subjects. In addition, paired data for the homologous detectors were analyzed to determine left/right ratios. Figure 9 indicates probe locations. Higher flows are seen on the left side from frontal through mid-central regions. The error ratios or detector pairs F and G indicate no statistically significant differences between left and right for the Obrist k₁ computations even though the mean ratios indicate a higher flow on the right side. The deviation ratio of k₁ L/R is essentially the same from frontal to occipital; for the H/A₁₀.₆ computations it is greatest in frontal to midtemporal and significantly less in the occipital regions. Generally occipital probes detect less isotope and, therefore, have lower count rates; this may account for k₁ variability in that region.

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for lower and residual errors of 0.0052 and 0.029 respectively). The H/A<sub>10.5</sub> data for the same subjects (fig. 11a and b) showed a high correlation of right to left flow values. The high count data yielded a r of 0.95 while the lower count data a r of 0.89, with residual variability of 0.00020 and 0.00064 respectively. In fact, if one point were removed from the lower count rate data, both correlations would have been almost identical. The best fit curves indicated higher flow values on the left for both calculations.

Discussion

A major difficulty with multicompartmental analysis is that "noise" of any type reduces reliability
of flow values. Most investigators recognize the need for high detector count rates to avoid statistical variability. This is not easy to achieve in many patients, such as the elderly, where average CBF is low with occipital flows being the lowest. If there is a disturbance of flow to low flow regions, often it is not possible to obtain satisfactory count rates. Increased isotope dose (10 to 20 mc as compared to 3 to 5 mc for the internal carotid injection) and decreased detector collimation (38° for carotid injection to as high as 90° for inhalation have only partially solved this problem. It was for that reason the total counts for the head were used for most comparisons. We did not want to use \( k_1 \) values from peak count rates below 1000 per second (fig. 10).

There are two other sources of “noise.” End-tidal gas sampling is influenced by lung diffusion deficits; in many patients end-tidal \( \text{CO}_2 \) (and therefore apparent Xenon concentration) varies with respiration depth and immediately after a sigh. We have observed in patients that a deviation of one air curve point can change the value of \( k_1 \). While it is possible to correct

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**Table 2**

<table>
<thead>
<tr>
<th>Condition</th>
<th>( k_1 )</th>
<th>( H/A_{10.5} )</th>
<th>End tidal pCO(_2)</th>
<th>( k_1 )</th>
<th>( H/A_{10.5} )</th>
<th>End tidal pCO(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.16</td>
<td>0.49</td>
<td>30.6 mm Hg</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>.91</td>
<td>0.40</td>
<td>23.2 mm Hg</td>
<td>78</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>5% ( \text{CO}_2 ) Inhalation</td>
<td>1.70</td>
<td>0.70</td>
<td>42.8 mm Hg</td>
<td>147</td>
<td>143</td>
<td>140</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Detector pair</th>
<th>( \text{Mean } k_1 \pm \text{s.e.} ) Left</th>
<th>( \text{Mean } k_1 \pm \text{s.e.} ) Right</th>
<th>( \text{Mean } H/A_{10.5} \pm \text{s.e.} ) Left</th>
<th>( \text{Mean } H/A_{10.5} \pm \text{s.e.} ) Right</th>
<th>( \text{Mean ratio } \text{Left/Right} )</th>
<th>( \text{Deviation ratio } \text{Left/Right} )</th>
<th>( \text{Error ratio } \text{Left/Right} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.04 ± 0.06</td>
<td>1.02 ± 0.05</td>
<td>0.46 ± 0.02</td>
<td>0.46 ± 0.02</td>
<td>1.00</td>
<td>1.00</td>
<td>1.22</td>
</tr>
<tr>
<td>B</td>
<td>1.05 ± 0.06</td>
<td>0.96 ± 0.06</td>
<td>0.47 ± 0.03</td>
<td>0.44 ± 0.02</td>
<td>1.09</td>
<td>1.06</td>
<td>1.32</td>
</tr>
<tr>
<td>C</td>
<td>0.96 ± 0.04</td>
<td>0.95 ± 0.05</td>
<td>0.41 ± 0.02</td>
<td>0.40 ± 0.01</td>
<td>1.03</td>
<td>1.03</td>
<td>1.15</td>
</tr>
<tr>
<td>D</td>
<td>0.94 ± 0.05</td>
<td>0.93 ± 0.04</td>
<td>0.45 ± 0.02</td>
<td>0.43 ± 0.02</td>
<td>1.00</td>
<td>1.04</td>
<td>1.14</td>
</tr>
<tr>
<td>E</td>
<td>0.93 ± 0.05</td>
<td>0.89 ± 0.04</td>
<td>0.41 ± 0.02</td>
<td>0.39 ± 0.01</td>
<td>1.03</td>
<td>1.05</td>
<td>1.22</td>
</tr>
<tr>
<td>F</td>
<td>0.87 ± 0.04</td>
<td>0.99 ± 0.08</td>
<td>0.39 ± 0.02</td>
<td>0.40 ± 0.02</td>
<td>.92</td>
<td>1.00</td>
<td>1.28</td>
</tr>
<tr>
<td>G</td>
<td>0.80 ± 0.05</td>
<td>0.85 ± 0.06</td>
<td>0.39 ± 0.02</td>
<td>0.38 ± 0.01</td>
<td>.95</td>
<td>1.02</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Definitions: In Left/Right = \( z \), mean of \( Z \)'s = Mean Ratio; s.d. of \( Z \)'s = Deviation Ratio; s.e. of \( Z \)'s = Error Ratio.
FIGURE 9. Head detector probe placements with reference to standard EEG electrode locations where possible.

FIGURE 10. $k_1$ values of right side versus left side for two normal groups (three subjects each) having lowest and highest detector count rates (Obrist computation).
Air curve data partially for equipment and operator error, it is not possible to do the same for biological variability. This could be avoided by arterial sampling, but this would seriously detract from the basic technique. Very slight head motions are not easily recognized and yet can contribute significant “noise” and reduce measurement reliability. These problems, along with suboptimal count rates, gave our initial clinical data a degree of unreliability.

Our recirculation corrected height-over-area method is much less sensitive to “noise” than multicompartamental analysis. However, it is derived for a single compartment flow. The method is most accurate for flow studies of a single tissue compartment such as from positron emitter tomograms (PET). In computer model studies, we found only small errors were introduced using a normal range of arterial curves (intravenous bolus) for multicompartmental tissues. The greatest errors came from the end-of-curve time.

The analysis point for height and area divisions should be early in the curve since relative compartment loading is more proportional to flow initially. A compartment contribution to amplitude proportional to flow and partition coefficient is achieved only with intra-arterial bolus injection. With the intravenous bolus, peak counts from the highest flow compartments occur first with those from the slowest flow compartments last. In the two compartment model the peaks for the fast and slow compartments differ by about 0.1 and 0.2 minute for a bolus injection. This small time difference indicates that at detector peak count rate, relative contributions to curve height are still somewhat proportional to flow rates. An earlier data analysis point would have less unequal compartmental loading, but this is adversely influenced by two technical factors. The end-tidal sample does not simultaneously reflect the arterial concentration reaching a tissue element under the detector. Biological mechanics provide unpredictable time shifts between the observed end-tidal curve and the detector curve. A 0.1 minute difference in time of arrival to various tissue elements is normal. The effect of time differences is less with progressing time. A 0.1 minute error in the relative timing at head detector peak count rate could produce about a 2% error in flow where at half-way between zero and peak counts it could produce about a 12% error.

Any radiation scatter from the lungs and nasal passages are most significant in the early phases of the head curve when lung concentrations are highest and head counts still low. Such scatter will contribute some error to our measurement, but this is a second order effect; a 10% overestimation of head curve area from beginning to peak would cause about a 3% over-estimation of flow.

The utility of our approach for multicompartamental flows is shown by comparison with two-compartamental flow determinations. Obrit $k_s$ and our recirculation corrected $H/A$ flow values provide the same information. The excellent correlation between $k_{ave}$ and $H/A$ show the correction for recirculation.
by both methods is nearly equivalent. Our $k_1$ values for the normal subjects using intravenous $^{133}$Xe input are comparable with those reported by Obrist$^{15}$ using $^{133}$Xe inhalation. Sensitivity to age and $CO_2$ is provided by both methods. The Obrist computation requires extensive curve fitting and higher detector count rates for stable compartmental analysis.

When looking at regional cerebral flow values, the $H/A_{10.5}$ values are more stable than $k_1$ values. Yet they reflect changes in flow and correlate with $k_1$ over a large flow range. This does not indicate that $k_{ave}$ computed from $k_1$, $k_2$, $P_1$, and $P_2$, is not as stable as the $H/A_{10.5}$ values. In fact Figure 4 indicate that $H/A$ and $k_{ave}$ are very similar for whole head curves.

The left hemisphere of the brain$^{14}$ showed higher flows than the right (table 3, figs. 10, 11). This observation is more strongly supported by the $H/A_{10.5}$ flow values than by $k_1$ values, though this may be peculiar to our small set of data. Our data shows inter regional flow differences in the precentral and parietal regions (probe pairs C and G in figure 9) as reported by other investigators.$^{15}$ Table 4 summarizes that data. Paired data analysis (t test) for both flow methods indicated a more positive difference between the two regions for $H/A_{ave}$ though its regional percentage difference was smaller ($p = 0.017$ for $k_1$ data and $p = 0.005$ for $H/A_{10.5}$ data). Our higher standard deviations for $k_1$ are probably due to: fewer subjects, larger subjects age range, and lower head count rates.

We did not translate $k_1$ values to flow by estimating

**Table 4** Flow Data for Precentral and Parietal Areas of Fifteen Normals in this Study, and Flows of Another Study

<table>
<thead>
<tr>
<th>Data by</th>
<th>Left precentral</th>
<th>Right precentral</th>
<th>Right parietal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obrist, et. al. (15) $k_1$</td>
<td>$0.94 \pm 0.11$ S.D.$^*$</td>
<td>$0.93 \pm 0.11$ S.D.$^*$</td>
<td>$0.83 \pm 0.10$ S.D.$^\dagger$</td>
</tr>
<tr>
<td>This study $k_1$</td>
<td>$0.96 \pm 0.15$ S.D.</td>
<td>$0.95 \pm 0.20$ S.D.</td>
<td>$0.85 \pm 0.22$ S.D.</td>
</tr>
<tr>
<td>This study $H/A_{10.5}$</td>
<td>$0.410 \pm 0.061$ S.D.</td>
<td>$0.401 \pm 0.053$ S.D.</td>
<td>$0.382 \pm 0.056$ S.D.</td>
</tr>
</tbody>
</table>

$^*$48 young controls.
$^\dagger$35 young controls.
λ, the Xe blood-brain partition coefficient. However, λ is important for repeat studies with changing hemoglobin. Recent information indicates a difference in λ between normal tissue and tumor. For the H/A_{10.8} a reasonable estimate of mean λ is 1 to 1.2 so that H/A_{10.8} values might be considered as cc/gm/min. An estimated mean flow value of 46 cc/100 gm/min for our younger normal subjects is within the range established by intracarotid injection.

The use of a 10.5 minute head curve is an attempt to minimize scalp effects and to produce a usable flow value with least calculations. Figure 12 shows the percent of curve area remaining versus time for various k values. Normal grey matter flow has k = 1 typically while normal white matter flow has k = 0.26. For normal flows, without scalp contamination, the 10.5 minute duration can be expected to introduce an overestimation of about 5% in mean flow and about 20% at one-half normal flow. Scapulation will lower the flow values. Using a single flow model for the multicompartmental brain may tend to lower the estimated mean flow, especially where grey and white matter are equally sensed.

There are conditions where the entire curve is needed, such as brain death, to avoid significant errors in flow estimates. It may be that the rationale for H/A_{10.8} will be supplanted by the more precise H/A_{6}. Clinical studies will evaluate this point.

Reviews of the inhalation and intravenous injection methods indicate that compartmental analysis techniques have not totally satisfied the need for clinically accurate regional information. The H/A_{10.8} recirculation values are less sensitive to statistical counting errors and biological interferences. This approach will provide more regional resolution by allowing a greater degree of detector collimation.

Non-invasive methods are not sufficiently established to fully evaluate new rCBF techniques. Comparison with the internal carotid injection of 180Xe is needed. Some researchers have compared their non-invasive methods in this way. However, data from such studies have not been persuasive. They have neither determined the number of accurate clinical correlations with regional information nor have they indicated the number of false positives or false negatives introduced by the variability of their methods. Our initial clinical correlations indicate H/A flow values reflect patient status reliably. Results of comparisons with the intracarotid technique will follow this publication.

Acknowledgment

The help by Dr. Walter Obst is as indicated in Appendix I is gratefully appreciated.

References

3. Olesen J, Paulson OB, Lassen NA: Regional cerebral blood flow in man determined by the initial slope of the clearance of intra-arterially injected 133 Xe. Stroke 2: 519-540, 1971

Appendix 1

An assumption needed to derive our recirculation corrected H/A computation is that the head curve area resulting from a given
arterial dose remains constant throughout the measurement. In that case, the head curve area from the first half of an arterial input dose will be the same as for the second half. (At head curve peak about one-half of the isotope has been delivered for an intravenous bolus injection). This assumption is inherent in the Obrist computation since $p_1$ and $p_2$ are determined by fitting a plane through all calculation points using the same values. The fact that the Obrist model works well in terms of curve fitting suggests the assumption is valid at least for reasonably short arterial input functions.

We derived a $H/A$ type computation for a non-bolus arterial input using areas as indicated in Figure 13, where:

- $A_a$ = Area due to $C_a(t)$ from time 0 to t which equals $\int_0^t C_a(t) \, dt$.
- $A_t$ = Area remaining due to input of $C_a(t)$ from time 0 to t. (If at any time, the arterial input suddenly dropped to zero, the head curve would decrease in an exponential form starting with the curve height at that time).
- $A_g$ = Area due to $C_a(t)$ from time $t$ until $C_a(t)$ is zero.
- $a$ = area arterial curve prior to analysis time,
- $b$ = area arterial curve after analysis time.

If $u = \frac{\text{Area Total Head Curve}}{\text{Area Total Arterial Curve}}$, then $A_a + A_t = ua$ and $A_e = ub$.

Then

$$A_e = \text{Area due to } C_{\text{air}}, \text{ from time } t \text{ until } C_{\text{air}} \text{ is zero.}$$

$$a = \text{area arterial curve prior to analysis time.}$$

$$b = \text{area arterial curve after analysis time.}$$

If $u = \frac{\text{Area Total Head Curve}}{\text{Area Total Arterial Curve}},$ then $A_a + A_t = ua$ and $A_e = ub$.

Then

$$A_e = \text{Area due to } C_{\text{air}}, \text{ from time } t \text{ until } C_{\text{air}} \text{ is zero.}$$

$$a = \text{area arterial curve prior to analysis time.}$$

$$b = \text{area arterial curve after analysis time.}$$

If $u = \frac{\text{Area Total Head Curve}}{\text{Area Total Arterial Curve}},$ then $A_a + A_t = ua$ and $A_e = ub$.

Then

$$A_e = \text{Area due to } C_{\text{air}}, \text{ from time } t \text{ until } C_{\text{air}} \text{ is zero.}$$

$$a = \text{area arterial curve prior to analysis time.}$$

$$b = \text{area arterial curve after analysis time.}$$

Substituting equation (4) into equation (3) yields equation (1) in the text or:

$$k = \frac{\text{Area Total Head Curve}}{\text{Area Total Arterial Curve}} \times \frac{\text{Area Arterial Curve}}{0 \text{ to Analysis Point}} - \frac{\text{Area Head Curve}}{0 \text{ to Analysis Point}}$$

The computation is derived for a single flow. However, two or more underlying flows would not alter the basic computation, but would present limitations on the accuracy and validity of the model. For this reason, there are two conditions where our non-bolus arterial input computation will not work at all: 1) Where the mean transit time of the arterial input approaches the mean transit time of the mean head flow (therefore, we keep the input function as short as possible), and 2) Use of an analysis point where arterial concentrations have approached zero, since slower flow components will dominate the $C(t)$ value. If the peak concentrations for the various flow components occur nearly together, and the analysis point is peak amplitude, the mean flow calculated should be nearly the same as for an instantaneous input. However, the choice of analysis point (t) is not limited to the peak of the head curve. In order not to lose fast flow components in the mean, one should choose the analysis time near the head curve peak. Significantly before head curve peak, small time errors between arterial and head curve (such as introduced by end-tidal sampling) would cause large calculation errors. At $C(t)$ peak the highest flow tissue areas just have passed peak concentration. In the normal flow ranges, waiting one minute past that point reduces calculated mean flow as much as 50% for models using $k_1 = 0.98, k_2 = 0.23$ with $\lambda_t/\lambda_s = 0.5$. With $\lambda_t/\lambda_s << 1$ slower flows still dominate after curve peak; only about 27% of the peak fast flow amplitude would remain one minute after head curve peak for a $k$ of 1 where there is a rapid return of arterial concentration to zero. The peak head curve has the highest count rate, and therefore the best counting statistics for the absolute value of $C(t)$. 

Figure 13. Area relationships for recirculating tracer input and a resulting head curve.

\[
\begin{align*}
\text{Area Total Head Curve} & = \text{Area Total Arterial Curve} \times \frac{\text{Area Arterial Curve}}{0 \text{ to Analysis Point}} - \frac{\text{Area Head Curve}}{0 \text{ to Analysis Point}} \\
\end{align*}
\]
For the mentioned reasons we chose to analyze data at the head curve peak and use the shortest of arterial input functions possible achievable by non-arterial means.

The choice of a 10.5 minute analysis time reduces the numerical effect of non-cerebral flow without introducing significant errors within expected flow ranges. It is possible to correct for the missing tail of the curve after the 10.5 minute cutoff by estimating the tail area from the end slope.

After reviewing this paper Walter Obrist pointed out a derivation of Eq. (1) starting with the Fick equation

$$\frac{dC(t)}{dt} = k (\lambda a C_{a} - C_{B})$$  \hspace{1cm} \text{Eq. (5)}

where $C_{a}$ = arterial time function of indicator concentration. $C_{V}$ = venous time function of indicator concentration.

$t$ = time.

$C_{H}$ = head concentration at time $t$.

$\lambda$ = tracer partition coefficient = equilibrium tissue conc. / equilibrium blood conc.

$k$ = flow related decay constant = $F / \lambda W$ (F is flow and W the tissue weight).

$\alpha$ = proportionality constant that accounts for detector sensitivities for head and arterial counting.

For a finite arterial input:

$$\int_{0}^{T} C_{a}(t) dt = \int_{0}^{T} C_{V}(t) dt$$

so that

$$C_{H} = k \int_{0}^{T} C_{a}(t) dt - \int_{0}^{T} C_{V}(t) dt$$

This does assume equilibration of tracer in tissue and venous blood at all times. Rewriting Eq. (5) and integrating we get

$${C_{H}}_{t} = k \left[ \int_{0}^{T} C_{a}(t) dt \frac{\int_{0}^{T} C_{a}(t) dt}{\int_{0}^{T} C_{V}(t) dt} - \int_{0}^{T} C_{V}(t) dt \right]$$ \hspace{1cm} \text{Eq. (6)}

which is equivalent to Eq. (1).

Obrist further suggests a correction for the missing area at the end of the curve at time $z$ based on the following approach:

$$Q = \frac{\int_{0}^{T} C_{a}(t) dt}{\int_{0}^{T} C_{V}(t) dt}$$

where $T$ is curve height analysis time. If $C_{a}$ is end of head curve height, eq. (6) can be written

$${C_{H}}_{z} = k Q \int_{0}^{T} C_{a}(t) dt + kQ \int_{0}^{T} C_{V}(t) dt - k \int_{0}^{T} C_{V}(t) dt$$

Assuming that the tail of the curve is represented by a single exponential having the same value as $k$, then

$$f_{s}C_{B}e^{-k(t-s)}dt = \frac{C_{H}}{k}$$

so that

$$C_{H} = Q \int_{0}^{T} C_{a}(t) dt - \int_{0}^{T} C_{V}(t) dt$$

This correction for the missing head curve tail would somewhat underestimate the area for multicompartmental flows where $k$ is likely to be a higher flow constant than the actual tail. However, with low counts at time $z$, $C_{H}$ may be more accurately determined than a single fitted exponential.

Editors Note

This paper presents an innovative method for handling the data in CBF calculations following intravenous 133Xenon injection. Rather than wait for “Letters to the Editor” it was decided to solicit some brief discussion to offer in conjunction with the presentation of this interesting report. Dr. Niels A. Lassen has submitted that which follows:

Comment on paper by Namon et al

The study by Namon and coworkers present a new method of calculating cerebral blood flow from Xenon-133 curves recorded over the head after i.v. injection. The method is based on making a number of simplifying assumptions, one of which consists in assuming that the ratio $u$ of the area under head counts and arterial input is constant. The study argues well for some of these shortcuts, but omits to mention others. The method has, however, a number of very attractive features namely: being based on integrals, and using the entire curve.

The method neglects the contribution of scattered counts from the airways that are (attempted) corrected for in the analysis of Jablonski et al. (Acta Neurol. Scand. 60: 216-217, 1979). An attractive feature of the new method is the fact that only one parameter, the time constant $1/k$ is being evaluated and used to calculate the mean blood flow. The evidence of the usefulness of the approach is presented in form of a comparison with standard forms of analysis of curves. However, such a comparison cannot be very satisfactory as a true “gold standard” is lacking. A comparison to the classical Kety-Schmidt method using Xenon-133 inhalation and jugular sampling (preferably bilateral sampling) would be desirable.

A purely pragmatic approach, as an analysis of data obtained in various patient groups, might also be of some value.

Niels A. Lassen, M.D.
Department of Clinical Physiology
Copenhagen
Cerebral blood flow studies in man using recirculation corrected height/area (H/A) computations for intravenous injection of 133Xenon.

R Namon, O M Reinmuth and R Schwelm

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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