Estimating Total Cerebral Blood Flow From the Initial Slope of Hydrogen Washout Curves

BY T. F. DOYLE, B.S., A. N. MARTINS, M.D., AND A. I. KOBRINE, M.D.

Abstract:
An initial slope index of total cerebral blood flow, measured by the hydrogen clearance technique, shows a high correlation with flows calculated by bicompartmental analysis. In 247 flow measurements done on 41 rhesus monkeys, a linear regression analysis between these two methods of calculating flow shows a correlation coefficient of 0.928 with a standard error about y values of ± 7.63. The initial slope index is not only faster but does not require that a steady state be maintained for ten minutes.

Additional Key Words
normocapnia bicompartmental analysis hypoxia hypoxia hypercapnia

Introduction
Sveinsdottir et al.1 made the comparison between regional cerebral blood flow values calculated by an initial slope index method and by the stochastic method of height-over-total-area. They concluded that the two-minute initial index method, although theoretically erroneous, contained essentially the same information as that obtained from the more laborious, but more theoretically correct, stochastic method.

This report concerns the correlation between total cerebral blood flow values calculated by the initial slope index method and by bicompartmental analysis. An initial index of flow would be valuable in calculating total cerebral flow in that the assumption of a ten-minute steady state would not have to be made, and minor variations of baseline would have only negligible effect.

Methods
Our method of measuring total cerebral blood flow using hydrogen clearance and an electrode in the torcular Herophili has been described elsewhere.2 Part of the monkey’s skull at inion was removed and an electrode was passed through the dura into the torcular Herophili and anchored in place with methyl methacrylate. The reference electrode was a self-tapping stainless-steel screw passed into the frontal bone. Hydrogen was added to the inspired gas mixture at the endotracheal tube entrance in a concentration that varied from 5 to 25 vol %, but was constant for each flow determination. Hydrogen was usually given for 10 minutes, but in some experiments the period of inhalation was varied from 5 to 30 minutes. At the end of a predetermined period, hydrogen flow was stopped abruptly and the recording of its clearance from the torcular blood was begun. The data used here were derived from 247 total cerebral blood flow studies done on 41 rhesus monkeys.

Flows were obtained during states of normocapnia, hypocapnia, and hypercapnia and ranged from 14 to 196 ml/100 gm per minute. It was determined earlier23 that 40 seconds after hydrogen inhalation was stopped, arterial hydrogen concentration decreased to less than 10% of the original concentration; therefore, data from the first 40 seconds of the washout curve were not used.

Theoretical Considerations
The rate at which hydrogen is washed out of the tissue is proportional to the blood flow through the tissue.4 If the tissue being sampled is homogenous, then the equation for the washout curve is monoexponential and blood flow can easily be calculated from the formula:

\[ f = \frac{-k}{X} \]

where f is the flow in milliliters per gram per minute, X is the blood: tissue partition coefficient, which for hydrogen is close to unity,5 and k is the rate constant. The rate constant or slope can easily be obtained from the formula:

\[ k = \frac{\ln C_2 - \ln C_1}{T_2 - T_1} \]

C1 and C2 are any values on the curve at time T1 and T2.

The brain is not composed of homogenous tissue, however; the clearance curve is biexponential and can be analyzed by the stochastic method of height-over-total-area or by bicompartmental analysis,6 such as was used for this report.

BICOMPARTMENTAL ANALYSIS
For this method, the data are graphed on semilogarithmic graph paper and the biexponential curve is separated, by


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standard curve stripping techniques, into the two component exponentials representing the fast and slow flow components, \( y = Ae^{k_1 t} + Be^{k_2 t} \).

The average total flow, \( \bar{f} \), is then calculated from the formula:

\[
\bar{f} = \frac{A + B}{A + B}
\]

where \( \bar{f} \) = average total blood flow, \( A = y \) intercept of the fast component, \( B = y \) intercept of the slow component, and \( k_1 \) and \( k_2 \) = rate constants (or slopes) of the fast and slow components, respectively.

**Initial Slope Index**

To use the initial slope index, we assume that \( k_1 = k_2 = k \); that is, that the initial part of the washout curve can be fitted by a straight line, \( k \) is then calculated from formula (2) and \( \bar{f} \) from formula (1). Data from the first two minutes of the clearance curve were used.

**Results**

A linear regression analysis of the two methods of calculating flow from the same data shows a high correlation coefficient, 0.928 (fig. 1). Flows in the normal range, centering about 52 ml/100 gm per minute, tended to be similar when calculated with either method. The two-minute slope index tended to underestimate higher flows and overestimate lower flows, in comparison with flows calculated by bicompartamental analysis. The slope did not differ significantly from 1.0, but the difference between the intercept and zero was very highly significant (\( P < 0.001 \)).

To determine whether flows calculated by either method differ in variability, data were selected from 12 experiments (61 flows) in which physiological parameters such as blood gases, blood pressure and temperature were kept stable for the duration of the experiment. In these instances, flow values would be expected to remain constant. The variation coefficient \( \frac{\text{standard deviation} \times m}{\text{mean value}} \) was calculated for each experiment, for each method of calculating flow, and then averaged. The variation coefficient for the bicompartamental method was 13.9 which did not differ significantly from 13.0 for the initial slope index method. Also, there was no correlation between the magnitude of the flow values and the variability.

Linear regression analysis showed that the initial index of flow had a higher correlation to the slow compartment of flow, 0.7612 (fig. 2), than to the fast component, 0.6001 (fig. 3).

**Discussion**

The initial slope index would be a correct measure of total blood flow only if the clearance curves were monoexponential, i.e., if \( k_1/k_2 = 1 \). If \( k_1 \) and \( k_2 \) differ...
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A linear regression analysis of the slow flow component (ordinate) and total flow calculated by initial slope index (abscissa), \( n = 241 \), correlation coefficient 0.7612 ± 8.79 SD about y values.

A linear regression analysis of the fast flow component (ordinate) and total flow calculated by initial slope index (abscissa), \( n = 241 \), correlation coefficient 0.6001 ± 17.4 SD about y values.
by as much as 3, they can still be fitted quite well with a single exponential. Our data yield $k_j/\lambda$ ratios ranging from 1.7 to 15 with a mean of 3.97 ± 0.15 SD. It is surprising, therefore, how well these approximations of flow agree with the values derived from bicompartamental analyses. Flows close to 52 ml/100 gm per minute (the mean total cerebral blood flow value) tend to be identical when measured by either method. However, lower flows tend to be overestimated and high flows underestimated when calculated by the initial slope index method. A correction factor (bicompartamental value = 1.35 initial slope value —17) can easily be applied for very high and very low flow values.

Conclusions
Total cerebral blood flow values measured by hydrogen clearance, when estimated from the initial two-minute slope, agree quite well ($r = 0.928$) with those values calculated by the theoretically more correct bicompartamental analysis. This method of flow estimation has the advantage of requiring only a two-minute steady state; and because the data dealt with are from the early part of the washout curve, minor variations of the baseline have little or no effect.

References
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