Regional Cerebral Blood Flow by
133Xenon Inhalation

PRELIMINARY EVALUATION OF AN INITIAL SLOPE INDEX IN PATIENTS WITH UNSTABLE FLOW COMPARTMENTS

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Abstract:
Repeated measurements of regional cerebral blood flow (rCBF) were made by the short (ten minutes) 133Xenon inhalation technique and bicompartmental analysis in 11 patients with cerebrovascular disorders, mainly acute cerebral infarction. rCBF was measured 3 to 11 times during one to two weeks. The blood flow of the fast compartment (f₁) was calculated as well as the relative weight of this compartment (w₁, assumed to correspond to gray matter). In addition a new flow index, the Initial Slope Index (ISI) modified for the inhalation technique, was used. This index of predominantly gray matter flow was calculated from a one-minute epoch of the early part of the clearance curve corrected for recirculation. In three of the patients the f₁ and ISI varied in parallel and the w₁ showed generally only minor variations from one measurement to the other. However, in the other eight patients fluctuation of the w₁ and f₁ values were seen which often showed no meaningful relation to the clinical course. The observed w₁ changes indicated that some tissues (slowly perfused gray matter and/or rapidly perfused white extracerebral tissues) fluctuate between the fast and the slow compartment. In such cases the f₁ values obtained cannot be used for comparison between measurements, since they represent flow rates of varying tissues and do not always represent a true gray matter blood flow. In these patients the ISI, which is independent of such weight changes, showed moderate and clinically likely variations.

Additional Key Words
compartmental analysis
initial slope index
Xenon clearance
stroke
gray matter weight

Introduction
The Xenon inhalation technique, which was introduced by Mallett and Veall¹,² and later modified by Obrist and co-workers,³-⁴ allows repeated measurements of regional cerebral blood flow (rCBF) in the same patient over a prolonged period. The usefulness of serial rCBF measurements in the treatment and care of patients with acute stroke has recently been discussed in a preliminary communication from our laboratory.⁵ The purpose of the present paper is to discuss methodological difficulties involved in the bicompartmental analysis of short (ten minutes) Xenon inhalation curves⁶ recorded from 11 patients with cerebrovascular disorders. A new index of rCBF, the Initial Slope Index (ISI)⁶,⁷ modified for the inhalation technique, will be used.

Methods
Nine of the 11 patients included in the study had cerebral infarction, one had subarachnoid hemorrhage due to an aneurysm of the left internal carotid artery, and one had an aneurysm of the basilar artery. Brief case histories will be given in conjunction with the rCBF results. Three to 11 rCBF studies were made in each patient during one to two weeks. The first rCBF measurement was made in most cases on the first day after the onset of the acute symptoms.

Calculation of rCBF
A two-compartmental analysis was made using the basic equation⁸:

\[ N_1(t) = \alpha w_1 K_1 e^{-K_1 t} \int_0^t C_2(u) e^{-K_1 u} du \]  

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where \( t = \) a given time after the start of Xenon inhalation, \( N_i(t) = \) counts obtained from the \( i:th \) tissue component at time \( t \) (\( i = 1, 2 \)), \( a = \) a proportionality constant, \( w_i = \) relative weight of the \( i:th \) tissue component (\( w_1 + w_2 = 1 \)), \( \lambda_i = \) tissue-blood partition coefficient for the \( i:th \) tissue, \( k_i = \) decay constant for the \( i:th \) component, \( C_A(t) = \) concentration of isotope in expired air (= arterial blood) at time \( t \).

The program solves for \( K_1 \) and \( K_2 \) and, in addition, gives estimates of \( \alpha w_1 \lambda_1 = p_1 \) for each of the two compartments. (The reader is referred to Obrist et al.\(^2\) for details of the calculations.) The first compartment is supposed to consist of gray matter. By multiplying \( K_i \) with \( \lambda_i \) (corrected for hemoglobin\(^9\)) the blood flow of rapidly perfused tissues \( f_i \) can be estimated. The exact value of \( \lambda \) for the second compartment, however, cannot be determined due to the influence of extracerebral tissues and consequently no calculation of the blood flow of slowly perfused tissues can be made.

The uncertainty of the \( \lambda \) for the second compartment also precludes an exact calculation of the fractional weights of the two compartments. However, in the present study an approximate \( w_i \) was calculated using a standard \( \lambda_i = 0.8 \) and \( \lambda_2 = 1.5 \) (\( \lambda \)-white at Hb = 15 gm %\(^9\)) and using the formula

\[
   w_i = \frac{p_i/\lambda_1}{p_i/\lambda_1 + p_2/\lambda_2} \cdot 100 \quad (p_i = \alpha w_i \lambda_i)
\]

This approximate \( w_i \) calculation will be used only for comparison between measurements in the same patient and the same cerebral region.

### The Initial Slope Index

An estimate of \( rCBF \) from the slope of the initial part of the clearance curve has been used with advantage for the intraarterial Xenon injection technique.\(^6\),\(^7\) With the inhalation technique, the observed head curve cannot be used directly for calculation of the ISI due to its distortion by recirculation. A curve which corresponds to the observed data but is without any influence of recirculation, however, can be reconstructed from the biexponential solution according to the formula

\[
   N_i(t) = N_i(x)e^{-K_i(t-x)} + N_{2i}(x)e^{-K_2(t-x)}
\]

where \( N_i(t) = \) total counting rate corrected for recirculation at any time \( t \) (minutes), \( N_i(x) = \) counting rate of the first compartment at time \( x \) (= start of the biexponential analysis), \( N_{2i}(x) = \) counting rate of the second compartment at time \( x \).

As is illustrated in figures 1 and 2, the ISI is calculated from the two-minute to three-minute interval of the curve. The ISI is defined as the slope constant (K-value) of a monoexponential function connecting the points \( N(2) \) and \( N(3) \) and is calculated according to the formula

\[
   ISI = \frac{\ln N^f(2) - \ln N^f(3)}{100}
\]

As will be discussed in detail later, the ISI is an index of the blood flow of all tissues recorded, but is highly dominated by the gray matter blood flow and very little influenced by extracerebral components.

**Calculation of the Initial Slope Index (ISI).** A typical head curve is shown with start of biexponential analysis at time \( x \) (= start-fit time). The solid line indicates the fitted curve (equation 1) with recirculation included. The dashed line represents the recirculation corrected curve (equation 3). The two to three-minute interval of this curve is used for calculation of ISI.

**Calculation of ISI.** The dashed line represents the two to three-minute interval of the recirculation corrected curve from figure 1 (semilogarithmic scale). The two components constituting the curve are shown below. It is evident that the first compartment (mainly gray matter) highly dominates the ISI (see Discussion).
Results

In three of the patients, all with acute cerebral infarction, the flow and weight values were relatively stable. The other eight patients (Nos. 1 through 8) showed considerable variations of the relative weights of the two components during the measurement series. As will be discussed subsequently, such variations make the interpretations of the concomitant f₁ changes difficult and suggest the use of the new flow parameter, the ISI. The results from these eight patients will be described in detail below.

Patient No. 1 was admitted with minor right hemiparesis which showed regression during the first week of hospitalization. During this period the f₁ and ISI showed increases in both hemispheres (see fig. 3). After an initial increase following the progression of infarction on Days 8 to 10 the flow values diminished and later stabilized. The patient's clinical course essentially paralleled these flow values proceeding to complete hemiplegia and aphasia with no recovery. Particularly the ISI showed significantly lower flow values in the left, clinically most affected, hemisphere. The w₁ values were stable in the right hemisphere but showed a decrease in the left hemisphere in the later measurements, possibly indicating that some parts of the gray matter due to the infarction were included in the slow compartment.

The results from Patient No. 2 are shown in figure 4. The patient had an acute right hemiplegia and aphasia which persisted without any change throughout her hospital stay. The ISI showed only small fluctuations during the investigation period (15 days). The w₁, however, showed an increase in the left (affected) hemisphere of about 75% from the first to the fourth study, while the f₁ decreased by 40%. It is obvious from the figure that there is a negative correlation between the f₁ and the w₁ values.

Patient No. 3 (fig. 5) had an initially mild right hemiparesis with clinical worsening on Days 2 and 7. Some subsequent improvement occurred. The flow results showed an initial increase followed by decreases and later stabilization. The w₁ showed only moderate variations except for Measurement No. 5 on the seventh day when the w₁ in-
creased by 25% in the clinically unaffected hemisphere. The disability of the patient reached its maximum on this day. Simultaneously a marked decrease in \( f_i \) was seen with only a moderate decrease of ISI.

Patient No. 4 (Fig. 6) had a subarachnoid hemorrhage due to an aneurysm of the left internal carotid artery on the day before the first measurement. During the first hospital week the patient showed considerable clinical improvement.

During this period the ISI increased by 43% while the \( f_i \) increased by only 25%. A Crutchfield clamp was placed on the left common carotid artery on the seventh day and the artery was gradually narrowed until occluded on Day 10. Immediately after the operation, decreases of flow and weight values were seen followed by augmentations especially in the right nonaffected hemisphere.

The results from Patients Nos. 5 through 8 are shown in Table 1. Marked variations of \( w \) are seen in these patients, all of whom were in fairly stable clinical conditions during the four studies. The ISI showed small variations while the \( f_i \) fluctuated markedly.

**Discussion**

**THE BIEXPOENTIAL ANALYSIS**

In the present study the \( w \) values showed marked changes from one measurement to the other in many cases. Such fluctuations indicate that the fraction of "fast" and "slowly" perfused tissues changes between the measurements. The biexponential model assumes that all the gray matter is included in the fast compartment and that the white matter and the extracerebral...
tissues together constitute the slow compartment. If this model would fit all the data presented here, the \( w_i \) changes observed would indicate anatomical changes in the cerebral tissues measured. An increase in \( w_i \) could be caused by the disappearance of slowly perfused tissues, or by the absence of blood flow in part of these tissues. With regard to the clinical pictures such changes seem less likely in the present series of patients. A decrease in \( w_i \) can be caused by a loss of gray matter (without similar changes in white matter) due to infarction, atrophy, etc. Such decreases have been demonstrated by the intra-arterial injection technique in patients with organic brain disorders of different etiology. The weight changes generally showed good correlations to clinical and pathoanatomical changes. In the present study organic changes in the gray matter might explain the decreases of \( w_i \) seen in Patient No. 1, who showed marked progression during the study period. This explanation, however, seems less likely in all the other cases with regard to the clinical picture. This is especially true in cases where the \( w_i \) fluctuated several times (e.g., Patient No. 4).

More likely explanations for the observed variations in \( w_i \) imply an improper distinction between gray and white extracerebral tissues in the bicompartimental analysis. Tissues with intermediate flow rates (slowest gray tissues and fastest white extracerebral tissues) seem to fluctuate between the two compartments causing variations in \( w_i \) and \( f_i \). Such fluctuations have been reported also for the intra-arterial technique by Iliff and co-workers. They found that the weight of the fast component decreased by about 20% during hypcapnia in relation to normocapnia in patients with ischemic cerebrovascular disease. Thus, the distinction between the gray and the other tissues seems to constitute a general problem in the bicompartimental analysis of clearance curves from pathological brains. However, there is evidence indicating that a proper distinction can be made by the intra-arterial technique in the normal brain.

Fluctuations in \( w_i \) seriously limit the possibilities of making meaningful comparisons between the flow values. This is true if the weight changes are due to anatomical or physiological changes as well as if they are caused by a faulty curve analysis. One flow value might represent a pure gray matter blood flow while another indicates the flow of a mixture of gray, white, and extracerebral tissues. In such a case the first \( f_i \) can be considered a different flow parameter than the second.

The difficulties encountered in the separation of the flow of the gray matter from that of slower perfused tissues can be expected to increase at lower flows because of increasing overlap between flow rates of the different compartments. In the present study large variations of \( w_i \) were also seen at normal flow rates (e.g., Patient No. 4), indicating that in the diseased brain such difficulties might be encountered over a large span of flow levels. The mathematical possibilities for a proper separation of the compartments in cases of low flow can be expected to increase if the period of analysis was extended from 10 minutes to 15 or 20 minutes. However, then the influence of extracerebral tissues on the tail of the curve will increase, causing a low \( K_2 \) and an underestimation of \( K_R \). Biexponential analysis of 20-minute Xenon inhalation curves from normal brains has been shown to result in an underestimation of the gray matter flow by about 25%. The absence of energy discrimination of the pulses from the detectors in our present system might have aggravated the difficulties with the biexponential analysis by increasing the influence of extracerebral tissues. This influence, however, can be assumed to be rather constant between the measurements and can hardly explain the variations seen in the present data.

THE INITIAL SLOPE INDEX

In view of the problems encountered with the biexponential analysis, the ISI was tried as an index of flow. It was clearly demonstrated in figure 2 that the two to three minutes' slope, on which the calculation of the ISI is based, is highly dominated by the clearance of isotope in rapidly perfused tissues. Out of the total decrease in countrate of 1,850 cpm, 84% is due to clearance of the first component. Results from three-compartmental analysis show that the third (extracerebral) component has a minimal influence on the early part of the curve from which the ISI is calculated. Thus it can be concluded that the ISI is an index of primary gray matter blood flow with negligible extracerebral contamination.

The crucial question is whether the ISI is relatively independent of the weight changes described above. Twelve curves from Patients Nos. 3 and 4 were subjected to a special analysis in order to make an empirical test of the ISI with respect to \( w_i \) changes and changes in the total duration of the analyzed curve. These curves, which all gave seemingly proper bicompartimental results at full-length analysis (one-minute inhalation + ten-minute clearance), were shortened from the tail end and analyzed by means of the ordinary program. It is evident from table 2 that even moderately shortened curves gave pronounced fluctuations in the \( w_i \) and \( f_i \) values, variations similar to those found in some of the present patients (e.g., Patient No. 2). The ISI, however, was very stable and varied maximally 4% for the shortest curves. Considering these results together with the fact that the ISI is calculated from a curve based on both compartments added together, it can be concluded that the ISI is not influenced by fluctuations in \( w_i \) caused by faulty curve analysis. It is also evident that the ISI can be calculated with accuracy even from very short curves.

The present results showed in principal two types of covariation of the flow and weight parameters. In
two patients (Nos. 1 and 4) the $f_i$ and $w_i$ varied in parallel, a decrease of $f_i$ was accompanied by a decrease in $w_i$, and vice versa. In these two patients, who were the only two with more marked clinical changes, a flow decrease of the gray matter seems to cause the slowest part of the gray matter to be included in the slow compartment. Since only the fastest part of the gray matter is included, the $f_i$ will be faster than the true gray matter flow. The ISI is not influenced by such weight changes and thus the relative (percent) size of the variations will be larger for $f_i$, as is demonstrated clearly in Patient No. 1 (see fig. 3). In such cases the ISI is a more sensitive parameter than the $f_i$.

In the other six patients, the variations in $w_i$ showed a negative correlation with $f_i$. In these cases (e.g., Patient No. 2) a decrease of $w_i$ probably implied the transfer of slowly perfused gray matter to the second compartment, which caused a false increase of $f_i$ not influencing the ISI. A $w_i$ increase would then imply an increased content of slowly perfused tissue in the first compartment lowering the $f_i$. In these cases the ISI showed more moderate changes, probably more representative of the true flow changes in the brain tissue.

The present principle for calculating the ISI was chosen after several other methods of calculation had been tried and evaluated. An ISI might be calculated from the one-minute recirculation corrected slope following the start-fit time as an alternative to the present fixed time interval (two to three minutes). Such an index, however, is substantially influenced by such weight changes and thus the relative (percent) size of the variations will be larger for $f_i$, as is demonstrated clearly in Patient No. 1 (see fig. 3). In such cases the ISI is a more sensitive parameter than the $f_i$.

Maximal and minimal values in parentheses.

<table>
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<th>End of analysis (min)</th>
<th>$f_i$ (%)</th>
<th>$w_i$ (%)</th>
<th>ISI (%)</th>
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<td>(150-3)</td>
<td>(104-96)</td>
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References

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