133Xenon Inhalation Method: Significance of Indicator Maldistribution for Distinguishing Brain Areas with Impaired Perfusion

An Index for Total Flow

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SUMMARY This paper introduces a new index for the assessment of regional cerebral blood flow. The index is proportional to total flow, and is obtained from the ratio of regional count rate to arterial blood flow per unit mass of tissue per minute. It accounts for brain tissue partly or totally deprived of its blood supply. Examples of clinical application are reported.

A good correlation with the findings of computer-assisted tomography has been found.

THE CLINICAL APPLICATION of the 133Xe inhalation method for the assessment of regional cerebral blood flow (CBF) in cerebrovascular disease is still limited by methodological difficulties.

In addressing the problem of indicator maldistribution in ischemic brain regions 1-4 commonly referred to as "look through" phenomenon or artifact 4-6, 133Xe has been cited as a better alternative to 133Xe if the surface of the brain is directly accessible. 4, 5 However, for non-invasive measurements of CBF, the converse appears to be true. The primary characteristic emission of 85Kr is predominantly 1.9 particle

Calculation Of rCBF

Clearance curve analysis was operationally carried out in accordance with the two-compartment model developed by Obrist and co-workers.10-12 By means of the resulting set of parameter values \( p_i, p_2, k_1, \) and \( k_2, \) reconstruction of the curve fitted through the data points originally recorded was then accomplished to obtain the fitted value of the total count rate \( N_i(t) \) at any given time \( t \) from start-fit to end-fit time. This was done using the following equations (1, 2):

\[
N_i(t) = p_i \int C_A(u) \cdot e^{-k_i(t-u)} du
\]

where \( N_i(t) \) is the count rate accounted for by the \( i \)-th compartment at time \( t, \) not corrected for recirculation; \( t = a \) given time after start of \( ^{133}\text{Xe} \) inhalation; \( p_i = \) weighting coefficient of the \( i \)-th compartment according to Obrist's assumptions; \( C_A(t) = \) isotope concentration in the entidal expired air (≈ arterial blood10-12) at time \( t; k_i = \) decay constant of the \( i \)-th compartment.

\[
N_i(t) = \sum_{i=1}^{2} N_i(t).
\]

In the concept of the two-compartment model the rCBF-parameters \( f_i \) (ml/100g/min) and \( w_i \) (%) are derived by means of the following relations (3-5):

\[
f_i = \lambda_i \cdot k_i,
\]

where \( \lambda_i \) represents the blood-brain tissue partition coefficient for gray and white matter, adjusted for hemoglobin concentration (e.g. \( \lambda_{\text{gray}} = 0.8 \) and \( \lambda_{\text{white}} = 1.5 \) for a hemoglobin concentration of 15g%). The parameter \( f_i \) is the normalized flow rate of the \( i \)-th compartment. The relative weight of the first compartment, \( w_1, \) is determined by

\[
w_1 = \frac{p_1/f_1}{p_1/f_1 + p_2/f_2} \cdot 100,
\]

where \( w_1 = 100 - w_2. \)

The values for \( f_i \) and \( w_i, \) are readily obtained from equations (3) to (5) by using the computer solutions for \( p_i \) and \( k_i, \) and the hemoglobin adjusted \( \lambda_i. \) To the extent that the basic assumption of the two-compartment model is valid — i.e. that a faster clearing compartment, considered to represent mainly cerebral gray matter, is separated from a slower clearing compartment, considered to represent white matter and extracerebral tissue — the two-compartmentally derived rCBF-parameters will provide meaningful results. Risberg et al.14 and Obrist et al.15 recognized, however, that in certain pathological states, where compartmental boundaries shift, the concept may not hold true. From the equations given above it can be easily seen that the outcome of \( f_i \) and \( w_i \) depends essentially upon the proper substitute for the \( \lambda_i \) related to the decay constants \( k_i, \) for each compartment. Under pathological circumstances, where reduced perfusion of gray matter may show up in the second compartment and increased perfusion of white matter — e.g. due to reactive hyperemia — may reveal itself in the first compartment according to the order of magnitude of their clearance rates, the association of \( \lambda_i \) to \( k_i, \) and \( \lambda_o \) to \( k_o, \) is not suitable. Such situations are well known under the term "slippage" which describes the manifestation of clearance rates of tissue fractions of gray or white matter in the wrong compartment of the two-compartment model. This phenomenon introduces a source of considerable uncertainty in the analysis of rCBF results. In a series of about 1,200 measurements in 280 stroke patients we found it generally difficult to achieve conclusive interpretation of impaired rCBF based solely upon \( f_i \) and \( w_i. \)

Nevertheless the two-compartment model provides an excellent parameterized fit to the clearance curves from which a useful new set of parameters can be derived to describe rCBF. By rearranging we obtain from equations (1) and (2):

\[
\sum_{i=1}^{2} \frac{p_i}{f_i} = \sum_{i=1}^{2} \int t C_A(u) \cdot e^{-k_i(t-u)} du
\]

The quotient on the right-hand side of equation (6) is a constant and independent of indicator dose. Its physiological meaning is more readily elucidated by considering the parameters represented by the coefficients \( p_i. \) Referring to Obrist,13

\[
p_i = \alpha \cdot w_i \cdot f_i,
\]

where \( w_i \) is the relative weight and \( f_i \) the normalized flow rate of the \( i \)-th compartment. The proportionality constant \( \alpha \) implies a whole product of different coefficients, i.e. A, B, C, D, W, etc., most of which cannot be readily assessed in vivo. For example, the coefficient \( A \) relates units of count rate to concentration, \( B \) accounts for differences in counting geometry, C for differences in detector sensitivity, D for regional differences of skull thickness, etc., whereas \( W \) accounts for the absolute weight of brain tissue in the field of view of a detector. Most of these coefficients, although partly subjected to biological variations, are generally assumed to be reasonably constant and reproducible from subject to subject and from measurement to measurement in the same subject. They are commonly lumped together into a single coefficient that is in the following denoted by \( \beta. \) The coefficient \( \beta, \) however, certainly represents a biological variable which contributes essentially to the size of \( p_i. \) Its product with the relative weight \( w_i \) is the absolute weight \( W_i \) of the tissue under observation. Equation (7) can thus be rewritten as

\[
p_i = \beta \cdot W_i \cdot f_i.
\]

The normalized flow rate \( f_i \) (ml/min/100g) is given by the ratio of total flow \( F_i \) (ml/min) to total tissue weight perfused \( W_i(g), \) thus

\[
p_i = \beta \cdot W_i \cdot \frac{F_i}{W_i} = \beta \cdot F_i
\]

In a two-compartment system,

\[
\sum_{i=1}^{2} p_i = \beta \sum_{i=1}^{2} F_i.
\]

The sum of the two-compartmental \( p_i \) is thus proportional to total flow (ml/min) in the tissue under observation. Since \( \beta \) is considered to be a constant for a given recording system,
NEW INDEX FOR rCBF/Blauenstein et al.

Methods

The clearance of $^{133}\text{Xe}$ was measured by the Obrist inhalation method. The technical details of the procedure and the specifications of our system are described elsewhere. In brief, two lead shielded blocks enclosing seven detectors each in a fixed parallel array were placed perpendicularly to the two lateral planes of the subject's head. This provides an optimal alignment of corresponding probes to cover homologous regions in both hemispheres in the approximate locations shown in the sketch of figure 3. The use of a Plexiglas grid system assured reproducibility of positioning of the subject's head relative to the detectors in sequential measurements to within ±0.5 cm. The scintillation detectors consisted of NaI(Tl) crystals with $\frac{3}{8}$" diameter and $\frac{3}{4}$" length, being recessed behind 1" long cylindrical lead collimators with an inner diameter of $\frac{3}{4}$". The electronic windows of the pulse height analyzers were set to encompass both gamma and x-ray radiation, i.e. from 20 to 100 kev. The systemic arterial carbon dioxide tension (Paco$_2$) was analyzed from arterial blood samples in patients and was estimated from the endtidal points of the capnographic recordings (Beckman LB-2) of the expired air sample in normal subjects. The mean arterial blood pressure (MABP) was calculated as diastolic pressure plus one-third of the pulse pressure. The computerized axial transverse tomography (CT-scan) was performed in standard fashion (EMI-scanner).

Material

Normal reference data for $\Phi$ and $S$ were obtained from 46 right-handed healthy volunteers with a mean age of 24±5.5 (SD) years, ranging from 18 to 43 years (1 woman, 45 men). On 32 of the subjects two rest measurements were performed on consecutive days; 14 volunteers underwent a single measurement at rest. Normal reference values for $f_i$ and $w_i$ are described elsewhere.

To illustrate the significance of a parameter for total flow in the assessment of abnormal indicator delivery, three examples were arbitrarily chosen from more than 1,200 rCBF measurements on 280 patients with cerebrovascular disease: (1) cerebral hemiatrophy; (2) ischemic cerebral infarction in association with transient ischemic attacks; (3) unilateral ischemic cerebral infarction with progression, followed by a second infarction in the contralateral hemisphere. The related case histories are mentioned together with the rCBF data in the following section.

Results

Normal Subjects

The results of the 78 rCBF measurements performed under rest conditions on 46 healthy right-handed subjects are summarized in table 1 and figure 1. Since two rCBF measurements were performed on each of 32 subjects, they were weighted by a factor of 0.5; together with the single measurements on the remaining 14 subjects a sample size of $N = 46$ was obtained. $\Phi$ is bilaterally highest in the pre-central (superior-frontal), inferior-frontal, and centro-temporal regions. The interhemispheric asymmetries pre-frontally, centro-temporally, and temporop-occipitally are statistically

the sum of the $p_i$ can be used as an index for total flow hereafter referred to as $\Phi$ for convenience. Note that the calculation of $\Phi$ does not require the knowledge of the blood-brain tissue partition coefficients $\lambda_i$. It is recognized that contamination by radiation from the contralateral hemisphere ("cross-talk") and from ipsilateral regions adjacent to the tissue cone under observation (scatter radiation) interferes with an experimentally ideal measurement of $\Phi$.

The constant $\beta$ depends largely upon the technical characteristics of the monitoring devices of a given recording system. Absolute values of $\Phi$ are thus not immediately reproducible in different laboratories using the $^{133}\text{Xe}$ inhalation method as long as $\beta$ is not specified. Inter-laboratory communication, however, can be obtained by use of dimensionless ratios where the analyzed parameters are expressed as a percentage of reference values represented, e.g., by homologous regions of the contralateral hemisphere, by the ipsilateral hemispheric mean value, or by analogous regions of preceding measurements in the same subject. In the figures of this paper the regional values for $\Phi$ are expressed as a percentage of the total sum of $\Phi$ for all 14 regions considered.

The index for total flow, $\Phi$, is determined by both the size of the compartments and their flow rates. A large tissue fraction with low perfusion rates and a small one with high perfusion rates may yield the same total flow. In order to distinguish such differences in perfusion rates, a parameter for flow rate is needed. This can be derived from the $p_i$, as ordinate values and the $k_i$ as decay constants, expressing the first-minute decrease of the $p_i$ as a percentage of the sum of the initial ordinate values — denoted by $S$ — according to the equation

$$S = \frac{p_1(1 - e^{-k_1t}) + p_2(1 - e^{-k_2t})}{p_1 + p_2} \cdot 100, \quad (11)$$

where $t = 1$ minute. The proportionality constant $\beta$ implied in $p_i$ according to equation (10) cancels out on the right-hand side of equation (11). It follows that:

$$S = \frac{F_1(1 - e^{-k_1t}) + F_2(1 - e^{-k_2t})}{F_1 + F_2} \cdot 100, \quad (12)$$

where $F_i$ represents the absolute flow for each compartment. Referring to Obrist's definition of the fractional flow, $FF$, equation (12) can be rewritten as

$$S = FF_1(1 - e^{-k_1t}) \cdot 100 + FF_2(1 - e^{-k_2t}) \cdot 100. \quad (13)$$

Note that like the index for total flow $\Phi$, this flow rate $S$ does not require the knowledge of the blood-brain tissue partition coefficients $\lambda_i$. The parameter $S$ is similar to other indices reported in the literature. Historically the concept of an initial slope has been well established for many years for the $^{133}\text{Xe}$ injection method. To date the attempts to apply it to the inhalation method, however, have been limited by the necessity to correct for recirculation of indicator. This in turn requires a monitoring time of much more than two minutes after start of clearance to obtain a proper estimate of $k_i$ and in turn a suitable parameter set $p_i$ and $k_i$. 

$\Phi$ cancels out on the right-hand side of equation (10)
NORMAL SUBJECTS (N = 46)

**TABLE 1**

Regional Cerebral Blood Flow Indices for Total Flow ($\Phi$) and Flow Rate ($S$) in 46 Right-handed Healthy Subjects

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>G</th>
<th>H</th>
<th>Mean</th>
<th>S.E.</th>
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<td></td>
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<td>45</td>
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</tr>
<tr>
<td>10</td>
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<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>40.4</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Figure 1.** Regional cerebral blood flow indices for total flow ($\Phi$) and flow rate ($S$) in 46 right-handed healthy subjects. In this and the following figures, the regional values for $\Phi$ are expressed as a percentage, $\Phi\%$, of the total sum of $\Phi$ of all 14 regions. * = Statistically significant interhemispheric differences. The solid line refers to the left hemisphere, the broken line to the right. The letters A through H refer to the brain regions shown in the sketch of figure 3: (A) pre-frontal; (B) pre-central, superior-frontal; (C) inferior-frontal; (D) Rolandic; (E) centro-temporal; (G) parietal; (H) temporo-occipital.

significant at the level of $p < 0.0001, 0.047$, and $< 0.0001$, respectively. The hemispheric mean of $\Phi$ is significantly higher on the left side ($p = 0.034$). The interhemispheric correlation coefficients of six of the seven pairs of homologous regions range from 0.859 to 0.962, that of the temporo-occipital regions is 0.672. The hemispheric means of $\Phi$ show an almost complete interhemispheric correlation ($r = 0.967$). $S$ is bilaterally highest in the frontal lobe, gradually declining in size from the pre-frontal to the temporo-occipital regions. The interhemispheric asymmetry inferior-frontally is statistically significant ($p = 0.001$), that of the hemispheric means of $S$ reaches a level of $p = 0.076$.

**Figure 2.** Pneumoencephalogram of case 1 (atrophy of the right cerebral hemisphere). Left: antero-posterior view, supine position. The frontal horn and the body of the right lateral ventricle is markedly enlarged. Right: postero-anterior view, prone position. The occipital horn of the right lateral ventricle is considerably enlarged.

**Patients**

**Case 1: Atrophy of a Cerebral Hemisphere**

A 22-year-old woman with mental retardation and chronic left hemiparesis was referred for evaluation because of progressing mental deterioration and worsening of the seizure disorder from which she had been suffering since age 8. The pneumoencephalogram (fig. 2) and carotid angiogram revealed atrophy of the right hemisphere. The results of the rCBF measurement are shown in table 2 and figure 3.

The interhemispheric correlation coefficients of the seven homologous regions range from 0.859 to 0.917, that of the hemispheric mean values is 0.982.

**Table 1** Regional Cerebral Blood Flow Indices for Total Flow ($\Phi$) and Flow Rate ($S$) in 46 Right-handed Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>L</th>
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<tbody>
<tr>
<td></td>
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<td>S.E.</td>
<td>Mean</td>
<td>S.E.</td>
<td>Mean</td>
<td>S.E.</td>
<td>Mean</td>
<td>S.E.</td>
</tr>
<tr>
<td>A</td>
<td>*358</td>
<td>17</td>
<td>332</td>
<td>16</td>
<td>50.9</td>
<td>0.8</td>
<td>50.9</td>
<td>0.7</td>
</tr>
<tr>
<td>B</td>
<td>446</td>
<td>18</td>
<td>439</td>
<td>15</td>
<td>49.2</td>
<td>0.7</td>
<td>49.3</td>
<td>0.7</td>
</tr>
<tr>
<td>C</td>
<td>475</td>
<td>16</td>
<td>474</td>
<td>14</td>
<td>*47.8</td>
<td>0.6</td>
<td>48.7</td>
<td>0.7</td>
</tr>
<tr>
<td>D</td>
<td>375</td>
<td>15</td>
<td>377</td>
<td>15</td>
<td>46.0</td>
<td>0.6</td>
<td>46.0</td>
<td>0.7</td>
</tr>
<tr>
<td>E</td>
<td>*453</td>
<td>14</td>
<td>469</td>
<td>16</td>
<td>46.4</td>
<td>0.6</td>
<td>46.9</td>
<td>0.6</td>
</tr>
<tr>
<td>G</td>
<td>399</td>
<td>12</td>
<td>398</td>
<td>14</td>
<td>45.9</td>
<td>0.6</td>
<td>45.8</td>
<td>0.7</td>
</tr>
<tr>
<td>H</td>
<td>*384</td>
<td>10</td>
<td>347</td>
<td>11</td>
<td>43.5</td>
<td>0.6</td>
<td>43.5</td>
<td>0.6</td>
</tr>
<tr>
<td>HM</td>
<td>*413</td>
<td>14</td>
<td>405</td>
<td>13</td>
<td>47.1</td>
<td>0.6</td>
<td>47.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Mean Paco 40.4 ± 2.3 (SD) mm Hg; mean MAP 95.0 ± 12.4 (SD) mm Hg.

Statistically significant interhemispheric differences. S.E. = standard error. The letters A through H refer to the brain regions shown in the sketch of figure 3. HM = hemispheric mean; L/R = left/right hemisphere.
$\phi$ is 20.4% lower than the left. The right hemispheric mean of $S$, however, is only 2.6% lower than the left. $S$ indicates a comparable size of the clearance rates in both hemispheres, while $\phi$ reveals a considerable interhemispheric asymmetry. Since $\phi$ is proportional to total flow, the larger left hemisphere of this patient reveals the bigger total flow than the atrophic right hemisphere, as would be expected from the radiological findings (fig. 2). The flow per unit of time and of tissue mass, as implied in $S$, is, however, approximately similar for both hemispheres. The main rCBF finding in this case is, therefore, the interhemispheric asymmetry in total perfusion of either hemisphere and not an essential difference in the perfusion rate per unit of tissue mass. To illustrate the salient features of $\phi$ and $S$, their behavior in three homologous brain regions is described in detail:

Pre-frontally (A) and inferior-frontally (C). The interhemispheric differences of $S$ are in the same direction as those of $\phi$, but of much smaller magnitude. $S$ of the right-sided regions (A) and (C) is only 1.1% and 1.9%, respectively, lower than that of the left-sided homologous regions. $\phi$ in contrast is 23.7% and 22.4% smaller, respectively. Because of lack of a weighting factor, $S$ does not show the pronounced interhemispheric asymmetry evidenced by $\phi$.

Temporo-occipitally (H). In contrast to the findings in regions (A) and (C), the parameter $S$ is temporo-occipitally 23% higher on the right side, whereas $\phi$ is 5% smaller on the right side compared with the left. Apparently, the parameterized estimate of total flow, $\phi$, is in the right temporo-occipital region lower than in the left despite the distinctly higher perfusion rate on the right side evidenced by $S$. The parameters $\phi$ and $S$ combine suggest diagnostically relative hyperperfusion of a small tissue mass in the right temporo-occipital region.

The two-compartmentally derived parameters $f_1$ and $w_t$ are also given in table 2. Since they are supposed to be highly dominated by gray matter flow represented in the fast clearing first compartment, a comparison with $\phi$ and $S$ is of interest. The latter parameters are not predicated on separation of fast and slow compartments and are, therefore, not subjected to the phenomenon of slippage. The flow rate $f_1$ shows pre-frontally and inferior-frontally the higher values in the right atrophic hemisphere, in contrast to $S$. The relative weight $w_t$ is consistently lower on the right side than on the left. Its interhemispheric asymmetries for homologous regions, however, do not correlate in size with those revealed by $\phi$.

Case 2: Small Cerebral Ischemic Infarction in Association with Transient Ischemic Attacks

A 60-year-old right-handed man with a history of transient loss of speech two years prior to admission was referred for weakness of the right arm lasting half a minute, and incoherent speech lasting a few hours. During his hospital course he developed intermittent dysphasia, dysarthria, and numbness in the right hand, but no motor weakness. The CT-scan performed one day after occurrence of the first attack revealed an area of diminished density in the left temporo-parietal region; the cerebral ventricles and sulci appeared mildly to moderately enlarged (fig. 4). A left carotid angiogram carried out eight days after the first episode showed a 30% stenosis of the left internal carotid artery without evidence of ulceration; there were marked arteriosclerotic irregularities in the cavernous and distal portion of the internal carotid artery, but no intracranial abnormalities were otherwise found. The results of the rCBF measurement performed on the same day as the CT-scan are shown in table 3 and figure 5.

Both $\phi$ and $S$ indicate in this patient severely impaired rCBF mainly in the distribution of the left middle cerebral artery (regions B, C, D, E, and G). Based upon the CT-scan an area of indicator maldistribution may be expected in the left temporo-parietal region. $\phi$ reveals the most pronounced interhemispheric asymmetries in the regions E, G, and B with 30%, 22%, and 20%, respectively, lower values on the left side than on the right. The corresponding values for $S$ are 17%, 13%, and 12%. In the centro-temporal region E the

\[\begin{array}{cccccc}
\text{A} & 291 & 222 & 45.7 & 45.2 & 73 & 76 & 43 & 37 \\
\text{B} & 320 & 243 & 41.9 & 38.1 & 67 & 63 & 40 & 35 \\
\text{C} & 353 & 274 & 41.9 & 41.1 & 69 & 73 & 40 & 33 \\
\text{D} & 225 & 179 & 36.7 & 33.1 & 59 & 55 & 34 & 28 \\
\text{E} & 305 & 220 & 39.7 & 35.5 & 61 & 58 & 45 & 36 \\
\text{G} & 191 & 176 & 35.5 & 34.9 & 58 & 55 & 32 & 28 \\
\text{H} & 180 & 171 & 33.0 & 40.6 & 56 & 79 & 26 & 26 \\
\text{HM} & 206 & 212 & 39.2 & 38.2 & 63.3 & 66.0 & 37.1 & 31.7
\end{array}\]

TABLE 3 rCBF in Case 2: Cerebral Ischemic Infarction in the Left Hemisphere in Association with Transient Ischemic Attacks

- Paco 43.5 mm Hg; MAP 128 mm Hg.
- Labels as in table 1.

\[\begin{array}{cccccc}
\text{L} & \text{R} & \text{L} & \text{R} & \text{L} & \text{R} \\
\text{A} & 179 & 178 & 34.6 & 35.5 & 50 & 53 & 34 & 33 \\
\text{B} & 213 & 267 & 33.1 & 37.5 & 46 & 57 & 36 & 34 \\
\text{C} & 256 & 272 & 33.4 & 34.8 & 51 & 51 & 33 & 36 \\
\text{D} & 163 & 201 & 31.2 & 33.4 & 49 & 50 & 27 & 31 \\
\text{E} & 191 & 272 & 28.5 & 34.3 & 41 & 50 & 34 & 37 \\
\text{G} & 177 & 227 & 27.9 & 31.9 & 45 & 45 & 26 & 35 \\
\text{H} & 225 & 253 & 30.9 & 32.3 & 44 & 46 & 35 & 35 \\
\text{HM} & 201 & 239 & 31.4 & 34.2 & 46.6 & 50.3 & 32.1 & 34.4
\end{array}\]
FIGURE 4. CT-scans, slices 2B, 3A, 3B, and 4A, of case 2 (ischemic infarction in the left hemisphere in association with transient ischemic attacks). An area of diminished density is seen in the left temporo-parietal area. The ventricles and cerebral sulci are mildly to moderately enlarged.

30% reduction of $\Phi$ compared with the contralateral side is due to not only the 17% reduction in the perfusion rate, but also to an apparent loss of tissue mass perfused. The same may hold true for the left parietal (G) and precentral (B) regions. Comparable extensive interhemispheric differences are not disclosed by $I_t$ and $W_t$.

Case 3: Progression of a Unilateral Ischemic Cerebral Infarction Followed by a Second Infarction in the Contralateral Hemisphere

A severe left hemiparesis developed in a 72-year-old diabetic woman 12 hours prior to admission and progressed to a persistent hemiplegia 58 hours after onset. On the

FIGURE 5. Regional cerebral blood flow in case 2 (ischemic infarction in the left hemisphere in association with transient ischemic attacks). Labels as in figure 1.
seventh day of the course the patient became aphasic and hemiplegic on the right side as well. The CT-scan obtained on the third and eleventh day after onset are shown in figure 6. The first scan coincided temporally with the progression of the left hemiparesis to hemiplegia. It showed a circumscribed low density area in the right hemisphere. The second scan was performed four days after the occurrence of the right hemiplegia and aphasia. It showed an extensive low density area in the left hemisphere in addition to the initially found small low density area in the right hemisphere. Serial rCBF measurements correlated well with the stepwise progression in the clinical course which ultimately proved fatal. The results for Φ and S are shown in table 4 and presented graphically for the regional Φ and S in figures 7 and 8, respectively, and for the hemispheric means of Φ in figure 9.

The initial rCBF measurement (#1) performed 18 hours after onset showed impaired flow in the distribution of the right middle cerebral artery characterized by lower values of either Φ or S or both mainly in the right-sided Rolandic (D),

### Table 4. rCBF in Case 8: Progression of an Ischemic Infarction in the Right Cerebral Hemisphere, Followed by a Second Infarction in the Contralateral Hemisphere Which Occurred Between Measurements #5 and #6

<table>
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FIGURE 6. CT-scans of case 3 (progression of a right-sided ischemic cerebral infarction, followed by a second infarction in the contralateral hemisphere). Left: low density area in the right hemisphere on the third day after onset. Right: extensive low density area in the left hemisphere on the eleventh day after onset, in addition to the initially found circumscribed low density area in the right hemisphere.
Regional cerebral blood flow in case 3. Time course of $\Phi$ through six consecutive measurements ($\#1$ through $\#6$). The regional values for $\Phi$ are expressed as a percentage, $\Phi\%$, of the total sum of $\Phi$ of all 14 regions. $HS =$ hemispheric sum of $\Phi\%$. The letters $A$ through $H$ refer to the brain regions shown in the sketch of figure 3. The solid lines refer to the left hemisphere, the broken lines to the right.

centro-temporal (E), and parietal (G) regions, compared with the left. In the second ($\#2$) and third ($\#3$) measurements 26 and 46 hours after onset, the interhemispheric asymmetries of $\Phi$ and $S$ between homologous regions varied in size and orientation throughout the hemispheres, revealing either moderate aggravation, attenuation, or even inversion of the asymmetries found in the initial ($\#1$) measurement. The progression of the neurological deficit from left hemiparesis to hemiplegia occurred between the third ($\#3$) and fourth ($\#4$) measurements. It was followed by a distinct aggravation and spatial extension of the interhemispheric asymmetries of both $\Phi$ and $S$ in measurement $\#4$, with the symptomatic hemisphere showing the lower values. Remarkably, the small asymmetry of the temporo-occipital regions, which predominantly represent vertebro-basilar/posterior cerebral circulation, remained relatively constant.

Table 4 and figures 8 and 9 indicate that the clinical worsening was also accompanied by a distinct general increase of both $\Phi$ and $S$. This is not obvious in figure 7 because it expresses regional $\Phi$ values as a percentage of the sum of these 14 values. (It may be speculated that in this instance the general flow increase contributed to the focal and perifocal edema in the lesion area thus worsening the functional deficit.) The fifth ($\#5$) rCBF measurement, performed 55 hours after the first progression of the neurological deficit,
revealed a peculiar attenuation or even reversal of the interhemispheric asymmetries, accompanied by a marked reduction of \( \Phi \) and \( S \) in all regions. Two days later the patient developed an extensive infarction in the left hemisphere, as documented by the CT-scan obtained four days later (fig. 6). The last rCBF measurement (6), performed 10 days after the disastrous cerebrovascular event in the left hemisphere, disclosed a decrease of the mean hemispheric \( \Phi \) of 45% and 32% on the left and right side, respectively, compared with the preceding rCBF measurement \( \Phi \) (fig. 9). The interhemispheric asymmetries were most pronounced in the regions A, B, D, E, and G. The parameter \( S \) declined simultaneously in both hemispheres to a similar degree, except in the inferior-frontal region C where the right side decreased more than the left. The reduction of the mean hemispheric S from the fifth to the sixth measurement was bilaterally 25%. In this instance the greater impairment of the blood supply to the left hemisphere was disclosed by \( \Phi \) and not by \( S \).

### Discussion

**Proportionalized Total Flow, \( \Phi \)**

Høgest-Rasmussen and co-workers\(^1\) discussed the problem of indicator maldistribution in acute apoplexy, referring to the fact that the \( \text{\textsuperscript{133}} \text{Xe} \) injection method accounts only for perfused tissue. They considered that the observed counting rate from a region containing an ischemic focus would be less than that for the same region with normal perfusion. They noted, however, that in practice this "lack of counts" had not appeared to be of value. Our experience with the \( \text{\textsuperscript{133}} \text{Xe} \) inhalation method does not corroborate this view. The introduction of a weighting factor for indicator delivery to the brain tissue under observation turns out to be highly useful in distinguishing brain areas with impaired perfusion. The count rate from a brain region divided by the convolution of the arterial input of tracer to that region (see equation 6) is proportional to total flow which is responsible for the total amount of indicator delivered to brain tissue. It provides meaningful complementary information about rCBF not contained in clearance constants or normalized flow rates.

Any level of total flow will be proportionally indicated by the magnitude of the regional count rate regardless of the magnitude of the underlying determinants. The more voluminous the vascular bed the larger the total flow will be. It seems, therefore, plausible that \( \Phi \) recorded from the bulkiest parts of the brain will yield the largest values. In the normal subjects the highest values of \( \Phi \) occur in the pre-central, inferior-frontal, and centro-temporal regions of both hemispheres which is in accordance with their anatomical size and blood supply (fig. 1). A shrunken vascular bed in an atrophic hemisphere in turn will carry less total flow as exemplified in case 1 (fig. 3). Any reduction in size of the vascular bed necessarily diminishes total flow, e.g. ischemic sequestration of brain tissue by thrombo-embolic vascular occlusion reduces the original capacity of the vascular bed and thus \( \Phi \) as illustrated by cases 2 and 3 (figs. 5, and 7–9). Any space-demanding process, particularly brain edema, may reduce the potential size of the vascular bed and thus \( \Phi \). This may hold true as well for severely increased intracranial pressure of any cause which decreases the capacity of the vascular bed by its extrinsic compressive force.

An empirical approach may be helpful in the assessment of the informational value of \( \Phi \). If one postulates that the sensitivity of a parameter to detect rCBF differences in the brain can serve as a rating scale for its usefulness, then \( \Phi \) appears to be superior to the other parameters available at present. As reported elsewhere\(^2\) the rCBF indices \( f_1, w_1, FF_1, \) and ISI reveal in normal subjects significant interhemispheric differences only in the inferior-frontal regions. \( \Phi \) in the present series of normals (table 1, fig. 1), however, indicates statistically significant interhemispheric asymmetries in the pre-frontal, centro-temporal, and temporo-occipital regions. Although these asymmetries are small in comparison to the standard error of the corresponding regional mean values, they are nonetheless statistically significant due to the strong interhemispheric correlation of \( \Phi \). Remarkably, \( \Phi \) in the inferior-frontal regions is not different between the two hemispheres despite the statistically significant difference of the flow rate \( S \). Hence, it appears that \( \Phi \) contains different information about rCBF than \( S \), implying conceptually total flow and not flow per unit of tissue mass.

**Influence of the Blood-Brain Tissue Partition Coefficient \( \lambda_i \)**

At present there is no way to assess in vivo the appropriate set of \( \lambda_i \) in a given subject at a given time for all tissue fractions of a given brain region. Moreover, experimentally determined \( \lambda_i \) for gray and white matter cannot reliably be related to the clearance constants derived, as mentioned earlier in connection with slippage. Thus, the substitution of \( \lambda_i \) into the equations to calculate rCBF would not contribute to the clarification of the rCBF data obtained. Rather it may result in unrecognized distortions which can be very misleading in the interpretation of rCBF and its correlation to clinical findings. The unavailability of individually appropriate sets of \( \lambda_i \) is, however, no handicap to arrive at useful data. The original and basic information about rCBF is contained in the clearance curves themselves.

As shown above the computer-analysis of the clearance curves by Obrist's model\(^10,12\) provides directly the coefficients \( p_i \) from which the new parameter for total flow, \( \Phi \), can be derived without any knowledge of the \( \lambda_i \) involved. The proportionality constant \( \beta \) implied in the \( p_i \) is independent of the \( \lambda_i \). A breakdown of the \( p_i \) into their physiological components represented by the absolute tissue weights \( W_i \) and the flow rates \( f_i \) that would require the substitution of \( \lambda_i \) is not needed to obtain the parameter for total flow. As exemplified by case 3, \( \Phi \) does not behave erratically in successive rCBF measurements despite progressive cerebrovascular pathology rendering ample cause for shifts in compartmental boundaries and alterations of \( \lambda_i \) due to ischemic infarction. The six rCBF measurements appear to correlate well with the clinical course of the patient.

**Influence of "Cross-Talk"**

The contamination of unilateral regional measurements of \( \text{\textsuperscript{133}} \text{Xe} \) clearance by radiation from the opposite hemisphere, as implied in the term "cross-talk," influences...
the outcome of \( \Phi \) to a substantial degree. The higher the count rate in the contralateral regions the more undesired counts will be picked up by the monitoring device in the ipsilateral region. Thus, \( \Phi \) in its uncorrected form will always reveal a value higher than is expected without cross-talk. Recent studies carried out in our laboratory indicate that the rCBF parameters can be partially corrected for cross-talk so that they are more useful for clinical purposes. Among the various parameters \( \Phi \) is the most sensitive to cross-talk. It is, therefore, remarkable that it nonetheless discloses inter-hemispheric differences of rCBF not found with the other parameters.21

Flow Rate, S

Several initial slope indices have proven useful in the calculation of rCBF. In the \(^{133}\)Xe injection method an initial one- or two-minute slope plotted semilogarithmically against time provides a rapid means of comparing regions in the same hemisphere.15,16 In the inhalation method, however, the effects of recirculation of indicator preclude the direct use of this approach. Accordingly, the principle was modified to calculate the initial slope index, ISI, for the inhalation method.14 While this modification is based on computed \( k_1 \) and \( k_2 \) which have been corrected for recirculation, it is also based on the total count rate \( N_T (x) \), i.e. explicitly its two-compartmental components \( N_T (x) \) at start-fit time \( x \) which may range from 1.3 to 2.9 minutes. The fixation of the computed slope of ISI to the arbitrary time interval between the second and third minute after start of \(^{133}\)Xe inhalation14 produces variation in the relative contribution of the two compartments, thus giving rise to methodological distortion of the rCBF data. In order to avoid such distortion the parameter S was introduced as an index for the normalized flow rate. As a single rCBF parameter it is of limited value as are other normalized flow rate indices. In combination with \( \Phi \), however, it may provide clinically useful information about regional cerebral blood flow.

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