For many years, regional cerebral blood flow (rCBF) has been measured successfully on a routine basis using various radioactive inert gas methods, although some of the underlying assumptions of the model (e.g., complete and instantaneous equilibration of the indicator gas between capillary blood and tissue, homogeneous perfusion of each compartment) may not always be fully valid, especially in pathologic tissue, and the distribution coefficient cannot be determined by external detection of radiation in two-dimensional projections. Despite those limitations injection of radioactive inert gases into the internal carotid artery allows rCBF measurements with reasonable accuracy. High spatial resolution can be achieved either by means of a gamma-camera or by a multicylindrical system.

In order to avoid arterial puncture noninvasive pro-
cedures for measuring rCBF were developed, but those techniques incurred other problems, e.g., separation of extracerebral ("third compartment") flow from cerebral flow, correction for recirculating activity and radiation scattered from the airways. In 1975 Obrist et al. described a method designed to overcome the major difficulties. That approach essentially requires inhalation of Xe-133 for 1 min, followed by a 10 min washout period, continuous recording of both cranial activity and endtidal air activity as an estimate of arterial isotope concentration, bicompartimental deconvolution starting when the air curve has dropped to 10 to 20% of its peak value.

Several modifications of the original method have been proposed, e.g., intravenous injection of Xe-133 instead of inhalation yielding equivalent results in normal subjects, and utilization of a gamma-camera in lieu of multiple detectors for optimum selection of regions of interest as well as for rapid visual detection of artifacts. Because of the complexity of physiological and technical variables involved, however, accuracy of noninvasive rCBF measurements remains limited, and problems are accentuated by application of the technique to patients with cerebrovascular disease. From among the principal sources of error, this study focuses on the influence of counting rates and on consequences of high recirculating activity. Although some data as to the effect of counting statistics on accuracy of noninvasive flow measurements are available, they are limited to certain assumptions about recirculating activity. The latter variable, however, also affects rCBF measurements, as described quantitatively in the present report.

Methods

All calculations are based on data from rCBF measurements in 50 patients, selected at random from a larger series of routine examinations carried out in this laboratory. All patients were suspected to suffer from cerebrovascular disorders, their age ranged between 17 and 75 years, with a mean of 53.8 years.

Following slow intravenous bolus injection of 20–30 mCi Xe-133 in normal saline solution, brain activity was continuously measured for 11 min with a gamma-camera in a lateral view, while expired air activity was counted with a separate detector. Expiratory CO₂ concentrations were recorded continuously during flow measurements. Sampling intervals were 0.01 min for expired air and 0.1 min for brain activity. On-line data acquisition and processing was performed by a PDP 11/34 mini computer system.

On the curve of expiratory air activity versus time the peaks representing endtidal xenon concentration were selected, interpolated at intervals of 0.1 min, and smoothed by a weighted 7-point running means procedure. A recirculation ratio Q then was calculated, representing the amount of late recirculating activity relative to initial arterial activity, from two integrals — the first from maximum to 1 min after maximum, the second from 1 min to 8 min after maximum (fig. 1) — according to

\[
Q = \frac{\int_{t_1}^{t_2} C_a(t) \, dt}{\int_{t_0}^{t_1} C_a(t) \, dt}
\]

with \( C_a(t) \) = endtidal air activity at time \( t \) and 
\( t_0 = \) time at maximum \\
\( t_1 = t_0 + 1 \) min \\
\( t_2 = t_0 + 8 \) min

Standard CBF parameters were determined for the whole hemisphere applying the method of Obrist et al. Pertinent patient data are summarized in table 1.

As a first step in calculations of the variance of CBF measurements, for each of the 50 patients an idealized head activity curve \( C(T) \) was constructed by inserting the measured endtidal air activity curve, and the calculated values for \( k_1, k_2, P_1 \) and \( P_2 \) into the convolution equation.

\[
C(T) = \sum_{i=1}^{2} P_i \cdot \int_0^T C_a(t) e^{-k_i(T-t)} \, dt
\]

Those curves then were adjusted to mean counting rates of 5,000, 10,000, 20,000, 50,000, and 100,000 cpm, and superimposed with appropriate Gaussian noise (S.D. equaling the square root of counts per sample) for simulation of counting statistics. This procedure was repeated 100 times at each level, and flow values were calculated each time using Obrist's algorithm with a start-of-fit point at 15% of maximum endtidal air activity. The average ratio of peak to mean counting rates of head curves during the entire sampling period of 11 min was \( 1.929 \pm 0.2418 \).

Following elimination of non-converging fits, mean and standard deviation of flow to the first (\( F_1 \) and

![Figure 1. Example of a plot of endtidal air activity \( C_a \) (arbitrary units) versus time \( t \). Areas corresponding to the integrals from maximum to 1 min after maximum and from 1 min to 8 min after maximum are marked.](image-url)
second compartment ($F_2$), relative weight of the first compartment ($W_1$), mean flow (MF) representing the weighted mean of $F_1$ and $F_2$, initial slope (IS), and height-over-area equivalent flow ($\text{CBF}_{15}$) were computed for the above simulation data of each case, using the formulas compiled by Obrist and Wilkinson. The dependence of the standard deviation of flow parameters on counting rate and recirculation ratio was determined by linear regression analysis, following a linearizing logarithmic transformation of standard deviation and countrate. Additional simulations were performed at the 20,000 cpm level with normal flow values ($F_1 = 80.9$, $F_2 = 20.1$, MF = 46.1 ml/100 g/min; $W_1 = 41.9\%$) for all patients, based only on the individual endtidal activity curves. Those simulations were carried out both with a common start-of-fit point at 15% of maximum endtidal air activity and with a constant start of fit at 1.5 min after the beginning of the measurement. Significance was assessed by means of appropriate t-tests for linear regression, or by generalized F-statistics for multiple regressions.

**Results**

1. Influence of Variable Countrates and Recirculation

At each counting rate level a highly significant linear regression of the logarithm of the standard deviation of each flow parameter on recirculation was found ($p < 0.001$ in all cases), indicating an exponential error increase at higher recirculation. In order to assess the combined effect of both parameters, multiple regressions of the logarithm of the standard deviation as dependent variables, on recirculation ratio and logarithm of counting rate as independent variables, were computed (table 2, fig. 2). A significant ($p < 0.05$) dependence was found for all flow parameters except for $W_1$ even when estimated under the most conservative assumption of only one degree of freedom for countrate variation. For ease of comparison of the magnitude of the effect on the different flow parameters, the range on the S-axis in Fig. 2 was scaled to represent 40% of the original mean value of the respective parameter. While standard deviations of $F_1$, $F_2$, MF, and IS showed a very similar dependence on countrate and recirculation ratio, $\text{CBF}_{15}$ was considerably more stable. The standard deviation of $W_1$ was relatively small as compared to the other flow parameters. In general, there was an exponential increase of scatter at higher recirculation ratios, while the influence of counting rate was of lesser weight.

Beside the increase in parameter variance, recirculation also caused failure to converge in a considerable

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean $S$</th>
<th>Regression equation</th>
<th>$F_{49.1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_1$ (ml/100g/min)</td>
<td>6.25</td>
<td>$\log S = 0.784 \times Q - 0.516 \times \log C + 2.503$</td>
<td>398.4*</td>
</tr>
<tr>
<td>$F_2$ (ml/100g/min)</td>
<td>1.88</td>
<td>$\log S = 0.671 \times Q - 0.442 \times \log C + 1.744$</td>
<td>263.3*</td>
</tr>
<tr>
<td>MF (ml/100g/min)</td>
<td>2.78</td>
<td>$\log S = 0.859 \times Q - 0.516 \times \log C + 2.109$</td>
<td>599.0*</td>
</tr>
<tr>
<td>$W_1$ (%)</td>
<td>2.28</td>
<td>$\log S = 0.815 \times Q - 0.460 \times \log C + 1.797$</td>
<td>151.2</td>
</tr>
<tr>
<td>IS</td>
<td>4.7</td>
<td>$\log S = 0.844 \times Q - 0.561 \times \log C + 2.534$</td>
<td>303.4*</td>
</tr>
<tr>
<td>$\text{CBF}_{15}$ (ml/100g/min)</td>
<td>1.99</td>
<td>$\log S = 0.938 \times Q - 0.603 \times \log C + 2.276$</td>
<td>419.4*</td>
</tr>
</tbody>
</table>

*p < 0.05.
TABLE 3  Percentage of Correctly Converging Fits

<table>
<thead>
<tr>
<th>Counting rate (cpm)</th>
<th>Q ≤ 0.4</th>
<th>0.4 &lt; Q ≤ 0.6</th>
<th>0.6 &lt; Q ≤ 0.8</th>
<th>0.8 &lt; Q ≤ 1.0</th>
<th>1.0 &lt; Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,000</td>
<td>100.0</td>
<td>97.0</td>
<td>84.3</td>
<td>72.0</td>
<td>72.6</td>
</tr>
<tr>
<td>10,000</td>
<td>100.0</td>
<td>99.8</td>
<td>94.7</td>
<td>91.0</td>
<td>81.2</td>
</tr>
<tr>
<td>20,000</td>
<td>100.0</td>
<td>99.9</td>
<td>98.1</td>
<td>92.3</td>
<td>94.0</td>
</tr>
<tr>
<td>50,000</td>
<td>100.0</td>
<td>96.8</td>
<td>95.8</td>
<td>99.2</td>
<td>98.4</td>
</tr>
<tr>
<td>100,000</td>
<td>100.0</td>
<td>100.0</td>
<td>99.9</td>
<td>97.7</td>
<td>95.8</td>
</tr>
<tr>
<td>Total # of fits at each level</td>
<td>400</td>
<td>1600</td>
<td>1900</td>
<td>600</td>
<td>500</td>
</tr>
</tbody>
</table>

number of simulation runs (table 3). Those runs were not included in the calculation of standard deviations, but their occurrence indicates possible bias in actual measurements. Although convergence was more dependable at higher countrates, even at a mean counting rate of 100,000 cpm the fit procedure did not converge in a few cases of substantial recirculation.

2. Influence of flow values

While in the above stimulation runs original flow values varied from patient to patient, in order to obtain data representative of measurements in cerebrovascular disease, a very similar regression of the logarithm of standard deviation S on recirculation ratio Q was obtained when flow values were kept constant. As shown in figure 3, for normal MF at the 20,000 cpm mean countrate level the correlation is even closer (fig. 3b, log S = −0.235 + 2.182 × Q, t49 = 13.842, p < 0.001) than for varying flow (fig. 3a, log S = −0.298 + 2.066 × Q, t49 = 10.684, p < 0.001), and the calculated standard deviations are of the same magnitude. This demonstrates that the increase of variance is not an effect of the variability of flow values. Accordingly, there was no correlation between flow values and recirculation rates in this patient group.

3. Influence of Start-of-fit time

As expected, there was a close correlation between recirculation ratio Q and start-of-fit time T (fig. 4, T = 1.247 + 2.558 × Q, t49 = 12.5, p < 0.001). In order to distinguish the relative magnitude of the influences of those two variables, a simulation series was run at the 20,000 cpm level with constant start-of-fit time (1.5 min after beginning of measurement) and normal flow values. Regression analysis (table 4) revealed a strong linear dependence (p < 0.001) of the error of F2 and W, on recirculation ratio, while that of F, (p < 0.01) and MF (p < 0.02, fig. 5) was much weaker, but still significant. No significant dependence, however, was found for the errors of IS and CBF on recirculation at constant start-of-fit time. All fits converged properly even at the highest recirculation rates. Correspondingly, in those stimulation runs using the 15% of maximum criterion, at this countrate level failure to converge did not occur at start-of-fit times below 2.5 min.

Discussion

In order to quantify the variance of rCBF-results, simulation of decay statistics was performed already by Obrist et al., when introducing the bicompartimental inhalation method. Their simulations, however, were based on a single arbitrary endtidal air curve only. A coefficient of variation of 3% at a peak counting rate of 60,000 cpm was obtained for F,. Since that peak counting rate corresponds to a mean counting rate of 31,104 cpm, and that coefficient of variation translates into a standard deviation of 2.4 ml/100 g/min at a normal F, value of 80 ml/100 g/min, a recirculation ratio of 0.25 can be estimated from the regression
Figure 4. Regression line and 95% confidence limits of start-of-fit time $T$ (min) according to the 15%-of-maximum criterion, on recirculation ratio $Q$.

Equations for the curve of expired air activity chosen by those authors. This recirculation ratio corresponds to a start-of-fit time of 1.9 min according to the 15% criterion which is not far from the 1.6 min start-of-fit time chosen by Obrist et al.

Unfortunately, in the present series of rCBF measurements utilizing the i.v. method much higher recirculation ratios and, therefore, later start-of-fit times were observed. This finding corresponds with studies on the reproducibility of intravenous rCBF measurements in patients with cerebrovascular disease: Mean differences of $-0.12 \pm 9.6$ ml/100 g/min for regional $F_1$ between two measurements performed at an average interval of 2 hours were reported by Thomas et al., and Meric et al. found $F_1$-differences of $0.0 \pm 12.1$ for the left and $-0.4 \pm 11.8$ ml/100 g/min for the right hemisphere within a 30 min interval, both variations being considerably higher than those obtained by Obrist et al. in healthy volunteers ($-0.5 \pm 5.3$ ml/100 g/min) using the Xenon inhalation technique.

This discrepancy may at least in part be explained by the fact that even slight disturbances of pulmonary function lead to a delay of Xenon washout in the lungs, which situation may be more common in a group of elderly patients suffering from cerebrovascular disease, than in a group of normal persons. Another occasional source of high recirculation may be partial retention of tracer in peripheral veins, a problem unique to the i.v. procedure.

The exponential behavior of the increase in scatter obviously is caused by delay of the start-of-fit time at high recirculation, since recirculation itself only leads to a linear increase of the standard deviation of bicomartmental flow parameters, especially of $F_2$ and $W_1$, while non-compartmental parameters are not affected. Thus there seem to be two major determinants of the resulting error: While a late start-of-fit primarily leads to uncertainty in estimates of gray matter flow, it also affects IS, MF, and $F_2$, recirculating activity causes uncertainty of a lesser degree mainly in compartment separation and estimation of white matter flow.

Although on account of the present simulation results a very early start-of-fit would appear desirable, some objections must be considered. In comparative intravenous and intracarotid rCBF studies Meric et al. demonstrated that for start-of-fit times earlier than 3 min there is some overestimation of gray matter flow in cerebrovascular patients, which phenomenon was explained by those authors on the basis of radiation scattered from the airways and of variable circulatory delay between end-tidal and cerebral arterial tracer appearance. In attempts to minimize these effects by introduction of additional variables, variance may be enlarged even further and therefore, it remains doubtful if real improvement can be achieved. Extending measuring time to 14 or 15 min may stabilize results especially in low flow states. This effect seems to be mainly due to a reduction in compartmental slippage, being reflected in the variance of $W_1$, but the procedure probably does not eliminate the error in estimates of $F_2$ caused by late start-of-fit. It may, however, improve convergence probability at high recirculation rates, since curve fitting is then based on a greater number of points.

In this study variation of simulation results was caused by different decay statistics only, while in an actual measurement additional sources of error are to be expected which have been discussed extensively in the literature. Scattered radiation from the airways, as mentioned above, but also extracerebral activity in scalp and bone marrow, as well as radiation from the

**Table 4** Dependence of Standard Deviation $S$ (ml/100 g/min) of Flow Parameters on Recirculation Ratio $Q$ at Constant Start-of-fit Time (1.5 min)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression equation</th>
<th>$t_{0.05}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_1$ (ml/100 g/min)</td>
<td>$S = 2.248 + 0.511 \times Q$</td>
<td>2.944t</td>
</tr>
<tr>
<td>$F_2$ (ml/100 g/min)</td>
<td>$S = 0.523 + 0.350 \times Q$</td>
<td>10.494*</td>
</tr>
<tr>
<td>MF (ml/100 g/min)</td>
<td>$S = 0.849 + 0.157 \times Q$</td>
<td>2.523</td>
</tr>
<tr>
<td>$W_1$ (%)</td>
<td>$S = 0.551 + 0.280 \times Q$</td>
<td>7.491*</td>
</tr>
<tr>
<td>IS</td>
<td>$S = 2.007 + 0.178 \times Q$</td>
<td>0.981</td>
</tr>
<tr>
<td>CBF$_{15}$ (ml/100 g/min)</td>
<td>$S = 0.740 + 0.004 \times Q$</td>
<td>0.065</td>
</tr>
</tbody>
</table>

* $p < 0.001$, $t_p < 0.01$, $t_p < 0.02$. 

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opposite hemisphere may obscure cerebral activity washout. Furthermore, flow distribution never is fully homogeneous within the two compartments. Especially under pathological conditions there may be significant overlap between compartments causing slippage of flow values and compartmental weights which is easily detected on a graphic display of the quality of fit. Moreover, disturbances of circulatory or pulmonary function may lead not only to delayed Xenon washout, but also to false estimates of arterial from endtidal Xenon concentration. Unfortunately, trapping of gas in parts of the lungs seems to be quite common even in healthy elderly people, and its complex influence on noninvasive rCBF measurements has not been assessed as yet. Therefore, the equations described in this report only yield the lower limits of inaccuracy.

Considering all those aspects the following conclusions may be drawn. Among the sources of error in noninvasive bicompartamental rCBF measurements high recirculation is a serious problem. Its effect can be kept within acceptable limits, if the start-of-fit time is not allowed to exceed 2.5 min, for which a corresponding standard deviation of 4.65 (F), 2.04 (MF), and 1.39 (CBF) ml/100 g/min respectively at a mean countrate of 20,000 cpm is calculated from the regression equation. Using the 15%-of-maximun-activity criterion this limit is reached at a recirculation ratio of approx. 0.5 which is still below the mean value of the present patient group. Nevertheless, it appears to be a suitable compromise between the systematic errors, caused by airway scatter and variability of circulatory delay, from too early a start-of-fit, and the exponential increase of variance when start-of-fit is delayed. Errors may be further minimized, although to a lesser extent, by increased countrates and prolonged measurements. Since variance of non-compartmental flow parameters is not increasing for constant start-of-fit, those parameters should be preferred if recirculation is high.

Acknowledgement

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References

Effect of recirculation and regional counting rate on reliability of noninvasive bicompartamental CBF measurements.

K Herholz