Spectrum Subtraction Technique for Minimizing Extracranial Influence on Cerebral Blood Flow Measurements by 133Xenon Inhalation

JARL RISBERG, PH.D., BARBARA P. UZZELL, PH.D., AND WALTER D. OBRIST, PH.D.

SUMMARY Estimates of regional cerebral blood flow (rCBF) by the 133Xe inhalation method are influenced by isotope contamination from slow clearing extracerebral tissues. Subtraction of x-ray (31 keV) from gamma-ray counts (81 keV) has been suggested as a means of yielding clearance curves that are relatively free of such contamination. In the present study, rCBF measurements based on the total 133Xe spectrum (x-ray plus gamma) were compared with those derived from the subtracted spectrum (x-ray minus gamma) in 20 young controls, using a two-compartmental analysis of the clearance curves. In comparison with addition, the subtraction data gave substantially higher estimates of blood flow for the slow (second) compartment. This, along with a shift in the relative weights of the two compartments, indicated a decreased contribution of slow tissue components, consistent with a reduction in extracerebral contamination. Blood flow values obtained by subtraction were in good agreement with those reported for the intracarotid injection method. A limitation of the subtraction technique, however, is the relatively high dose of isotope required for adequate signal-to-noise ratios.

ONE SOURCE OF ERROR in the measurement of regional cerebral blood flow (rCBF) by 133Xe inhalation is contamination of the clearance curves by radioactivity from extracerebral tissues, particularly the scalp. Although the clearance of 133Xe from such tissues is dominated by very slow components (decay constants of .02 to .05), faster clearance rates are also present which overlap with those of the cerebral white matter. This overlap precludes an exact calculation of white matter blood flow, as well as the relative tissue weights for both gray and white matter.

In many applications of the technique, e.g., the study of functional changes in brain activity, fast flow rates (assumed to represent gray matter in the normal brain) are of primary interest. This fast flow is considered not to be significantly influenced by extracerebral contamination. In other largely clinical applications of the technique, an accurate estimate of slower flow rates arising from damaged tissue is of primary importance. In such studies, extracerebral contamination may present a significant problem, so that efforts to minimize it become desirable. One approach is the use of a spectrum subtraction technique, as proposed by Oldendorf and by Crawley and coworkers. This technique, based on the differential absorption of 133Xe photons at two energy levels, involves subtraction of 31 keV x-rays from 81 keV gamma-rays, a procedure aimed at reducing the influence of superficial (primarily extracranial) tissues. The present study was designed to evaluate the adequacy and usefulness of the subtraction technique. A preliminary report has been given earlier.

Methods

Cerebral blood flow estimates were made on 20 normal young volunteers, age 21-26 years. Only a brief description of the 133Xe inhalation method will be given here, since it has been described in detail elsewhere. 133Xe mixed with air (5 mCi per liter) was inhaled for one minute through a face mask. Radiation from the frontal, temporal, central and occipital regions of the left hemisphere was recorded for 16 minutes following the start of inhalation by 4 NaI scintillation detectors, 1.5 cm in diameter with 1.0 cm of lateral collimation. The output from each detector was fed in parallel to a discriminator set to accept pulses above 60 keV (gamma range), and to a pulse height analyzer with the energy window set at 10-50 keV (x-ray range). The pulses were then integrated over 8 second epochs and stored in a Nuclear of Chicago multichannel analyzer for later computer processing on an IBM 1130. The arterial concentration of 133Xe was estimated from radioactivity sampled at the end-tidal peaks of the expired air. Arterial Pco2 was estimated from the same air samples by a Godart capnograph, which yielded a mean value of 36.5 mm Hg for the group.

The system described above resulted in two clearance curves from each of the 4 detectors, one for gamma-rays and one for x-rays. The two curves were both added to each other (gamma + x-ray), and subtracted (gamma - x-ray). Addition produced the wide-spectrum clearance curves usually recorded with this method, which could then be compared with those obtained by subtraction. In the subtraction procedure, a normalizing factor was used to equalize the counting efficiency of the detector for x-rays and gammarays at the surface of the scalp. This factor, which varied from 0.80 to 1.20 between detectors, was calculated from the ratio of gamma to x-ray counts recorded from a 133Xe source immediately in front of the detectors. The stability of the normalizing factor was checked by measurements close in time to the rCBF determinations. The observed x-ray count rates were multiplied by this normalizing factor before subtraction from the gamma count rates. The subtraction procedure provides a zero count rate for radiation originating at the surface, and maximum count rates for radiation emitted from tissue approximately 2.5 cm below the surface. Count rates obtained at the peak of the clearance curves averaged 262 X 10^6 cpm for addition, and 94 X 10^6 cpm for subtraction. All curves were subjected to a two-compartmental analysis, described in detail elsewhere.
Curve fitting was carried out to 11 minutes following the start of inhalation. The following parameters were computed:

\( f_1 \): An estimate of gray matter blood flow obtained by multiplying the decay constant of the fast compartment (\( k_1 \)) by the tissue blood partition coefficient for gray matter (\( \lambda \text{gray} = 0.80 \) at normal hemoglobin levels).

\( f_2 \): An estimate of white matter blood flow obtained by multiplying the decay constant of the slow compartment (\( k_2 \)) by the tissue blood partition coefficient for white matter (\( \lambda \text{white} = 1.50 \)). This estimate assumes no extracerebral contamination, a condition that should be approximated by the subtraction technique.

\( w_1 \): The relative tissue weight of the fast compartment. \( w_2 \) is the corresponding weight for the slow compartment (\( w_1 + w_2 = 1 \)).

\( T \): The weighted mean flow of the two compartments (\( T = w_1 f_1 + w_2 f_2 \)).

\( f_1/ \): The "fractional flow" of the fast compartment, i.e., fraction of the total blood flow contributed by the gray matter (\( f_1/ = w_1 f_1/(w_1 f_1 + w_2 f_2) \)).

### Results

Results are summarized in table 1, which is based on an average of the 4 probes. All rCBF parameters gave higher values for the spectrum subtraction than for the spectrum addition analysis. In order to compare the rCBF variables, differences between addition and subtraction were expressed in percentage ((subtraction - addition)/addition). Large differences of 22 to 24% were obtained for \( w_1 \), \( f_2 \), and \( T \), while small differences of 4 to 5% were obtained for \( f_1 \) and \( f_1/ \). As shown in table 1, the rCBF parameters based on spectrum subtraction were in good agreement with those obtained by the intracarotid injection method in normal subjects.^{13} Spectrum addition, however, yielded more discrepant values. Whereas the relative tissue weight of the fast compartment (\( w_1 \)) was essentially the same for subtraction and intracarotid injection (approximately 50%), the addition analysis resulted in considerably lower values of about 40%. The finding of a relatively large fast compartment by the subtraction technique is consistent with a reduction in size of the slow compartment due to elimination of extracerebral components.

Figure 1 presents regional differences between the addition and subtraction analysis, expressed in percent. As in the case of the 4-probe average (table 1), each brain region gave larger percent differences for \( w_1 \), \( f_2 \), and \( T \) than for \( f_1 \) and \( f_1/ \). Values for \( w_1 \), \( f_2 \), and \( T \) were consistently higher in the central region than in other areas. The particular orientation of the detector may account for this discrepancy, since it viewed the convexity of the head where the contribution of scalp and bone are probably greater.

### Discussion

The present findings confirm the earlier results of Crawley and coworkers^{11} and demonstrate clearly that the spectrum subtraction technique is an effective way of decreasing the influence of extracerebral tissues on rCBF measurements by \(^{133}\)Xe inhalation. As might be expected, the largest differences between subtraction and addition were in estimates of the slow compartment flow (\( f_2 \)), in the relative tissue weight (\( w_1 \)), and in the mean flow (\( T \)), all of which is consistent with a reduced contribution from slow extracerebral tissues. In con-

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spectrum Addition</th>
<th>Spectrum Subtraction</th>
<th>Difference</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_1^* ) (ml/100g/min)</td>
<td>75.1 ± 8.0</td>
<td>72.2 ± 7.0</td>
<td>2.9 ± 2.7</td>
<td>4.0</td>
</tr>
<tr>
<td>( f_1/ ) (percent)</td>
<td>.798 ± .021</td>
<td>.750 ± .023</td>
<td>.038 ± .012</td>
<td>4.0</td>
</tr>
<tr>
<td>( w_1 ) (percent)</td>
<td>50.0 ± 2.0</td>
<td>40.3 ± 2.5</td>
<td>9.5 ± 2.2</td>
<td>19.0</td>
</tr>
<tr>
<td>( f_2 ) (ml/100g/min)</td>
<td>18.8 ± 1.8</td>
<td>15.3 ± 1.4</td>
<td>3.4 ± 1.3</td>
<td>22.9</td>
</tr>
<tr>
<td>( T ) (ml/100g/min)</td>
<td>46.8 ± 4.9</td>
<td>38.3 ± 3.8</td>
<td>8.5 ± 2.5</td>
<td>22.2</td>
</tr>
</tbody>
</table>

*When corrected to a Paco of 38.6 mm Hg (same as intracarotid injection), the \( f_1^* \) values for subtraction and addition were 83.0 and 79.8, respectively.

**All differences are significant at the .001 level.**
trast, blood flow ($f_1$) and fractional flow ($f_2$) of the fast compartment were influenced only to a limited extent by the subtraction procedure, which is consistent with earlier observations that this compartment is insensitive to changes in extracranial flow.1,3,9

In order to assess the extent to which extracerebral components were eliminated by the subtraction technique, curve fitting was extended to later portions of the curve, i.e., end fit times (EFT) greater than the usual 11 minutes. A progressive reduction in average flow values was obtained ($f_1 = 72.1$ and 69.5, $f_2 = 17.6$ and 16.7, for EFT of 13.5 and 16.0 minutes, respectively), with little change in the $w_1$ values ($w_1 = 50.4$ and 50.9 for EFT of 13.5 and 16.0 minutes, respectively). On the other hand, analyses of both intracarotid injection data and pure two-compartment synthetic curves revealed no change in flow measurements with changes in EFT. The sensitivity of the flow parameters to changes in EFT in the spectrum subtraction technique suggested that extracerebral contamination was not totally eliminated, and that the tail of the curves still contained unwanted slow components.

The residual extracerebral influence after subtraction might be attributed to the presence of scattered gamma radiation originating from distant sources outside the geometric field of measurement. In the studies described above, wide energy ranges were used in recording both gamma-rays (above 60 kev) and x-rays (10-50 kev). Such "wide windows" increase the amount of scattered radiation recorded, thus increasing the possibility of extracerebral influence. The importance of this factor was studied in a separate series of 4 normal subjects where, in addition to wide windows, narrow windows were applied to the same detector. The narrow windows were set at 75 kev and above for gamma radiation and at 25-35 kev for x-ray. The results indicated little change in rCBF parameters due to the introduction of narrow energy ranges. Sensitivity to variations in EFT, however, decreased. Differences between the 11 minute and 16 minute curves were 4.2% for $f_1$ and 8.6% for $f_2$ with narrow windows, compared to 7.3% and 10.8%, respectively, for wide windows. Thus, the use of narrow energy discrimination slightly improves the efficiency of the spectrum subtraction technique.

The main disadvantage of spectrum subtraction is that it markedly increases the ratio of random statistical noise to count rate, which results in greater instability of the computed blood flow parameters. Whereas the variance in count rate for subtraction is the same as addition, the mean count rate is approximately one-third. This signal to noise ratio can, however, be made comparable to that of a standard $^{133}$Xe inhalation study by increasing the $^{133}$Xe dose and/or widening the geometric field of detection. While larger doses of $^{133}$Xe limit the number of rCBF determinations in the same subject, wider geometric fields reduce the spatial resolution of the method. In the present study, the $^{133}$Xe dose was double that usually given (5.0 mCi/l) compared to 2.5 mCi/l, and the geometric field of the detector was increased by employing 1 as opposed to 2 cm of lateral collimation. Blood flow measurements obtained on the 4 subjects with narrow windows required a $^{133}$Xe dose about 7 times greater than normal. Use of more standard 2 cm collimation in the spectrum subtraction technique would require a six-fold increase in dose (15 mCi/l) for wide spectrum windows and a 21-fold increase (52 mCi/l) for narrow windows, compared with the usual concentration. It is clear that such large doses severely restrict the general applicability of the spectrum subtraction technique.

References

Spectrum subtraction technique for minimizing extracranial influence on cerebral blood flow measurements by 133xenon inhalation.

J Risberg, B P Uzzell and W D Obrist