Focal Cerebral Ischemia Measured by the Intra-Arterial $^{133}$Xenon Method

Limitations of 2-Dimensional Blood Flow Measurements

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SUMMARY The limitations of 2-dimensional isotope techniques in the study of focal cerebral ischemia were investigated using the intra-carotid $^{133}$xenon injection method and a 254 multidetector scintillation camera. To make sure that the detectors “look” directly on infarcted areas, only patients with infarcts involving cortical surface structures were included in the study. Eleven such patients were found among 43 consecutive patients with completed stroke, all investigated with CT-scan. The blood supply to the infarcted areas was evaluated using 3 different approaches: 1) The first minute washout of $^{133}$xenon (rCBF), 2) the initial distribution of isotope during the first 5 sec and 3) the cumulated counts recorded during 15 min. Compton scatter and the “look through phenomenon” were responsible for the majority of counts recorded from the infarcted areas and the blood flow recorded was found to be grossly overestimated and much more influenced by the blood flow in the surroundings than in the ischemic area itself. However, using the 3 approaches, infarcted areas were always disclosed by our equipment.

It is concluded that 2-dimensional isotope technique is not reliable for quantifying focal ischemic lesions. The method should be limited to the qualitative demonstration of the ischemic lesions for which it is fully reliable.

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eluded the recordings would have reflected mainly blood flow in overlaying perfused brain tissue.

Methods

rCBF (Wash-Out Rate of \(^{133}\)Xenon)

The rCBF was measured by injecting \(^{133}\)xenon in the internal carotid artery and recording the clearance (wash-out) of the isotope from the brain using 254 externally placed detectors.

The scintillation camera has 254 individual detectors each consisting of a NaJ crystal (8 mm in diameter) in connection with a photo-multiplier, an amplifier and a lower level discriminator at approximately 20 keV.\(^{19}\)

The detectors are arranged in an orthogonal matrix with 19 columns and 14 rows on a slightly curved spheric surface. The center to center distance between each detector is 1.0 cm. The camera is collimated by a slightly curved 4 cm thick lead slab with 254 cylindrical holes (8 mm in diameter) corresponding to the camera detectors.

The rCBF investigations were carried out in conjunction with direct carotid angiography. Using the Seldinger technique, a heparinized polyethylene catheter was introduced into the internal carotid artery. About 5–10 mCi \(^{133}\)xenon dissolved in 2 ml of isotonic saline was injected as a bolus and the clearance of the isotope was recorded by the 254 detectors.

Corresponding to each detector, 254 clearance curves corrected for background and remaining activity are displayed in a semilogarithmic system on a TV-monitor. rCBF is calculated from the initial part of the clearance curves (from 12 to 60 sec after the bolus injection) using the equation: rCBF = \[ D \times 0.87 \times 2.30 \times 100 \text{ ml/100 g/min} \] where D is the numerical value of the slope of the clearance curve in base 10 logarithm, 0.87 is the brain blood partition coefficient of \(^{133}\)xenon for brain cortex and normal hematocrit blood, 2.30 is the conversion factor from decimal to natural logarithm, 100 is the conversion factor needed to obtain CBF per 100 g brain tissue.

The flow values calculated from these clearance curves are displayed on a TV-monitor as a schematic 2-dimensional picture of the hemisphere (fig. 1). The image is made of 254 colored squares representing absolute flow values on a 16-level color scale. Increasing the systemic blood pressure (BP) by continuous i.v. infusion of angiotensin. During this procedure BP was monitored continuously via the carotid catheter.

Definition of Ischemic Areas Based on Isotope Angiography (Initial Distribution of \(^{133}\)Xenon)

In addition to the rCBF measurement, the 254 detector camera is able to monitor the initial distribution of the injected isotope.

In every second after the bolus injection the total number of counts in each of the 254 detectors is recorded and displayed on a TV-monitor as a schematic 2-dimensional picture of the hemisphere after correction for field uniformity. The picture is made of 254 colored squares each representing the total number of counts recorded during one second on a 16-level color scale.

Such pictures representing the isotope distribution during the first 5 sec after the injection comprise our so-called isotope angiogram. It shows the initial distribution of the isotope before the wash-out of the isotope starts (fig. 2). In principle, it is cerebral angiography in which \(^{133}\)xenon has replaced conventional contrast medium.

Ischemic areas in this study were defined as areas of abnormal low isotope filling on the isotope angiogram 5 sec after isotope injection. Figure 3 shows the normal isotope distribution as scaled in percent of the mean count rate. The picture is an average picture obtained from 13 normal subjects. (All had been in-

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**Figure 1.** Upper panel: Flow map from a normal subject showing the regional cerebral blood flow scaled in percent of the mean hemispheric blood flow.

Lower panel: Flow map showing a large ischemic area in the posterior part of the brain scaled in percent of the mean hemispheric blood flow. Case 6 in the present series.
Investigated in order to exclude intra-cranial tumors or cerebrovascular disorders; they were all considered normal at the time of investigation on the basis of cerebral angiography, isotope scan, CT-scan and clinical neurological examination. The percentage count rate recorded by the detectors in the middle part of the matrix is high and this percentage decreases rapidly towards the peripheral part of the detector matrix. This pattern is due to the relatively large volume of brain tissue in the tissue cones covered by the detectors in the middle, and the relatively small volume of brain tissue in the tissue cones covered by the peripheral detectors. It is, therefore, not possible to assign a fixed over-all count rate limit for hyper- as well as hypoperfusion as this is highly dependent upon the localization of the areas.

Ischemic areas on the isotope angiogram have been defined by visual inspection as areas receiving abnormally small amounts of the isotope bolus, i.e., obvious defects in the isotope angiogram (fig. 2).

The blood supply to these ischemic areas was evaluated in 3 ways:

1. First Minute Wash-Out Approach (rCBF):

The cerebral blood flow recorded by the detectors covering these ischemic areas was investigated using the initial slope index method. The blood flow to be expected in normal man in each of the 11 ischemic areas was studied in the same group of 13 normal subjects. Table 1 shows the blood flow to be expected in each of these 11 ischemic areas expressed as a percent of the mean hemispheric blood flow. Blood flow values recorded in the ischemic areas below 3 standard deviations were considered significantly decreased (fig. 1).

2. Initial Distribution of 138 Xenon (Isotope-Angiogram)

An average picture of the normal initial isotope distribution, expressed in percent of the mean count rate 5 sec after isotope injection in the same 13 normal subjects, was constructed (fig. 3). The isotope distribution in areas corresponding to the ischemic areas therefore could be calculated and compared to the initial count rate in the ischemic areas (fig. 4).

3. Cumulated Counts over 15 min (Cumulated Count Map)

The total counts recorded by each detector during

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**TABLE 1: Expected rCBF In Ischemic Areas**

<table>
<thead>
<tr>
<th>Case</th>
<th>Expected normal rCBF (rCBF) in 9 ischemic areas, % of mean hemispheric blood flow</th>
<th>rCBF - 3SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>105 ± 2.5%</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>106 ± 3.9%</td>
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<td>3</td>
<td>97 ± 3.6%</td>
<td>87%</td>
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<td>4</td>
<td>98 ± 3.9%</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>99 ± 3.1%</td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>98 ± 4.2%</td>
<td>85%</td>
</tr>
<tr>
<td>7</td>
<td>98 ± 2.9%</td>
<td>89%</td>
</tr>
<tr>
<td>8</td>
<td>94 ± 3.0%</td>
<td>85%</td>
</tr>
<tr>
<td>9</td>
<td>95 ± 2.4%</td>
<td>88%</td>
</tr>
</tbody>
</table>

The blood flow to be expected, in normal man, in 9 ischemic infarcts. The blood flow is expressed as a percent of the mean hemispheric blood flow (rCBF) ± SD and is an average of 13 normal subjects. Blood flow values below (rCBF - 3 SD) of the mean hemispheric blood flow is considered significantly decreased.
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FIGURE 4. Upper panel: 5 sec. isotope-angiogram showing an ischemic area in the posterior part of the brain as present in case 6.
Lower panel: Cumulated count map from the same patient, showing the same ischemic area in the posterior part of the brain.

15 min reflects the amount of perfused brain tissue and comprises our “cumulated count map.” Such a cumulated count map, expressed in percent of the mean count constructed as an average of the map in 13 normal subjects, is shown in figure 3. The total amount of counts recorded during 15 min in the ischemic areas, therefore, could be compared to the corresponding areas in this normal average map (fig. 4).

Evaluation of Blood Supply in a Hypothetical, Non-perfused and Trans-hemispheric Infarct:

Compton scatter seriously affects all 3 isotope methods described. In the case of a totally ischemic area comprising the entire tissue cone of a detector, Compton scatter would indicate that a wash-out curve nevertheless was recorded: the count rate would be low but its wash-out rate in a semilogarithmetic plot would be the same as that in the tissue where the scatter originated. Hence the focal rCBF measured by the first-minute wash-out approach will be that of the nonfocal perfused areas. The other established modes of calculating rCBF would give equally misleading results because the bicompartmental analysis and the stochastic analysis (the height over area for 15 min) are also based on relative aspects of the curve, viz., the absolute count rate is not used in the calculations.

The 2 other isotope methods used in the evaluation of the blood supply to ischemic areas were devised to circumvent this problem which cannot be solved by eliminating the scatter. Compton scatter from soft gamma rays cannot be effectively excluded by energy discrimination. The scatter can be reduced, but this does not change the shape of the semilogarithmic recorded curve over the infarct. Compton scatter affects also the 2 other methods although they both are based on absolute parameters: the initial count rate (5-sec isotope-angiogram) and the cumulated counts over 15 min (cumulated count map). In the following we attempt to evaluate the influence of scatter on these 2 methods. The approach used is that of assessing the results to be expected by both methods in a hypothetical, non-perfused trans-hemispheric infarct.

The analysis is based on isotope studies made in the vertex projection in normal subjects (fig. 5). In this projection half of the detectors look at the right hemisphere and the other at the left. As only one hemisphere receives isotope during a study, the noninjected hemisphere may be considered an area of total ischemia since it receives no isotope (lack of cross midline isotope supply was assured by angiography). As seen in figure 5 the non-injected hemisphere has a low-but-not-zero initial count rate and cumulated count over 15 min.

In the patients with stroke the ischemic areas most often appear as a wedge-shaped segment reaching the peripheral detectors. We used our vertex studies to evaluate the effect of Compton scatter in a hypothetical, non-perfused and trans-hemispheric infarct simulating a wedge-shaped infarct with a right angle and being perfused from the 2 sides and not from the third. This was done by adding the contribution of Compton scatter from the 2 perfused sides of the hypothetical infarct (fig. 6).

FIGURE 5. Upper panel: Vertex projection. 5 sec. isotope-angiogram in a normal subject. Note the count rate recorded from the non-perfused hemisphere (percent of the mean count).
Lower panel: Vertex projection. Cumulated count map in the same normal subject (percent of the mean count).
Results

The infarct-localization seen on the first CT-scan examination in the 11 patients is shown in table 2. According to the patient selection criteria, all infarcts reached the cortical surface on the convexity. All the infarcts were localized in the part of the brain supplied by the middle cerebral artery and appeared to correspond to the supply area of one or more main arterial divisions of this artery. Massive involvement of deep structures was evident in several patients, some of which may be considered trans-hemispheric (see table 2).

The 5-sec isotope angiogram showed areas with abnormally decreased isotope distribution in 9 of the 11 patients. The localization of these areas (considered to be ischemic) corresponded in all 9 cases to infarcted areas on CT-scan (table 2). In the remaining 2 patients no ischemic areas were found on 5-sec angiogram. Instead, focal areas with a pronounced increase of isotope uptake were found corresponding to the infarcted areas on CT-scan. In accordance with the findings on the isotope angiogram, the blood flow recorded from these areas was extremely high despite being localized to areas of frank infarction. Both patients showed no occlusions of significant arteries and they were considered to be cases of post-ischemic hyperemia. They are, therefore, beyond the scope of the present study.

The 9 Ischemic Infarcts

Conventional (x-ray) cerebral angiography showed stem or branch occlusions in the territory of the middle cerebral artery in all 9 patients. Isotope brain scintigraphy with Tc\textsuperscript{99m} showed, also in all 9, an activity accumulation corresponding to the infarcts seen on CT-scan. Electroencephalography revealed focal low frequency activity with a fair correspondence to the infarcts seen on CT-scan.
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TABLE 3 Isotope Angiogram and Cumulated Count Map

<table>
<thead>
<tr>
<th>Case</th>
<th>Ischemic areas</th>
<th>Corresponding normal areas</th>
<th>Hypothetical non-perfused infarcts</th>
<th>Ischemic areas</th>
<th>Corresponding normal areas</th>
<th>Hypothetical non-perfused infarcts</th>
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<tbody>
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<td>122</td>
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<td>104</td>
<td>44</td>
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<td>117</td>
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</table>

Isotope distribution in ischemic areas in 9 infarcted brains, in 9 hypothetical transhemispheric non-perfused infarcts of the same size and in the corresponding normal areas. The 5 sec. isotope angiogram expresses the initial distribution of isotope. The cumulated count map expresses the sum of counts during 15 min.

Initial Distribution of Isotope (5-sec) in the Ischemic Infarcts

The average count rate in the 9 ischemic areas, expressed as a percent of the mean count rate of the surrounding perfused brain on 5-sec isotope angiogram, is tabulated in table 3. The corresponding average count rate in normal man for each of these 9 areas is also given. The abnormally low count rate in the ischemic areas relative to the expected count rate in corresponding normally perfused areas is clearly shown. The abnormally low bolus distribution at 5 sec is obvious.

The average count rate in the hypothetical transhemispheric infarcts of the same size is also listed in table 3. The count rate recorded from the ischemic areas and the count rate recorded from the hypothetical non-perfused infarcts do not differ significantly except in two patients (Nos. 2 and 5). In these 2 patients the infarcts were surrounded by perfused tissue on all sides and the count rate in the corresponding hypothetical infarcts are, therefore, underestimated.

Cumulated Counts in Ischemic Infarcts

In the ischemic areas on the cumulated count map the amount of counts recorded over 15 minutes was clearly subnormal in 7 of 8 patients so studied (in one patient movements invalidated the 15 min recording). Only in patient 2 no obvious difference was found. This infarct was the smallest in this series (covering only 11 detectors) and was localized in the middle of the hemisphere being surrounded by perfused tissue from all sides. In contrast to the findings on the 5-sec angiogram the cumulated counts actually recorded in these 7 patients were always higher (average 73%) than the counts recorded in the corresponding hypothetical infarcts.

rCBF Recorded Over Ischemic Infarcts

The average blood flow recorded over the ischemic infarcts ranged from 14 to 37 ml/100 g/min with a mean value of 28 ml/100 g/min (table 4). The number

TABLE 4 CBF (Wash-out Method)

<table>
<thead>
<tr>
<th>Case</th>
<th>CBFI during rest</th>
<th>During</th>
<th>No. of detect</th>
<th>% of mCBF</th>
<th>mCBF</th>
<th>During</th>
<th>No. of detect</th>
<th>% of mCBF</th>
<th>mCBF</th>
<th>During</th>
<th>No. of detect</th>
<th>% of mCBF</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ml/100 gr/min.</td>
<td>hypertension</td>
<td>ml/100 gr/min.</td>
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<td>m/100 gr/min.</td>
<td>hypertension</td>
<td>ml/100 gr/min.</td>
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<td>ml/100 gr/min.</td>
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<tr>
<td>1</td>
<td>35 ± 4</td>
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</table>

Cerebral blood flow in the ischemic areas and in the surrounding non-ischemic brain during rest and during hypertension.

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of detectors involved in these areas ranged from 11 to 78 (table 4). The mean blood flow recorded in these areas were always significantly decreased below the expected \( rCBF \) minus 3 standard deviations (cf. the section on methods). Thus, when using the initial slope index method, ischemic infarcted areas were in all patients revealed as areas with a statistically significant blood flow decrease.

The blood flow recorded in the ischemic areas and the average blood flow in the surrounding brain during induced hypertension is also shown in table 4.

No correlation was found between the initial (5-sec) count rate per detector in the ischemic areas and the blood flow values measured, \((\text{correlation coefficient } r = 0.01)\) both expressed in percent of the values to be expected. On the other hand, a good positive correlation was found between the blood flow recorded in the ischemic areas and the average blood flow in the non-infarcted brain areas, as shown in figure 7 \((r = 0.85)\). A similarly good positive correlation was found between the blood flow measured in the ischemic areas and in the non-ischemic brain areas during hypertension \((r = 0.84, \text{fig. 8})\). A positive correlation was found between the blood flow change in the ischemic areas from rest to hypertension and the similar blood flow changes in the surrounding non-ischemic brain areas \((r = 0.77)\).

**Discussion**

All infarcts investigated in this series were localized immediately under the detector head. This would appear to give the best possibility for measuring the blood flow in infarcted brain tissue with our 2-dimensional instrument. Like other 2-dimensional detector devices it is unsuited for measurement of blood flow in deeply localized lesions, because of overlying perfused tissue and tissue absorption.

The blood flow values recorded over the ischemic areas ranged from 14 to 37 ml/100 g/min and averaged 28 ml/100 g/min. This is distinctly subnormal and statistically significantly decreased relative to the mean hemispheric blood flow. However, even much lower flow values must prevail in these areas, in that the low flow values we recorded grossly overestimates the blood flow in the infarcted brain tissue.

\( rCBF \) to be Expected in an Ischemic Infarct

In most of the cases the initial count rate recorded from the ischemic infarcts did not differ much from the initial count rate recorded from the hypothetical trans-hemispheric infarcts. It should be emphasized that these hypothetical infarcts only give a rough impression of the count rate to be expected from non-perfused areas, due mainly to Compton scatter. It is, however, impressive that no difference was seen suggesting that practically all the initially recorded counts from such areas originate from tissue outside the ischemic area. In other words, the infarcted tissues are not, or at the most very slowly, perfused.

Nevertheless average blood flow values ranging
from 14 to 37 ml/100 g/min were measured. These values are not in accordance with the ischemic thresholds of rCBF for loss of normal electrical activity and cell death. During temporary clamping of the carotid artery Boysen found that blood flow values below 18-23 ml/100 g/min were inadequate for maintenance of normal EEG activity. Morawetz et al. used the hydrogen clearance technique in experimental stroke models. In their studies blood flow below the level of 10-12 ml/100 g/min for 2 or 3 hours resulted in infarction and cell death.

The infarcted areas in this study were manifested by severe, persisting, neurological deficits, persisting low absorption areas on CT-scan, EEG abnormalities, occluded arteries on angiography and isotope accumulation on isotope-scan in all the patients. For these reasons flow values averaging 28 ml/100 g/min do not reflect the blood flow in the ischemic areas investigated.

**Comments on the Low rCBF Values Recorded Over Infarcts**

If no isotope at all reaches the infarcted area and if the infarct does not overlie an area receiving isotope, then Compton scattered radiation from non-infarcted parts of the brain would be the main source of the counts recorded over the infarct. In this case the rCBF recorded locally would be totally erroneous, viz., pertaining entirely to the wash-out of 133Xe of non-infarcted brain tissue. However, our study clearly shows that the blood flow recorded from the ischemic areas always was significantly lower than in the non-infarcted areas. Thus, the counts recorded locally cannot entirely stem from Compton scatter of 133Xe in the non-infarcted brain.

a) The infarcts receive some isotope and hence the rCBF recorded is a weighted average of the slow wash-out of this isotope and the faster wash-out rate of Compton scattered radiation. The isotope may reach the infarct by collateral arteries, by diffusing in from veins draining other areas but lying in close contact to the infarct, and by diffusing in from the much better perfused border zones. The cumulated count map (the sum of counts over 15 min) showed in all patients more counts over the infarcted areas than expected from Compton scatter (the sum of all counts over 15 min in the hypothetical infarcts). This supports the idea of slow arrival of small amounts of isotope to the infarcted areas.

b) The radiation measured over the infarct partly stems from isotope deposited in low flow areas, areas with a lower flow than average in non-infarcted areas. In the superficial infarcts studied a look-through to underlying slowly perfused white substance might be considered.

c) A slow wash-out of 133Xe reaching the infarcts would be expected if the blood flow was normal but the partition coefficient increased. Since the acute change in tissue composition is edema reducing (slightly) the partition coefficient, this possibility can be discarded. The dilution effect of the edema should be mentioned, as edema is always present in infarcted areas, and increases the volume of the infarct. It can be considered as a new nonperfused compartment of the infarcted area. The blood flow measured per tissue unit (100 g brain tissue) will decrease with increasing edema.

No correlation could be demonstrated between counts recorded from the 5-sec isotope angiogram and the blood flow recorded from the ischemic areas. A good positive correlation was found between the degree of blood flow in the surrounding non-focal brain and the blood flow measured in the ischemic area. When the blood flow changed in the surroundings due to alterations in the systemic blood pressure, the blood flow recorded from the ischemic areas changed in the same direction. These findings taken together indicate that the blood flow recorded from the ischemic areas is heavily influenced by the blood flow in the surroundings and probably less by the blood flow in the ischemic area itself. The recorded blood flow values, far above the thresholds for normal electrical activity and cell necrosis, further support these findings.

The present clinical study amplifies the conclusions reached by Hanson et al. and Donley et al. in their experimental study of focal ischemia in monkeys: Compton scatter and the look-through phenomenon invalidates rCBF measurements by radioactive inert gases using the conventionally externally placed stationary detectors. This critique is valid regardless of the mode of the isotope administration: intra-arterial injection, intravenous injection or inhalation. The 2 latter modes of isotope administration labelling both hemispheres simultaneously, accentuate the look-through effects.

For these reasons rCBF measurements, by the 2-dimensional techniques, cannot be considered quantitative in stroke. Not only is the ischemic flow level severely overestimated but even the directional change with physiological intervention might be erroneous: the recorded flow is massively influenced by counts (and hence by flow values) in non-infarcted areas of the brain. These methods cannot be used to study pharmacological effects on the blood flow in ischemic lesions as the results will be massively influenced by blood flow changes in surrounding non-ischemic brain tissue.

Despite the severe limitations, our equipment was able to disclose and map the cortical infarcts. Isotope angiography (initial distribution of 133Xe injected intra-arterially) was even superior to conventional x-ray angiography.

To study rCBF reliably in patients with focal cerebral ischemia, local deposition of a freely diffusible isotope is the best way to avoid interfering factors. In the closed skull, only activation of atoms by accelerated heavy particles render this possible, a procedure much too costly and complex for clinical use. Emission tomography with inert radioactive gases is currently being developed in order to circumvent some of the disadvantages of the 2-dimensional rCBF techniques. Using coincidence counting of positrons from inhaled 75Krypton, Yamamoto et al. obtained wash-
out curves from a slice of brain tissue. Our own group uses a fast-rotating single photon emission tomograph for measuring the wash-out of inhaled 133 xenon in 3 slices of the brain simultaneously. Both methods are primarily used to study patients with focal cerebral ischemia, in particular, patients in whom reconstructive vascular surgery is under consideration. However, while these tomographic approaches avoid the look-through phenomenon, Compton scatter interference cannot be entirely avoided.

References
Focal cerebral ischemia measured by the intra-arterial 133xenon method. Limitations of 2-dimensional blood flow measurements.

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