Regional Cerebral Blood Flow Measurement With Intravenous $[^{15}O]$Water Bolus and $[^{18}F]$Fluoromethane Inhalation

K. Herholz, MD, U. Pietrzyk, PhD, K. Wienhard, PhD, I. Hebold, MD, G. Pawlik, MD, R. Wagner, PhD, V. Holthoff, MD, P. Klinkhammer, MD, and W-D. Heiss, MD

In 20 patients with ischemic cerebrovascular disease, classic migraine, or angiomas, we compared paired dynamic positron emission tomographic measurements of regional cerebral blood flow using both $[^{15}O]$water and $[^{18}F]$fluoromethane as tracers. Cerebral blood flow was also determined according to the autoradiographic technique with a bolus injection of $[^{15}O]$water. There were reasonable overall correlations between dynamic $[^{15}O]$water and $[^{18}F]$fluoromethane values for cerebral blood flow ($r=0.82$) and between dynamic and autoradiographic $[^{15}O]$water values for cerebral blood flow ($r=0.83$). We found a close correspondence between abnormal pathologic findings and visually evaluated cerebral blood flow tomograms obtained with the two tracers. On average, dynamic $[^{15}O]$water cerebral blood flow was 6% lower than that measured with $[^{18}F]$fluoromethane. There also was a general trend toward a greater underestimation with $[^{15}O]$water in high-flow areas, particularly in hyperemic areas, probably due to incomplete first-pass extraction of $[^{15}O]$water. Underestimation was not detected in low-flow areas or in the cerebellum. Absolute cerebral blood flow values were less closely correlated between tracers and techniques than cerebral blood flow patterns. The variability of the relation between absolute flow values was probably caused by confounding effects of the variation in the circulatory delay time. The autoradiographic technique was most sensitive to this type error. (Stroke 1989;20:1174–1181)

Intravenous bolus injection of oxygen-15–labeled water ($[^{15}O]$water) was suggested for the measurement of cerebral blood flow (CBF) by Ter-Pogossian et al. and was adapted for positron emission tomography (PET) by Raichle et al. These authors described an autoradiographic technique essentially using the total activity delivered to the brain during the first 40 seconds after bolus arrival as a measure of CBF. Alpert et al. suggested recording the wash-in and washout phases of $[^{15}O]$water in the brain by dynamic PET and used these data to calculate CBF. Several algorithms and modifications have since been proposed for that purpose.

However, water is not freely permeable in brain tissue. Its extraction coefficient was measured using the autoradiographic technique by comparison with freely diffusible tracers in monkeys and humans. A value of approximately 0.8 was determined, causing some underestimation of CBF, particularly in high-flow areas. We compared the performance of $[^{15}O]$water with that of a freely diffusible tracer, $[^{18}F]$fluoromethane using dynamic PET. We were interested in the correlation of rCBF estimates obtained with the two tracers ($[^{18}F]$fluoromethane vs. $[^{15}O]$water) and the two techniques (dynamic vs. autoradiographic) and tried to analyze differences with respect to the underlying causes and their consequences for the clinical application of the methods.

Subjects and Methods

We studied 20 consecutive patients (10 men, 10 women) with a mean age of 45 (SD 15.3) years who were examined for suspected cerebrovascular disease. Informed consent was obtained from every patient. Clinical diagnoses were ischemic attacks with reversible symptoms in nine, ischemic stroke in five, angioma in three, vasculitis in one, transient global amnesia in one, and migraine in one patient. Thus, a wide range of CBF values was covered in healthy and pathologic brain tissue.
We used a four-ring/seven-slice positron tomograph with an in-plane resolution of 7.8 mm and a slice thickness of 11 mm (Scanditronix PC-384, Uppsala, Sweden). Measurements were carried out in a resting state, with the eyes closed but not blindfolded and the ears unplugged, in a room with dimmed light and low, steady noise caused by the technical equipment. Before their PET studies, the patients were familiarized with the laboratory environment and procedure. Teflon cannulas were inserted into a radial artery for blood sampling and into an antecubital vein for tracer injection. A breathing face mask covering the nose and mouth was applied, and the patient was then moved into the tomograph and CBF was measured with \([^{15}O] Wagner\) and \([^{18}F] FM\) in sequence without changing the patient’s position. Arterial blood samples for blood gas determinations were obtained at the beginning of the first and at the end of the second measurement.

For the first tracer, approximately 50 mCi (1,850 MBq) \([^{15}O]W\) was rapidly injected through the antecubital cannula. Blood sampling and sequential PET scanning were started immediately after injection of the tracer. Blood samples of 1–2 ml were drawn as rapidly as possible during the first 2 minutes and afterwards at intervals from 30 seconds to 1 minute, for a total measurement time of 5 minutes. Twenty PET scans (12 lasting 10, six lasting 20, and two lasting 30 seconds) were acquired. After completion of the \([^{15}O]\)W measurement, approximately 10–15 minutes elapsed before the total brain count rate was <1% of peak activity, at which time the second measurement could be started.

For the second tracer, the breathing system was switched to rebreathing in a closed system containing 30–50 mCi (1,100–1,850 MBq) \([^{18}F] FM\). The breathing system was equipped with a soda lime \(CO_2\) absorber and a continuous oxygen supply to maintain the oxygen concentration at 21%. After 2 minutes, the breathing system was disconnected and the patient breathed room air and exhaled the \([^{18}F] FM\) into a large inflatable reservoir. Blood sampling and sequential PET scanning were started at the beginning of the \([^{18}F] FM\) inhalation using a protocol similar to that of the \([^{15}O] W\) bolus study. Total measurement time was 10.6 minutes; 20 PET scans (eight lasting 20 seconds and 12 lasting 40 seconds) were acquired.

All blood samples were drawn into preweighed syringes, were weighed again, and were counted over 30 seconds in an automatic cross-calibrated well counter. PET counts and blood counts were corrected for isotope decay. Counts per gram was converted to counts per milliliter assuming a blood density of 1.06 g/ml.

The dynamic \([^{15}O] W\) and \([^{18}F] FM\) data were analyzed with reference to the general theory of CBF measurement of Kety,\(^1\) in which total tissue activity \(C_T\) at time \(t\) is given by

\[
C_T(t) = C_{at} \int_0^t C_{at}(\tau) e^{-\lambda t} d\tau
\]

where \(C_{at}(\tau)\) is arterial activity at time \(\tau\) and \(\lambda\) is the tissue–blood partition coefficient. All arterial blood curves were shifted by 7 seconds to account for the earlier arrival of tracer in the brain than in the distal radial artery. That circulatory delay time had been determined as an average prior to regional cerebral blood flow (rCBF) analysis by comparing the tracer arrival in blood samples with ratemeter plots that monitored the total count rate recorded by the PET scanner. CBF and CBF/A were determined pixel by pixel using nonlinear least squares fitting of the model equation to the measured data.\(^10\)

For the autoradiographic technique, the first four scans of the dynamic \([^{15}O] W\) measurement were summed. This corresponds to a total measurement time of approximately 40 seconds, which was suggested by Raichle et al\(^2\) as the most appropriate for this technique. The autoradiographic analysis proceeded in two steps. For a fine grid of 128 CBF values (range 0–160 ml/100 g/min), the corresponding theoretical tissue activity was determined by integration of Equation 1 over the measurement time. The local (rCBF) value was then determined by comparing the theoretical values with the measured activity in each pixel. A fixed \(\lambda\) of 0.95 ml/g was used.

Identical sets of geometrically defined regions of interest that could be adapted to the individual anatomy by a semiautomatic procedure\(^12\) were placed on CBF images obtained with both techniques. The regions were designed to outline the cortical territories of the anterior, middle, and posterior cerebral arteries as described for tomographic brain slices by Damasio.\(^13\) Additional regions mapped the striatum, thalamus, brainstem, cerebellum, and centrum semiovale. Territorial values were calculated by averaging corresponding regions across several slices, with appropriate weighting for region size.

Data are reported as mean±SD. Statistical analysis (correlations and analyses of variance [ANOVA]) was performed using a commercial software package (SAS Institute, Cary, North Carolina). If the data were not normally distributed, rank transformations or nonparametric statistics were used as indicated.

**Results**

**Comparison of Tracers**

Global CBF (excluding only areas with major hyperperfusion rCBF > 100 ml/100 g/min) was significantly lower, by 6%, when measured with \([^{15}O]W\) than with \([^{18}F] FM\) (40.6±8.4 and 43.4±9.8 ml/100 g/min, respectively; \(p=0.029\) by Wilcoxon’s sign rank test). There were no differences in \(PaCO_2\) between tracers (37.1±2.98 and 37.0±4.38 mm Hg, for \([^{15}O] W\) and \([^{18}F] FM\), respectively; \(p=0.91\) by repeated-measures ANOVA). ANOVA of territorial CBF revealed that the relation between tracers differed in...
different vascular territories (Huynh-Feldt corrected \( p = 0.0002 \) for the interaction between territory and tracer by repeated-measures ANOVA). The greatest underestimation was found in the striatum and thalamus (CBF approximately 8% lower with \([^{15}O]\)water), whereas there was no significant difference between tracers in the white matter, the territory of the posterior cerebral artery, or the cerebellum.

As expected because of the incomplete first-pass extraction of water, a general trend toward lower \([^{15}O]\)water:
\([^{18}F]\)fluoromethane rCBF ratios was observed in high-flow areas (striatum, thalamus) relative to low-flow areas (Figure 1). The cerebellum, however, did not conform to that general rule; its \([^{15}O]\)water:
\([^{18}F]\)fluoromethane rCBF ratio was significantly larger than that in the supratentorial structures (1.07 vs. 0.92, \( p = 0.0001 \) by Wilcoxon’s sign rank test), although average \([^{18}F]\)fluoromethane rCBF was quite similar (43.7±8.76 in the cerebellum vs. 43.6±10.1 ml/100 g/min in the supratentorial structures).

The Pearson correlation coefficient between \([^{18}F]\)fluoromethane and \([^{15}O]\)water rCBF in all normal brain regions \((n=962)\) was \( r = 0.82 \) (Figure 2, top); that between \([^{18}F]\)fluoromethane and \([^{15}O]\)water global CBF was \( r = 0.84 \). The correlation coefficients of territorial CBF are given in Table 1. To analyze rCBF patterns and to eliminate the influence of variation in average CBF, normalized rCBF relative to global CBF was calculated for each patient and each tracer. The overall correlation between these normalized values in all supratentorial regions was \( r = 0.90 \). As shown in Figure 2, bottom, the correlation was particularly good in regions with low and medium flow, but high-flow areas showed greater scatter. The high correlation is also reflected by the close correspondence between the forebrain rCBF pattern obtained by the two tracers, as illustrated in Figure 3.

Major hyperperfusion was observed in two of the three patients with angiomas and in one of the five ischemic stroke patients (who had postischemic hyperemia 1 day after the onset of an ischemic stroke in the right middle cerebral artery territory). Areas of hyperperfusion were seen equally well with both tracers, but rCBF was underestimated with \([^{15}O]\)water (77.2, 74.2, and 93.9 compared with 110.0, 121.3, and 129.8 ml/100 g/min with \([^{18}F]\)fluoromethane). Corresponding areas of relative hyperperfusion were also seen with both tracers in an ischemic stroke patient with a recent infarct in the left posterior cerebral artery territory \(([^{15}O]\)water rCBF of 41.0 vs. \([^{18}F]\)fluoromethane rCBF of 44.3 ml/100 g/min). Corresponding areas of hypoperfusion were found in the remaining three patients with ischemic stroke, in three of the nine patients with transient symptoms (all studied after cessation of clinical symptoms), in the patient with transient global amnesia (moderate bilateral hyperperfusion of the posterior cerebral artery territory including the mesial temporal cortex), and in the patient with classic migraine (bilateral posterior hyperperfusion). No rCBF abnormalities were found in six of the nine patients with transient ischemic attack and in one patient with a very small angioma (<1 cm in diameter). There was generally a close correspondence between pathologic findings and rCBF findings with both tracers, as illustrated by three examples in Figure 4.

Fitted values of \( \lambda \) were consistently lower by an average of 6% for \([^{15}O]\)water than for \([^{18}F]\)fluoromethane \((p<0.004\) by Wilcoxon’s sign rank test). Global and regional CBF and \( \lambda \) values are listed in Table 2.

**Comparison of Techniques**

Autoradiographic \([^{15}O]\)water rCBF was consistently lower than dynamic \([^{15}O]\)water rCBF (Table 2). There was a significant main effect of technique \((p=0.05)\) and significant territorial variation \((p<0.0002)\). Significantly different effects of technique in various territories were also observed (interaction of technique×territory, \( p < 0.0001 \)); the difference was largest in the cerebellum (autoradiographic rCBF 14.1% less than dynamic rCBF) and smallest in the centrum semiovale (4.5%) and brainstem (1%).

However, some reservations with respect to the significance of these findings are in order because we observed a strong influence of our assumptions about circulatory delay time on the results (Figure 5). In accordance with observations reported by Iida et al.,

\(^{14}\) a change in the circulatory delay time by only 3 seconds produced a change in CBF of up to...
The high sensitivity to circulatory delay time effects, which probably differ among patients, corresponded to a relatively low correlation between absolute autoradiographic and dynamic global CBF values \( r=0.77 \); the correlation between rCBF patterns was much closer \( r=0.95 \), and the overall correlation coefficient of absolute rCBF values between the two techniques was \( r=0.83 \). Our results, therefore, indicate that the dynamic and autoradiographic techniques are almost equivalent with regard to the rCBF pattern, but absolute rCBF values may differ considerably.

Discussion

Our data indicate a generally close relation between dynamic measurements of rCBF with

Table 1. Pearson Correlation Coefficients of Regional Cerebral Blood Flow in Vascular Territories of 20 Patients With Suspected Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Territory</th>
<th>Tracers</th>
<th>Comparing</th>
<th>Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral artery</td>
<td>0.82</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>0.84</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>0.83</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Striatum</td>
<td>0.73</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.75</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.80</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.84</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>0.83</td>
<td>0.79</td>
<td></td>
</tr>
</tbody>
</table>

Tracers, \([^{15}O]\)water and \([^{18}F]\)fluoromethane in dynamic positron emission tomography (PET); Techniques, dynamic and autoradiographic PET with \([^{15}O]\)water.

18% with the autoradiographic method, whereas the dynamic method was less sensitive.
[15O]water and [18F]fluoromethane. Absolute global CBF values were somewhat less closely correlated than the rCBF pattern, that is, rCBF normalized with respect to the individual global CBF. Interestingly, there was even less correspondence between global CBF when the dynamic and autoradiographic measurements of CBF with [15O]water were compared, although the measurements were based on the same PET data (except for different total measurement times), excluding the possibility of physiological variability.

The variability of the relation between absolute CBF values appeared to be due mainly to a high sensitivity of the [15O]water bolus method (particularly in the autoradiographic technique), to small errors in the correction for the circulatory delay time, which has been reported by Iida et al., Kanno et al., and Koeppe et al. We used a fixed time shift of 7 seconds as the time of tracer arrival in the radial artery cannula relative to its arrival in the brain. That time shift was determined as an average because we had only multiple arterial blood samples drawn manually at approximately 3-5-second intervals and were therefore not able to determine reliable circulatory delay times for each patient, as suggested by Iida et al. Their approach used au-

Figure 3. Four representative and corresponding cerebral blood flow (CBF) tomosgrams obtained with [15O]water (top) and [18F]fluoromethane (bottom) in 28-year-old woman with recent transient ischemic attack but apparently normal CBF at time of study. Slice levels (from left to right) are 14, 41, 55, and 82 mm above canthomeatal plane. Scaling of series is different, as indicated, to achieve corresponding appearance of forebrain structures. Relatively higher cerebellar CBF in [15O]water study can be seen in lowest slice.

Figure 4. Corresponding cerebral blood flow (CBF) tomosgrams obtained with [15O]water (top row) and [18F]fluoromethane (bottom row) in three patients with individually adjusted gray scales (range displayed below each tomogram). Patient's left side is on viewer's right. Left column: 45-year-old woman with 42-day-old ischemic stroke and hypoperfusion of left frontolateral cortex and basal ganglia. Middle column: 30-year-old woman with 2-day-old ischemic stroke and luxury perfusion of right perisylvian area. Right column: 48-year-old man with hyperperfused arteriovenous angioma in left striatum.
TABLE 2. Territorial and Global Values of rCBF and A for 20 Patients With Suspected Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Territory</th>
<th>rCBF (ml/100 g/min)</th>
<th>A (ml/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral artery</td>
<td>45.9±10.2</td>
<td>38.5±9.1</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>44.8±10.3</td>
<td>37.2±9.3</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>41.0±9.7</td>
<td>36.3±8.6</td>
</tr>
<tr>
<td>Striatum</td>
<td>51.4±13.2</td>
<td>39.9±9.7</td>
</tr>
<tr>
<td>Thalamus</td>
<td>55.6±14.4</td>
<td>41.0±10.5</td>
</tr>
<tr>
<td>Brainstem</td>
<td>40.3±8.4</td>
<td>36.5±10.0</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>43.7±8.7</td>
<td>39.9±10.7</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>21.6±5.1</td>
<td>20.6±5.8</td>
</tr>
<tr>
<td>Global</td>
<td>43.4±9.8</td>
<td>37.0±9.0</td>
</tr>
</tbody>
</table>

rCBF, regional cerebral blood flow; A, tissue–blood partition coefficient. Values are mean±SD.

matic on-line blood sampling, which also requires a correction for tracer dispersion in the sampling system. As yet, it is not known if individually determined circulatory delay times would improve the correlation between absolute CBF values.

The high sensitivity of the [15O]water bolus method to variations in circulatory delay time is not unexpected in view of the rapid changes of the input function during the measuring time. Using smoother input functions and the dynamic technique, as suggested by Lammertsma et al.,17 could ameliorate the problem.

The underestimation of [15O]water rCBF in most territories probably is due mainly to the incomplete first-pass extraction of the tracer.8,18 This interpretation is in accordance with the observed inverse relation between the supratentorial [15O]water: [18F]fluoromethane rCBF ratios and rCBF measured with [18F]fluoromethane because diffusion limitation exerts a larger effect under high-flow conditions with rapid capillary passage. If we approximate the extraction rate E by the dynamic [15O]water: [18F]fluoromethane rCBF ratio, we obtain an average E of 40.6/43.4=0.94. Inserting this value of E into the Renkin-Crone equation, as suggested by Herscovitch et al.,9 yields a permeability–surface area product for water of 118.9 ml/100 g/min, close to the value of 104 ml/100 g/min measured by Herscovitch et al.9 Yet, because of the high sensitivity of absolute [15O]water rCBF values to errors in estimates of the circulatory delay time and because of complex modeling problems involved in the accurate measurement of tracer extraction and permeability,19 such estimates of the permeability–surface area product probably are subject to considerable uncertainty.

The regional variation of the permeability–surface area product, however, certainly is more reliable, as indicated by the close correlation of the rCBF patterns between tracers and techniques. We found a significantly higher [15O]water:[18F]fluoromethane rCBF ratio in the cerebellum than in the supratentorial region, despite similar values of rCBF measured with [18F]fluoromethane (Figure 1). This may indicate that the permeability–surface area product, which controls the relation between CBF and tracer uptake,20 is larger in the cerebellum than in the supratentorial brain structures. This finding corresponds to a similar observation with respect to 2-[18F]fluoro-2-deoxyglucose (FDG) transport across the blood–brain barrier; the transport: phosphorylation ratio was significantly larger in the cerebellum than in the supratentorial structures, that is, carrier-mediated FDG transport in the cerebellum was larger than expected on grounds of hexose consumption.21 Furthermore, a higher density of capillaries in the
human cerebellum than in the supratentorial structures has been observed in anatomic studies. We may therefore conclude that the capillary surface area is larger in the cerebellum than in the supratentorial structures, facilitating extraction of diffusion-limited substances such as [15O]water and carrier-mediated transport of FDG. Of course, the extraction rate must not exceed 1. The [15O]water:[18F]fluoromethane rCBF ratio of 1.07 that we obtained in the cerebellum did not differ significantly from 1, but it may indicate that regional variations in the circulatory delay time could also contribute to regional variations in the relation between [15O]water and [15F]fluoromethane rCBF. In any case, relative rCBF values based on the cerebellum as a reference structure must be regarded as method-dependent.

The λ for [15O]water and [15F]fluoromethane we obtained by the dynamic technique are lower than respective in vitro values. A λ of approximately 1.0 ml/g has been derived from the work of Gatley et al. for [15F]fluoromethane whereas values between 0.90 and 0.96 ml/g have been reported for [15O]water. Similar findings of low λ for [15O]water have also been observed by Carson et al. and Blomqvist et al. in dynamic PET studies. Therefore, there may be minor insufficiencies of the model. The problems may be related to intercompartmental diffusion, for example, diffusion of tracer from gray to white matter, and possibly also to cerebrospinal fluid. Because we also observed the discrepancy between fitted and in vitro λ with [15F]fluoromethane, it probably is not caused solely by hypothetical subcompartments for diffusing and nondiffusing structure-bound water.

In conclusion, dynamic measurements of rCBF patterns with [15O]water and [15F]fluoromethane show a good correspondence in patients with suspected cerebrovascular disease. However, due to incomplete tracer extraction, absolute rCBF values are underestimated in most structures with [15O]water. That underestimation is absent in the cerebellum, probably because of its higher capillary density, and in low-flow areas. Another potential disadvantage of the intravenous [15O]water bolus method, particularly when the autoradiographic technique is used, is its high sensitivity to errors in estimates of the circulatory delay time between tracer appearance in peripheral arterial blood samples and in the brain. These disadvantages may be counterbalanced by the easier handling of the fluid tracer compared with the gaseous [15F]fluoromethane and by the rapid repeatability of [15O]water measurements due to its very short physical half-life.

References


KEY WORDS • cerebral blood flow • cerebrovascular disorders • tomography, emission computed.
Regional cerebral blood flow measurement with intravenous [15O]water bolus and [18F]fluoromethane inhalation.
K Herholz, U Pietrzyk, K Wienhard, I Hebold, G Pawlik, R Wagner, V Holthoff, P Klinkhammer and W D Heiss

Stroke. 1989;20:1174-1181
doi: 10.1161/01.STR.20.9.1174

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/9/1174

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/