Pathophysiologic Study of Chronic Infarcts with I-123 Isopropyl Iodo-Amphetamine (IMP): The Importance of Periinfarct Area


Seventeen chronic cerebral infarcts were investigated by a highly sensitive, dedicated brain single photon emission computed tomography system using I-123-Isoisopropyl iodoamphetamine (IMP). IMP uptake was measured 10 minutes, 2 hours, and 5 hours after injection, and regional cerebral blood flow was measured with 133Xe. In 4 cases a positron emission tomography system was used to measure the rCBF and the regional metabolic rate of oxygen with C15O2 and 18O2. The results obtained allowed us to identify 2 abnormal zones. One, the “central area,” was characterized by a severe decrease in IMP uptake and rCBF averaging 34% and 46% respectively and by a hypodense image on the x-ray computed tomography scan. The second, the periinfarct or “peripheral area” was characterized by a moderate decrease in IMP uptake and regional cerebral blood flow averaging 13 and 19% respectively; this area extended around the central area and had a normal density on computed tomography scan. The IMP hypofixation of the peripheral area observed at the 10th minute tended to disappear at the 5th hour. The volume of this area was often found to be quite large, covering more than 30% of a hemisphere whereas the central area did not exceed 25%. Volume appeared to be correlated with the neurological status of the patient. The nature of the peripheral area is not established with certainty. It may be caused by deafferentation of areas not directly affected by the ischemic insult and/or selective ischemic neuronal loss. The results stress the important role played by the peripheral area, which may be useful in establishing the prognosis and evaluating the efficacy of therapy in individual stroke cases. (Stroke 1987;18:21-29)

CEREBRAL single photon emission tomography (SPECT) has benefited from two major improvements in recent years. The first was the advent of I-123-isopropyl-iodoamphetamine (IMP), which can be considered the first real brain agent placed at the disposition of every nuclear medicine center. Its usefulness is recognized in cerebrovascular patients in obtaining both the localization and the extent of infarcts whether such infarcts are visible or not by x-ray computed tomography (CT). Because its sensitivity is so much higher than that of rotating cameras, acquisitions take only a few minutes and can be repeated easily. With this system, regional cerebral blood flow (rCBF) measured with 133Xe and IMP values can be obtained on the same areas of the tomographic slices.

Using this high-sensitivity SPECT system we studied 17 patients with chronic infarcts; a few were also studied with a positron emission tomography (PET) system. The results obtained emphasize the pathophysiologic importance of the periinfarct area in which IMP uptake, CBF, and metabolic activity are decreased.

Subjects and Methods

Two SPECT systems were used. All patients were studied with the Tomomatic 64, a hybrid bar-camera array system; a few were also studied using a rotating camera (GE-400 A) connected to a SIMIS 4 computer. Physical characteristics of both systems have been described in detail elsewhere. We will only detail here the "relative" sensitivity of the Tomomatic, which we found to be 20–25 times higher than that of the GE-400 A for 123I allowing for shorter acquisition times. With both systems "relative" sensitivity represents the count number of a 2-cm-thick brain slice taken at the same level with the same acquisition time and with measurements made approximately 2 hours after injection on 23 patients. Resolution of rotating cameras varies from 12 to 20 mm; with the collimator used it was 16–18 mm for the Tomomatic 64.

For IMP, 20- to 60-minute acquisitions were routinely made with the rotating camera at 30 or 60 minutes and between the 4th and 5th hour; with the Tomomatic 64, 3-minute acquisitions were made between 4 and 10 minutes and will be referred to as the 10th minute acquisition (IMP 10') at 2 hours (IMP 2H) and 5 hours (IMP 5H). At these three times a first acquisition provided three 2-cm-thick slices centered on planes OM + 20 mm, OM + 60 mm, and OM + 100 mm referred to as Slices 1, 3, and 5; a second acquisition immediately followed after moving the patient's bed 2 cm and provided the intermediate slices OM +
40 mm, OM + 80 mm, and OM + 120 mm referred to as Slices 2, 4, and 6. IMP was prepared from a commercial kit (ORIS, France) using an exchange reaction. Iso-80 mm was produced by the method already well validated, 1314 rCBF was computed; CBF^ images presented expressed the distribution of rCBF values pixel by pixel; 133Xe was delivered in gaseous form (IRE, Belgium). Since the Tomomatic 64 can acquire data from only 3 brain slices 2 cm apart at any time and since the technique of Xe inhalation was not repeated to obtain intermediate slices; rCBF^ was studied only on the OM + 20, + 60, and + 100 mm slices (Slices 1, 3, and 5). As a result we do not have flow values from slices OM + 40 mm, + 80 mm, and + 120 mm (Slices 2, 4, and 6). Because it is often outside the brain area, the slice OM + 120 mm was not used in the present study.

A PET system, ECAT II, was used to measure rCBF by the standard continuous C15O2 steady-state inhalation method (rCBF^). Regional cerebral metabolic rate of oxygen (rCMRO2) and regional oxygen extraction fraction (rOEF) were obtained by the 15O2 inhalation method.13,16

To facilitate comparing SPECT and PET results, decreases or increases in rCBF^, rCMRO2, rCBF^, and IMP activity on the side of the lesion were expressed in percent of the contralateral value, representing the degree of asymmetry. For rCBF^, rCMRO2, and rOEF, results were either relative, expressing the degree of asymmetry, or absolute. All patients were submitted to CT, CBF^, and IMP studies; 4 were also studied by PET. It was possible to compare SPECT, PET, and CT data by accurately repositioning the patient's head for each examination in such a way that slices were obtained at the same level. SPECT, PET, and CT studies were performed in the same week, and 4-vessel angiograms were performed in all patients during the chronic phase.

Seventeen patients (Table 1), 53-79 years old, with unilateral completed stroke were investigated at the chronic stage (3 months-6 years). All had a CT hypodense area in the affected hemisphere and were selected because their infarct was clearly seen around the OM + 60 mm level. This was done because OM + 60 mm is the only level at which we obtained SPECT and PET data. The middle cerebral artery (MCA) territory was involved in 16; the anterior cerebral artery (ACA) territory, in 1. The infarct was superficial in 13 patients, deep in 1, and both for 3; all but 1 had hemiplegia. Fourteen patients had tight stenosis or occlusion of the ipsilateral internal carotid artery (ICA). The remaining cases had no major lesions of the ipsilateral ICA; 1 of these 3 patients had an intracranial arterial occlusion. Embolic origin of the stroke was suspected in 14 patients; the association of both embolic and hemodynamic processes was found in 2 presenting a watershed image and a central territory lesional aspect.

<table>
<thead>
<tr>
<th>Patients' name/age/sex</th>
<th>Infarct</th>
<th>Side</th>
<th>Neck vessels</th>
<th>Neurological status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS/32/F 2 yr Left</td>
<td>LIC occlusion</td>
<td>RIC hypoplasia</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>DEC/75/F 1 yr Left</td>
<td>LIC occlusion</td>
<td>RIC stenosis &lt; 90%</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>WEL/72/M 7 mo Left</td>
<td>LIC occlusion</td>
<td>RIC arterial plaque</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>OLI/59/M 3 mo Left</td>
<td>LIC arterial plaque</td>
<td>RIC normal</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>COR/69/M 16 yr Left</td>
<td>LIC occlusion</td>
<td>RIC occlusion</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>GOU/69/M 2 yr Right</td>
<td>LIC occlusion</td>
<td>RIC occlusion</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>ISK/60/M 9 mo Left</td>
<td>LIC occlusion*</td>
<td>RIC stenosis &lt; 90%</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>PEP/63/M 3 yr Right</td>
<td>LIC occlusion</td>
<td>RIC occlusion</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>JUL/55/F 3 mo Left</td>
<td>LIC arterial plaque</td>
<td>RIC normal</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>BAR/65/M 5 mo Right</td>
<td>LIC stenosis &lt; 90%</td>
<td>RIC occlusion†</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>BEN/59/M 18 mo Right</td>
<td>LIC arterial plaque</td>
<td>RIC stenosis &gt; 90%</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>REN/75/M 11 mo Right</td>
<td>LIC arterial plaque</td>
<td>RIC stenosis &gt; 90%</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>COQ/69/F 4 mo Right</td>
<td>LIC stenosis &lt; 90%</td>
<td>RIC stenosis &gt; 90%</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>PRI/56/M 4 mo Right</td>
<td>LIC stenosis &lt; 90%</td>
<td>RIC stenosis &gt; 90%</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>LAR/66/F 1 yr Right</td>
<td>LIC normal</td>
<td>RIC dysplasia without stenosis</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>MEL/61/F 4 mo Right</td>
<td>LIC normal</td>
<td>RIC stenosis &gt; 90%</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>CLE/69/M 5 mo Left</td>
<td>LIC occlusion</td>
<td>RIC arterial plaque</td>
<td>—‡</td>
<td></td>
</tr>
</tbody>
</table>

Mean age 63

LIC: left internal carotid artery.
RIC: right internal carotid artery.
† An endarterectomy was performed on LIC, 8 months after infarct.
‡ An endarterectomy was performed on RIC, 2 months after infarct.
For the neurological status classification, see text.
In the group of patients suspected of embolism, the stroke occurred at the time of the occlusion in 4; in 1 the occlusion seemed to have been present for some time; 3 did not have any significant carotid lesion; 5 had a carotid stenosis; and in 1 the carotid occlusion was presumably concomitant with the stroke. The 2 patients with presumed hemodynamic and embolic origin of the stroke, 1 had a carotid occlusion concomitant with the stroke and 1 had a tight carotid stenosis.

Five normal subjects, 30-45 years old, were studied in order to establish the confidence limits of the asymmetry of homologous areas with IMP and rCBF_Xe and normal values of rCBF_Xe. Three of them also had IMP images at 24 hours, and their results were used to study normal IMP kinetics.

Neurological deficit or disability was classified with the stroke and 1 had a tight carotid stenosis. In the group of patients suspected of embolism, the stroke occurred at the time of the occlusion in 4; in 1 the occlusion seemed to have been present for some time; 3 did not have any significant carotid lesion; 5 had a carotid stenosis; and in 1 the carotid occlusion was presumably concomitant with the stroke. In the 2 patients with presumed hemodynamic and embolic origin of the stroke, 1 had a carotid occlusion concomitant with the stroke and 1 had a tight carotid stenosis.

The limits of the normal difference interval may be defined by the sum of the normal difference mean plus 1 standard deviation (SD). For 114 pairs of symmetrical areas taken on IMP images of 10 minutes, 2 hours, and 5 hours, and then more slowly to reach a maximum at 3-4 hours, which is maintained for at least 24 hours. In 3 normal subjects, the mean decay-corrected values of the entire slice OM + 60 mm at 2 hours, 5 hours, and 24 hours, compared with those found at 10 minutes, were respectively 134, 136, and 121%. This brain IMP activity curve was previously observed by Kuhl et al.3

IMP and rCBF_Xe distributions are practically symmetrical in normal subjects; however, small differences may be observed between homologous areas. The limits of the normal difference interval may be defined by the sum of the normal difference mean plus 1 standard deviation (SD). For 114 pairs of symmetrical areas taken on IMP images of 10 minutes, 2 hours, and 5 hours, and 34 on CBF_Xe images in 5 normal subjects, the normal mean difference + 1 SD was 5.4% for IMP and 9% for rCBF_Xe. Values greater or lower than the normal contralateral values by 6% for IMP and 10% for rCBF_Xe will be considered abnormal. In the same normal subjects mean cortical rCBF_Xe measured on 36 area pairs on the slice OM + 60 mm was 48.1 ± 3.4 ml/min/100 g (mean ± SD).

### Table 2. IMP Uptake and rCBF Values in 17 Patients With Chronic Infarct

<table>
<thead>
<tr>
<th>Patient</th>
<th>rCBF_Xe (%)</th>
<th>IMP 10' (%)</th>
<th>IMP 2H (%)</th>
<th>IMP 5H (%)</th>
<th>Area size*</th>
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<tbody>
<tr>
<td>CAS</td>
<td>37</td>
<td>31</td>
<td>27</td>
<td>22</td>
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<tr>
<td>DEC</td>
<td>42</td>
<td>25</td>
<td>16</td>
<td>10</td>
<td>5</td>
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<tr>
<td>WEI</td>
<td>48</td>
<td>38</td>
<td>39</td>
<td>31</td>
<td>9†</td>
</tr>
<tr>
<td>OLI</td>
<td>36</td>
<td>23</td>
<td>21</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>COR</td>
<td>26</td>
<td>27</td>
<td>20</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>GOU</td>
<td>52</td>
<td>28</td>
<td>31</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>ISK</td>
<td>55</td>
<td>46</td>
<td>43</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>PEP</td>
<td>44</td>
<td>43</td>
<td>40</td>
<td>43</td>
<td>14</td>
</tr>
<tr>
<td>JUI</td>
<td>51</td>
<td>39</td>
<td>28</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>BAR</td>
<td>58</td>
<td>50</td>
<td>49</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>BEN</td>
<td>37</td>
<td>25</td>
<td>22</td>
<td>15</td>
<td>8†</td>
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<tr>
<td>REN</td>
<td>54</td>
<td>38</td>
<td>38</td>
<td>29</td>
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<tr>
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<td>FRI</td>
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<td>28</td>
<td>25</td>
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<td>12</td>
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<td>LAR</td>
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<td>15</td>
<td>6</td>
</tr>
<tr>
<td>MEL</td>
<td>71</td>
<td>45</td>
<td>54</td>
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<td>25</td>
</tr>
<tr>
<td>CLE</td>
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<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>34</td>
<td>30</td>
<td>24</td>
<td>11</td>
</tr>
</tbody>
</table>

**Note:**
- rCBF_Xe, IMP 10', IMP 2H, IMP 5H were measured on slice OM + 60 mm. Values presented express the decrease measured on central and peripheral area in percent of contralateral symmetrical area. Central and peripheral area volume was measured on the 5 slices: OM + 20, + 40, + 60, + 80, and + 100 mm.
- Area size is expressed in % of a hemisphere.
- Peripheral area too small on slice OM + 60 mm; measurements not made.

**Results**

**Normal Subjects**

When IMP is injected in a peripheral vein, the brain activity, corrected for decay, increases sharply for 30 minutes and then more slowly to reach a maximum at 3-4 hours, which is maintained for at least 24 hours. In 3 normal subjects, the mean decay-corrected values of the entire slice OM + 60 mm at 2 hours, 5 hours, and 24 hours, compared with those found at 10 minutes, were respectively 134, 136, and 121%. This brain IMP activity curve was previously observed by Kuhl et al.3

IMP and rCBF_Xe distributions are practically symmetrical in normal subjects; however, small differences may be observed between homologous areas. The limits of the normal difference interval may be defined by the sum of the normal difference mean plus 1 standard deviation (SD). For 114 pairs of symmetrical areas taken on IMP images of 10 minutes, 2 hours, and 5 hours, and 34 on CBF_Xe images in 5 normal subjects, the normal mean difference + 1 SD was 5.4% for IMP and 9% for rCBF_Xe. Values greater or lower than the normal contralateral values by 6% for IMP and 10% for rCBF_Xe will be considered abnormal. In the same normal subjects mean cortical rCBF_Xe measured on 36 area pairs on the slice OM + 60 mm was 48.1 ± 3.4 ml/min/100 g (mean ± SD).
FIGURE 1. Patient BAR right sylvian infarct. rCBF xe, x-ray CT, and IMP images correspond to the slice OM + 60 mm. The central area situated in the right posterior parietal zone presents a marked decrease in rCBF xe and IMP uptake without redistribution and a hypodense image on CT scan. The peripheral area occupying the right cortical and subcortical frontoparietal zone presents a moderate decrease in IMP uptake with a redistribution that is almost complete at 5 hours, a normal CT scan image, and a moderately decreased rCBF. For absolute values see Table 1.

and in most cases also in extensive periinfarct areas. We found that degree of hypofixation allowed differentiation of these areas. To avoid confusion with terminology based on pathophysiological data, we will use purely descriptive terms when referring to these zones: The infarct zone will be called the “central area” and the periinfarct zone will be referred to as the “peripheral area.” Values presented for IMP, rCBF, rCMRO2, and OEF were measured on the slice OM + 60 mm, which is also referred to as Slice 3.

CENTRAL AREA. The central area was characterized by two features: First, a maximal decrease in both IMP uptake and rCBF (Table 2, Figures 1 and 2), and second, a marked hypodensity on the CT scan (CT + image). The IMP and CBF values representative of the central area were measured in a large region of interest (ROI) of 5–9 cm² enclosing the lowest IMP uptake and rCBF and the limits of CT + image. Results are shown in Table 2. The mean value of IMP uptake was decreased by 34, 30, and 24% respectively at 10 minutes, 2 hours, and 5 hours. For all patients the IMP 10' and IMP 5H were decreased respectively by at least 20 and 10%; the slight decrease regression observed between 10 minutes and 5 hours reflected a tracer redistribution. When individual results were examined, this redistribution was found in 14 patients but was not observed in 3. Volume of the central area of each patient was evaluated by adding together the areas with maximal IMP 10' decrease found on the five IMP slices, i.e., over the whole brain (Figure 4); results were expressed in percent of the affected cerebral hemisphere volume. The mean value for 17 patients was 12% of a hemisphere. When infarct age was taken into account, mean value for infarcts 3–12 months old was 12%; for infarcts older than one year it was 9% (Table 2). No correlation was found between central area volume and neurological deficit.

Mean decrease of rCBF xe in the central area was 46% with large individual variations from -26 to -71%. The rCBF xe was decreased by at least 25% and was always more pronounced than that of IMP. Mean ratio of the IMP decrease at 10 minutes to that of rCBF was 0.74. Regional CMRO2, rCBF xe, and OEF were measured in 4 patients by the PET method. In these patients the mean decrease was 65% for rCMRO2, 65% for rCBF xe, 2% for OEF, 52% for rCBF xe, and 42 and 38% for IMP uptake at 10 minutes and 5 hours respectively (Table 3).

PERIPHERAL AREA. The peripheral area surrounded the central area and was characterized by two features: First, a moderate decrease in IMP uptake and rCBF xe, and second, a normal CT scan image (Figures 1 and 2).

In most of the patients, the peripheral area was large;
Table 3. rCBF<sub>O2</sub>, rCBF<sub>x</sub>, rOEF, rCMRO<sub>2</sub>, and IMP Uptake Values in 4 Chronic Infarcts

<table>
<thead>
<tr>
<th>Patient</th>
<th>rCBF&lt;sub&gt;O2&lt;/sub&gt; (L/R) (%)</th>
<th>rCBF&lt;sub&gt;x&lt;/sub&gt; (L/R) (%)</th>
<th>rOEF (L/R) (%)</th>
<th>rCMRO&lt;sub&gt;2&lt;/sub&gt; (L/R) (%)</th>
<th>IMP&lt;sub&gt;10'&lt;/sub&gt; (L/R) (%)</th>
<th>IMP&lt;sub&gt;5H&lt;/sub&gt; (L/R) (%)</th>
<th>rCBF&lt;sub&gt;O2&lt;/sub&gt; (L/R) (%)</th>
<th>rCBF&lt;sub&gt;x&lt;/sub&gt; (L/R) (%)</th>
<th>rOEF (L/R) (%)</th>
<th>rCMRO&lt;sub&gt;2&lt;/sub&gt; (L/R) (%)</th>
<th>IMP&lt;sub&gt;10'&lt;/sub&gt; (L/R) (%)</th>
<th>IMP&lt;sub&gt;5H&lt;/sub&gt; (L/R) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAR</td>
<td>-63 (30/11)</td>
<td>-58 (36/16)</td>
<td>0</td>
<td>-62 (54/-54)</td>
<td>-50 (54/-54)</td>
<td>-41 (54/-54)</td>
<td>-29 (25/20)</td>
<td>-21 (42/3)</td>
<td>5* (55/-52)</td>
<td>-33 (55/-52)</td>
<td>-23 (55/-52)</td>
<td>-9  (55/-52)</td>
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<tr>
<td>GOU</td>
<td>-55 (31/14)</td>
<td>-52 (50/24)</td>
<td>+5* (59/-62)</td>
<td>-53 (59/-62)</td>
<td>-28 (59/-62)</td>
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<td>(Area too small, values not measured)</td>
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<tr>
<td>ISK</td>
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<td>-55 (25/55)</td>
<td>-6* (51/-54)</td>
<td>-66 (51/-54)</td>
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<td>-19 (52/64)</td>
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<tr>
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<td>-2</td>
<td>-65</td>
<td>-42</td>
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<td>-24</td>
<td>-21</td>
<td>+2</td>
<td>-23</td>
<td>-16</td>
<td>-7</td>
</tr>
</tbody>
</table>

*Insignificant decrease or increase.

rCBF<sub>O2</sub>, rCBF<sub>x</sub>, rOEF, rCMRO<sub>2</sub>, and IMP uptake were measured on the slice OM + 60 mm; values in the table express decrease (or increase) measured on central and peripheral areas in percent of the contralateral symmetrical area.

For rCBF<sub>O2</sub> and rCBFx, results in parentheses represent absolute rCBF values in ml/min/100 g for the left and right side.

For rOEF, results in parentheses represent absolute rOEF values for the left and right side.

However, in 2 patients it was very small, representing a narrow rim surrounding the central area and in 1 other it was too small to be studied on Slice 3 but was larger on Slices 2 and 4.

Regional IMP and CBF values representative of the peripheral area were measured in a ROI of 5-9 cm<sup>2</sup> taken within the limits of the IMP hypofixation zone and at a distance from the central area (Table 2). Mean IMP uptake was decreased by 13% at 10 minutes, 9% at 2 hours, and 6% at 5 hours, with large individual variations. For all patients IMP 10' was decreased by 20% or less. Between 10 minutes and 5 hours, a redistribution of tracer occurred, sometimes resulting in a complete disappearance at 5 hours of the early hypofixation. When individual IMP values were considered (Figure 3), redistribution was complete in 4 patients (IMP 5H uptake being symmetrical), and incomplete in 10 patients (IMP 5H remaining asymmetrical). The volume of this zone was evaluated by adding together the areas with moderately decreased IMP 10' uptake and normal CT scan image on the 5 IMP SPECT slices, i.e., the whole brain (Figure 4). Peripheral area volume was less than 30% of the hemisphere volume for 8 patients, between 30 and 60% for 8 patients, and more than 60% for 1 (Table 2). Although not very accurate, this evaluation nevertheless documents the large extent of the peripheral area. The territory occupied by this area corresponded approximately to the whole MCA territory or to that of some of its branches in 14 patients and to the ACA territory in 1. In 2 cases it spread out of the MCA territory toward the frontal areas, without angiographic ACA occlusion and CT lesion of ACA territory. In no case was the occipital lobe involved.

Mean rCBF<sub>x</sub> was also moderately decreased by an average of 19%, and in spite of large individual variations, rCBF was decreased by less than 25% for all patients except 1. This patient had a peripheral area rCBF decreased by 35%, lower than the threshold; but in this case, the central area size on the OM + 60 mm slice was very large and the peripheral area reduced to a narrow strip. The high value observed could be a consequence of the 16-mm resolution of the SPECT.
system. As for the central area, rCBF\textsubscript{Xe} was more depressed than the 10-minute IMP uptake, with a ratio of IMP 10' to rCBF\textsubscript{Xe} of 0.68.

Of the 4 patients examined with PET, only 3 showed a peripheral area large enough to be studied (Table 3). The mean change was $-23\%$ for rCMRO\textsubscript{2}, $-24\%$ for rCBF\textsubscript{Ob}, $+2\%$ for rOEF, $-21\%$ for rCBF\textsubscript{Xe}, and $-16$ and $-7\%$ for IMP uptake at 10 minutes and 5 hours. Hence, the discrepancy between rCBF\textsubscript{Ob} and rCBF\textsubscript{Xe} previously found in the central area was not observed in the peripheral area. The size of the hypoperfused area measured on Slices 1, 3, and 5 closely corresponded to that of the hypofixation area as seen on the 10-minute IMP image. In other words, the peripheral area was fairly well demarcated with both techniques.

No correlation was found between IMP uptake decrease in the peripheral area and the status of the patients (Tables 1 and 2). However, the volume of the peripheral area correlated with neurological status. Patients with a complete remission, Grade I, had the smallest peripheral areas (2–25%); patients with Grade II had large peripheral areas (20–40%); and patients with severe sequelae, Grade III, had the largest peripheral areas (31–59%) (Table 1, Figure 5). The results obtained suggest that size of the peripheral area correlates with infarct age; mean size was 8% in infarcts older than 1 year, and 37% for infarcts 3 months to 1 year old (Table 2). In fact, the large dispersion of the results and the finding of large peripheral areas in old infarcts in recent observations not included in this study indicate that such correlation does not exist. Three patients were excluded from these correlation studies; 1 (WEI) because of 2 localizations of the same infarct, 1 (BEN) because of 2 infarcts of different age, and 1 (CLE) whose neurological deficit could not be accurately graded because he did not return for the last examination.

When combining results from central and peripheral areas, significant linear correlations between decreases in rCBF\textsubscript{Xe} and IMP uptake were found with $r = 0.88$, 0.90, and 0.81 for IMP 10', 2 hours, and 5 hours respectively (Table 4). For rCMRO\textsubscript{2}, the number of patients (5) was too small for a meaningful correlation study. We therefore combined the results obtained on these patients with those of 5 other patients with chronic infarcts that were not included in Tables 2 and 3 because the infarcts were mainly visible on a level other than OM + 60 mm. Regional CMRO\textsubscript{2} was somewhat more closely correlated to 2-hour IMP uptake with $r = 0.84$, $n = 63$, than to 10-minute and 5-hour IMP uptake, which had respective $r$ values of 0.79 with $n = 63$ and 0.80 with $n = 56$ (Table 4). In the same group of 9 patients absolute values of rCBF\textsubscript{Xe}

![Figure 4. Schematic relations between the central and peripheral areas; the peripheral area surrounds the central area. In most cases the peripheral area is larger than the central area.](image)

![Figure 5. Correlation between the peripheral area volume and neurological status. The peripheral area volume tends to be largest in cases with severe sequelae (Grade III) and smallest in cases with complete recovery (Grade I). Even though the number of patients is small, the fact that the gradings for the peripheral area volume and for neurological status were each assessed by a different observer who was unaware of the results of the other increases the value of the observed correlation. Three cases were excluded, 2 because they had 2 infarct localizations and 1 because his neurological deficit could not be graded accurately.](image)
and rCMRO$_2$ were well correlated with $r = 0.78$, $n = 126$.

Discussion

Since the introduction of IMP by Winchell et al., IMP hypofixation has been observed in chronic infarct areas that are hypodense on CT scan and also in areas found normal on CT scan.$^{2,4,6,7}$ Studying early and delayed periods following injection of IMP, the results obtained confirmed that 2 regions could be differentiated, the central or infarct core area and the peripheral or peri-infarct area. The central area, characterized by an important decrease of IMP, perfusion, and metabolic activity as well as by the ever-present hypodensity on CT scan, corresponded to the infarct core. The IMP hypofixation sometimes persisted unchanged from 10 minutes to 5 hours or in many cases partially regressed. The peripheral area surrounding the central area was characterized by a moderate decrease in IMP uptake, perfusion, and metabolic activity and in every case by a normal density on CT scan. The IMP hypofixation tended to disappear at 5 hours, and the size of this area frequently extended over a large part of a cerebral hemisphere. Practically, the marked decrease characterizing the central area is easily differentiated from the slight decrease in the peripheral area, and, if necessary, threshold values for IMP uptake and rCBF may be used.

The mean rCBF decrease of 19% found in the peripheral area may seem very small to have neurological consequences and persist for several years. Such low values might be due to the way in which the results are expressed; if contralateral values used as normal reference were already low, decrease in the infarct side would be less marked. This eventuality would be plausible in elderly patients with a history of cerebrovascular disease.$^{18}$ To evaluate this possible error, the peripheral area rCBF$_{x}$ decrease was expressed in percent of the mean value found in normal subjects. In 5 normal subjects 30–45 years of age, rCBF$_{x}$ was measured on 4 or 5 cortical areas on both sides of the slice OM + 60 mm. The mean value was 48.1 ml/min/100 g ± 3.4. When rCBF$_{x}$ values for the peripheral area were expressed in percent of this "normal" rCBF$_{x}$, mean decrease was 17% instead of 19% found when compared with the individual contralateral rCBF$_{x}$. Both decreases are of the same order of magnitude although the age of normal subjects differed. The same slight rCBF$_{0}$ and rCMRO$_{2}$ decrease was found with PET in peripheral areas (Table 3), confirming the validity of SPECT results.

The finding that neurological status correlates with peripheral area volume and not with central area volume is interesting. "Neurological status" here means the evaluation of both neurological deficit and psychological disability, which were rated with the scale used. This correlation may have prognostic value.

In the central area the marked decrease of IMP uptake, blood flow, and metabolism accompanied by CT hypodensity is certainly due to a loss of tissue following ischemic necrosis. The lesser decrease of IMP uptake compared to CBF decrease and the partial redistribution observed are probably due to the limited spatial resolution of SPECT systems. Part of the redistribution could also be attributed to fibroblastic tissue eventually remaining in the infarct core. In the peripheral area the moderate and parallel decrease in IMP uptake, blood flow, and metabolism without any CT hypodensity is not due to a typical infarction. This area tended to be clearly demarcated from normal tissue on the IMP, CBF, or CMRO$_2$, images. In most cases the concerned area respects boundaries of the major arterial supply regions, involving MCA or ACA territories.

Is the peri-infarct area caused by chronic inadequate oxygen supply due to a critically lowered CBF? This concept of a chronic ischemic penumbra is not compatible with parallel depression of CBF$_{0}$ and of CMRO$_2$ with normal OEF found by PET in 3 cases (Table 3). A preferential CBF depression, a state of chronic "misery perfusion"$^{19}$ could have been expected. It has been reported that CBF must decrease by approximately 50% — the so-called perfusion reserve$^{20}$ — before CMRO$_2$, and neuronal function begin to decrease. Not one of the 17 patients showed such a CBF$_{x}$ reduction (Table 2). It should also be recalled that 3 patients had no major lesions of the ipsilateral ICA or of the intracranial arterial tree in the chronic state here discussed. All these 3 patients had extensive peri-infarct areas, and chronic hypoxia can be ruled out.

Is the peripheral area due to a state of deafferentation that silences it? Such a process was described for the cerebellum and the crossed cerebellar diaschisis$^{21}$; it is characterized by a moderate decrease in CBF, CMRO$_2$, and IMP 10' as found for the peripheral area. But two differences were found: The IMP 10' hypofixation was still visible at 2 hours in the peripheral area but had disappeared in cerebellar diaschisis; the peripheral area corresponded to a vascular territory. Such distribution should not be expected in deafferentation. However, these two objections did not appear definitive since the difference in IMP kinetics was not always found and limits of the peripheral area were extended to an adjacent non-occluded territory in 2 patients. We conclude then the intrahemispheric diaschisis hypothesis does not seem to be the main mechanism explaining the peripheral area, but it cannot be ruled out.

Can the perifinarc area be regarded as the sequela of an acute ischemic penumbra? In 1983 Lassen et al$^{22}$ reported 2 stroke cases with stem occlusion of the middle cerebral artery; both patients had deep infarcts with a minimal perfusion of approximately 20 ml/100 g/min in the superficial cortical layers as measured in the acute phase. At autopsy several months later both showed extensive neuronal loss without frank infarction in the same cortical areas. This condition of selective neuronal loss with preservation of tissue structure may explain the peri-infarct areas in our 15 chronic cases. With this concept these areas represent incomplete infarction in the penumbral zone surrounding the infarct in the acute phase (the "expenumbra").
This hypothesis will be briefly discussed. It postulates that the perinfarct area represents an area of incomplete ischemic damage affecting some nerve cells and synapses. Incomplete infarction of this type is well described in cases of global cerebral hypoxia but only rarely in cerebral ischemia. In fact, in a recent autopsy study patients with ischemic stroke where selective neuronal loss in perinfarct areas was specifically sought, no evidence of extensive areas of this kind was found. This study may imply that massive neuronal loss as seen in the 2 cases reported by Lassen et al is not very frequent; however, it may have overlooked more subtle changes, as even 10 or 20% neuronal loss is easily overlooked, particularly if the cortical volume decreases. In the classical studies of Astrup et al defining the ischemic penumbra, complete and immediate recovery of electrical activity was found when CBF is increased after 2 hours of flow reduction. It should be noted, however, that electrical recovery does not preclude selective neuronal damage that eventually may result in cell death. Studies by Strong et al and Mies et al illustrate this point and emphasize the damage resulting from prolonged penumbral flow conditions.

Having argued that the peripheral area may have been critically ischemic in the acute phase, the fact that its perfusion is adequate in the chronic state, compared to metabolic needs, suggests a satisfactory reestablishment of local blood flow. Development of collateral blood flow in the weeks following an occlusion of the ICA has been described. The impact of ICA occlusion is maximal in the acute phase. It may therefore be that cases with extensive areas of acute penumbra surrounding the infarct will nevertheless have adequate CBF compared to the decreased metabolic demands months after the stroke. The rise in tissue oxygen tension and normalization of initially acid pH, which presumably results from such improvement in local blood flow, may well be essential in the recovery of function of the remaining neurons.

Experimental studies in normal animals have shown that very early cerebral uptake of IMP was well correlated with CBF and led us to consider this compound as an excellent CBF indicator. In humans the similarity observed between early IMP images and CBF images and the correlation between 10-minute IMP uptake and CBF reported here may be accepted as further evidence of this hypothesis. However, the poor correlation observed in normal animals after 30 minutes and the redistribution observed over time in chronic infarcts may be factors opposing this interpretation. In subacute infarcts rCBF decrease following “luxury perfusion” was frequently accompanied by an increase of IMP uptake in the same areas. These discrepancies indicate that accumulation of IMP is dependent not only on CBF but probably also on a number of other factors, including metabolic activity, neuronal density, glial condition, blood-brain barrier permeability, and local pH. In situations where CBF and metabolic activity are coupled, as in normal brain and chronic infarct, early IMP uptake is well correlated with CBF and CMR02. However, in CBF–CMR02 uncoupled situations, like in subacute infarcts after luxury perfusion, such correlation often disappears and IMP can no longer be considered a reliable CBF indicator. Despite these uncertainties the present study demonstrates the value of IMP imaging in investigating and understanding the pathophysiology of stroke sequelae.

The data presented demonstrate the existence in the chronic cerebral infarct of a peripheral area that surrounds the infarct area. Although exhibiting only a minor decrease in CBF and metabolism, the peripheral area seems responsible for a significant part of the patient’s symptoms and is correlated to neurological status of the patient. This region can most probably be considered to have suffered less damage than the central area, since its CT image is strictly normal, and could be considered as potentially recuperable.

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