Original Contributions

Blood Flow and Vascular Reactivity in Collaterally Perfused Brain Tissue
Evidence of an Ischemic Penumbra in Patients with Acute Stroke

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SUMMARY In a group of 48 patients with completed stroke, 8 patients had viable collaterally perfused brain tissue which was accessible for rCBF recordings with a two dimensional technique. All 8 had deep subcortical infarcts on CT-scan, and angiographic occlusion of the arteries normally supplying the infarcted territory. The brain tissue overlying the deep infarcts appeared normal on CT-scan and was supplied by collateral circulation. rCBF was measured in all within 72 hours after the stroke. The intra-carotid Xe-133 injection method and a 254 multidetector camera were used to study rCBF.

Relatively ischemic low flow areas were a constant finding in the collaterally perfused tissue. In 6 of the patients, the collaterally perfused part of the brain had low flow values comparable to those of an “ischemic penumbra” (viable, but functionally depressed brain tissue due to inadequate perfusion).

Autoregulation was impaired in all of the collaterally perfused areas while the CO₂-response always was preserved. Steal phenomena were not seen. In the surrounding brain tissue, autoregulation was normal in 5 patients and impaired in 3 while the CO₂-response seemed to be normal.

The results confirm the experimental finding of an ischemic penumbra associated with acute cerebral infarcts and suggest that early restoration of the blood flow in acute stroke patients might improve recovery and prognosis in selected patients.

Cerebral Arterial Occlusion may lead to different degrees of tissue damage depending on the collateral blood supply to the resultant ischemic tissue.¹⁻⁵ The blood flow in the area may decrease to such an extent that cell death ensues; but it is also possible that collateral flow, while insufficient for normal cell function, may be sufficient to preserve the cellular viability. Viable but non functional tissue located adjacent to an ischemic infarct has been denoted the ischemic penumbra.⁶⁻⁷

Such an ischemic penumbra, demonstrated in animal stroke models,¹⁻⁷ might prove important in man because restoration of the blood flow to such areas in stroke patients might restore normal cell function and thereby facilitate recovery and improve the prognosis. The frequency of occurrence, size and vascular reactivity of such areas in stroke patients are unknown, as to date they have been investigated in only a few selected cases.⁵⁻¹⁰

The present study analyses regional cerebral blood flow (rCBF) in a group of stroke patients in whom a region of collaterally perfused brain tissue was angiographically identified following a cerebral arterial occlusion.

Because the intracarotid Xenon-133 injection method used in this study does not record rCBF reliably unless the detectors “look” directly on viable brain tissue, patients were selected in whom collateral flow sufficed to avoid frank necrosis of superficial cortical areas.

Patients

The study population comprises 8 patients with collaterally perfused brain tissue which was considered present and accessible for rCBF investigations if the following 3 criteria were fulfilled:

CT-scan
1) A cerebral infarct was located deep in the hemisphere without involvement of the overlying cortex which appeared normal (fig. 1).

Cerebral Arteriography
2) An occlusion of the artery normally supplying the territory in which the infarct was located (fig. 2). All 8 patients had occlusion in the territory of the middle cerebral artery (MCA).

3) A delayed filling of arteries in the “occluded” territory from other sources than the occluded artery (here termed collateral circulation, figure 3).

In that way it was assured that the detectors looked directly on collaterally perfused viable brain tissue i.e. the brain tissue overlying the infarcts.

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The 8 patients were selected from a consecutive series of 48 patients with completed stroke all below the age of 75 years and all admitted to hospital within 72 hours after the acute onset of symptoms (intracranial hematoma and transient ischemic attacks were not included in the study).

The investigation programme tended to be the same in all patients in this series:

1) Cerebral arteriography and rCBF measurements within 24 hours of admission.

2) CT-scan approximately 24 hours after the arteriography, repeated after 14 days and 6 months.

3) The patients were examined clinically every day during the first week after admission, and again 2 weeks, 3 months and 6 months after the stroke.

Methods

Cerebral Arteriography

The patients were premedicated with diazepam 10 mg intramuscularly. Under local anesthesia using 5 ml 1% Lidocain® the common carotid artery was punctured and the angiography was performed. With the Seldinger technique, the needle was then replaced by a heparinised polyethylene catheter, the tip of which was placed in the internal carotid artery. The rCBF study was then performed.

rCBF

The rCBF investigations were carried out in connection with the carotid angiography as described above. 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.

The scintillation camera has 254 individual detectors each consisting of a NaJ crystal (8 mm in diameter, center to center distance 10 mm) in connection with a photo-multiplier, an amplifier and a lower level discriminator at approximately 20 keV. The camera is collimated by a slightly curved 4 cm thick lead slab with 254 cylindrical holes corresponding to the detectors of the camera.

rCBF was calculated using the initial slope index method and displayed on a TV-monitor as a schematic two-dimensional picture of the hemisphere (fig. 4). The image was made up of 254 coloured squares representing absolute flow values on a 16 level colour scale.

The investigations were carried out in a quiet room with the patient relaxing as much as possible. The eyes were covered and the ears were plugged ("rest" study).

Immediately after the injection of the isotope, a blood sample for pCO₂ determination was taken from the internal carotid artery and the intraarterial blood pressure was measured. Autoregulation was tested by increasing the mean arterial blood pressure (MAP) 20–40 mm Hg by continuous i.v. infusion of angiotensine. During this procedure, MAP was monitored continuously via the carotid catheter.

Definition of Hyperemic and Ischemic Areas

Areas with abnormal (high or low) blood flow were defined in the following way. An average flow map from 12 normal subjects was constructed. The variation of the regional blood flow in this average flow map, expressed as a standard deviation (SD), was 7%. Therefore, areas (more than 4 detectors) with blood flow values more than 2 SD = 14% below the mean hemispheric blood flow were defined as ischemic and areas with blood flow values more than 14% above the mean hemispheric blood flow were defined as hyperemic.

The average flow map from the 12 normal patients, expressed in percent of the mean hemispheric blood flow, was compared to the 8 individual flow maps in the series. If the blood flow in these individual cases (expressed in percent of the mean hemispheric blood flow) was more than 14% higher or lower than the normal blood flow in the area this area was defined as hyperemic or ischemic. It should be stressed in this context that hyperemia and ischemia in this study are defined as relative terms — relative to the mean hemispheric blood flow. It will appear from the results and the discussion that most of the areas termed ischemic in this study also are ischemic in terms of absolute flow.
values (ml/100 gr/min). Only one of the hyperemic areas was hyperemic in terms of absolute flow values.

Brain areas outside the ischemic and hyperemic areas were denoted non ischemic/non hyperemic areas.

Autoregulation was considered impaired when induced hypertension increased CBF by more than 12.2% (this is 2.26 times the coefficient of variation seen with this test in 9 normal subjects and hence corresponds to $p = 0.05$).

**TABLE 1.** Regional Cerebral Blood Flow During "Rest"

<table>
<thead>
<tr>
<th>Patients</th>
<th>PaCO₂ mm Hg</th>
<th>MAP mm Hg</th>
<th>Interval stroke rCBF hours</th>
<th>Non ischemic/ non hyperemic areas ml/100 gr/min SD</th>
<th>Ischemia ml/100 gr/min SD Range Detect.</th>
<th>Hyperemia ml/100 gr/min SD Range Detect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49.0</td>
<td>117</td>
<td>72</td>
<td>48 7</td>
<td>36 5  22–45  52</td>
<td>67 5  58–77  61</td>
</tr>
<tr>
<td>2</td>
<td>39.0</td>
<td>105</td>
<td>36</td>
<td>32 5</td>
<td>25 3  21–29  29</td>
<td>38 4  35–50  14</td>
</tr>
<tr>
<td>3</td>
<td>41.1</td>
<td>118</td>
<td>48</td>
<td>36 4</td>
<td>30 2  26–33  23</td>
<td>42 3  37–49  16</td>
</tr>
<tr>
<td>4</td>
<td>38.0</td>
<td>110</td>
<td>10</td>
<td>30 5</td>
<td>24 3  19–28  44</td>
<td>43 2  39–45  10</td>
</tr>
<tr>
<td>5</td>
<td>36.1</td>
<td>85</td>
<td>64</td>
<td>33 5</td>
<td>26 3  20–29  36</td>
<td>40 6  34–48  42</td>
</tr>
<tr>
<td>6</td>
<td>40.4</td>
<td>92</td>
<td>44</td>
<td>25 3</td>
<td>19 3  15–26  61</td>
<td>41 4  31–35  27</td>
</tr>
<tr>
<td>7</td>
<td>44.1</td>
<td>92</td>
<td>32</td>
<td>64 6</td>
<td>44 4  39–50  11</td>
<td>— — — — — —</td>
</tr>
<tr>
<td>8</td>
<td>44.3</td>
<td>120</td>
<td>64</td>
<td>55 6</td>
<td>49 2  46–52  17</td>
<td>66 3  62–71  12</td>
</tr>
</tbody>
</table>

**FIGURE 3.** Cerebral angiograms in patients 5 (left) and 4 (right) demonstrating the collaterally filling of the arteries in the "occluded" territory (see figure 2).

**FIGURE 4.** rCBF during rest, induced hypertension and spontaneous hyperventilation in patients 5 (left) and 4 (right). Note the flow values around 20 ml/100 gr/min, the impaired autoregulation and the preserved CO₂-response in both patients.
CT-scan
CT-scan was performed with an EMI 1010 scanner using the 160 × 160 matrix. The patients were investigated before as well as after contrast administration.

Results
Cerebral angiographies and rCBF investigations were performed from 10 to 72 hours after the onset of symptoms (average 54 hours, table 1). All 8 patients had ischemic areas on the flow map and in 7 both hyperemic and ischemic areas were seen. The location and relative size appear from table 2 in which also the corresponding infarcts on CT-scan are shown.

The occlusions were located in the stem of the middle cerebral artery in 3 patients (no. 1, 5, 6) in the origin of major branches in 3 patients (no. 2, 3, 4) and peripherally in the vascular tree in 2 patients (no. 7, 8).

The ischemic areas were always located within the collaterally perfused areas while the hyperemic areas always were located outside the collaterally perfused areas. The CT-scans the angiograms and the flow maps in two typical patients are shown in figures 1, 2, 3, 4.

Ischemic Areas
Location and Size
Ischemic areas were identified in all 8 patients in cortex overlying the deep infarcts and noted to be collaterally perfused on the angiograms. The extent of the ischemic areas was always considerably larger than the lateral projection of the infarct. This difference was most pronounced in the posterior and superior part of the ischemic areas which included large areas without underlying infarction. The size of the ischemic areas ranged from 11 to 61 detector fields; 22 to 122 cm

Blood Flow in ‘Resting’ State
The blood flow in the 8 ischemic areas is given in table 1. Average flow ranged from 19 to 36 ml/100 gr/min. in the 6 patients with major occlusions and from 44 to 49 ml/100 gr/min. in the two patients with minor occlusions. None of the detectors measured blood flow values below the estimated lower limit for cellular viability (10-12 ml/100 gr/min., Morawetz et al. 1978).³

Blood Flow During Induced Hypertension
During induced hypertension MAP was increased by 20–40 mm Hg (table 3). The average blood flow in the ischemic areas increased significantly (more than 12.2%) in all of the patients (table 3).

The blood flow was, in each case, corrected for changes in pCO₂ based on a subsequent rCBF study during spontaneous hyperventilation or inhalation of 5% CO₂ (see below). In patient no. 6 a CO₂ reactivity study was not performed but the blood flow increase during induced hypertension was so marked in the ischemic area that a correction for the recorded 1 mm Hg change of pCO₂ would not influence the results and conclusions obtained, i.e. impaired autoregulation.

In the non ischemic/non hyperemic areas the blood flow increase in 7 patients during induced hypertension; the increase was significant (more than 12.2%) only in 3 cases. The blood flow increase in the ischemic areas was in all patients considerably higher than in the non ischemic/non hyperemic areas (table 3).

In conclusion: The autoregulation was clearly impaired in large parts of all the collaterally perfused

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Table 2. The Localization of infarcts on CT-Scan and the Localization of Ischemic and Hyperemic Areas on the Flow Map

<table>
<thead>
<tr>
<th>Patients</th>
<th>CT Scan</th>
<th>Flow map</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
</tr>
<tr>
<td>8</td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
</tr>
</tbody>
</table>
blood flow increase. The relative blood flow decrease is not cor-
rected. In the remaining 5 patients detectors re­
paired in the area this is the most likely explanation for
the increase. In the remaining 5 patients detectors re­
tector fields were present in 7 of the 8 patients and were
always located outside the collaterally perfused areas
(table 2). Infarcts were not seen in hyperemic regions
or in the brain deep to them (table 2).

Blood Flow in Resting State

Average blood flow ranged from 30 to 67 ml/100 gr/ min. (table 1). In one patient (patient 1) the hyperemia
was associated with capillary blush and early venous

Blood Flow During Hypo/Hypercapnia

In 6 patients paco2 was decreased by spontaneous
duced hypertension the Co2 response was preserved in
all the ischemic areas.

In conclusion: The Co2-response was preserved in
all the ischemic areas investigated. Paradoxical re­
sponses (steal or inverse steal) were not observed.

Hyperemic Areas

Location and Size

Hyperemic areas ranging in size from 10 to 61 de­
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areas as an elevation of MAP always resulted in a
significant elevation of the blood flow. Autoregulation
was also impaired, but to a much lesser degree in the
non ischemic/non hyperemic area.

Blood Flow During Hypo/Hypercapnia

In 6 patients paco2 was decreased by spontaneous
hyperventilation. In these the blood flow decreased from 2.5% to 4.4% per mm Hg in the ischemic areas
(table 4). The decrease is, however, an underestima­tion as MAP increased in 4 patients during the hyper­
ventilation therefore counteracting the decrease as au­
toregulation was impaired in all the ischemic areas.

In only a few individual detector fields blood flow increases were recorded during hyperventilation. In patient no. 1, eight such detector fields were adjoining.

Average blood flow ranged from 30 to 67 ml/100 gr/ min. (table 1). In one patient (no. 4) paco2 was increased during
hyperventilation. The blood flow increased 3.8% per mm Hg in the ischemic areas compared to 1.1% per mm Hg in the non ischemic/non hyperemic areas. MAP increased also, but when compared to the study performed during induced hypertension the Co2-inha­
nlation still resulted in a blood flow increase (of 1.9% per mm Hg) in the ischemic area.

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Blood Flow in Resting State

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TABLE 3 (Continued)

<table>
<thead>
<tr>
<th>ml/100 gr/min</th>
<th>SD</th>
<th>Range</th>
<th>Detect.</th>
<th>CO₂ correct. ml/100 gr/min</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>5</td>
<td>48-69</td>
<td>61</td>
<td>71</td>
<td>6% ↑</td>
</tr>
<tr>
<td>38</td>
<td>5</td>
<td>31-50</td>
<td>14</td>
<td>47</td>
<td>24% ↑</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>33-46</td>
<td>16</td>
<td>40</td>
<td>5% ↓</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>35-46</td>
<td>10</td>
<td>40</td>
<td>7% ↓</td>
</tr>
<tr>
<td>42</td>
<td>13</td>
<td>28-58</td>
<td>42</td>
<td>42</td>
<td>5% ↑</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>35-49</td>
<td>27</td>
<td>42</td>
<td>2% ↑</td>
</tr>
<tr>
<td>28</td>
<td>5</td>
<td>17-38</td>
<td>56</td>
<td>not corrected</td>
<td>7% ↓</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>5</td>
<td>59-72</td>
<td>12</td>
<td>64</td>
<td>3% ↓</td>
</tr>
</tbody>
</table>

Blood Flow During Induced Hypertension

The blood flow increased significantly in the hyperemic areas in one patient (no. 2). In the remaining 6 patients the changes were slight and insignificant (within the 12.2% limit, table 3).

In conclusion: The autoregulation seemed to be normal in the remaining patients in hyperemic areas. The hyperemias were only relative to the mean hemispheric blood flow in these patients.

Blood Flow During Hypo/Hypercapnia

During hyperventilation the blood flow decreased in 5 patients from 4.3% to 8.7% per mm Hg (table 4). In one patient (no. 4) the blood flow decrease was negligible (0.5% per mm Hg).

During Inhalation of 5% CO₂

In patient 3 the blood flow increase was also negligible (1.0% and 0.7% respectively in 2 hyperemic areas). Also the blood flow increase in the non isch-

emic/non hyperemic areas was minimal (1.2% per mm Hg).

In conclusion: CO₂-response was preserved in most hyperemic areas but seemed to be impaired in 2 patients.

Clinical Features of the Patients

A schematic description of the acute clinical symptoms, the clinical development and the clinical outcome at 6 months is given in table 5. When the symptoms are compared to the location of the infarcts it appears that at least three patients (nos. 2, 3, 6) exhibited neurological symptoms which could not be readily explained by the CT-lesion. These patients had a sensory (fluent) aphasia but the CT-lesion was located around Broca's area. The collaterally perfused areas included, however, in all three patients Wernicke's area. The clinical state was unstable in 6 of the patients all of whom had a period of temporarily neurological deterioration during the first week after the stroke. In 3 patients the worsening period started before the angiography had been performed and in 3 patients the worsening period started after the angiography had been performed. Except for two patients (nos. 4, 6) the clinical recovery was excellent as these 6 patients were independent of care 6 months after the stroke.

Discussion

Methodological Considerations

Collaterally perfused brain tissue occurred in many more of the 48 patients than the 8 patients selected for the present study. Many patients with MCA occlusion and infarcts involving cortical convexity structures (reported elsewhere) showed angiographic evidence of some degree of collateral circulation. The patients selected in the present study were, however, the only patients in which such collaterally perfused brain tissue was readily accessible for reliable rCBF-recordings (with little interference from the infarcted area) according to the following considerations:

1) The equipment used measures rCBF reliably only if the detectors "look" directly on perfused tissue underneath the skull. The collaterally perfused brain tissue therefore must include cortical structures on the convexity in order to be examined reliably.

2) The main pre-requisite for measuring blood flow is that the tracer (Xe-133) gains access to the tissue to be studied, in other words that the tissue is perfused. This can only be a priori assumed in tissues that, although sparsely perfused, remain alive. The tissue to be examined must be without necrotic, infarcted areas, i.e. the tissue must appear normal on CT-scan, without hypodense areas and without areas enhancing after contrast administration.

3) In order to assess that the perfusion is solely due to collateral circulation, the artery normally supplying the tissue must be occluded.

4) A very low flow probably exists in the infarct but its influence on the washout curves must be very small. First, as previously shown, because the count rate recorded from cortical infarcts with the present tech-

TABLE 4 (Continued)

<table>
<thead>
<tr>
<th>ml/100 gr/min</th>
<th>SD</th>
<th>Range</th>
<th>Detect.</th>
<th>CBF change pr mm paCO₂</th>
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<tbody>
<tr>
<td>51</td>
<td>5</td>
<td>49-60</td>
<td>61</td>
<td>6.7% ↓</td>
</tr>
<tr>
<td>25</td>
<td>4</td>
<td>16-30</td>
<td>14</td>
<td>8.7% ↓</td>
</tr>
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<td>45</td>
<td>5</td>
<td>39-54</td>
<td>12</td>
<td>1.0% ↑</td>
</tr>
<tr>
<td>45</td>
<td>5</td>
<td>39-53</td>
<td>12</td>
<td>0.7% ↑</td>
</tr>
<tr>
<td>41</td>
<td>8</td>
<td>29-57</td>
<td>42</td>
<td>0.5% ↑</td>
</tr>
<tr>
<td>35</td>
<td>5</td>
<td>26-42</td>
<td>27</td>
<td>5.6% ↓</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>4</td>
<td>36-43</td>
<td>12</td>
<td>4.4% ↓</td>
</tr>
</tbody>
</table>
nique does not differ from that expected from Compton scattered radiation. This must apply also to deep infarcts. Second, because the tissue absorption of radiation from Xe$^{133}$ is considerable (halved by the square of the distance from the detectors).

Studying stroke patients with infarcts involving cortical convexity structures, it was recently shown that two-dimensional recording of CBF with Xenon-133 is practically useless in quantifying blood flow in densely ischemic brain tissue (infarction). First because of Compton scattered radiation from surrounding perfused brain tissue, second because of the look through phenomenon. Although the influence of these phenomena cannot be excluded completely in the present cases their influence is much reduced when measuring blood flow in the collaterally perfused ischemic brain areas here studied: The cortical convexity structures are perfused as they did not infarct and the deep infarcts constitute a barrier for radiation from even deeper structures.

Because of the above mentioned selection criteria the study does not attempt to investigate the incidence of such collaterally perfused ischemic brain tissue in an acute stroke population. However, the existence of 8 such patients in a population of 48 stroke patients, indicates the quantitative importance of such brain tissue in acute stroke patients.

Evidence of an Ischemic Penumbra

In an experimental study Symon et al 1974 included the MCA in baboons. In addition to infarction in the Sylvian opercular region, much larger low flow areas in viable tissue were found extending posteriorly and superiorly from the infarcts. The 6 patients in this study with an occlusion of the stem or of major branches of MCA may be the clinical counterpart of this experimental study. The location and size of the low flow areas were the same as in the experimental study of Symon and coworkers.

Brain tissue surrounding an acute cerebral infarct
which was viable, but non functional because of inadequate blood flow, was denoted the ischemic penumbra by Symon and colleagues. In their experimental model (the anaesthetized baboon) the evoked somatosensory response in the cortex was completely abolished at flow values below 15 ml/100 gr/min. while frank infarction developed only in brain tissue which immediately after an occlusion had flow rates less than 10 ml/100 gr/min. The ischemic penumbra therefore was considered to represent brain tissue with blood flow between 10 and 15 ml/100 gr/min. Recently, however, Jones and coworkers in an awake stroke model (the baboon) showed that after permanent occlusion when blood flow was between 18 and 23 ml/100 gr/min. neurological deficits were reversible at any time if normal perfusion was restored. For clinical use we therefore suggest the ischemic penumbra to be the brain tissue with blood flow between 10 and 23 ml/100 gr/min.

At flow levels of 20–30 ml/100 gr/min. the initial slope method overestimates the blood flow by 10%. When the overestimation induced by Compton scattered radiation from better perfused parts of the brain is included it becomes clear that ischemic areas with flow levels comparable to those of an ischemic penumbra may exist in the present group of patients with major MCA occlusions.

The patients with a sensory aphasia but no CT lesion in the relevant area support this concept. As the areas relevant for the neurological deficits were included in the collaterally perfused brain tissue a temporary functional depression might explain the temporary neurological deficits (the sensory aphasia).

The conspicuously high number of patients experiencing a temporary neurological deterioration during the first week after the stroke also points to a functional depression of the collaterally perfused tissue. A slight decrease in the perfusion pressure (due to a decrease in MAP and/or to an increase in local tissue pressure because of the development of edema in and around the underlying deep infarct) might decrease the blood flow and increase the amount of brain tissue being functionally depressed.

The clinical and experimental findings support the concepts of a functionally depressed state in some parts of the collaterally perfused brain tissue. However, it must be emphasized that a definite proof based on the present data is not possible as the duration of the blood flow increase during induced hypertension might be too short (less than 5 min.) to improve the clinical state. If a sustained increase in collateral flow would fail to ameliorate the clinical state then one either would be lead to conclude that the 1) collaterally perfused tissue was functionally isolated from manifesting itself due to the "undercutting" caused by the completely infarcted deeper tissue or that 2) it had suffered incomplete infarction, i.e. neuronal death without emolition.

**Regulation of Blood Flow in Collaterally Perfused Brain Tissue**

**Autoregulation** of the cerebral blood flow was clearly impaired in the collaterally perfused tissue. The increased blood flow measured during induced hypertension cannot be attributed solely to Compton scattered radiation from better perfused areas because: 1) the ischemic areas, in particular those due to major occlusions, were large, 2) the increase was in all cases higher in the ischemic areas than in the remainder of the hemisphere and 3) the hyperemic areas in the better perfused surroundings did not show a significant blood flow increase during induced hypertension in 6 of 7 patients. Therefore, there is no doubt that the blood flow in collaterally perfused brain tissue (including an ischemic penumbra) also in stroke patients can be increased by increasing MAP. This clinical finding is in accord with the experimental findings of Denny-Brown and Meyer 1957 and the experimental findings of Symon et al 1976, in which autoregulation was impaired in and around the ischemic penumbra.

The CO\textsubscript{2}-response was preserved in all ischemic areas investigated and the response was similar to that
of the non ischemic/non hyperemic areas. As was the case for autoregulation, the changes cannot be attributed only to changes in Compton scattered radiation from better perfused areas because: 1) the ischemic areas were fairly large and 2) the decrease of blood flow during hyperventilation appeared, despite an accompanying SAP increase which would tend to counteract the blood flow decrease because of the impaired autoregulation in the ischemic areas.

If the CO₂-response was abolished in the vessels within the ischemic area and preserved only in the surrounding non ischemic brain tissue then the inverse steal phenomenon should appear during hyperventilation, i.e., a paradoxical blood flow increase would occur in the ischemic area particularly in the patients in whom MAP also increased. Such paradoxical responses were not seen. The vessels within the collaterally perfused tissue, therefore, most likely react in a normal fashion to pACO₂ changes. Whether the CO₂-reactivity is normal or reduced to some extent is difficult to evaluate because of the Compton scattered radiation that after all influences the recordings.

This finding agrees with the finding of Nakagawa et al. 1981 who studied CO₂-reactivity in moderately ischemic, non infarcted brain tissue after MCA occlusion in the dog. Increasing pACO₂ to 55 mm Hg increased the blood flow in the ischemic areas indicating preservation of the CO₂-reactivity also in slowly perfused brain tissue. After MCA occlusion in the baboon Symon et al. 1974 found the CO₂-reactivity to be preserved, although reduced, in brain tissue with a blood flow of 23 ml/100 gr/min. In the most densely ischemic tissue however CO₂-reactivity was abolished, and paradoxical flow responses occurred. A similar finding was obtained by Ott et al. 1975 after direct injection of Xenon-133 into the distal stump of the occluded MCA in the baboon.

Blood Flow in the Non Ischemic Brain Tissue

Hyperemic areas occurred in 7 patients always outside the collaterally perfused brain tissue. It should be emphasized in this context that the hyperemic areas were defined on the basis of statistics only. Particularly in the 5 patients with major MCA occlusions and normal angiography in the hyperemic areas one cannot exclude the possibility that the hyperemic areas in fact represents normally perfused brain tissue. The non ischemic/non hyperemic areas may represent brain tissue with a perfusion pressure between that of the "normal" hyperemic areas and the definitely abnormal ischemic areas.

CO₂-response appeared normal in the hyperemic areas in all but two patients (no. 3, 4). The observation in patients 3 and 4 does not need to be a manifestation of an impaired CO₂-response. Hyperventilation exerts a decompressive effect on the brain which may change the tissue pressure locally and enhance the perfusion pressure in formerly compressed brain tissue. Such a development might compensate for the vasoconstrictive effect of hyperventilation. The reverse phenomenon might occur during hypercapnia.

Concluding Remarks

In a previous study of the same stroke population, we found that hyperemic areas were always seen in the proximity of a cerebral infarct when cortical convexity structures were involved. However, the hyperemic areas were never located posterior-superior to the cortical infarcts. This is explained by the present study: These areas posterior-superior to a cortical infarct lie down-stream of the occlusion and are probably collaterally supplied areas with a low perfusion pressure (the ischemic penumbra). Although these areas biochemically are prepared to produce a hyperemia (due to accumulation of vasoactive metabolites and severe acidosis) the local perfusion pressure is insufficient to support one. Anterior to the infarct (up-stream), the circulation and perfusion pressure is normal or nearly normal and able to create a hyperemic area (fig. 5).

Similar hyperemic areas were not seen in the present series probably because the infarcts were located deep in the hemisphere. Blood flow abnormalities are, as mentioned, seen best with two-dimensional techniques if the abnormalities are located superficially in the brain directly underneath the detectors.

Because of the occurrence of focal hyperemia around and particularly within acute cerebral infarcts we suggested previously that induced hypertension should be avoided in the acute state of cerebral infarction: Hypertension may increase edema, blood volume and tissue pressure in the hyperemic area. Considering the present result, which indicate the presence of an ischemic penumbra in some acute stroke patients it would be justified also to suggest the reverse: that hypotension also should be avoided. As hypertension in fact increases the blood flow in the ischemic penumbra induced hypertension might benefit tissue survival in this area. Although the perfusion seems to be sufficient for cellular viability in the major part of the
collaterally perfused ischemic area a borderzone of threatened brain tissue must exist — a borderzone which might survive if induced hypertension increases blood flow to the area. Thus changing the blood pressure in the setting of an acute stroke seems to be a twofold sword. Elevation benefits the ischemic penumbra and harms the hypopermja area by augmenting local edema, lowering benefits the hyperemia and harms the penumbra.

Jones et al. 1981 have shown that the development of infarction was a function of intensity as well as of duration of ischemia. They therefore suggested that early restoration of blood flow in acute stroke patients might improve recovery by avoiding cell damage due to prolonged ischemia. Positron emission tomography studies in stroke patients support this concept. Critical flow (high oxygen extraction combined with low blood flow) in infarcts and their borderzones were measured in early stages while a low or normal oxygen extraction combined with low blood flow and low CMRO2 were found later. The finding of extensive pressure passive non-infarcted low flow areas in the acute stroke patients here presented indicating that increasing perfusion pressure locally might improve clinical outcome further supports the suggestions of Jones and coworkers. But whether acute surgical revascularization can achieve this theoretically predicted improvement in neuronal survival in an ischemic penumbra has yet to be determined.

References


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