Focal Cerebral Hyperemia in Acute Stroke

Incidence, Pathophysiology and Clinical Significance

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SUMMARY In a consecutive study comprising 41 patients with completed stroke of less than 72 hours duration, cerebral angiography and measurements of the regional cerebral blood flow (rCBF) were performed within 24 hours after admission. The rCBF study was done using the 133-Xenon intracarotid injection method and a 254 multi-detector camera. CT scan was done 24 hours after the rCBF study.

Focal cerebral hyperemia was found in 16 patients. The study revealed 3 different types of hyperemia: 

Border-zone hyperemia, surrounding ischemic areas, was seen in patients with occluded arteries on angiography, presumably resulting from accumulation of acid metabolites in the border-zone of acute infarcts.

Postischemic hyperemia was seen in patients without occlusion, presumably due to recanalization of a prior occluded artery. Remote hyperemia was found distant from the infarcted area, presumably due to local tissue pressure on brain tissue.

Cortical infarcts (10 patients) all had extensive hyperemic areas. Because the 254 detector camera has an excellent resolution in the cortical surface, our findings strongly suggest that all acute cerebral infarcts are, in fact, associated with hyperemic areas. The hyperemic areas are often extensive and vascular reactivity is commonly impaired. It is suggested that treatment aimed at reducing blood flow in hyperemic areas might improve prognosis.
12.2% (this is 2.26 times the coefficient of variation seen with this test in 9 normal subjects and hence corresponds to \( p = 0.05 \)).

Autoregulation is considered false if: 1) induced hypertension decreases the blood flow more than 12.2% or if 2) induced hypertension does not change the blood flow more than 12.2% together with impaired CO\(_2\) response.\(^{17,18}\)

In case of intact CO\(_2\) response the rCBF values obtained during hypertension were corrected to the PaCO\(_2\) at rest, implying a correction of 4% flow change for each 1 mm Hg of PCO\(_2\).\(^{18}\)

Definition of Hyperemia

Larsen et al.\(^{18}\) using the same technique as in the present study, measured resting rCBF repeatedly in a group of 24 normal subjects. Mean CBF was 49 ml/100 g/min in the left hemisphere and 55 ml/100 g/min in the right hemisphere. The random experimental error for the left hemisphere was 3.2 ml/100 g/min and 4.8 ml/100 g/min for the right hemisphere. Expressed as a coefficient of variation the random error for the left hemisphere was 6.5% and for the right hemisphere 8.7%. We, therefore, define focal cerebral hyperemia as areas where rCBF, compared to the mean hemispheric blood flow, is increased more than \( 3 \times 6.5 \approx 20\% (p = 0.01) \) for the left hemisphere and more than \( 3 \times 8.7 \approx 26\% (p = 0.01) \) for the right hemisphere.

Based on the same data we define absolute focal hyperemia as rCBF > 49 + 3 \times 3.2 = 59 ml/100 g/min in the left hemisphere and as rCBF > 55 + 3 \times 4.8 = 69 ml/100 g/min in the right hemisphere (\( p = 0.01 \)).

Isotope-Angiogram

In addition to the rCBF measurements, the 254-detector camera is able to monitor the distribution of the injected isotope from the time of injection until the study is finished.

In every second after the bolus injection the total number of counts in each of the 254 detectors is registered and displayed on the TV monitor as a schematic 2-dimensional picture of the hemisphere with 254 color squares, each representing the total number of counts during one second on a 16 level color scale. Such pictures, representing the isotope distribution during the first 5 seconds after the injection, comprise our isotope-angiogram and show the arterial distribution of the isotope before washout of the isotope (fig. 1).

The isotope-angiogram does not show the site of the arterial occlusion but shows the resultant low or non-perfused areas as well as the highly perfused areas in cases with focal hyperemia (fig. 1).

Results

The rCBF measurements revealed areas of focal cerebral hyperemia in 16 of the 41 patients, i.e., in 39%. These 16 were investigated from 10 to 84 hours after onset of stroke (table 1). The results of the rCBF studies during rest appear in table 1. Absolute hyperemia was seen in 6 patients in whom the mean flow in the hyperemic areas ranged from 67 to 103 ml/100 g/min. The hyperemias in the remaining 10 patients were only relative and ranged from 28 to 54 ml/100 g/min.

Ischemic areas in the 16 instances of focal cerebral hyperemia were defined as areas of abnormal low isotope filling on the isotope-angiogram 5 seconds after injection of 133-Xenon. Such ischemic areas were seen in 13 patients while 3 did not have ischemic areas.

In all but one of the 16 (patient No. 11) some of the semilogarithmic recorded 2 minutes clearance curves appeared as bending curves irrespective of the magnitude of the hyperemic blood flow.

CT scan showed hypodense areas involving the cortical surface in 10 of the 41 patients and all these 10 had areas of focal cerebral hyperemia (100%).

The CT scan showed hypodense areas without cortical involvement in 25 of the 41 patients. Only 4 of these 25 patients had areas of focal cerebral hyperemia (16%). The CT scan was normal in the remaining 6 patients and 2 of these had areas of focal cerebral hyperemia (33%). According to the findings on the CT scan the hyperemic areas could be separated into 4 different groups:

**Group I: 7 Patients (Nos. 1–7)**

The hyperemic areas were localized adjacent to, and in close topographic relation to low absorption areas.
**Group II: 2 Patients (8-9)**

The hyperemic areas were localized corresponding to the low absorption areas on CT scan.

**Group III: 2 Patients (10-11)**

The hyperemic areas were present without any low absorption areas in the hemisphere investigated.

**Group IV: 5 Patients (11-16)**

The hyperemic areas were localized remote from, and without any topographic relation to low absorption areas.

The results in these 4 groups will be further presented separately.

**Group I: (Patients Nos. 1-7)**

*Hyperemic areas localized adjacent to and in close topographic relation to low absorption areas on CT scan (borderzone hyperemia).*

The low absorption areas in this group always involved the cortical surface, and cerebral angiography in all patients showed occlusion of the middle cerebral artery (total or branch occlusion).

The isotope-angiogram showed in all patients an area of very low isotope filling adjacent to, and in close topographic relation to, an area with abnormally high and fast isotope filling — an area corresponding to the hyperemic area surrounding low flow areas on the flow map. Comparing the CT scan and the flow map, the hyperemic areas were localized in close topographic relation to the low absorption areas on CT scan. The localization of the lesions are shown in table 3 and figures 1, 2, 4.

The hyperemic areas were always relative hyperemias, rCBF ranging from 28 to 54 ml/100 g/min except in patient 7 where the hyperemia was absolute: 67 ml/100 g/min (table 1).

Autoregulation was tested in all 7 and the results appear in table 2. In the hyperemic areas autoregulation was impaired in 3. In the remaining 4 the blood flow increase did not exceed 12.2% or even decreased during hypotension reflecting normal or “false” autoregulation (patient 7).

Measurements of reactivity to changes in Pao2 were carried out in only 2 patients (3 and 4). The results are shown in table 2. In patient 3, the CO2 response was clearly normal. In patient 4 the blood flow increase did not exceed 12.2% or even decreased during hypotension reflecting normal or “false” autoregulation (patient 7).

**Table 1** Regional Cerebral Blood Flow During Rest in 16 Stroke Patients with Cerebral Hyperemia

<table>
<thead>
<tr>
<th>Case</th>
<th>Interval stroke</th>
<th>Areas of hyperemia</th>
<th>No. of detectors</th>
<th>Areas of ischemia</th>
<th>No. of detectors</th>
<th>rCBF</th>
<th>% of rCBF</th>
<th>Non focal brain</th>
<th>% of rCBF</th>
<th>Non focal brain</th>
<th>% of rCBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72 h</td>
<td>54 ± 7</td>
<td>47-71</td>
<td>19</td>
<td>35 ± 4</td>
<td>28-40</td>
<td>69</td>
<td>36 ± 7</td>
<td>28-44</td>
<td>136</td>
<td>150%</td>
</tr>
<tr>
<td>2</td>
<td>14 h</td>
<td>51 ± 3</td>
<td>45-56</td>
<td>11</td>
<td>30 ± 4</td>
<td>26-41</td>
<td>11</td>
<td>37 ± 6</td>
<td>26-45</td>
<td>206</td>
<td>138%</td>
</tr>
<tr>
<td>3</td>
<td>38 h</td>
<td>44 ± 2</td>
<td>41-47</td>
<td>16</td>
<td>28 ± 5</td>
<td>20-34</td>
<td>52</td>
<td>33 ± 4</td>
<td>23-42</td>
<td>160</td>
<td>133%</td>
</tr>
<tr>
<td>4</td>
<td>24 h</td>
<td>46 ± 13</td>
<td>33-75</td>
<td>50</td>
<td>23 ± 5</td>
<td>16-33</td>
<td>47</td>
<td>22 ± 5</td>
<td>13-33</td>
<td>141</td>
<td>209%</td>
</tr>
<tr>
<td>5</td>
<td>36 h</td>
<td>51 ± 4</td>
<td>45-65</td>
<td>28</td>
<td>30 ± 5</td>
<td>17-35</td>
<td>37</td>
<td>39 ± 5</td>
<td>21-46</td>
<td>143</td>
<td>131%</td>
</tr>
<tr>
<td>6</td>
<td>48 h</td>
<td>28 ± 4</td>
<td>23-41</td>
<td>69</td>
<td>14 ± 5</td>
<td>4-22</td>
<td>79</td>
<td>18 ± 5</td>
<td>0-22</td>
<td>91</td>
<td>156%</td>
</tr>
<tr>
<td>7</td>
<td>62 h</td>
<td>67 ± 9</td>
<td>58-93</td>
<td>42</td>
<td>37 ± 6</td>
<td>27-47</td>
<td>39</td>
<td>46 ± 6</td>
<td>29-56</td>
<td>157</td>
<td>146%</td>
</tr>
<tr>
<td>8</td>
<td>10 h</td>
<td>103 ± 12</td>
<td>87-144</td>
<td>69</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>60 ± 15</td>
<td>37-85</td>
<td>176</td>
<td>172%</td>
</tr>
<tr>
<td>9</td>
<td>84 h</td>
<td>75 ± 10</td>
<td>64-91</td>
<td>15</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>50 ± 6</td>
<td>40-65</td>
<td>234</td>
<td>150%</td>
</tr>
<tr>
<td>10</td>
<td>15 h</td>
<td>85 ± 7</td>
<td>77-102</td>
<td>36</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>58 ± 7</td>
<td>45-71</td>
<td>194</td>
<td>147%</td>
</tr>
<tr>
<td>11</td>
<td>12 h</td>
<td>67 ± 5</td>
<td>60-77</td>
<td>63</td>
<td>36 ± 8</td>
<td>22-48</td>
<td>47</td>
<td>47 ± 7</td>
<td>30-59</td>
<td>115</td>
<td>143%</td>
</tr>
<tr>
<td>12</td>
<td>40 h</td>
<td>85 ± 11</td>
<td>60-107</td>
<td>52</td>
<td>31 ± 6</td>
<td>17-41</td>
<td>39</td>
<td>41 ± 7</td>
<td>20-56</td>
<td>132</td>
<td>207%</td>
</tr>
<tr>
<td>13</td>
<td>24 h</td>
<td>46 ± 6</td>
<td>39-57</td>
<td>29</td>
<td>26 ± 5</td>
<td>17-34</td>
<td>43</td>
<td>30 ± 7</td>
<td>17-39</td>
<td>151</td>
<td>153%</td>
</tr>
<tr>
<td>14</td>
<td>10 h</td>
<td>43 ± 3</td>
<td>37-60</td>
<td>28</td>
<td>26 ± 3</td>
<td>21-33</td>
<td>24</td>
<td>30 ± 6</td>
<td>20-37</td>
<td>143</td>
<td>143%</td>
</tr>
<tr>
<td>15</td>
<td>64 h</td>
<td>43 ± 3</td>
<td>40-51</td>
<td>28</td>
<td>31 ± 3</td>
<td>24-35</td>
<td>35</td>
<td>32 ± 5</td>
<td>21-41</td>
<td>157</td>
<td>134%</td>
</tr>
<tr>
<td>16</td>
<td>44 h</td>
<td>32 ± 3</td>
<td>31-39</td>
<td>19</td>
<td>21 ± 5</td>
<td>9-27</td>
<td>33</td>
<td>25 ± 4</td>
<td>13-31</td>
<td>181</td>
<td>128%</td>
</tr>
</tbody>
</table>
FIGURE 2. Upper panel: Patient 7. Flow map 62 hours after onset of stroke. The blood flow is shown in percent of the hemispheric mean flow. A borderzone hyperemia surrounds an ischemic area involving the left parietal lobe. Lower panel: Flow map 10 hours after onset of stroke. The blood flow is shown in percent of the hemispheric mean flow. A large hyperemic area is seen in the temporal and parietal region. The blood flow in the surrounding tissue is normal (60 ml/100 g/min) and ischemic areas are not seen. The hyperemic area corresponds to a low absorption area on CT scan - therefore a case of post-ischemic hyperemia.

Group II: (Patients 8-9)

Hyperemic areas localized corresponding to the low absorption areas on CT scan.

The low absorption areas in this group also involved the cortical surface. Cerebral angiograms showed no occlusion of significant arteries, and capillary blush and early venous filling in these 2 patients were the only signs of an acute vascular lesion.

The isotope-angiogram did not show any ischemic areas. Both patients showed areas of extremely high and fast isotope-filling areas corresponding to the pronounced hyperemic areas on the flow map. Comparing the CT scan and the flow map, the low absorption areas and the hyperemic areas were in the same place. The localization of the lesions is shown in table 3 and figures 2, 5.

The hyperemias in both cases were absolute hyperemias, the rCBF averaging 75 and 103 ml/100 g/min (table 1).

The tests of autoregulation and CO₂ response in these two patients are shown in table 2. Induced hypertension did not give rise to increased blood flow in the hyperemic area (table 2). CO₂ response was clearly impaired in patient 8 because the blood flow only changed 1% per mm Hg during hyperventilation. The CO₂ response was probably also impaired in patient 9 as hyperventilation resulted in a blood flow decrease of 5.2% per mm Hg change. This suggests that the CO₂ response might be considered normal, but the blood flow decreased 8% per mm Hg during hyperventilation in the surrounding brain. This marked difference in the CO₂ response indicates that it...
TABLE 2  Autoregulation and CO₂ Response in the Hyperemic Areas of 16 Stroke Patients with Focal Cerebral Hyperemia

<table>
<thead>
<tr>
<th>Case</th>
<th>BP change hypertension (mm Hg)</th>
<th>Autoregulation</th>
<th>%rCBF increase during hypertension</th>
<th>BP change during hyperventilation</th>
<th>pCO₂ change during hyperventilation</th>
<th>CO₂ response</th>
<th>%rCBF change per mm Hg pCO₂ in hyperemia</th>
<th>%rCBF change per mm Hg pCO₂ in non focal brain</th>
<th>CO₂ response in hyperemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+35</td>
<td>impaired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+18</td>
<td>normal*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+21</td>
<td>impaired</td>
<td>+1</td>
<td>+3.5</td>
<td>+6.5%</td>
<td>+3.4%</td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+20</td>
<td>impaired</td>
<td>+10</td>
<td>+6.8</td>
<td>+2.6%</td>
<td>+2.9%</td>
<td>impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+23</td>
<td>normal*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+10</td>
<td>0%</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+41</td>
<td>false</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>+20</td>
<td>false</td>
<td>+7</td>
<td>+5.9</td>
<td>+1.0%</td>
<td>0.0%</td>
<td>impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>+23</td>
<td>false</td>
<td>+10</td>
<td>+2.3</td>
<td>+5.2%</td>
<td>+8.9%</td>
<td>impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>+35</td>
<td>normal</td>
<td>0</td>
<td>+9.1</td>
<td>+7.0%</td>
<td>+5.5%</td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>+30</td>
<td>normal</td>
<td>+21</td>
<td>+3.6</td>
<td>+6.2%</td>
<td>+3.6%</td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>+45</td>
<td>normal</td>
<td>+5</td>
<td>+2.7</td>
<td>+3.5%</td>
<td>+4.5%</td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>+38</td>
<td>normal*</td>
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<td></td>
</tr>
<tr>
<td>14</td>
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<td>false</td>
<td>+15</td>
<td>+4.8</td>
<td>+0.5%</td>
<td>+4.5%</td>
<td>impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>+46</td>
<td>normal</td>
<td>+5</td>
<td>+2.7</td>
<td>+4.3%</td>
<td>+4.6%</td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>+40</td>
<td>false</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*False autoregulation cannot be excluded because CO₂ response was not tested
**Autoregulation uncertain because CO₂ response was not tested.

was impaired in the hyperemic area. As the blood flow did not change significantly during hypertension there was probably false autoregulation. The BP decreased 10 mm Hg during hyperventilation and the blood flow decrease in the hyperemic area is therefore most likely the result of this BP decrease.

The CO₂ response was impaired in both the patients and, as the blood flow did not change significantly during induced hypertension, "false" autoregulation was considered present. Recanalization of occluded arteries is believed to be the cause of these hyperemias and they are, therefore, denoted post-ischemic hyperemia.

Group III: (Patients 10-11)

Hyperemic areas present without any low absorption areas on CT scan.

Low absorption areas were not seen and the CT scan appeared completely normal in both patients. Cerebral arterial occlusion was present in patient 11 but not in patient 10. In both a pronounced capillary blush and early venous filling without signs of arterial occlusion were seen in the hyperemic areas.

The isotope-angiogram showed high and fast isotope-filling in the hyperemic areas in both cases. The localization of these lesions are shown in table 3 and figure 3.

The hyperemias in both patients were absolute hyperemias, rCBF averaging 85 and 67 ml/100 g/min (table 1). Autoregulation and CO₂ response were normal in both patients (table 2).

The hyperemic areas in both patients are believed to be of the same origin as in group 2, i.e., recanalization of an occluded artery therefore denoted post-ischemic hyperemia.

Group IV: (Patients 12-16)

Hyperemic areas localized remote from, and without any topographic relation to low absorption areas.

The low absorption areas on CT scan in this group involved the cortical surface in one patient, No. 12. In the remaining 4 (13-16) the low absorption areas were without cortical involvement (deep lesions).

Patient 12. The CT scan was normal in the hy-

![Figure 5. Patient 8. CT scan 34 hours after onset of stroke. A large low absorption area with cortical involvement in the left hemisphere. This area corresponds to the hyperemic area seen on the flow map.](image-url)
peremic area. Cerebral angiography showed a pronounced capillary blush and early venous filling in the hyperemic area in which the vascular tree was intact without occlusion. A medial branch occlusion was seen in the area corresponding to a low absorption area on CT scan. The isotope-angiogram showed an area of very low isotope-filling corresponding to the low absorption area on CT scan while the isotope distribution to the hyperemic area was extremely fast and high. Comparing the CT scan and flow map, the hyperemic area was localized distant from the low absorption area but it seemed to merge with a borderzone hyperemia surrounding the ischemic lesion as seen in group I.

The localization of the lesions are shown in table 3. The hyperemia was absolute (85 ml/100 g/min). Autoregulation as well as CO₂ response were normal (table 2).

The hyperemia in this case is most likely due to recanalization of an occluded artery as in group II and III, therefore it is classified as post-ischemic hyperemia with persisting occlusion of (another) branch.

Patients 13–16. The CT scan was normal in the hyperemic areas in these 4. Cerebral angiography showed occlusions corresponding to the low absorption areas localized deep on CT scan. In the hyperemic areas the vascular tree was intact without occlusions. The isotope-angiogram showed areas of relatively low and delayed isotope-filling in all these patients, but the focal ischemias were not as pronounced as in group I. The hyperemic areas also showed relatively high and fast isotope-filling but never so prominent as in group I, II and III.

Comparing the CT scan and flow map, the hyperemic areas were localized remote from and without any topographic relation to the low absorption areas. The localization of the lesions are shown in table 3 and figure 3, 6.

Autoregulation and CO₂ response were normal in one patient. “False” autoregulation with impaired CO₂ response was seen in one patient. In the remaining 2 CO₂ response was not tested. Autoregulation was apparently normal in one and “false” in another (table 2).

The pathophysiology in these 4 patients is not clear. They are denoted remote hyperemias.

**Discussion**

In this study initial slope index was used to calculate rCBF. This method of calculation presupposes that the semilogarithmic recorded clearance curves appear monoeponential during the first minute of recording. In areas of focal cerebral hyperemia several curves showed a downward convex configuration during the first minute of recording. The basis for using the initial slope index is, therefore, no longer present. The steepness of the slope depends on the time interval used in calculation of the slope, i.e., the calculated blood flow will be higher if a shorter time interval is used. For this reason, the blood flow values presented in this study are minimum values of the true blood flow in the hyperemic areas and they should be considered as a semiquantitative manifestation of a high blood flow rather than as absolute figures.

An overabundant cerebral blood flow relative to the metabolic needs of the brain tissue has been denoted "the luxury perfusion syndrome" (Lassen, 1966) and
in several clinical studies this term has been used syn-
Onomous with focal cerebral hyperemia.14.7.10 In
these studies, as well as in the present study, the ex-
stistence of luxury perfusion in areas of cerebral
hyperemia is not formally proved because reliable
measurements of the arterio-venous oxygen deficit
from these areas are generally not possible in studies
of human stroke.
Luxury perfusion in areas of hyperemia in ex-
perimental stroke models is well established as the
phenomenon of red veins associated with areas of ex-
perimental ischemia and post-ischemic hyper-
emia.21-28 The concept of luxury perfusion in the
hyperemic areas has further been supported using
positron emission tomography in the study of cerebral
metabolism and rCBF in acute stroke.28 Despite the
increased blood flow in the hyperemic areas the oxy-
gen consumption was significantly decreased focally.

The incidence of focal cerebral hyperemia in acute
stroke has hitherto been unknown because consecutive
series of patients investigated within a well defined
period of time have not been available. The incidence
of focal cerebral hyperemia in non-consecutive series
varies with the time from onset of stroke to the rCBF
study. The incidence is high in series investigated early
after onset of stroke. In the study of Christensen et al.,9
33% of patients investigated within 24 hours had hyperemia and in the study of Paulson 1970.8 50% of
patients investigated within 3 days after stroke had it.
Focal cerebral hyperemia was found in only 10% of
patients investigated within 2 and 16 months after
onset of stroke by Uemura et al.,10 and by Cronquist.9
Focal cerebral hyperemia must be considered as a
common but transient phenomenon most frequently
found in the acute phase of stroke. This conclusion
from the data in the literature is confirmed in our con-
secutive early studies of patients in whom focal
cerebral hyperemia was seen in 39%. The true inci-
dence of hyperemia in our series is probably con-
iderably higher. Infarcts involving the cortical sur-
face as demonstrated on CT scan were consistently
associated with areas of focal cerebral hyperemia —
but infarcts localized in the deep grey and white struc-
tures were associated with focal cerebral hyperemia in
only 4 of 25 patients (16%).

The result of rCBF measurements using the initial
slope method are a manifestation of the fast flow com-
ponent in the brain, i.e., the grey substance, and the
absorption of radiation within cerebral tissues means
that flow in the outer layers of cortex is recorded with
the highest efficiency. The rCBF recorded is, there-
fore, mainly a manifestation of the blood flow in the
lateral cortical mantle of the hemisphere. This is
presumably the reason for the finding of focal cerebral
hyperemia in all patients with cortical infarction and
the much less frequent demonstration of focal cerebral
hyperemia in association with infarction deep in the
hemisphere.
Focal cerebral hyperemia seems to divide into 3
groups:
Borderzone Hyperemia. Areas of hyperemia sur-
rrounding ischemic areas.
Post-ischemic Hyperemia. Hyperemic areas in brain
tissue without arterial occlusion but localized to areas
of infarction seen on CT scan, or to areas of marked
capillary blush and early venous filling on cerebral
angiography.
Remote Hyperemia. Hyperemic areas in apparently
normal brain tissue, as revealed by CT scan and
cerebral angiography, remote from an ischemic lesion.
Borderzone Hyperemia. Hyperemic areas adjacent
to areas of ischemia are common findings in experimen-
tal models of acute focal cerebral ischemia.22, 24, 27-29
Such hyperemic areas have been examined histo-
pathologically by Yamaguchi et al.25, 29 Morpho-
logical changes were either absent or mild in the
hyperemic areas indicating that areas of slightly im-
paired, as well as unimpaired, tissue can be found in
the areas with borderzone hyperemia. This is presum-
ably also the case in the borderzone hyperemic areas
in our study as indicated by the varying degree of im-
paired vascular reactivity in these patients, ranging
from areas of normal autoregulation to areas of im-
paired CO2 response and "false" autoregulation.
These results suggest that borderzone hyperemic areas
are threatened areas with a potential for survival.
Borderzone hyperemia is probably caused by a
combination of several mechanisms. One is spread of
acid metabolites from an ischemic region, suggested
by Lassen7 and supported in experimental stroke
models.27, 28 The accumulation of acid metabolites
results in vasodilatation and varying degree of im-
paired vascular reactivity depending on the degree of pH
decrease. Another mechanism is the clearance of aggre-
gates of blood elements formed earlier in small
blood vessels, as demonstrated by Yamaguchi and
Waltz 1971.28
Borderzone hyperemia was found in all patients
with areas of low absorption involving the cortical sur-
face areas on CT scan. These are areas where bor-
derzone hyperemia is detectible with the 254-detector
The finding strongly suggests that areas of ischemia in acute cerebral infarction always have areas of borderzone hyperemia.

Post-ischemic Hyperemia. Post-ischemic hyperemia is a common finding in experimental stroke models when the blood flow is restored in an obliterated artery after a period of ischemia. In patients with cerebral infarction hyperemia is also found after proved recanalization of occluded arteries.

In the present study post-ischemic hyperemia was found in 5 patients (Nos. 8-12). Hyperemia of this kind is believed present when hyperemia is demonstrated in an area of low absorption on a CT scan and when cerebral angiography shows no vessel occlusion in that area (patients 8-9). If an occlusion disappears within a short time, restoring the blood flow, the ischemic episode is mild and low absorption areas on CT scan do not develop. Hyperemic areas in a normal area on CT scan, therefore, most likely exist. If an area of low absorption is not seen to correspond with the hyperemic area a capillary blush and early venous filling should be present for the occurrence of a post-ischemic hyperemia (patients 10-12). This has been a common finding in acute apoplexy and proven recanalized infarction.

The hyperemic areas in our 5 patients all were absolute hyperemias and the blood flow was significantly higher than the blood flow in borderzone hyperemias. A higher accumulation of acid metabolites and a higher perfusion pressure because of the intact vascular tree in these areas might explain this difference.

Post-ischemic hyperemia appears to be present in 2 forms. If tissue lesions in the form of hypodense CT areas are present, then the hyperemia is associated with abnormal vasomotor responses. If no CT abnormality is seen then the vasomotor responses are normal. The latter form appears to be the more benign.

Abnormal vasomotor responses with “false” autoregulation, as present in the 2 instances of post-ischemic hyperemia corresponding to low absorption areas on CT scan (patients 8-9), reflect a severe degree of brain damage. An increase of BP does not increase blood flow in these areas, most likely because of an increase in local tissue pressure caused by development of edema during hypertension ("false" autoregulation).

In the 3 patients with a normal CT scan in the hyperemic areas (patients 10-12) autoregulation and CO2 response were normal at the time of investigation, indicating that the ischemia prior to hyperemia has been a mild degree, without any harmful effects on the tissue involved.

Remote Hyperemia. It is well known that there is a global decrease of blood flow in brains suffering from acute apoplexy. The finding of focal cerebral hyperemia remote from the infarcted areas in 5 patients (Nos. 6, 13-16) is surprising and has to our knowledge not been described previously in patients with acute stroke.

Similar findings of remote hyperemias have been reported in rCBF studies in patients with intracranial tumors.

The cause of remote hyperemia is difficult to assess. The phenomenon was seen in only 5 of 35 patients with low absorption areas on CT scan (14%). A great deal of the brain is not seen with our equipment, particularly brain tissue near the skull and foramen magnum and the opposite hemisphere. Remote hyperemia could be transient and, perhaps, intermittent, and its occurrence could be more common than indicated in this study.

Mass displacement due to pressure gradients could be responsible for the hyperemia in these patients. Permanent or intermittent compression against unyielding anatomical structures might produce local ischemia and hyperemia or in adjacent tissues because of focal spread of acid metabolites. A mass effect manifested by ventricular compression was present in all the patients with remote hyperemia but it was also found in several patients without remote hyperemia.

Possible Therapeutic Implications

The concept of the borderzone as a threatened area with a potential to survive means that treatment of brain infarcts should not be directed exclusively toward ischemia, but toward the areas of hyperemia as well.

Cerebral infarcts of more than 24 hours duration are made up of 2 essentially different parts: one is ischemic, the other hyperemic.

In stroke models, treatment (induced hypertension, hyperventilation, barbiturates, etc.) directed at the ischemia, has been reported as successful if started immediately or shortly after onset of stroke.

Early treatment is only possible in rare clinical situations. Patients with stroke are admitted to the hospital several hours or even days after the onset of symptoms, and irreversible damage to the brain in the ischemic area is therefore established in most patients. Therapy then might be directed at creating the best conditions for survival of the hyperemic areas.

Because autoregulation is commonly impaired or is even “false” in the hyperemic areas, hypertensive episodes should be prevented in patients with acute stroke. On the other hand, slight hypotension in the acute stage of apoplexy could be beneficial because this would diminish the development of edema and blood engorgement in the hyperemic area.

The vessels in the hyperemic areas are dilated, and the ischemic part of the infarct is subject to strong vasodilator stimuli (acid metabolites). Vasodilating agents would be without much direct positive effect on the infarcted areas. Indirectly vasodilating agents might, nevertheless, be of some benefit in 2 ways: 1) The vasodilation could produce a slight hypotension, reducing flow and edema production in the hyperemic areas. 2) Vasodilation in the surrounding normal brain tissue could further reduce the blood flow in the hyperemia (and therefore also edema and blood engorgement) because of “steal” from the hyperemic to the surrounding normal brain tissue.
Therapy with vasoconstrictive agents might be harmful, as autoregulation is commonly impaired in the hyperemic areas. These agents would produce vasoconstriction only outside the hyperemic area resulting in "inverse steal" from the surrounding brain to the hyperemic area. An "inverse steal" might increase blood flow, blood engorgement and, therefore, also edema in the area of hyperemia.

References

Cerebral Extraction of N-13 Ammonia: Its Dependence on Cerebral Blood Flow and Capillary Permeability — Surface Area Product

Michael E. Phelps, Ph.D., Sung-Cheng Huang, D.Sc., Edward J. Hoffman, Ph.D., Carl Selin, M.S., and David E. Kuhl, M.D.

SUMMARY 15N-labeled ammonia was used to investigate 1) the cerebral extraction and clearance of ammonia, 2) the mechanism by which capillaries accommodate changes in cerebral blood flow (CBF) and 3) its use for the measurement of CBF. The unidirectional extraction of 15NH3 in rhesus monkeys was measured during PaCO2-induced changes in CBF and dog studies were performed using in vitro tissue counting techniques to examine 15NH3 extraction in grey and white matter, mixed tissue and cerebellum during variations in CBF produced by combinations of embolization, local brain compression, and changes in PaCO2. The single pass extraction fraction of 15NH3 varied from about 70 to 20% over a CBF range of 12 to 140 cc/min/100 g. Capillary permeability-surface area product (PS) estimates with a Renkin/Crone model show PS increasing with CBF. The magnitude and rate of increase in PS with CBF was highest in gray matter > mixed tissue > white matter. Tissue extraction of 15NH3 vs CBF relationship was best described by a unidirectional transport model in which CBF increases by both recruitment of capillaries and by increases of blood velocity in open capillaries. This saturable-recruitment model provides a possible explanation for the mechanism of flow changes at the capillary level. The net 15NH3 extraction subsequent to an i.v. injection increases non-linearly with CBF. Doubling or halving basal CBF produced from 35 to 50% changes in the 15N tissue concentrations with further increases in CBF associated with progressively smaller changes in 15N concentrations.

SINCE IT WAS originally proposed by Hunter et al.1-3 and Harper et al. (N-13) ammonia (15NH3)4 has been used as an imaging agent for the heart and brain with very little information available regarding what factors determine its tissue distribution. The rapid diffusion of 15NH3 through cerebral4-8 and myocardial capillaries and its rapid incorporation and trapping in the slowly turning over amino acid pools can potentially allow the use of this labeled substrate for imaging capillary perfusion, the study of the capillary flow mechanisms, or the study of ammonia and amino acid metabolism. However, due to the complexities involved in the extraction and retention of 15NH3 in these organs, more extensive studies are required to better understand the potential uses of this tracer.

Phelps et al.4 using positron computed tomography (PCT) with normal volunteers, showed that the relative 15N concentrations in structures of the brain were in good agreement with the relative capillary densities and/or cerebral blood flow (CBF). Subsequently, Phelps et al. 6 demonstrated in the monkey that the unidirectional extraction fraction of 15NH3 by the brain was 1) less than 100% at normal values of CBF, 2) inversely related to CBF, 3) unaffected by blood ammonia concentrations from 80 to 1400 µg% and insensitive to changes in arterial blood pH over the range of 7.2 and 7.7, 4) decreased by about 24% during hypoglycemic coma and 5) was limited by capillary permeability. Intravenously injected 15NH3 was proposed for estimation of capillary perfusion in brain and heart in analogy to the microsphere model with capillary occlusion by microspheres replaced by metabolic trapping of 15NH3.4,8

Cooper et al.7 found that the brain ammonia pool...
Focal cerebral hyperemia in acute stroke. Incidence, pathophysiology and clinical significance.

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