Reversible ischemia around intracerebral hemorrhage: a single-photon emission computerized tomography study

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Object. A zone of perilesional ischemia has been demonstrated around intracerebral hemorrhage (ICH) in numerous experimental models and in human studies. There is potential for perfusion recovery in the zone of perilesional oligemia around ICH. The authors sought to demonstrate, quantify, and study the chronological evolution of perilesional ischemic change in ICH in humans by measuring cerebral blood flow.

Methods. Eleven patients with spontaneous supratentorial ICH underwent two technetium-99m hexamethylpropyleneamine oxime single-photon emission computerized tomography (SPECT) scanning, one in the acute stage (within days of ictus) and the other in the late stage (6–9 months postictus). All patients in this study were treated nonsurgically. Methods of SPECT data analysis based on count differences in regions of interest can be difficult to apply to images with large space-occupying lesions such as ICH, because of the distortion of intracranial anatomy, midline shift, and alterations in the three-dimensional (3D) characteristics of the lesion over time (that is, absorption of the hematoma on the later studies). The authors used the following method: the late and early images were registered and aligned to a common 3D orientation and were normalized to maximal counts. The late images were then compared voxel by voxel with the early ones. The region-growing algorithm was used to discern the difference between the two images, outlining voxels in the perihematoma region, with a signal improvement of at least 15% on the late image.

Discrete brain regions around the hematoma with at least a 15% improvement in radiotracer uptake (and hence perfusion) in the late images were observed in all cases. The mean volume of brain with a greater than 15% improvement in perfusion between the two studies was 34.8 cm³ (range 7.2–71.3 cm³). These volumes represent regions of the brain that were poorly perfused in the initial studies. This may represent a zone of reversible perilesional oligemia (penumbra) in ICH in humans.

Conclusions. This is the first study in which it is documented that some of the perilesional hypoperfused tissue around human ICH regains its perfusion in the long term, leading the authors to suggest that there may be a penumbra in human ICH. Medical or surgical therapeutic interventions could increase the volume of perilesional brain that recovers after the initial insult. The results of this study therefore support the concept that intervention in ICH has the potential to reduce the ultimate neurological deficit and improve outcome.

Key Words • intracerebral hemorrhage • single-photon emission computerized tomography

Animal models of ICH have shown that blood produces ischemia in the parenchyma and that surrounding this an area of edema, oligemia, and hemorrhagic necrosis develops.³⁴,²³,³² Hypoperfusion has been demonstrated around human ICH in the acute state with SPECT and PET scanning.¹⁰,¹¹ Whether any of this perilesional hypoperfused tissue survives in the long term is not known. A zone of reversible perilesional oligemia (the penumbra) has been demonstrated in ischemic stroke in humans.²,¹⁰,⁴² If there is a penumbra around an ICH, it is possible that the neurons in it, as in the penumbra in ischemic stroke, may be electrically silent but retain membrane integrity, and they may be potentially recoverable if perfusion is restored. Indeed, animal experiments have shown that medical,¹²,³² radiological,¹⁰ or surgical interventions¹⁰,²³ may reduce the neurological damage after ICH.

We studied the changes in CBF that accompany human ICH, with particular reference to the serial changes that occur in the region surrounding the hematoma, by using ⁹⁹mTc-HMPAO SPECT scanning (Amersham International plc.).

Clinical Material and Methods

Patient Population

Patients with spontaneous supratentorial ICH were studied using ⁹⁹mTc-HMPAO SPECT scanning. This study was approved by the local ethics committee, and informed consent (or relatives’ assent) was obtained either from the patients or their relatives if the patients were not well enough to give it. Prospectively collected data from 11 consecutive patients are presented (Table 1); all patients were treated...
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nonsurgically. Two SPECT studies were performed in all patients, first in the acute stage (within days of ictus) and then in the late stage (6–9 months postictus).

**Methodology Used for SPECT Studies**

Five hundred megabecquerels of $^{99m}$Tc-HMPAO was injected approximately 10 minutes before image acquisition. Images were acquired using a triple-headed gamma camera (Prism model 3000XP; Picker, Cleveland, OH) equipped with ultrahigh-resolution fan-beam collimators. Three 10-minute acquisitions were made using a $128 \times 128$ matrix and 120 flip angles, and then the acquisitions were summed to give a single 30-minute data set. Slices were reconstructed 3.56 mm thick by using a ramp filter and were then filtered using a three-dimensional Butterworth filter of order 13 at a cutoff of 0.2 mm per pixel. The slices were then zoomed onto a $64 \times 64$ matrix with 4 mm per pixel. The data set was manually aligned to correct for left/right tilt and rotation, and slices were aligned approximately parallel to the anterior commissure–posterior commissure line to facilitate further analysis. The data were then transferred to a diagnostic workstation (Hermes Nuclear, Stockholm, Sweden) for subsequent analysis.

The late images were registered to the acute images by using an iterative method that minimizes the count difference between the two after normalizing each to its maximal count. Scaling was constrained during the registration. Following registration, all the axial slices demonstrating radionuclide uptake defects were saved separately for analysis. One slice above and one below the defects were also saved.

The late images were then compared voxel by voxel with the early ones. The region-growing algorithm was used to discern the differences, outlining voxels that differed between the two images by a predefined threshold.

We used the difference-based region-growing method to identify voxels in the perihematoma region that demonstrated a signal improvement of at least 15% on the late image. The maximum blood flow in the human brain is up to 85 ml/100 g/min. Therefore, on any SPECT image the area of maximal radionuclide uptake corresponds to a CBF of up to 85 ml/100 g/min, and the area of minimal radionuclide uptake corresponds to a CBF of nearly 0 ml/100 g/min. A change of 15% would therefore correspond to a CBF change of up to 12 ml/100 g/min. The figure of 15% was chosen because at least 15% of normal CBF is required to maintain structural integrity of brain cells.

A large ROI that encompassed the clot and extended considerably into well perfused brain was drawn on the early images and copied to the late images. Parts of brain outside this region of interest were masked. This was done for two reasons: first, because our objective was to study CBF changes in the brain surrounding ICH, and second, to avoid the confounding effects of the widespread remote CBF changes (diaschises) affecting the ipsilateral and contralateral hemisphere that are known to occur in human ICH.

Voxels representing less than 40% radiotracer uptake on the initial image and corresponding voxels with the same three-dimensional location on the late image were excluded from analysis. By doing so, we excluded regions that represented hematoma cavity and CSF spaces on the initial scan and corresponding regions on the late image. As a result, any brain tissue that may have moved back into the hematoma cavity on the late image as a result of clot resorption was not included in the analysis. Any brain tissue that may have moved into a space occupied by CSF on the acute image was also excluded. By applying various lower thresholds, we discovered that 40% was optimal for complete exclusion of regions consisting of CSF and hemorrhage. Changes at the lower end entail a much larger change in HMPAO uptake per milliliter per 100 g per minute than changes at the upper end. Exclusion of all areas with radiotracer uptake of less than 40% therefore also improves the accuracy of our measurements.

The observed improvement in perfusion therefore could not have been caused by any of the following: 1) movement of normal brain back into the hematoma cavity following clot resorption; 2) movement of normal brain into an area occupied by a ventricle or other CSF space on the acute scan; or 3) movement of normal brain across the ROI boundary. Because deposition of the radionuclide varies in the same patient at different times, it may not be valid to compare radionuclide uptake by the same areas of the brain in temporally separated scans. This problem was overcome by normalizing the images on the basis of the maximal count.

**Results**

Improvement in perilesional brain perfusion was observed in all patients between the first and second studies (Table 1 and Fig. 1). All these patients were treated nonsurgically. The mean volume of brain with 15% or more improvement in perfusion between the two studies was 34.8 cm$^3$ (median 33.7 cm$^3$, range 7.2–71.3 cm$^3$). These volumes represent regions of brain that were underperfused in the earlier studies and thus constitute a zone of reversible ischemia, the so-called penumbra. Multivariate analysis for other independent variables, for example, the location of hemorrhage, was not appropriate because of the sample size.

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**Table 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Clot Vol (cm$^3$)*</th>
<th>Site of ICH</th>
<th>Interval (mos)$^\dagger$</th>
<th>Penumbra Vol (cm$^3$)$^\ddagger$</th>
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<tbody>
<tr>
<td>1</td>
<td>79, F</td>
<td>12</td>
<td>rt frontal</td>
<td>7</td>
<td>35.2</td>
<td></td>
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<tr>
<td>2</td>
<td>77, M</td>
<td>30</td>
<td>rt parietal</td>
<td>7</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>78, M</td>
<td>30</td>
<td>rt parietal</td>
<td>6</td>
<td>32.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>79, F</td>
<td>19</td>
<td>lt occipital</td>
<td>6</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>57, F</td>
<td>27</td>
<td>lt parietal</td>
<td>6</td>
<td>71.3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>50, M</td>
<td>18</td>
<td>rt basal ganglia</td>
<td>6</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>26, F</td>
<td>2</td>
<td>lt basal ganglia</td>
<td>9</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>66, M</td>
<td>40</td>
<td>rt frontal</td>
<td>9</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>42, M</td>
<td>10</td>
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<td></td>
</tr>
<tr>
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<td>66, M</td>
<td>42</td>
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<tr>
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<td>63, F</td>
<td>60</td>
<td>lt parietal</td>
<td>6</td>
<td>53.6</td>
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</table>

* Clot volume on initial SPECT scan.
† Approximate interval between the two SPECT scans.
‡ Volume of perilesional brain regions with a 15% or more increase in radionuclide uptake on the second compared with the first SPECT scan.

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J. Neurosurg. / Volume 96 / April, 2002
Discussion

Analysis of SPECT Data in ICH

In analyzing SPECT data in ICH, it is difficult to determine at times whether the observed defect in radionuclide uptake is due to clotting or to ventricular or perilesional ischemia. In addition, when comparing late scans with earlier studies in the same patient, the clot may have been resorbed and thus the perfusion defect caused may look much smaller than that seen on the initial scan. An analysis based on isotope counts or count ratios in ROIs normalized against other parts of the brain could show more perfused brain in the late scan, which in fact may be a reflection of the absence of the clot and movement of the normal brain surrounding it, that had been previously distorted by clot and/or edema into the hematoma cavity. It is difficult under these circumstances to determine the proportion of any observed increase in radiotracer uptake that is due to improvement in perfusion, or the proportion that is due to shifting of normal brain into the hematoma cavity because of resorption of the clot. By excluding regions from analysis with less than 40% signal on the initial image, we excluded any brain that would have moved back into the hematoma cavity. As the clot is resorbed and brain tissue returns to this region, the brain also moves from a still wider area into the region of previously adjacent compressed brain.

Did this phenomenon affect our results? We believe that it did not for the following reasons: first, eight of the 11 patients in this study had lobar hemorrhages. Of these, in five patients the clots were close to, but not completely reaching the cortical surface. In these patients, therefore, a rim of cortex was sandwiched between the clot and the skull (Fig. 1). This rim of cortex could not have participated in the brain shifts alluded to earlier and moved out of and then back into the ROI, because it was confined by the skull. In all five of these patients, this rim of cortex showed significant improvement between the immediate and delayed studies (Fig. 1). This improvement cannot be explained on the basis of movement of normal brain into the ROI. Second, improvement in perfusion was seen in patients with very small clots (Case 7, clot volume 2 cm³). Such a small clot is unlikely to exert significant brain compression and deformation, and the improvement seen is again difficult to explain on the basis of brain movement. It therefore seems

Fig. 1. Case 10. The first column consists of CT images from the day of ictus; the second shows SPECT images obtained the same day. The third and the fourth columns show late CT and SPECT images obtained on the same day. The last column shows the late SPECT images in gray scale. The difference-based region-growing (DBRG) method has been applied to the rightmost images to identify volumes of perilesional brain regions with a greater than 15% increase in radionuclide uptake compared with the initial study. These regions are shown in red.
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that the improvement that we observed was a real change in perfusion.

Coregistration with CT scans can be helpful under these circumstances, but in practice we found that with ICH, the shape of the defect on late CT scans may not be spherical or ellipsoid, and in fact it can be very irregular. Sometimes, instead of an isolated defect, there is atrophy of the ipsilateral hemisphere with an increase in the size of the ventricle and other CSF spaces. This is because the areas of poor perfusion in ICH are very large. The complex phenomenon of moving and deforming tissue with a gradient of CBF cannot be fully addressed by CT–SPECT coregistration. Also CT–SPECT coregistration is not required for calculation of penumbra volume when analyzing images with the difference-based region-growing method. Other methods of SPECT image analysis that do not require CT–SPECT coregistration have been described.21

The concept of region growing22 has been widely applied to analysis of medical images over the last 18 years.16,17 It has been validated and found to be useful for volume measurement from SPECT images.20,34 It should be remembered, however, that lesion volumes obtained from SPECT images are close approximations and not absolutely exact.

The resolution of images in our series was 8 mm. This causes a blurring effect around the clot and creates a transition zone where there may in fact be a sharp boundary. This blurring effect at the edges is unlikely to have significantly affected our study for the following reasons: first, the interval between the initial and late scans is approximately 6 months. By this time, the hematoma has been resorbed and the shape of the defect has changed. As a result, the transition zone of the initial image is not being compared with the transition zone of the late scan. Coregistration of the penumbra with the initial images in our series showed that it extended into well-perfused brain, far beyond the transition zone. Second, if the observed difference was caused solely by resolution effects, one would expect to see a complete ring of penumbra in each case. This has not been the case in the majority of patients in our series. Third, by specifying a lower threshold of at least a 40% uptake, a significant proportion of the transition zone is excluded from analysis. Therefore, it seems that the observed differences are not effects of resolution; they appear to be caused by a real difference in isotope uptake/perfusion.

We normalized the early and late images with each other on the basis of maximal counts. Normalizing on the basis of total counts has the drawback that total counts may be substantially affected by the lesion (ICH). Normalizing on the basis of maximal counts assumes that maximal counts are located in the normal part of the brain and that therefore the analysis is not affected by the disease, although ICH is known to cause widespread remote CBF changes (depression). In the unlikely event that the CBF in all brain regions is diminished by the ICH in the acute stage, and that no regions with normal CBF remain, our methodology of normalizing on the basis of maximal counts would reduce the isotope counts in the late image. We would thus underestimate the improvement. It is therefore unlikely that this method could either show improvement when there is in fact no change, or overestimate the improvement.

Penumbra in Human ICH

Central to the concept of the penumbra is the potential for recovery of the tissue that constitutes it.2,7,12 A CBF-based study of the penumbra in human ICH should therefore demonstrate that there is hypoperfused brain in the parenchyma surrounding the clot in the acute stage and that some of this hypoperfused perilesional brain survives in the long term. Serial CBF studies are thus needed, and the last of these must be performed at least a few months postictus to allow all the acute and subacute CBF changes to settle down; a number of researchers have shown that regional CBF continues to change for weeks following ICH.35–37,45 In a large number of animal experiments it has been shown that there is ischemia around the hematoma in ICH.2,20,33,44 Hypoperfusion has also been demonstrated around human ICH.9,18,25,31,40,41

A number of investigators have documented serial CBF changes in human ICH.9,11,28,30,35,36,38,39,41,45 Information from these investigations indicates that after the hemorrhage, the CBF of the ipsilateral hemisphere, and sometimes the contralateral hemisphere as well, continues to decrease for many weeks. In the majority of instances this is followed by a partial recovery. These studies, however, do not provide sufficient evidence for penumbra in human ICH for the following reasons: first, they do not document the CBF changes in the perilesional zone. Instead, either the mean CBF of both hemispheres or of the ipsilateral hemisphere has been recorded by the majority of researchers. Widespread CBF changes in the remote parts of the ipsilateral hemisphere, contralateral hemisphere, and the cerebellum have been shown to occur following ICH.9,11,18,24,27,37,39,40 Any assessment of the mean CBF of either one or both hemispheres is likely to be substantially affected by this phenomenon. In addition, none of the investigators accounted for resolution of the clot on later CBF studies. Second, in some cases18,45 the improvement in mean ipsilateral or bilateral hemispheric CBF was seen soon after surgical intervention. Surgical trauma has been shown to induce a transient rise in CBF in patients with ICH13,28 and this factor therefore further confuses the results of these investigations.

Mayer, et al.,19 evaluated perilesional ischemia by using SPECT scanning, but their work did not include a follow-up study in the chronic stage; their first scan was obtained at 18 hours and the second at 72 hours postictus. This is too early to assess any long-term changes. In addition, the method they used (flow deficit) to measure volumes from SPECT scanning21 is not recommended for use in conditions in which there is either distortion of brain or the possibility of remote CBF effects from the lesion, both of these conditions apply to ICH. The volume of brain that showed improvement was small (mean 8 ml), and the improvement could have been due to the partial volume effect, for which a correction was not made.

The design of the study is therefore crucial in addressing the issue of penumbra in human ICH. This is the first study in which it is documented that some of the perilesional hypoperfused tissue around human ICH regains its perfusion in the long term, which leads us to suggest that there may be a penumbra in human ICH. Future investigations with well-designed positron emission tomography studies could provide more comprehensive information (CBF as well as metabolism) and help in clarifying the issue further. It is possible that therapeutic interventions could increase the volume of perilesional brain that recovers after the initial
insult. Our data provides the rationale for the concept that intervention in ICH has the potential to reduce the ultimate neurological deficit and to improve outcome.

Conclusions

By analyzing data from serial SPECT scans in patients with ICH who were treated nonsurgically, we have been able to confirm the presence of ischemia around ICH and demonstrate that some of the ischemic perilesional brain recovers its perfusion in the long term. This has not been demonstrated before. This zone of reversible oligemia (penumbra) points to the presence of sublethally injured brain in the vicinity of the ICH. Therapeutic interventions, medical or surgical, could increase the volume of the injured brain that recovers after the initial insult. In this study we therefore support the concept that intervention in ICH may reduce the final neurological deficit.

Appendix

The International Surgical Trial in Intracerebral Haemorrhage (ISTICH) is designed to determine whether a policy of early surgical evacuation of the hematoma in patients with spontaneous supratentorial ICH will improve outcome compared with initial conservative treatment. So far, more than 670 patients have been recruited in more than 100 centers; more are needed. Any centers wishing to participate should contact stich@ncl.ac.uk.

Acknowledgments

We are grateful to neurosurgeons in Newcastle, who permitted us to study their patients.

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Dr. Siddique was supported by grants from the Stroke Association (United Kingdom) and the Medical Research Council of the United Kingdom.

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