Natural history of the spontaneous reperfusion of human cerebral infarcts as assessed by $^{99m}$Tc HMPAO SPECT


Abstract

Objective—Little is known about the effect of spontaneous reperfusion of human cerebral infarcts. Single photon emission computerised tomography (SPECT) data were analysed from a study using $^{99m}$Tc HMPAO ("$^{99m}$Tc hexamethylpropyleneamine oxime") in human cerebral infarction for the frequency of reperfusion and to see if it affected infarct size, oedema, haemorrhagic transformation, or functional outcome.

Methods—Fifty sequential cases of ischaemic stroke were studied with 124 $^{99m}$Tc HMPAO SPECT at around one day, one week, and three months after stroke along with detailed clinical and functional assessments.

Results—Visually apparent reperfusion occurred in 14 of 50 patients (28%) with a mean delay of 5.8 days and reperfusion was seen in seven others in whom it was identified on the basis of changes in perfusion deficit volume. It occurred in 13 of 23 embolic events but only in three of 23 other events. In only two cases did spontaneous reperfusion occur early enough to preserve tissue or function. Reperfusion did not otherwise reduce infarct size, or improve clinical or functional outcome, and was not associated with oedema but an association with haemorrhagic transformation was suggested. Reperfusion significantly decreased the apparent perfusion defect as measured by SPECT one week from the ictus, but was mostly non-nutritional and transient. The mean volume of tissue preserved by nutritional reperfusion was 10 cm$^3$, but this was unequally distributed between cases. Late washout of $^{99m}$Tc HMPAO from areas of hyperaemic reperfusion may be a good prognostic marker but is a rare phenomenon and too insensitive to be of general applicability.

Conclusions—Spontaneous reperfusion after cerebral infarction occurs in 42% of cases within the first week but is associated with clinical improvement in only 2%. It has few adverse consequences although it may be associated with haemorrhagic transformation.

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Keywords: SPECT; reperfusion; cerebral infarction; natural history

Impairment of cerebral blood flow is the underlying abnormality in cerebral infarction and its restoration is crucial in preserving neural tissue. This is the basis of thrombolytic therapy but recent data have shown that non-nutritional reperfusion after streptokinase is harmful. However, little is known about the natural history of spontaneous reperfusion. Luxury reperfusion was first recognised in 1966. Several studies have described reperfusion but either have not considered its clinical consequences or the clinical details have been scant. Its frequency and timing in unselected stroke cases are not well documented. The natural history of reperfusion may suggest a maximum time from onset at which reperfusion can be nutritional and result in clinical improvement or tissue preservation. It will also indicate the degree to which reperfusion is determined by aetiology (thrombotic v embolic infarction), or associated with oedema or haemorrhagic transformation.

$^{99m}$Tc hexamethylpropyleneamine oxime ("$^{99m}$Tc HMPAO, Exametazine, Ceretec, American International) is a validated proportional indicator of cerebral blood flow. As part of a prospective study investigating the patterns of change in cerebral blood flow and their clinical correlates in acute stroke, we performed 124 high resolution SPECT scans using $^{99m}$Tc HMPAO. The subjects were 50 consecutive, unselected patients with ischaemic stroke admitted to a district general hospital. As serial assessments of clinical status, perfusion defect and infarct volume determined by both SPECT and CT were available, we analysed the data to determine the natural history and consequences of spontaneous reperfusion in human cerebral infarction.

Various indices measurable from $^{99m}$Tc HMPAO SPECT have been proposed as prognostic indicators but the most recent work has suggested that these add little or nothing to the prognosis determined by simple clinical examination. The redistribution of $^{99m}$Tc HMPAO after hyperaemic reperfusion has been proposed as a prognostic marker and we performed early and late scans after HMPAO injection on five occasions to further evaluate this.

Patients and methods

The study was prospective and carried out on sequential patients with first stroke admitted to a general teaching hospital. We have previously reported the methods. Briefly, a full neurological examination and SPECT, using
99Tcm HMPAO and the NOVO 810 scanner, which is a dedicated multidetector tomo-
graphic head scanner with a resolution of 9 mm full width at half maximum in the plane of the
scan, were carried out as soon as possible after
the infarct. The clinical assessment included
the Canadian neurological scale21 and, for
functional evaluation, the Barthel index. 22 Sub-
sequent assessments were around one week
and three months after stroke. Brain CT was
carried out usually between three and seven
days. Echocardiography, carotid duplex Dop-
pler studies, and ECG were also carried out.

Scans were inspected with full knowledge of
the x ray CT result and clinical picture. Reper-
fusion was identified from SPECT by visual
inspection in the first instance.

Reperfusion was defined as either:
(1) an absolute increase in 99Tc" HMPAO
uptake in the affected volume defined by the
CT, MRI, or later SPECT. This type of reper-
fusion, which we have termed absolute hyper-
aemia, could therefore be identified on any
scan without the need for an earlier scan show-
ing decreased 99Tc" HMPAO uptake (fig 1).

(2) Relative increase in 99Tc" HMPAO
uptake in the affected volume (“relative reper-
fusion”), in one or more 99Tc" HMPAO
SPECT; compared with the same volume in an
earlier SPECT (fig 2).

Absolute hyperaemia was readily identified; in
addition the serial SPECT for all the patients
without absolute hyperaemia were scrutinised
for relative reperfusion. Absolute hyperaemia
was confirmed and quantified using circular
regions of interest twice the resolution of the
scanner (18 mm) in diameter. These were
placed manually over the whole of the affected
region and the equivalent contralateral region.
The mean counts from the region of interest on
each side were averaged and the ratio abnor-
mal: normal calculated. If reperfusion occupied
only part of the volume of the infarct, the
reperfused portion of the volume was tested
separately. The criterion confirming relative
reperfusion and hyperaemia was that the
change between the reperfused and non-
reperfused scans was >2 SD outside the refer-
ence range for right to left difference. 23 In ad-
inon, we noted any case in which the apparent
perfusion defect was lower in the second
SPECT than either the first or third SPECT;
we interpreted this as suggesting lesser degrees
of reperfusion, detectable only by volume
measurements.

The measurement of perfusion defects has
been described previously. 16 The brain CT was
examined for oedema and haemorrhagic inf-
arction. Oedema was deemed to be present if
there was effacement of the sulci overlying the
infarct or compression or displacement of
adjacent structures on the CT.

The aetiology was based on the history,
ECG, echocardiogram, and duplex Doppler as
embolic (cardiac or artery to artery) or throm-
botic (occlusion in situ). SPECT results were
not used to classify the aetiology. Lacunes were
not considered to have a unique pathogenesis
and infarcts consistent with low flow (water-
shed infarcts) were classified according to the
primary aetiology. Embolic infarcts had to be
of sudden onset when the mode of onset was

Figure 1 Absolute hyperaemia 1.1 days after a middle
cerebral artery embolism.

Figure 2 Relative reperfusion: a right posterior cerebral artery infarct scanned 1.7 days after onset (left) shows a large
perfusion deficit with almost complete resolution of the perfusion defect on the second scan (right) at 8.7 days.
known and the deficit maximal at onset. A
source (either cardiac or artery to artery) of
embolus had to be present without pre-
eminent evidence of a thrombotic cause.
Gradual onset was considered incompatible
with an embolic aetiology. When the mode of
onset was uncertain (insufficient informa-
tion or the patient woke with the deficit) the cause
was diagnosed as embolic if there was a
substantial cause of embolism without substan-
tial evidence of a thrombotic cause. Lesions of
deep perforating arteries without a source of
embolism were diagnosed as thrombotic (and
were often lacunar). Cases with conflicting
aetiological evidence were left unclassified.
Whereas occlusion of branches of the major
cerebral arteries is thought to be most
commonly embolic, this factor was subordi-
nated to the speed of onset such that a branch
occlusion arising slowly was classified as
thrombotic. Otherwise, branch occlusion was
considered to favour an embolic aetiology.

Patients with and without reperfusion were
compared for perfusion defect, aetiology,
oedema, and haemorrhagic infarction.

In some cases in which hyperaemia was
seen, the second scan was repeated about six
hours later without further injection of $^{99}$Tc
HMPAO, looking for evidence of redistribu-
tion of $^{99}$Tc HMPAO. The changes within
these volumes were heterogeneous. These
small focal changes were analysed using
individual regions of interest, which were not
summed together. This analysis was confined
to grey matter. Typically one or two slices from
each pair of scans were chosen for more
detailed study, the region of interest being
placed manually with the closest possible
match for anatomical site and the percentage
change in counts per region of interest
betweentheearlyandlatescanscalculated.We
adjusted for decay by using the ratio of the
total counts in the slices studied.

<table>
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</table>

H = hyperaemic; R = relative; V = detected on volume measurements only; X = no evidence for reperfusion.
Results
In the 50 consecutive patients with ischaemic stroke who entered the study 124 SPECT scans were taken. Table 1 shows details of scanning times and perfusion defect measurements. Fourteen cases (28%) exhibited reperfusion, which was hyperaemic in eight (57%). Infourof the eight, reperfusion was seen on the first SPECT but involved only part of the volume of the infarct in three of the four. In six of 14 patients (43%), reperfusion was relative and seen on the second SPECT. Reperfusion was never seen on the three month scan. Table 2 shows details of HMPAO uptake in the reperfused regions. Reperfusion inferred from an apparent fall in the perfusion defect in the second SPECT compared with both the first and third SPECT in seven further cases of the 26 cases in which this could be sought (having completed all three scans with no visible reperfusion and with the infarct visible on at least the first and third scans). As these cases were self selecting for survival to three months, primary analysis counted these cases as not reperfused; secondary analysis included them as reperfused. This did not materially alter the findings.

Perfusion defect volumes were not normally distributed (table 1). The SPECT perfusion defect decreased between the first and second scans without reaching significance. There was an increase in perfusion defect between the second and third examinations (medians 6 and 19 cm³ respectively, p<0.001, Wilcoxon signed ranks). We calculated early reperfusion volumes (first−second scan perfusion deficit 15.3 (SD 40.4) cm³, late reperfusion (second−third month scan −22.0 (SD 31.5) cm³), and total reperfusion (first−third scan−10.1 (SD 19.5) cm³). Thus the mean decrease in the perfusion defect of 15 cm³ in the first week was followed by an increase of 22 cm³ by three months—that is, in the 33 cases for whom there are complete data, nutritional reperfusion amounted to 10 cm³ and non-nutritional to 12 cm³.

Analyses for CT infarct volume and for clinical outcome using the Canadian neurological scale score at each clinical examination and the Barthel index at the final examination showed no differences between those with and without reperfusion. Similarly,

Table 2 Abnormal/normal "TC" HMPAO uptake ratios for those cases in which reperfusion was identified.

<table>
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<td>Wash</td>
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</table>

H = hyperaemic; R = relative as defined in the text.
measures of nutritional and non-nutritional reperfusion had no association with outcome.

Reperfusion was without effect on the incidence of oedema, which was identified in 14 (29%) of the 49 cases with CT (p=0.684; \( \chi^2 \) with Yates’ correction). As oedema was not seen in small lesions for reasons that may be artefactual, the data were reanalysed for lesions above 20 cm\(^3\) but this made no difference (p=0.325; \( \chi^2 \) with Yates’ correction).

Haemorrhagic transformation was seen in six cases (12%) and reperfusion was present in four of these (p=0.078, \( \chi^2 = 13.1 \) with Yates’ correction), suggesting an association between these, but with small numbers.

We classified the aetiology in 46 cases (92%). Of these, 13 of 23 embolic lesions and three of 23 thrombotic cases were reperfused (p=0.049, \( \chi^2 = 6.04 \)). The statistical significance increased (p=0.0173, \( \chi^2 = 8.1 \)) when reperfusion inferred from volume measurements was included. Embolic lesions were neither more often haemorrhagic nor oedematous than thrombotic lesions.

Reperfusion was identifiable on the first SPECT in four cases. In only one case did early reperfusion preserve neuronal tissue so that it remained functional and connected, so influencing the clinical course. In one other case there was early haemorrhagic reperfusion limited to the superficial cortical part of an embolic lesion which survived according to \( ^{99} \text{Tc} \)-HMPAO uptake at three months. However, it had no clinically detectable function, presumably because it was disconnected from the remainder of the brain as the surrounding tissues were infarcted.

CASE REPORT

A 59 year old female right handed librarian with a five year history of well treated hypertension and no other stroke risk factors reported two episodes of one minute duration of expressive aphasia and one episode of one minute of right sided tingling in the six months

Figure 5  Repeat SPECT six hours after injection of \( ^{99} \text{Tc} \)-HMPAO (fig 4) shows partial washout of \( ^{99} \text{Tc} \)-HMPAO, most striking at the centre of the lesion (arrowhead).

Figure 6  Final SPECT in the case shown in figs 4 and 5, performed 25 days later, showing a modest perfusion deficit in the centre of the region previously showing the most intense reperfusion.

Figure 7  First SPECT in case 2, at 0.8 days, showing a perfusion deficit in the anterior part of the middle cerebral artery territory, with a zone of hyperaemia posterior to this and a zone of decreased perfusion in the parieto-occipital region. The basal ganglia and adjacent regions are not reperfused.

Figure 8  Final SPECT in case 2, at 106 days, showing that the central part of the region is preserved, corresponding to the hyperaemic region in fig 7, but that it is surrounded by infarcted tissue and is presumed to be functionally disconnected.
before presentation. On the day of presentation she woke unable to speak but with full comprehension. She had no weakness or sensory disturbance and walked normally to her telephone to dial her workplace, but on being answered could not speak. Her speech began to be disturbed and walked normally to her workplace. Twenty-four hours after onset her speech on bedside testing was normal in content and without errors but slow. There was minimal right upper motor neuron facial weakness and a mild right sided cortical sensory deficit but no other signs. SPECT showed an average 24% increase in 99Tcm HMPAO retention in the cortical distribution of the left middle cerebral artery compared with the right (fig 1). Full haematological investigation, chest radiography, ECG, and carotid duplex Doppler were normal. Echocardiography disclosed an enlarged left atrium. At five days, CT showed slight cortical low density on one slice, SPECT was normal and no clinical signs remained. Neuropsychological assessment showed only impaired verbal fluency. Brain MRI at six weeks showed increased signal limited to the white matter (fig 3). Despite aspirin, she had a further similar event two months after the first but with less complete recovery on neuropsychological evaluation. She was anticoagulated. SPECT at 48 hours after the second event showed increases averaging 12% (range 8% to 54%) in the left middle cerebral artery cortical territory (fig 4). A further scan six hours later (fig 5) showed partial washout of 10% overall (not significant), but it was limited to the central zone, where the volumes had the highest uptake. Here the excess retention fell from 54% to 26%. A final SPECT one month later showed persisting perfusion deficits consistent with patchy infarction at the centre of the affected volume (fig 6).

Repeat scans six hours after injection, looking for redistribution of 99TcHMPAO after hyperaemic reperfusion, were carried out on five occasions (table 2). The case described above was the only one in which substantial redistribution was seen. After the first event there was an overall increase in retention, from 124% to 131% of the opposite side but in some individual regions of interest at the centre of the lesion there was evidence of washout reaching a maximum of −27%. More peripherally there was an increase in uptake. At the second event there was slight overall washout, from 112% to 110% of the opposite side but focally this reached a maximum of −35%. In the other cases studied there were no significant global or focal changes in retention, focal changes ranging between between −13% and +6%. These figures lie within the 95% confidence intervals for small regions of interest. In one case there was a non-reperfused region and here there was a significant increase in retention, from +31 to +42% in individual regions of interest.

**Discussion**

In this study 28% of cases exhibited reperfusion directly visible on SPECT and a further 14% had evidence of reperfusion deduced from perfusion deficit volume measurements. This proportion is in keeping with other studies done at a similar time after stroke, suggesting similar criteria for defining reperfusion. Nevertheless, the meaning of “reperfusion” seen with 99TcHMPAO is uncertain. Its uptake is dependent not only on local cerebral blood flow but also intracellular glutathione, although more recent evidence suggests a primary role for the extracellular redox state. Furthermore, three case reports suggest that 99TcHMPAO may overestimate cerebral blood flow. However, there has been no conclusive confirmation of this report. Some support comes from four cases of acute infarction imaged with both PET and 99TcHMPAO SPECT. In two cases, 99TcHMPAO retention exceeded that expected from the PET study, although in both these cases the 99TcHMPAO study was done two days after the PET. In the other two cases, where the 99TcHMPAO and PET studies were separated by only one day, the findings were concordant. The authors, therefore, cannot conclusively confirm spurious hyperfixation. However, uncertainty over this point means that our comments may apply only to phenomena found with 99TcHMPAO. Similarly, we have avoided the term “luxury perfusion” because its meaning varies according to the technique used to identify it. Originally it was a simple increase in cerebral blood flow above that normally expected at that site. With the arrival of metabolic studies and PET, the term was equated with a low oxygen extraction ratio irrespective of local cerebral blood flow. The importance of the distinction was shown by Baron et al; a low oxygen extraction ratio was...
found in 82% of infarcts less than 31 days old, but, in these, cerebral blood flow was decreased in 52%, normal in 34%, and increased in only 14%.

The mean time of the 14 SPECT scans showing reperfusion was 5.8 days from onset and 10 of these had earlier scans that did not show reperfusion, suggesting that spontaneous reperfusion usually occurs after the first day. This is supported by most studies that have identified spontaneous reperfusion, which usually report its occurrence within two weeks of the ictus. One study reported that one third of cases had reperfused within 18 hours of onset. However, two thirds were embolic. This unusually high proportion may explain the finding.

In the two cases in which reperfusion was early enough to preserve tissue, both showed reperfusion in the first scan. In one it was patchy, probably reflecting distal migration of embolic fragments and the surviving tissue was disconnected from the rest of the brain, rendering it functionally useless (figs 7–9). Functionally beneficial spontaneous reperfusion is therefore rare, occurring in one in 50 cases and these findings are consistent with other work. Volumetric analysis suggests that the mean benefit of spontaneous reperfusion is the preservation of 10 cm³ of tissue, corresponding to the nutritional reperfusion reported by Infeld et al.1

Perhaps more important in view of the increasing interest in thrombolytic treatment is the demonstration in one case that early reperfusion may enable full recovery, even after a total middle cerebral artery event. In the case report above, symptoms were present for three hours, and probably longer, as they were present on waking. However, as the clinical deficit was limited to dysphasia despite changes throughout the middle cerebral artery territory, it seems likely that reperfusion had already occurred by the time of awakening and this is supported by the association of early reperfusion with embolic events. The extensive cortical changes on MRI, with only trivial dysphasia, suggest that the cortex underwent a change detectable on MRI that did not involve extensive neuronal loss, perhaps a form of incomplete infarction. Similar cases have rarely been reported. In a study of reperfusion after cerebral infarction using radioactive xenon, three cases were identified without deficits on CT despite pronounced hyperaemia on xenon cerebral blood flow studies. One of these involved dysphasia lasting two days, akin to the case here.

The increase in CT infarct volume between the second day and a week probably reflects increasing oedema rather than infarct volume as the SPECT perfusion defect, detecting reperfusion, usually remained constant or decreased at one week, a common finding. Oedema, seen in 29% of cases, was not significantly associated with spontaneous reperfusion. This suggests that the ingress of oedema fluid is not driven by arterial perfusion, and we hypothesise that it arises by retrograde venous flow, or from the adjacent cerebral parenchyma.

Although the association between reperfusion and haemorrhagic transformation did not reach significance, four of six haemorrhagic infarcts were associated with reperfusion. We suspect that the failure to detect an association was a false negative due to small numbers, as an association has been suggested by others and is biologically plausible.

Costa and Ell25 reported that 18.5% washout of ¹¹⁵Te HMPAO from an infarct might reflect a good prognosis. Our single case in which this was seen supports this suggestion, but the full series of 50 cases show that it is rare. It is also inconsistent, not always being seen in reperfused tissue that survived and putty when it was, being restricted to the lesion’s centre. More peripheral areas that were reperfused and survived did not show washout; they exhibited either no change or a slight increase. The process underlying washout has not been fully explained. Usually after cerebral infarction, no change in ¹¹⁵Te content, or an increase due to the influx of free ¹¹⁵Te pertechnetate, is expected. A fall must represent a different process. Washout from an increased cerebral blood volume has been suggested as ¹¹⁵Te HMPAO is cleared from the plasma by the liver. However, the plasma volume available and its proportionate uptake could not account for washout of more than 6%. Leakage of converted ¹¹⁵Te HMPAO may offer a better explanation.26

We conclude that spontaneous reperfusion occurs in 42% of cases of cerebral infarction, usually between one day and one week after stroke. When all the cases are analysed volumetrically there is evidence for salvage of a mean of 10 cm³ of tissue by nutritional reperfusion, although most reperfusion is non-nutritional. Extensive preservation of tissue is rare (4% of cases) and requires very early reperfusion. Spontaneous reperfusion is not associated with cerebral oedema but may be with haemorrhagic transformation. The natural history of reperfusion mirrors the recent trials of thrombolytic therapy in which gainful reperfusion can only be shown after treatment within three hours and is bought at the cost of more frequent haemorrhagic transformation.

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SPECT and stroke reperfusion


